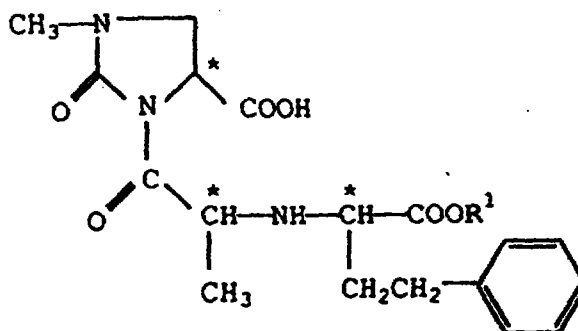


Description

This invention relates to a novel process for preparing optically active 2-oxoimidazolidine derivatives useful as pharmaceutical compounds.

This invention also relates to a novel intermediate of said 2-oxoimidazolidine derivative.

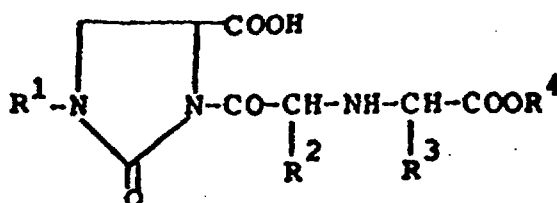
2-Oxoimidazolidine derivatives represented by the formula:



wherein R¹ represents hydrogen atom or a lower alkyl group and * represents an asymmetric carbon atom, are pharmaceutical compounds useful as hypotensors having excellent angiotensin converting enzyme (ACE) inhibitory activity.

The 2-oxoimidazolidine derivatives have three asymmetric carbons within the molecule, and their absolute configurations affect greatly the activity, and it has been known in the art that compounds of (S, S, S) configuration in which the absolute configurations of the three asymmetric carbon atoms are all (S) configurations are most preferred (Japanese Patent Publication No. 58233/1985 which corresponds to European Patent Application No. 0 095 163).

The novel compounds of EP-A-0 095 163 also have inhibitory activity against ACE and are useful to reduce or relieve angiotension related hypertension. The prior compounds are those of the formula:



wherein R¹ is lower alkyl or phenyl-lower alkyl, R² is lower alkyl, R³ is alkyl of one to 12 carbon atoms or phenyl-lower alkyl and R⁴ is hydrogen or lower alkyl, or a pharmaceutically acceptable salt thereof. The lower alkyl groups as disclosed in the prior specification may have 1, 2, 3 or 4 carbon atoms.

As a process for preparing compounds having such (S, S, S) configuration, in the above-mentioned patent specification, there is disclosed a process which comprises (1) reacting a (4S)-1-methyl-2-oxoimidazolidine-4-carboxylic acid ester with 2-bromopropionic acid chloride to form (4S)-1-methyl-3-(2-bromopropionyl)-2-oxoimidazolidine-4-carboxylic acid ester, (2) reacting this product with a (2S)-2-amino-4-phenylbutyric acid ester, then separating the compound of (S, S, S) configuration from the product, and subsequently (3) eliminating the ester residue.

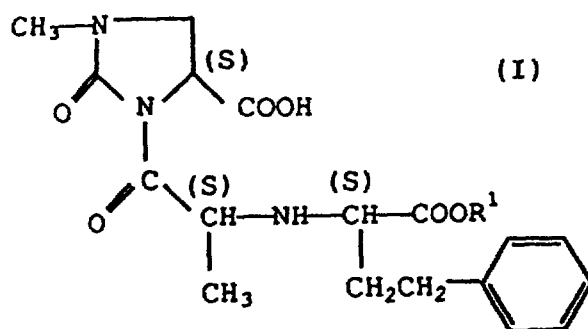
However, according to the above known method, in the condensation reaction of the step (2), the compound of (S, S, S) configuration and the compound of (S, R, S) configuration are formed, and also diastereo-selectivity is exhibited to give the compound of (S, R, S) configuration as the major product. For this reason, there have been involved drawbacks that separation of the compound of (S, S, S) configuration from the compound of (S, R, S) configuration is required for isolation thereof and also that the isolation yield of the (S, S, S) isomer is low.

Also, in the above known method, even when 2-bromopropionic acid chloride may be replaced with a compound of (S) configuration or (R) configuration, racemization and diastereoselectivity occur in the reaction of the step (2) to produce compounds of (S, S, S) configuration and (S, R, S) configuration, and also give the compound of (S, R, S) configuration as the major product, thus involving the same drawbacks as mentioned above.

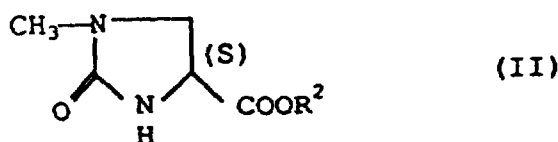
The present inventors, in view of the state of the art as described above, made various studies in order to establish a process which can prepare industrially advantageously 2-oxoimidazolidine derivatives of (S, S, S) configuration having potent activity, and consequently found that by use of a reactive derivative at the carboxyl group of (2R)-2-lower alkylsulfonyloxy (or arylsulfonyloxy)propionic acid in place of 2-bromopropionic acid in the above known method, no racemization occurs in the course of the reaction, and also the above (R) configuration is inverted to the (S) configuration in the condensation reaction with the (2S)-2-amino-4-phenylbutyric acid ester to give the desired 2-oxoimidazolidine-4-carboxylic acid derivative having (S, S, S) configuration stereoselectively and at high yield, to accomplish the present invention.

Thus, an object of the present invention is to provide a novel process for preparing 2-oxoimidazolidine derivative of (S, S, S) configuration. Another object of the present invention is to provide a novel intermediate of said 2-oxoimidazolidine derivative.

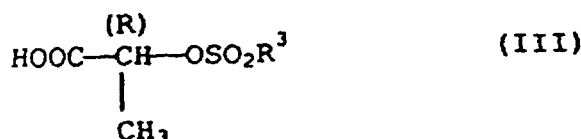
According to the present invention, the optically active 2-oxoimidazolidine derivative having (S, S, S) configuration of the formula:



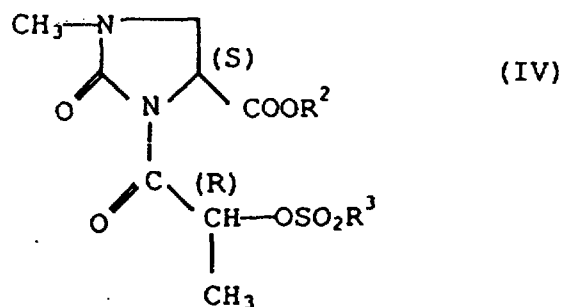
wherein R¹ represents hydrogen atom or a lower alkyl group, can be prepared by reacting a 2-oxoimidazolidine-4-carboxylic acid ester derivative having (S) configuration of the formula:



