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(54) **Title**: NOVEL CYCLOALKANONE β-SUBSTITUTED ALANINE DERIVATIVES

(57) **Abstract**: The present invention relates to cycloalkanone β-substituted alanine derivatives, a process for the preparation of cycloalkanone β-substituted alanine derivatives and the use of cycloalkanone β-substituted alanine derivatives in the preparation of enantiomerically enriched α-amino acids. Furthermore, the present invention relates to the preparation of pharmaceutically active products such as perindopril and ramipril using the novel cycloalkanone β-substituted alanine derivatives.

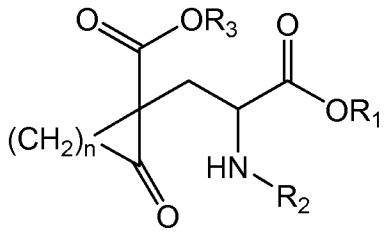
NOVEL CYCLOALKANONE β-SUBSTITUTED ALANINE DERIVATIVES

Field of the invention

The present invention relates to cycloalkanone β-substituted alanine derivatives, a process for the preparation of cycloalkanone β-substituted alanine derivatives and the use of cycloalkanone β-substituted alanine derivatives in the preparation of enantiomerically enriched α-amino acids.

Background

Cycloalkanone β-substituted alanine derivatives of the general formula [**1**] are versatile building blocks in many synthetic approaches towards a wide variety of medicines.

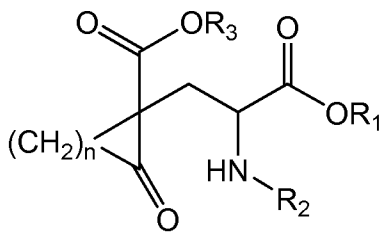


[**1**]

A particularly attractive application of cycloalkanone β-substituted alanine derivatives is the use in enzyme mediated synthesis of enantiomerically pure α-amino acids.

Detailed description of the invention

In the first aspect of the present invention, a new class of alanine derivatives is provided, namely compounds of the general formula [**1**]



[**1**]

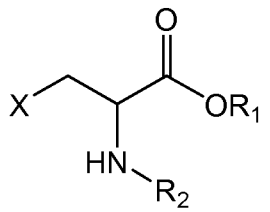
wherein R_1 is alkyl or hydrogen, R_2 is acyl, R_3 is alkyl or hydrogen and n is 1, 2, 3, 4, 5 or 6 or salts thereof.

In one embodiment R_1 and R_3 preferably are, independently, methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, benzyl or sec-butyl, R_2 is acetyl, phenylacetyl, carbobenzyloxy, formyl, propionyl or butyryl and n is 3 or 4.

In another preferred embodiment, the compound of the present invention is further converted into the ACE inhibitors perindopril or ramipril.

In the second aspect of the invention, a method for the preparation of the compounds of the first aspect is provided. It has been found that the cycloalkanone β–substituted alanine derivatives of the present invention can be successfully prepared starting from easily accessible compounds such as amino acids.

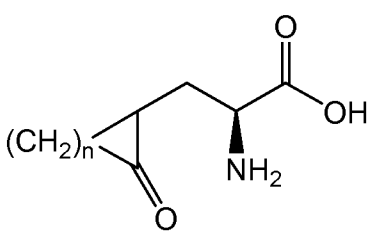
In a first embodiment of the second aspect, a compound of formula [**2**],



[**2**]

wherein R_1 is alkyl, R_2 is acyl and X is halogen, is treated with an amine or other base such as sodium or potassium methoxide, sodium or potassium ethoxide, etc, optionally followed by removal of amine salt followed by treatment with an ester of cycloalkanone-2-carboxylic acid in the presence of a catalytic amount of base to give the compound of general formula [**1**]. Preferably, R_1 is methyl, R_2 is acetyl and X is chlorine. It has been found that compounds [**2**] can be successfully prepared starting from easily accessible compounds such as amino acids like cysteine or serine using methods known to the skilled person.

In a second embodiment, the method as described in the first embodiment is further expanded by conversion of said compound of general formula [**1**] to give a compound of general formula [**3**]



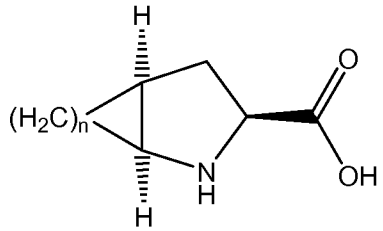
[**3**]

wherein n is 1, 2, 3, 4, 5 or 6 and which has the *S*-configuration at the nitrogen-substituted carbon atom, preferably with an ee-value >95%, more preferably >98%, most preferably >99.5%.