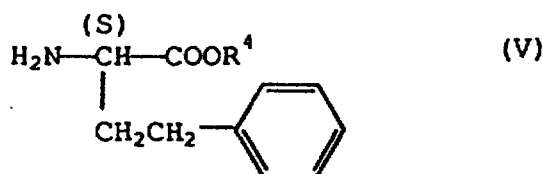
wherein R² represents a tert-butyl group or a benzyl group, with a reactive derivative at the carboxyl group of a propionic acid compound having (R) configuration of the formula:



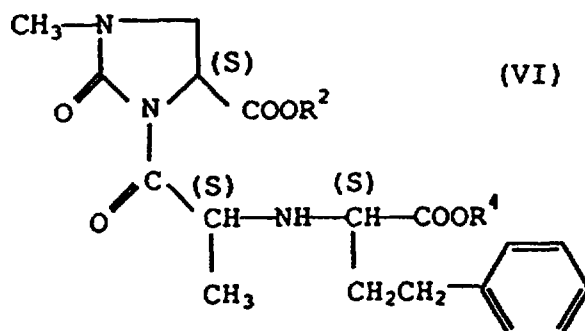
wherein R³ represents a lower alkyl group or an aryl group, to form a 3-acyl-2-oxoimidazolidine-4-carboxylic acid ester derivative having (S, R) configuration of the formula:



wherein R^2 and R^3 have the same meanings as defined above,
and reacting said compound with an amino acid ester derivative having (S) configuration of the formula:



wherein R^4 represents a lower alkyl group or a benzyl group,
to form a 2-oxoimidazolidine diester derivative having (S, S, S) configuration of the formula:



wherein R^2 and R^4 have the same meanings as defined above,
and subsequently eliminating R^2 from said compound and also when R^4 is a benzyl group further eliminating said benzyl group.

The condensation reaction between the 2-oxoimidazolidine-4-carboxylic acid ester (II) having (S) configuration and the reactive derivative at the carboxyl group of the propionic acid compound (III) having (R) configuration can be preferably practiced in an appropriate solvent in the presence of an acid acceptor. As the group represented by R^3 in the compound (III), lower alkyl groups such as methyl, ethyl, etc. and aryl groups such as phenyl, p-methylphenyl, etc. may be included, and as the reactive derivative at the carboxyl group of the compound (III), for example, active ester with N-hydroxysuccinic imide or acid halides such as acid chloride and an acid bromide may be included. As the acid acceptor, for example, potassium t-butoxide, sodium hydroxide, potassium hydroxide, etc. can be preferably used, and as the solvent, tetrahydrofuran, dioxane, dimethylformamide, etc. can be preferably used. This reaction should be preferably practiced under cooling to room temperature.

Thus, the compound (IV) having (S, R) configuration is obtained, and this compound is a novel compound.

The condensation reaction between the compound (IV) having (S, R) configuration obtained as described above and the amino acid ester (V) having (S) configuration should be preferably practiced in an appropriate solvent or without solvent in the presence of an acid acceptor. As the acid acceptor, it is preferable to use, for example, an alkali carbonate such as potassium carbonate, sodium carbonate, or an

organic tertiary amine such as triethylamine, tributylamine, N-methylmorpholine, etc., or alternatively, the compound (V) can be used in excess in place of the acid acceptor. As the solvent, for example, dimethyl sulfoxide, hexamethylphosphorylamide, dimethylformamide, etc. can be preferably used.

This reaction proceeds preferably at room temperature to under heating and only the (S, S, S) configuration isomer is produced stereoselectively and at good yield.

Elimination of tert-butyl group and/or benzyl group from the 2-oxoimidazolidine diester derivative (VI) having (S, S, S) configuration thus obtained can be practiced according to conventional methods. For example, elimination of tert-butyl can be practiced preferably by acid treatment, while benzyl group by catalytic reduction.

According to the process of the present invention as described above, only the optically active 2-oxoimidazolidine derivative having (S, S, S) configuration exhibiting potent angiotensin converting enzyme (ACE) inhibitory activity can be prepared stereoselectively and at good yield, and hence the process of the present invention is an industrially very advantageous process.

Example 1

(1) To a solution of D-lactic acid O-tosylate, namely (2R)-2-(p-toluenesulfonyloxy)propionic acid (1.15 g) in chloroform (5 ml) was added thionyl chloride (0.69 ml), and the mixture was heated under reflux for 3 hours. After the reaction mixture was concentrated under reduced pressure, chloroform was added to the residue, followed by reconcentration to give an acid chloride (residue A). On the other hand, (4S)-1-methyl-2-oxoimidazolidine-4-carboxylic acid t-butyl ester (1.08 g) was dissolved in tetrahydrofuran (12 ml), and potassium t-butoxide (607 mg) was added thereto under cooling at - 50 °C and the mixture was stirred for 20 minutes. To the solution was added a solution of the above acid chloride (residue A) in tetrahydrofuran (2 ml) at the same temperature, followed by stirring for 20 minutes. To the reaction mixture was added a mixed solution of ethyl acetate (6 ml), acetic acid (320 mg) and saturated aqueous sodium chloride (6 ml). The organic layer was taken by separation, washed successively with saturated aqueous sodium chloride, 5 % aqueous potassium carbonate, saturated aqueous sodium chloride, and then dried. Evaporation of the solvent, purification of the residue by silica gel chromatography (chloroform:ethyl acetate=2:1) and crystallization from n-hexane gave t-butyl (4S)-1-methyl-3-[(2R)-2-(p-toluenesulfonyloxy)propionyl]-2-oxoimidazolidine-4-carboxylate (1.48 g). Yield: 74 %, m.p.: 78 - 80 °C. $[\alpha]_D^{25}$: - 3.0° (C=1, chloroform)

IR $\nu_{\max}^{\text{Nujol}}$ (cm⁻¹):

35

1750, 1735, 1690

NMR (CDCl₃) δ : 1.46 (9H,s), 1.47 (3H,d,J=7Hz), 2.41 (3H,s), 2.87 (3H,s), 3.31 (1H,dd,J=4,9Hz), 3.70 (1H,t,J=9Hz), 4.50 (1H,dd,J=4,9Hz), 6.26 (1H,q,J=7Hz), 7.29, 7.80 (2H each, A₂B₂,J=7Hz).

(2) To ethyl (2S)-2-amino-4-phenylbutyrate (prepared from 0.86 g of hydrochloride thereof) were added dimethylsulfoxide (1 ml), triethylamine (0.65 ml) and the product of the above (1) (1.0 g), and the mixture was heated under stirring at 80 °C for 24 hours. To the reaction mixture was added saturated aqueous sodium chloride (3 ml), followed by extraction with ethyl acetate. The extract was washed with aqueous sodium chloride, and then dried. Evaporation of the solvent and purification of the residue by silica gel chromatography (chloroform:ethyl acetate=2:1) gave t-butyl (4S)-1-methyl-3-[(2S)-2-[N-[(1S)-1-ethoxycarbonyl-3-phenylpropyl]amino]propionyl]-2-oxoimidazolidine-4-carboxylate (950 mg) as colorless syrup. Yield: 87.8 %

50

IR $\nu_{\max}^{\text{Nujol}}$ (cm⁻¹):

3300, 1730, 1680

MS m/e: 461 (M⁺)

Maleic acid salt of this product:

55

m.p.: 122 - 124 °C (decompd.)

$[\alpha]_D^{25}$: - 58.2° (C=1, ethanol)

(3) To this product (500 mg) was added 15 % hydrochloric acid-dioxane solution (20 ml), and the mixture was stirred overnight. The crystals precipitated were collected by filtration, washed with ether to give

(4S)-1-methyl-3-[(2S)-2-[N-[(1S)-1-ethoxycarbonyl-3-phenylpropyl]amino]propionyl]-2-oxoimidazolidine-4-carboxylic acid hydrochloride (455 mg). Yield: 95 %, m.p.: 214 - 216 °C (decompd.).
 $[\alpha]_D^{25}$: - 64.1° (C = 1, ethanol)

IR $\nu_{\max}^{\text{Nujol}}$ (cm⁻¹) :

1720, 1695, 1640, 1610

MS m/e: 405 (M⁺)

Example 2

(1) To a solution of D-lactic acid O-tosylate (4.59 g) in tetrahydrofuran (50 ml) was added N-hydroxysuccinic imide (2.21 g). Then, under cooling, dicyclohexylcarbodiimide (3.96 g) was added, and the mixture was stirred at room temperature overnight. Insolubles were filtered off and the solvent was evaporated under reduced pressure to obtain an active ester (residue B) as oily substance. On the other hand, t-butyl (4S)-1-methyl-2-oxoimidazolidine-4-carboxylate (4.14 g) was dissolved in tetrahydrofuran (37 ml), and under cooling at - 50 °C, potassium t-butoxide (2.32 g) was added, followed by stirring for 20 minutes. Further, under cooling at - 50 °C, a solution of the above active ester (residue B) in tetrahydrofuran (10 ml) was added, and the mixture was stirred for 15 minutes. To the reaction mixture was added a mixed solution of ethyl acetate (24 ml), acetic acid (1.24 g) and saturated aqueous sodium chloride (24 ml). The organic layer was separated, successively washed with saturated aqueous sodium chloride, 5 % aqueous potassium carbonate and saturated aqueous sodium chloride and then dried. Evaporation of the solvent, purification of the residue by silica gel chromatography (toluene:ethyl acetate = 2:1) and crystallization from n-hexane gave t-butyl (4S)-1-methyl-3-[(2R)-2-(p-toluenesulfonyloxy)propionyl]-2-oxoimidazolidine-4-carboxylate (5.17 g). Yield: 64.5 %.

The physicochemical properties of this product are identical with those of the product obtained in Example 1 - (1).

Example 3

(1) D-lactic acid O-mesylate, namely (2R)-2-(methanesulfonyloxy)propionic acid (2.5 g) and t-butyl (4S)-1-methyl-2-oxoimidazolidine-4-carboxylate (3.42 g) were treated similarly as in Example 1 - (1), and the crude product was purified by silica gel chromatography (chloroform:ethyl acetate = 1:2) and crystallized from n-hexane to give t-butyl (4S)-1-methyl-3-[(2R)-2-(methanesulfonyloxy)-propionyl]-2-oxoimidazolidine-4-carboxylate (3.95 g). Yield: 75.8 %, m.p.: 97 - 100 °C.
 $[\alpha]_D^{25}$: - 3.2° (C = 2, chloroform)

IR $\nu_{\max}^{\text{Nujol}}$ (cm⁻¹) :

1740, 1700

NMR (CDCl₃) δ : 1.46 (9H,s), 1.61 (3H,d,J = 7Hz) 2.89 (3H,s), 3.02 (3H,s), 3.35 (1H,dd,J = 4,10Hz), 3.74- (1H,t,J = 10Hz), 4.58 (1H,dd,J = 4,10Hz), 6.35 (1H,q,J = 7Hz)

(2) This product (1 g) and ethyl (2S)-2-amino-4-phenylbutyrate (0.89 g) were treated similarly as in Example 1 - (2) to obtain t-butyl (4S)-1-methyl-3-[(2S)-2-[N-[(1S)-1-ethoxycarbonyl-3-phenylpropyl]-amino]propionyl]-2-oxoimidazolidine-4-carboxylate (1.2 g) as syrup. Yield: 91.1 %.

The physicochemical properties of this product are identical with those of the product obtained in Example 1 - (2).

Example 4

(1) D-lactic acid O-mesylate (1.97 g) and benzyl (4S)-1-methyl-2-oxoimidazolidine-4-carboxylate (2.27 g) were treated similarly as in Example 1 - (1), and the crude product was purified by silica gel chromatography (ethyl acetate) and crystallized from isopropyl ether to give benzyl (4S)-1-methyl-3-[(2R)-2-(methanesulfonyloxy)-propionyl]-2-oxoimidazolidine-4-carboxylate (3.01 g).

Yield: 80.8 %. m.p.: 98 - 102 °C

$[\alpha]_D^{25}$: - 5.0° (C = 2, chloroform)

IR $\nu_{\max}^{\text{Nujol}}$ (cm⁻¹):

1765, 1730, 1715, 1700

NMR (CDCl₃) δ : 1.61 (3H,d,J=7Hz), 2.86 (3H,s), 2.91 (3H,s), 3.36 (1H,dd,J=4,10Hz), 3.73 (1H,t,J=10Hz), 4.77 (1H,dd,J=4,10Hz), 5.20 (2H,s), 6.35 (1H,q,J=7Hz), 7.33 (5H,s)

MS m/z: 384 (M⁺)

(2) This product (1 g) and ethyl (2S)-2-amino-4-phenylbutyrate hydrochloride (950 mg) were treated similarly as in Example 1 - (2), and the crude product was purified by silica gel chromatography to give benzyl (4S)-1-methyl-3-[(2S)-2-[N-[(1S)-1-ethoxycarbonyl-3-phenylpropyl]amino]propionyl]-2-

oxoimidazolidine-4-carboxylate (850 mg) as colorless syrup. Yield: 65.9 %.

Maleic acid salt of this product:

m.p. 84 - 86 °C (recrystallized from ethyl acetateisopropyl ether)

$[\alpha]_D^{25}$: - 49.8° (C = 1, ethanol)

(3) This product (1 g) was dissolved in ethanol (30 ml), and catalytically reduced with addition of 10 % palladium-carbon (200 mg) under normal temperature and normal pressure for 3 hours. The catalyst was filtered off, and the solvent was evaporated. To the crystalline residue was added ether, and the product was collected by filtration to give (4S)-1-methyl-3-[(2S)-2-[N-[(1S)-1-ethoxycarbonyl-3-phenylpropyl]amino]propionyl]-2-oxoimidazolidine-4-carboxylic acid (780 mg). Yield: 95.4 %, m.p.: 140 °C.