Said conversion is carried out by hydrolysis of compound [**1**] followed by addition of cyanate. Preferably hydrolysis is carried out under acidic conditions, for instance using hydrochloric acid under reflux. Addition of cyanate is preferably carried out at neutral pH (*i.e.* 5.5 to 8.5, preferably 6 to 8, more preferably 6.7 to 7.5) using well-known cyanate sources of which KOCN and NaOCN are well-working examples. The resulting 3-(2-oxocycloalkyl)-2-ureidopropanoic acid is then converted into the compound of formula [**3**] in a bioconversion using a biocatalyst. Preferably, said bioconversion is carried out by the action of the enzyme carbamoylase. This enzyme may be used *in vitro* or *in vivo*. Alternatively, the carbamoylase is part of a system of more enzymes, for instance a hydantoinase, a carbamoylase and hydantoin racemase.

Alternatively, 3-(2-oxocycloalkyl)-2-ureidopropanoic acid can be converted to the corresponding hydantoin at low pH and elevated temperatures prior to the bioconversion as also hydantoins are good substrates for the enzyme system mentioned above.

In a third embodiment, the method as described in the second embodiment is further expanded by subjecting said compound of formula [**3**] to hydrogenation to give a compound of general formula [**4**]

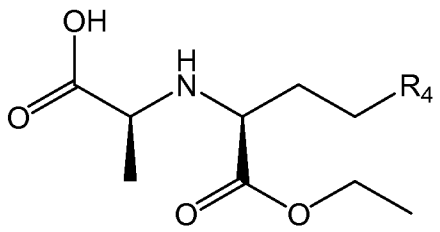


[**4**]

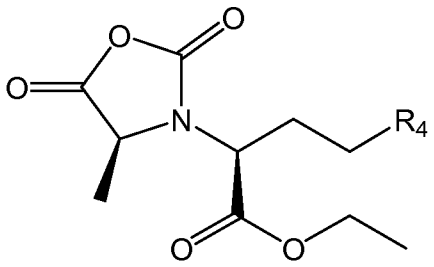
wherein n is 1, 2, 3, 4, 5 or 6 and which predominantly has the *S*,*S*,*S*-configuration, preferably >85%, more preferably >90%, most preferably >95%. Preferably, hydrogenation is carried out in the presence of a suitable metal-based heterogeneous catalyst or homogeneous catalyst. Metal-based heterogeneous catalysts can be, for instance, Pd on carbon or Pt on carbon. Metal-based homogeneous catalysts can be based on, for instance, Ru, Rh, Ir, and the like, with or without ligand. Hydrogenation can be carried out in a polar solvent such as water, methanol, ethanol, acetic acid or

mixtures thereof, under a pressure of hydrogen gas between 1 and 15 bar, preferably 8 to 12 bar, at a temperature between 0 and 80°C, preferably between 30 and 60°C.

In a fourth embodiment, the method as described in the third embodiment is further expanded by reacting said compound of general formula [**4**] with a carboxylic acid or with an activated carboxylic acid, preferably with an "activated" form of a compound of general formula [**5**] or with a compound of general formula [**6**]

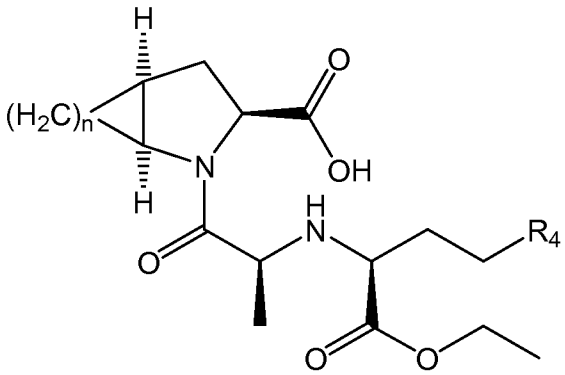


[**5**]



[**6**]

wherein R_4 is alkyl or aryl, preferably $-CH_3$ or phenyl, to give a compound of formula [**7**].



[**7**]

Optionally, the carboxylic acid group of compound [**4**] is protected prior to reaction with compound [**5**] or its activated form or [**6**] with the objective to circumvent unwanted side-reactions. The person skilled in the art is aware of the various protecting groups suitable for this purpose. Particularly suitable is protection of compound [**4**] as a benzyl ester or as a substituted benzyl ester. After reaction with compound [**5**] or [**6**], the resulting carboxylic acid protected derivative of compound [**7**] can be deprotected to furnish compound [**7**] using standard techniques. When the protecting group is a benzyl ester or as a substituted benzyl ester, deprotection can for instance be carried out using hydrogenation.

In the third aspect of the present invention, the compounds of the first aspect of the invention are used in the preparation of a medicament, preferably in the preparation of ramipril. Said uses can be accomplished through the method and intermediate products of the second aspect of the invention.

EXAMPLES

Example 1

Preparation of ethyl 1-(2-(methoxycarbonyl)-2-acetamidoethyl)-2-oxocyclopentanecarboxylate

1. Preparation of methyl 2-acetamidoacrylate

(*R*)-methyl 2-acetamido-3-chloropropanoate (30.0 g, 0.167 mol) was suspended in toluene (250 mL) and triethylamine (20.2 g, 0.200 mol) was added via addition funnel within 5-10 min and the mixture was heated at 45 °C for 6 h. The heterogeneous mixture was then cooled to 22°C and the triethylammonium chloride salt was filtered off quantitatively under suction and washed with fresh toluene (2 x 60 mL). The combined mother liquor and toluene washes are concentrated at 45°C to a final weight of approximately 245 g. This solution contains methyl 2-acetamidoacrylate, used as such in the next step.

2. Preparation of ethyl 1-(2-(methoxycarbonyl)-2-acetamidoethyl)-2-oxocyclopentanecarboxylate

To the solution obtained above containing methyl 2-acetamidoacrylate (approximately 23.9 g, 0.167 mol) was added ethyl 2-oxocyclopentanecarboxylate (31.1 g, 97%, 0.193 mol) and DBU (3.50 g, 0.023 mol) and the homogeneous solution was stirred for 18 h at 22°C. Then, 6 N aq. HCl (3.8 mL) was added and stirred and the phases were allowed to separate. The aqueous phase was discarded and the residual solution was concentrated to an oil weighing 58.4 g. A small amount of the oil was purified by silica gel flash chromatography to give the pure product as a mixture of two diastereomers. ^{1}H NMR ($CDCl_3$): δ 6.49 (d, 0.5H, one diastereomer), 5.81 (d, 0.5H, other diastereomer), 4.75-4.59 (m, 1H), 4.21-4.12 (m, 2H), 3.72 (s, 3H), 2.56-1.97 (m, 8H), 1.97 (s, 3H), 1.26 (t, 3H).

Example 2

Preparation of 3-(2-oxocyclopentyl)-2-ureidopropanoic acid

1. Preparation of 2-amino-3-(2-oxocyclopentyl)propanoic acid

The crude oil obtained in Example 1 containing ethyl 1-(2-(methoxycarbonyl)-2-acetamidoethyl)-2-oxocyclopentanecarboxylate (58.3 g) was dissolved in 2N aq. HCl (270 mL, 0.540 mol) and the solution was heated at 90-95°C for 7 h, during which time volatiles were removed under atmospheric pressure (mixture of methanol, ethanol, acetic acid and water). The resulting reaction mixture was cooled to 22°C and washed with MTBE (50 mL). The residual aqueous solution was concentrated to remove any dissolved MTBE to a final weight of 200 g, containing 2-amino-3-(2-oxocyclopentyl)propanoic acid and is used as such in the next step.

2. Preparation of 3-(2-oxocyclopentyl)-2-ureidopropanoic acid

The solution obtained in the previous step was cooled to 10°C and by slow addition of NaOH pellets (23.3 g, 0.582 mol), the pH was brought to 7.3. Then, potassium cyanate (14.9 g, 96%, 176 mmol) was added and the mixture was heated to 60°C. After 5.5 h, the solution was cooled to 6°C in an ice-bath and acidified with 5 N aq. HCl (38 mL) to pH 3.6 and was seeded with 20 mg product. The pH was further lowered to 1.7 with 5 N aq. HCl (19 mL) and the green-grey slurry was stirred for 15 min and then the product was collected on a filter under suction. The cake was washed with cold 1 N aq. HCl (2 x 30 mL), cold acetone (3 x 30 mL) and air-dried. Weight 21.7 g, 61% yield, purity >98% (HPLC). ^{1}H NMR: (DMSO-d_6, 300 MHz): δ 12.57 (br s, 1H), 6.22 (dd, 1H), 5.60 (br s, 2H), 4.23-4.04 (m, 1H), 2.27-1.40 (m, 9H).