$[\alpha]_D^{24}$: - 71.9° (C = 0.5, ethanol)

Example 5

(1) t-Butyl (4S)-1-methyl-3-[(2R)-2-(p-toluenesulfonyloxy)propionyl]-2-oxoimidazolidine-4-carboxylate (1 g) obtained in Example 1 - (1) and benzyl (2S)-2-amino-4-phenylbutyrate (1.55 g) were treated similarly as in Example 1 - (2) to give t-butyl (4S)-1-methyl-3-[(2S)-2-[N-[(1S)-1-benzyloxycarbonyl-3-phenylpropyl]amino]propionyl]-2-oxoimidazolidine-4-carboxylate (1.01 g) as colorless syrup. Yield: 82.3 %.

Maleic acid salt of this product:

m.p.: 108 - 112 °C.

$[\alpha]_D^{25}$: - 57.4° (C = 1, ethanol)

(2) This product (1.05 g) was dissolved in methanol (30 ml), and catalytically reduced with addition of 10 % palladium-carbon (300 mg) under normal temperature and normal pressure for 3 hours. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The crystals precipitated were collected by filtration, and washed with ether. Subsequently, this product was suspended in dioxane (10 ml), and 25 % hydrochloric acid-dioxane solution (10 ml) was added thereto, followed by stirring at room temperature overnight. The precipitated crystals were collected by filtration, dissolved in water and adjusted to pH 6 with sodium hydrogen carbonate. The precipitated crystals were collected by filtration, washed with water and dried to give (4S)-1-methyl-3-[(2S)-2-[N-[(1S)-1-carboxy-3-phenylpropyl]amino]propionyl]-2-oxoimidazolidine-4-carboxylic acid (664 mg). Yield: 88 %.

m.p.: 240 °C (decompd.)

$[\alpha]_D^{25}$: - 89° (C = 1, 5 % aqueous sodium hydrogen carbonate)

Example 6

(1) To a solution of D-lactic acid O-tosylate (2g) in chloroform (20 ml) was added thionyl chloride (2.39 ml), and the mixture was heated under reflux for 3 hours. The reaction mixture was concentrated under reduced pressure, then reconstituted with addition of chloroform to obtain an acid chloride (residue C). On the other hand, benzyl (4S)-1-methyl-2-oxoimidazolidine-4-carboxylate (2.21 g) was dissolved in tetrahydrofuran (25 ml), and under cooling at - 50 °C, potassium t-butoxide (1.06 g) was added under nitrogen gas stream, followed by stirring for 20 minutes. To this solution was added at the same temperature a solution of the above acid chloride (residue C) in tetrahydrofuran (4 ml), followed by stirring for 20 minutes. To the reaction mixture were added a mixed solution of ethyl acetate (15 ml), acetic acid (0.57 g) and saturated aqueous sodium chloride (15 ml). The organic layer was taken by separation, successively washed with saturated aqueous sodium chloride, aqueous 5 % potassium

carbonate, saturated aqueous sodium chloride, and then dried. Evaporation of the solvent and recrystallization of the residue from ethyl acetate gave benzyl (4S)-1-methyl-3-[(2R)-2-(p-toluenesulfonyloxy)-propionyl]-2-oxoimidazolidine-4-carboxylate (3.1 g). Yield: 82.8 %. m.p.: 153 - 155 °C.
 $[\alpha]_D^{25}$: + 2.5° (C=2, chloroform)

IR $\nu_{\text{max}}^{\text{Nujol}}$ (cm⁻¹) :

1740, 1730, 1695

NMR (CDCl₃) δ : 1.48 (3H,d,J=7Hz), 2.40 (3H,s), 2.82 (3H,s), 3.28 (1H,dd,J=4.10Hz), 3.68 (1H,t,J=10Hz), 4.66 (1H,dd,J=4.10Hz), 5.10, 5.26 (1Hx2,AB,J=12Hz), 6.24(1H,q,J=7Hz), 7.32 (5H,s), 7.25, 7.77 (2H each,A₂B₂,J=8Hz)

MS m/z: 460 (M⁺)

(2) This product (1 g) and benzyl (2S)-2-amino-4-phenylbutyrate (1.44 g) were treated similarly as in Example 1 - (2), and the crude product was purified by silica gel chromatography (chloroform:ethyl acetate=4:1) to give benzyl (4S)-1-methyl-3-[(2S)-2-[N-((1S)-1-benzyloxycarbonyl-3-phenylpropyl)-amino]propionyl]-2-oxoimidazolidine-4-carboxylate (0.82 g) as colorless syrup. Yield: 67.7 %.

Maleic acid salt of this product:

m.p.: 111 - 115 °C (decompd.)

$[\alpha]_D^{25}$: - 51.6° (C=1, ethanol)

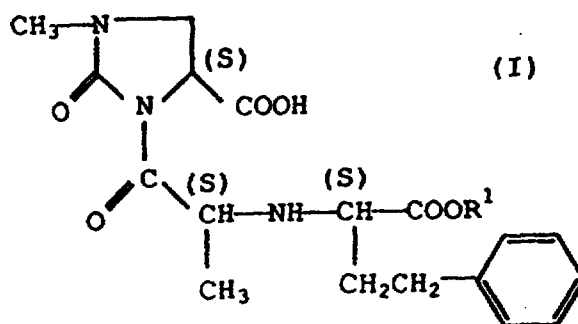
(3) This product (0.5 g) was dissolved in methanol (50 ml) and catalytically reduced with addition of palladium black (50 mg) under normal temperature and normal pressure for 3 hours. The catalyst was filtered off, and the solvent was evaporated. To the crystalline residue was added ether, and the product was separated by filtration to give (4S)-1-methyl-3-[(2S)-2-[N-((1S)-1-carboxy-3-phenylpropyl)amino]-propionyl]-2-oxoimidazolidine-4-carboxylic acid.

The physicochemical properties of this product are identical with those of the product obtained in Example 5 - (2).