Example 3

Preparation of (*S*)-2-amino-3-(2-oxocyclopentyl)propanoic acid

1. Transformation of pKECaroP-hyu1 construct into Escherichia coli RV308

- Thaw *Escherichia coli* RV308 aliquots (200 µl, super competent) on ice
- Add 15 µl LR reaction mix (see above)
- Incubate 30 minutes on ice
- Heat shock 1 minute 42°C
- Cool cells 2 minutes on ice
- Add 1 mL LB medium (5 g/l NaCl, 5 g/l yeast extract, 10 g/l tryptone)

- Incubate 1 h at 37°C
- Plate on LB agar plates supplemented with kanamycine (5 g/l NaCl, 5 g/l yeast extract, 10 g/l tryptone, 15 g/l agar, 50 mg/l kanamycine)
- Incubate 24 h at 28°C
- Isolate single colonies
-

2. Expression of Hyu genes in Escherichia coli RV308

Single clones from the transformation (see above) were used to inoculate 5 mL of 2xTY media (10 g/l yeast extract, 16 g/l tryptone, 5 g/l NaCl) supplemented with 0.05 g/l kanamycine and 1 mM $MnCl_2$ or $CoCl_2$, respectively. The culture was incubated at 28°C and 150 rpm for 24 h and then used for inoculation of 100 mL 2xTY media supplemented with 0.05 g/l kanamycine and 1 mM $MnCl_2$ or $CoCl_2$, respectively. The cultures were again incubated for 24–28 h under conditions previously mentioned and subsequently harvested by centrifugation (20 min, 5000 rpm, 4°C). The cell pellet was resuspended in 5 mL Tris-HCl (100 mM, pH 7), centrifuged again (20 min, 5000 rpm, 4°C) and the cells were frozen at –20°C.

3. Bioconversion

3-(2-oxocyclopentyl)-2-ureidopropanoic acid (13.5 g, 0.063 mol) was suspended in water (40 mL) and the pH was adjusted to 7.3 with 10.8 N aq. NaOH (6.3 mL). Then, $MnCl_2$ solution (3.75 mL, 100 mmol/L) was added and the solution was flushed with N_2 for 15 min. Then 60 g of wet cell slurry obtained according to 'Expression of Hyu genes in *Escherichia coli* RV308' (see above) was added. The reaction was stirred at 24°C for 22 h, after which time TLC indicated complete conversion to product. During this period, the pH was kept constant at 7.3 by addition of 5.4 N aq. H_3PO_4. Finally, the pH was lowered further to 4.0 by addition of 5.4 N aq. H_3PO_4. The reaction mixture was then centrifuged (12.500 rpm) and the clear solution thus obtained was further subjected to microfiltration (0.45 µ). The product 2-amino-3-(2-oxocyclopentyl)propanoic acid in solution has the *S* configuration at C2 with >99% ee (the other chiral center C4 is scrambled). This solution is used immediately in the next step (reduction).

Example 4

Preparation of (2*S*,3a*S*,6a*S*)-octahydrocyclopenta[b]pyrrole-2-carboxylic acid

To the aqueous solution obtained in Example 3 containing (*S*)-2-amino-3-(2-oxocyclopentyl)propanoic acid was added 5% Pt/C (3.0 g, 42% water-content) and the hydrogenation was performed under 10 bar of hydrogen gas pressure for 16 h at 70°C. At the end of the reaction, the catalyst was separated on filter paper under suction and the product (2*S*,3a*S*,6a*S*)-octahydrocyclopenta[b]pyrrole-2-carboxylic acid residing in solution was analyzed by HPLC. The diastereomeric ratio is 95:5. The product was purified from salts and other impurities on an ion-exchange column (Amberlyst 15, 80 mL/144 meq.). Elution was initially done with water to neutral pH to remove impurities. Then, the amino acid was eluted with 2N aq. NH_3 aq. and water to neutral pH. These aqueous fractions were combined and concentrated to give the product as an off-white solid. ^{1}H NMR (major diastereomer2*S*,3α*S*,6α*S*): (DMSO-d_6, 300 MHz): δ 10.54 (br s, 1H), 8.71 (br s, 1H), 4.22 (dd, 1H), 3.98 (t, 1H), 2.86-2.76 (m, 1H), 2.49-2.42 (m, 1H), 2.00-1.96 (m, 1H), 1.80-1.40 (m, 6H).

Example 5

Preparation of (2*S*,3a*S*,6a*S*)-benzyl octahydrocyclopenta[b]pyrrole-2-carboxylate, 4-toluenesulfonate (1:1) from (2*S*,3a*S*,6a*S*)-octahydrocyclopenta[b]pyrrole-2-carboxylic acid

In a round-bottom flask equipped with a Dean-Stark trap, (2*S*,3a*S*,6a*S*)-octahydrocyclopenta[b]pyrrole-2-carboxylic acid obtained in Example 4 (5.00 g, 32.2 mmol) was suspended in toluene (100 mL) and *p*-toluenesulphonic acid monohydrate (6.60 g, 34.7 mmol) and benzyl alcohol (15.0 mL, 15.6 g, 144 mmol) were added and the mixture was brought to reflux. The reaction was refluxed for 8 h and then allowed to cool to room temperature. A colorless solid precipitated. Most of the solvent was then removed *in vacuo* at 65°C. To the residual thick suspension, ethyl ether (200 mL) was added and the solid was collected on a filter (porosity #3) under suction and was further washed with ethyl ether (4 x 50 mL). The colorless product was allowed to air-dry. Weight 12.1 g, 90% yield.

Example 6

Preparation of N-[(*S*)-1-(ethoxycarbonyl)-3-phenyl-propyl]-L-alanylchloride HCl from N-[(*S*)-1-(ethoxycarbonyl)-3-phenyl-propyl]-L-alanine

N-[(*S*)-1-(ethoxycarbonyl)-3-phenyl-propyl]-L-alanylchloride HCl was synthesized from N-[(*S*)-1-(ethoxycarbonyl)-3-phenyl-propyl]-L-alanine and PCl_5 in CH_2Cl_2 at 0±3°C and precipitated by slow addition of cyclohexane as outlined in US 2006/0079698. Filitration was carried out under an atmosphere of nitrogen.

Example 7

Preparation of (2*S*,3a*S*,6a*S*)-octahydrocyclopenta[b]pyrrole-2-carboxylic acid, 1-[(2*S*)-2-[[(1*S*)-1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl], phenylmethyl ester from (2*S*,3a*S*,6a*S*)-benzyl octahydrocyclopenta[b]pyrrole-2-carboxylate

The toluenesulfonate salt prepared in Example 5 (6.00 g, 14.4 mmol) was suspended in CH_2Cl_2 (60 mL) and triethylamine (1.46 g, 14.4 mmol) was added at 0°C. The slurry was stirred for 30 min and then imidazole (2.94 g, 43.1 mmol) was added in small portions, followed by N-[(*S*)-1-(ethoxycarbonyl)-3-phenyl-propyl]-L-alanylchloride HCl prepared in Example 6 (5.28 g ,15.8 mmol). The reaction mixture was stirred for 2 h at 0°C and then allowed to warm to 20°C within 30 min and stirred at that temperature for 2 h. Water (60 mL) was then added and after vigorous mixing of the phases, the organic layer was separated and the aqueous layer was extracted once more with CH_2Cl_2 (60 mL). The combined organic layers were washed with aqueous saturated $NaHCO_3$ (60 mL), treated with charcoal (1 g) and dried over anhydrous Na_2SO_4 (5 g). After filtration of the salt and evaporation of the solvent *in vacuo* at 40°C, the product was obtained as a yellowish oil. This oil was redissolved in methanol (90 mL) and 5% Pd/C (0.50 g) was added and hydrogenation was performed under 2 bar of hydrogen pressure. After approx. 4 h, consumption of hydrogen ceased and the catalyst was filtered off on a pad of celite. Additional methanol was used to wash the celite (20 mL). The organic layer was removed *in vacuo* at 50°C. The residue was recrystallized from ethyl ether (100 mL) at 0°C. The product ramipril ([**7**], R_4 = phenyl) is a colorless solid. Weight 4.56 g, 70% yield.