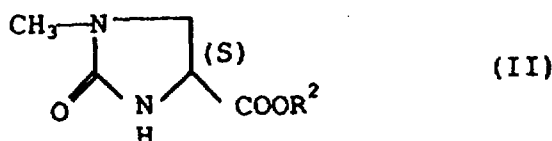
Claims

Claims for the following Contracting States : DE, GB, FR, IT, NL, SE, CH, LI, BE, AT, LU

1. A process for preparing an optically active 2-oxoimidazolidine derivative of the formula:



wherein R¹ represents hydrogen atom or a lower alkyl group,
 which comprises reacting a 2-oxoimidazolidine-4-carboxylic acid ester derivative having (S) configuration of the formula:



wherein R² represents a tert-butyl group or a benzyl group.



carbonate, saturated aqueous sodium chloride, and then dried. Evaporation of the solvent and recrystallization of the residue from ethyl acetate gave benzyl (4S)-1-methyl-3-[(2R)-2-(p-toluenesulfonyloxy)propionyl]-2-oxoimidazolidine-4-carboxylate (3.1 g). Yield: 82.8 %. m.p.: 153 - 155 °C.
 $[\alpha]_D^{25}$: + 2.5° (C=2, chloroform)

IR $\nu_{\text{max}}^{\text{Nujol}}$ (cm⁻¹):

1740, 1730, 1695

NMR (CDCl₃) δ : 1.48 (3H,d,J=7Hz), 2.40 (3H,s), 2.82 (3H,s), 3.28 (1H,dd,J=4.10Hz), 3.68 (1H,t,J=10Hz), 4.66 (1H,dd,J=4,10Hz), 5.10, 5.26 (1Hx2,AB,J=12Hz), 6.24(1H,q,J=7Hz), 7.32 (5H,s), 7.25, 7.77 (2H each,A₂B₂,J=8Hz)

MS m/z: 460 (M⁺)

(2) This product (1 g) and benzyl (2S)-2-amino-4-phenylbutyrate (1.44 g) were treated similarly as in Example 1 - (2), and the crude product was purified by silica gel chromatography (chloroform:ethyl acetate=4:1) to give benzyl (4S)-1-methyl-3-[(2S)-2-[N-((1S)-1-benzyloxycarbonyl-3-phenylpropyl)-amino]propionyl]-2-oxoimidazolidine-4-carboxylate (0.82 g) as colorless syrup. Yield: 67.7 %.

Maleic acid salt of this product:

m.p.: 111 - 115 °C (decompd.)

$[\alpha]_D^{25}$: - 51.6° (C=1, ethanol)

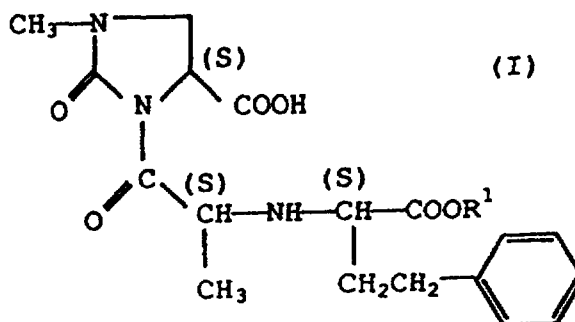
(3) This product (0.5 g) was dissolved in methanol (50 ml) and catalytically reduced with addition of palladium black (50 mg) under normal temperature and normal pressure for 3 hours. The catalyst was filtered off, and the solvent was evaporated. To the crystalline residue was added ether, and the product was separated by filtration to give (4S)-1-methyl-3-[(2S)-2-[N-((1S)-1-carboxy-3-phenylpropyl)amino]propionyl]-2-oxoimidazolidine-4-carboxylic acid.

The physicochemical properties of this product are identical with those of the product obtained in Example 5 - (2).

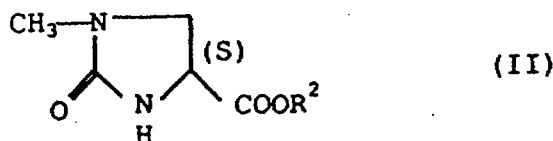
30 Claims

Claims for the following Contracting States : DE, GB, FR, IT, NL, SE, CH, LI, BE, AT, LU

1. A process for preparing an optically active 2-oxoimidazolidine derivative of the formula:



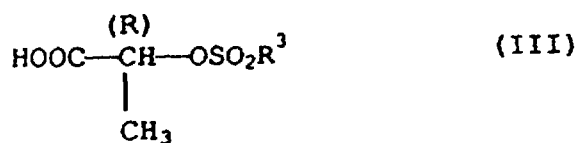
wherein R¹ represents hydrogen atom or a lower alkyl group, which comprises reacting a 2-oxoimidazolidine-4-carboxylic acid ester derivative having (S) configuration of the formula:



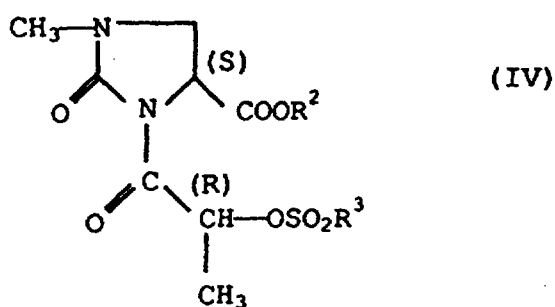
wherein R² represents a tert-butyl group or a benzyl group,



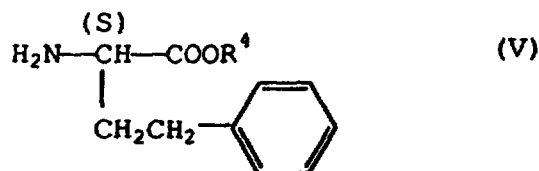
with a reactive derivative at the carboxyl group of a propionic acid compound having (R) configuration of the formula:



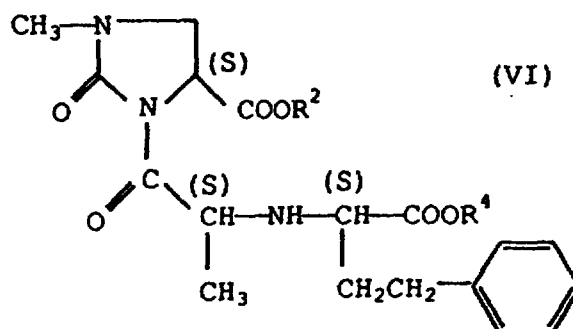
wherein R^3 represents a lower alkyl group or an aryl group to form a 3-acyl-2-oxoimidazolidine-4-carboxylic acid ester derivative having (S, R) configuration of the formula:



wherein R^2 and R^3 have the same meanings as defined above, and reacting said compound (IV) with an amino acid ester having (S) configuration of the formula:



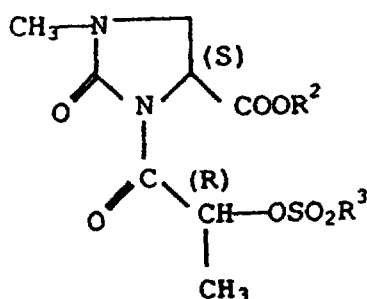
wherein R^4 represents a lower alkyl group or a benzyl group, to form a 2-oxoimidazolidine diester derivative having (S, S, S) configuration of the formula:



wherein R^2 and R^4 have the same meanings as defined above, and subsequently eliminating R^2 from said compound and also when R^4 is a benzyl group further eliminating said benzyl group.