Example 8

Preparation of ethyl 1-(2-(methoxycarbonyl)-2-acetamidoethyl)-2-oxocyclohexanecarboxylate

1. Preparation of methyl 2-acetamidoacrylate

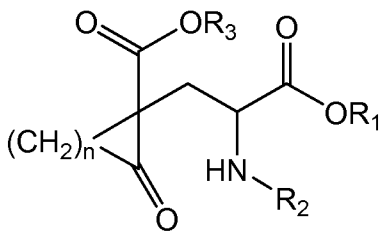
(*R*)-methyl 2-acetamido-3-chloropropanoate (30.0 g, 0.167 mol) was suspended in toluene (250 mL) and triethylamine (20.2 g, 0.200 mol) was added via addition funnel within 5-10 min and the mixture was heated at 45°C for 6 h. The heterogeneous mixture was then cooled to 22°C and the triethylammonium chloride salt was filtered off quantitatively under suction and washed with fresh toluene (2 x 60 mL). The combined mother liquor and toluene washes are concentrated at 45°C to an oil, which upon cooling to 22°C, crystallizes to a colorless solid. Weight 23.6 g, 99% yield. ^{1}H NMR ($CDCl_3$): δ 7.72 (br s, 1H), 6.60 (s, 1H), 5.88 (s, 1H), 3.84 (s, 3H), 2.11 (s, 3H).

2. Preparation of ethyl 1-(2-(methoxycarbonyl)-2-acetamidoethyl)-2-oxocyclohexanecarboxylate

Ethyl 2-oxocyclohexanecarboxylate (1.23 g, 95%, 6.85 mmol) was dissolved in dry THF (10 mL) at 0°C and a solution of *n*-BuLi in hexanes (15% w/w, 1.50 mL, 2.39 mmol) was added dropwise. After stirring the solution for 5 min, solid methyl 2-acetamidoacrylate (0.600 g, 4.19 mmol) was added and 5 min later, the cold bath was removed and the reaction was stirred for 4 days at 22°C. Then, acetic acid (0.140 mL) was added and the solution was stirred for 5 min and then concentrated *in vacuo* and the residue was purified by silica gel flash chromatography to give the product as a colorless oil (ca. 2:3 mixture of two diastereomers. Weight 850 mg, 65% yield ^{1}H NMR ($CDCl_3$): δ 6.53 (br d, 0.4H, minor diastereomer), 5.99 (d, 0.6H, major diastereomer),4.55 (ddd, 0.6H, major diastereomer), 4.37-4.23 (m, 0.4H), 4.21-4.04 (m, 2H), 3.65 (s, 3H), 2.55-2.36 (m, 3H), 2.32-2.08 (m, 2H), 2.00-1.90 (m, 1H), 1.90 (s, 1.8H, major diasteromer), 1.87 (s, 1.2H, minor diastereomer), 1.77-1.46 (m, 4H), 1.21 (t, 1.2H, minor diastereomer), 1.20 (t, 1.8H, major diastereomer).

CLAIMS

1. A compound of formula [**1**]

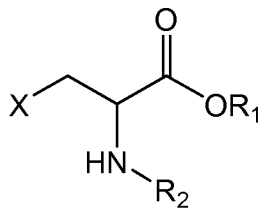


[**1**]

wherein R_1 is alkyl or hydrogen, R_2 is acyl, R_3 is alkyl or hydrogen and n is 1, 2, 3, 4, 5 or 6 or salts thereof.

2. Compound according to claim 1 wherein R_1 is methyl, R_2 is acetyl, R_3 is methyl or ethyl and n is 3 or 4.

3. Method for the preparation of the compounds of anyone of claims 1 to 2 comprising treatment of a compound of formula [**2**]



[**2**]

wherein R_1 is alkyl, R_2 is acyl and X is halogen with a base, followed by treatment with an ester of cycloalkanone-2-carboxylic acid in the presence of a catalytic amount of base.

4. Method according to claim 3 wherein amine salts are removed prior to said treatment with an ester of cycloalkanone-2-carboxylic acid.

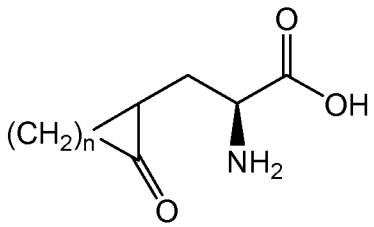
5. Method according to any one of claims 3 to 4 further comprising the steps of:

a) contacting said compounds of anyone of claims 1 to 2 with an acid or with hydroxide followed by acid;

b) contacting the product obtained in step a) with a cyanate;

c) contacting the product obtained in step b) with a carbamoylase,

to give a compound of the general formula [**3**]

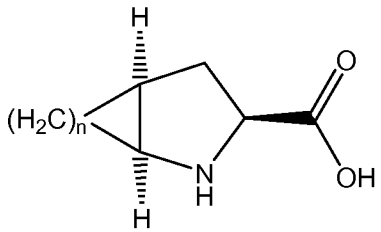


[**3**]

wherein n is 1, 2, 3, 4, 5 or 6.

6. Method according to claim 5 wherein in step c) also a racemase and/or a hydantoinase is present.

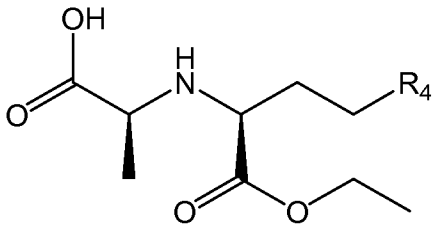
7. Method according to anyone of claims 5 to 6 further comprising subjecting said compound of general formula [**3**] to hydrogenation to give a compound of the general formula [**4**]



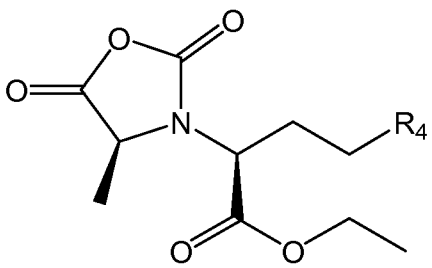
[**4**]

wherein n is 1, 2, 3, 4, 5 or 6 or salts thereof.

8. Method according to claim 7 further comprising contacting said compound of general formula [**4**] with a compound of general formula [**5**] or a compound of general formula [**6**]

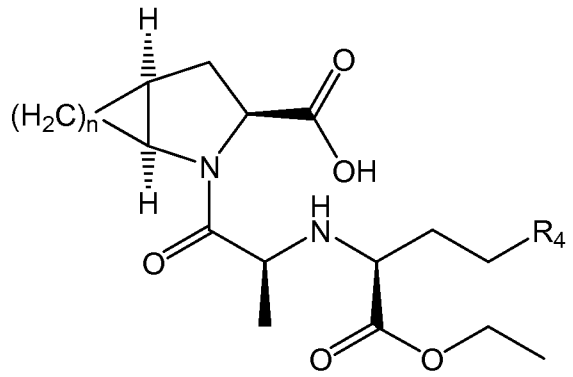


[**5**]



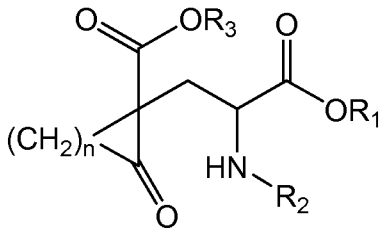
[**6**]

wherein R_4 is $-CH_3$ or phenyl, to give a compound of the general formula [**7**].



[7]

9. Use of a compound of general formula [1]



[1]

wherein R_1 is alkyl, R_2 is acyl, R_3 is alkyl and n is 3 or 4 in the preparation of ramipril and perindopril respectively.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/051312

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C233/47 C07D209/42 C07D209/52

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 C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2007/079871 A (SANOFI AVENTIS DEUTSCHLAND [DE]; BERK HOLGER [DE]; ZOCHER FRANK [DE];) 19 July 2007 (2007-07-19) page 4, line 21 - page 5, line 25 page 9, line 5 - line 11 claims 5,7	1,3,9
A	US 2006/149082 A1 (DUBUFFET THIERRY [FR] ET AL) 6 July 2006 (2006-07-06) paragraphs [0013] - [0029]	1,3,9

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[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

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"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
14 April 2009	21/04/2009

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	Fitz, Wolfgang

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/051312

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HAGIWARA H ET AL: "Domino Michael-O-alkylation reaction: one-pot synthesis of 2,4-diacylhydrofuran derivatives and its application to antitumor naphthofuran synthesis" JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1, CHEMICAL SOCIETY. LETCHWORTH, GB, vol. 22, 1 January 2001 (2001-01-01), pages 2946-2957, XP003016073 ISSN: 0300-922X page 41; table 4; compounds 5,15,48	1,3,9
A	EP 0 625 571 A (DEGUSSA [DE]) 23 November 1994 (1994-11-23) page 8, scheme 1	1,3,9

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