2. The process according to Claim 1, wherein R^3 in said compound (III) is a methyl group, an ethyl group, a phenyl group or p-methylphenyl group.
3. The process according to Claim 1, wherein said reactive derivative at the carboxyl group of the compound (III) is an active ester with N-hydroxysuccinic imide, an acid chloride or an acid bromide.
4. The process according to Claim 1, wherein said condensation reaction of the compound (II) and the compound (III) is practiced in the presence of an acid acceptor selected from potassium t-butoxide, sodium hydroxide or potassium hydroxide.
5. The process according to Claim 1, wherein said condensation reaction of the compound (II) and the compound (III) is practiced in the presence of a solvent selected from tetrahydrofuran, dioxane or dimethylformamide.
6. The process according to Claim 1, wherein said condensation reaction of the compound (II) and the compound (III) is practiced under cooling to room temperature.
7. The process according to Claim 1, wherein said condensation reaction of the compound (IV) and the compound (V) is practiced in the presence of an acid acceptor selected from potassium carbonate, sodium carbonate, triethylamine, tributylamine or N-methylmorpholine.
8. The process according to Claim 1, wherein said condensation reaction of the compound (IV) and the compound (V) is practiced in the presence of a solvent selected from dimethyl sulfoxide, hexamethylphosphoramide or dimethylformamide.
9. The process according to Claim 1, wherein said condensation reaction of the compound (IV) and the compound (V) is practiced at room temperature to under heating.
10. A 3-acyl-2-oxoimidazolidine-4-carboxylic acid ester derivative having (S, R) configuration of the formula:

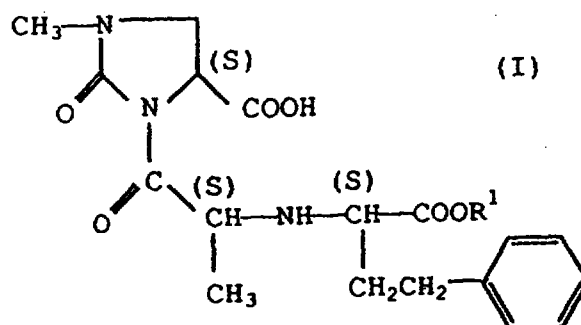


wherein R^2 represents a tert-butyl group or a benzyl group, and R^3 represents a lower alkyl group or an aryl group.

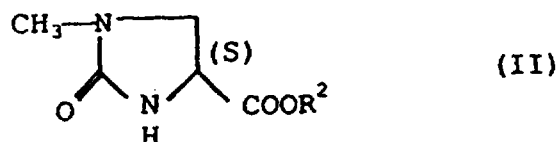


Claims for the following Contracting States : GR, ES

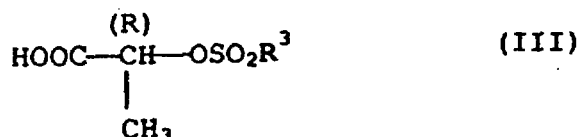
1. A process for preparing an optically active 2-oxoimidazolidine derivative of the formula:



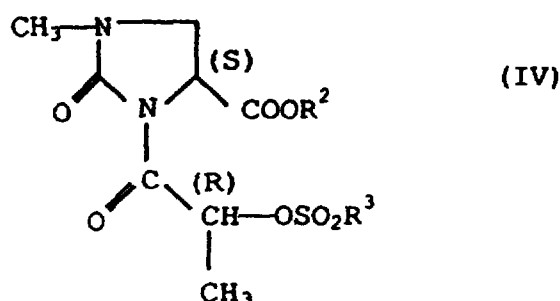
wherein R¹ represents hydrogen atom or a lower alkyl group,
which comprises reacting a 2-oxoimidazolidine-4-carboxylic acid ester derivative having (S) configuration of the formula:



wherein R² represents a tert-butyl group or a benzyl group,
with a reactive derivative at the carboxyl group of a propionic acid compound having (R) configuration of the formula:



wherein R³ represents a lower alkyl group or an aryl group
to form a 3-acyl-2-oxoimidazolidine-4-carboxylic acid ester derivative having (S, R) configuration of the formula:



wherein R² and R³ have the same meanings as defined above,
and reacting said compound (IV) with an amino acid ester having (S) configuration of the formula:



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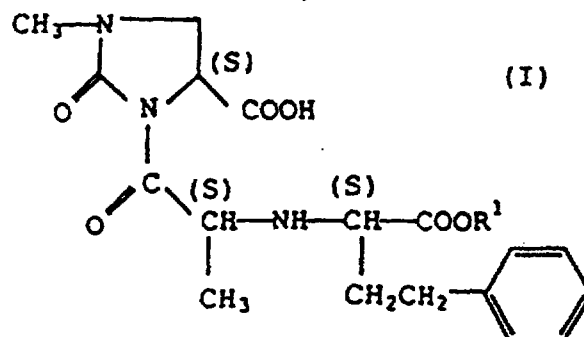
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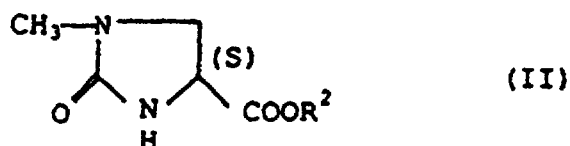
Patentansprüche

Patentansprüche für folgende Vertragsstaaten : DE, GB, FR, IT, NL, SE, CH, LI, BE, AT, LU

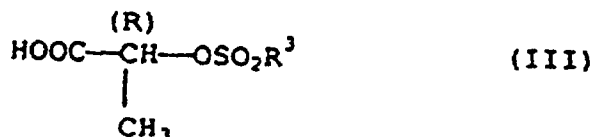
1. Verfahren zur Herstellung eines optisch aktiven 2-Oxoimidazolidinderivats der Formel:



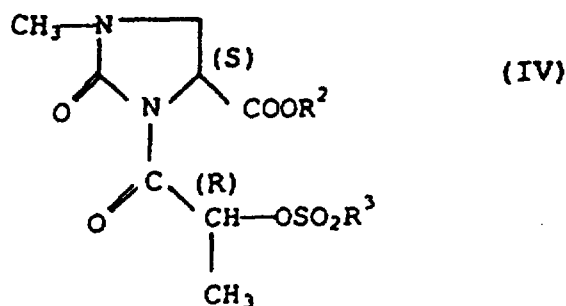
worin R¹ ein Wasserstoffatom oder eine niedere Alkylgruppe bedeutet,
umfassend die Reaktion eines 2-Oxoimidazolidin-4-carbonsäureesterderivats mit (S) Konfiguration und
der Formel:



worin R² eine tert.-Butylgruppe oder eine Benzylgruppe bedeutet,
mit einem reaktiven Derivat an der Carboxylgruppe einer Propionsäureverbindung mit (R) Konfiguration
und der Formel:

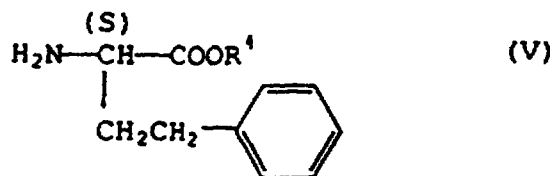


worin R³ eine niedere Alkylgruppe oder eine Arylgruppe bedeutet,
zur Herstellung eines 3-Acyl-2-oxoimidazolidin-4-carbonsäureesterderivats mit (S, R) Konfiguration und
der Formel:

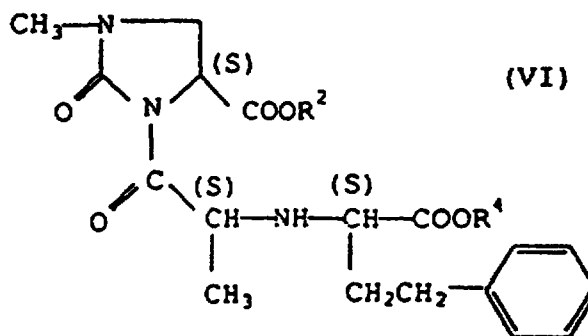




worin R^2 und R^3 die gleichen Bedeutungen wie oben definiert haben,
und Reaktion der Verbindung (IV) mit einem Aminosäureester mit (S) Konfiguration und der Formel:



worin R^4 eine niedere Alkylgruppe oder eine Benzylgruppe bedeutet,
zur Bildung eines 2-Oxoimidazolidindiesterderivats mit (S, S, S) Konfiguration und der Formel:



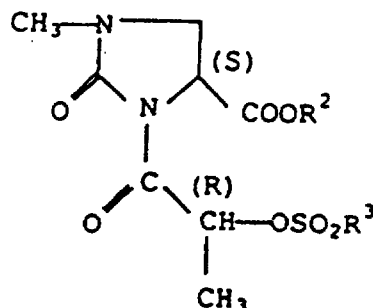
worin R^2 und R^4 die gleichen Bedeutungen wie oben definiert haben,
und anschließende Eliminierung von R^2 aus der Verbindung und wenn R^4 eine Benzylgruppe ist, auch
die weitere Eliminierung der Benzylgruppe.

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2. Verfahren nach Anspruch 1, worin R^3 in der Verbindung (III) eine Methylgruppe, eine Ethylgruppe, eine Phenylgruppe oder eine p-Methylphenylgruppe ist.
 3. Verfahren nach Anspruch 1, worin das reaktive Derivat an der Carboxylgruppe der Verbindung (III) ein Aktivester mit N-Hydroxysuccinimid, ein Säurechlorid oder ein Säurebromid ist.
 4. Verfahren nach Anspruch 1, worin die Kondensationsreaktion der Verbindung (II) und der Verbindung (III) in Gegenwart eines Säureakzeptors durchgeführt wird, ausgewählt aus Kalium-t-butoxid, Natriumhydroxid oder Kaliumhydroxid.
 5. Verfahren nach Anspruch 1, worin die Kondensationsreaktion der Verbindung (II) und der Verbindung (III) in Gegenwart eines Lösungsmittels durchgeführt wird, ausgewählt aus Tetrahydrofuran, Dioxan oder Dimethylformamid.
 6. Verfahren nach Anspruch 1, worin die Kondensationsreaktion der Verbindung (II) und der Verbindung (III) von Kühlen bis Raumtemperatur durchgeführt wird.
 7. Verfahren nach Anspruch 1, worin die Kondensationsreaktion der Verbindung (IV) und der Verbindung (V) in Gegenwart eines Säureakzeptors durchgeführt wird, ausgewählt aus Kaliumcarbonat, Natriumcarbonat, Triethylamin, Tributylamin oder N-Methylmorpholin.
 8. Verfahren nach Anspruch 1, worin die Kondensationsreaktion der Verbindung (IV) und der Verbindung (V) in Gegenwart eines Lösungsmittels durchgeführt wird, ausgewählt aus Dimethylsulfoxid, Hexamethylphosphorylamid oder Dimethylformamid.



9. Verfahren nach Anspruch 1, worin die Kondensationsreaktion der Verbindung (IV) und der Verbindung (V) von Raumtemperatur bis Erhitzen durchgeführt wird.

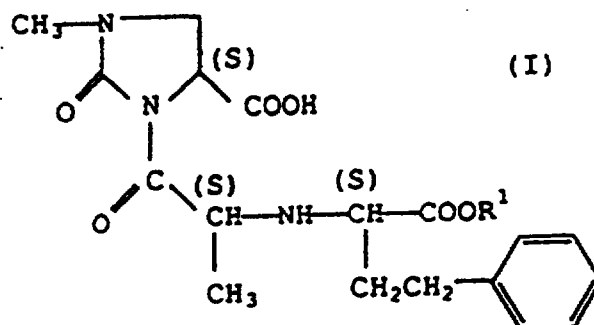
10. 3-Acyl-2-oxoimidazolidin-4-carbonsäureesterderivat mit (S, R) Konfiguration und der Formel:



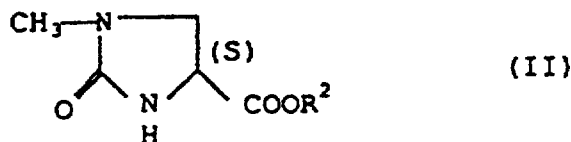
- 20 worin R² eine tert.-Butylgruppe oder eine Benzylgruppe bedeutet und R³ eine niedere Alkylgruppe oder eine Arylgruppe bedeutet.

Patentansprüche für folgende Vertragsstaaten : GR, ES

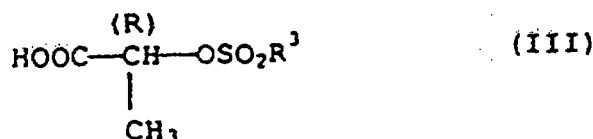
- 25 1. Verfahren zur Herstellung eines optisch aktiven 2-Oxoimidazolidinderivats der Formel:



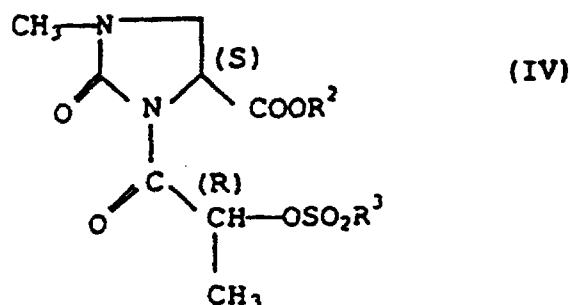
- 40 worin R¹ ein Wasserstoffatom oder eine niedere Alkylgruppe bedeutet, umfassend die Reaktion eines 2-Oxoimidazolidin-4-carbonsäureesterderivats mit (S) Konfiguration und der Formel:



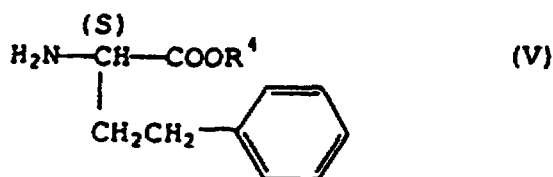
- 50 worin R² eine tert.-Butylgruppe oder eine Benzylgruppe bedeutet, mit einem reaktiven Derivat an der Carboxylgruppe einer Propionsäureverbindung mit (R) Konfiguration und der Formel:



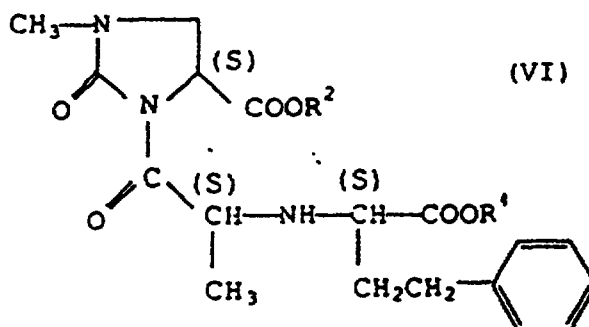
worin R^3 eine niedere Alkylgruppe oder eine Arylgruppe bedeutet,
zur Herstellung eines 3-Acyl-2-oxoimidazolidin-4-carbonsäureesterderivats mit (S, R) Konfiguration und
der Formel:



worin R^2 und R^3 die gleichen Bedeutungen wie oben definiert haben,
und Reaktion der Verbindung (IV) mit einem Aminosäureester mit (S) Konfiguration und der Formel:



worin R^4 eine niedere Alkylgruppe oder eine Benzylgruppe bedeutet,
zur Bildung eines α -Oxoimidazolidindiesterderivats mit (S, S, S) Konfiguration und der Formel:



worin R^2 und R^4 die gleichen Bedeutungen wie oben definiert haben,
und anschließende Eliminierung von R^2 aus der Verbindung und wenn R^4 eine Benzylgruppe ist, auch
die weitere Eliminierung der Benzylgruppe.

2. Verfahren nach Anspruch 1, worin R^3 in der Verbindung (III) eine Methylgruppe, eine Ethylgruppe, eine Phenylgruppe oder eine p-Methylphenylgruppe ist.

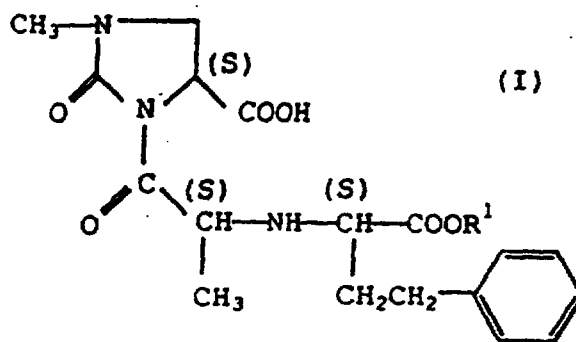


3. Verfahren nach Anspruch 1, worin das reaktive Derivat an der Carboxylgruppe der Verbindung (III) ein Aktivester mit N-Hydroxysuccinimid, ein Säurechlorid oder ein Säurebromid ist.
4. Verfahren nach Anspruch 1, worin die Kondensationsreaktion der Verbindung (II) und der Verbindung (III) in Gegenwart eines Säureakzeptors durchgeführt wird, ausgewählt aus Kalium-t-butoxid, Natriumhydroxid oder Kaliumhydroxid.
5. Verfahren nach Anspruch 1, worin die Kondensationsreaktion der Verbindung (II) und der Verbindung (III) in Gegenwart eines Lösungsmittels durchgeführt wird, ausgewählt aus Tetrahydrofuran, Dioxan oder Dimethylformamid.
6. Verfahren nach Anspruch 1, worin die Kondensationsreaktion der Verbindung (II) und der Verbindung (III) von Kühlen bis Raumtemperatur durchgeführt wird.
7. Verfahren nach Anspruch 1, worin die Kondensationsreaktion der Verbindung (IV) und der Verbindung (V) in Gegenwart eines Säureakzeptors durchgeführt wird, ausgewählt aus Kaliumcarbonat, Natriumcarbonat, Triethylamin, Tributylamin oder N-Methylmorpholin.
8. Verfahren nach Anspruch 1, worin die Kondensationsreaktion der Verbindung (IV) und der Verbindung (V) in Gegenwart eines Lösungsmittels durchgeführt wird, ausgewählt aus Dimethylsulfoxid, Hexamethylphosphorylamid oder Dimethylformamid.
9. Verfahren nach Anspruch 1, worin die Kondensationsreaktion der Verbindung (IV) und der Verbindung (V) von Raumtemperatur bis Erhitzen durchgeführt wird.

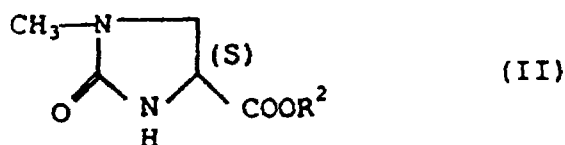
Revendications

Revendications pour les Etats contractants suivants : DE, GB, FR, IT, NL, SE, CH, LI, BE, AT, LU

1. Procédé de préparation d'un dérivé de la 2-oxoimidazolidine optiquement actif de la formule :



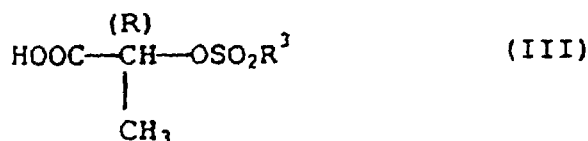
dans laquelle R¹ représente un atome d'hydrogène ou un radical alkyle inférieur, caractérisé en ce que l'on fait réagir un dérivé d'ester de l'acide 2-oxoimidazolidine-4-carboxylique possédant la configuration (S), de la formule :



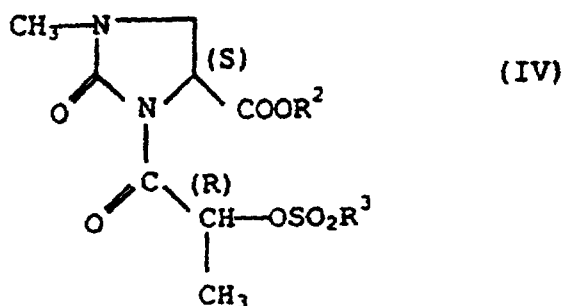
dans laquelle R² représente un radical tert-butyle ou un radical benzyle, avec un dérivé réactif au groupe carboxyle d'un composé de l'acide propionique possédant la



configuration (R), de la formule :

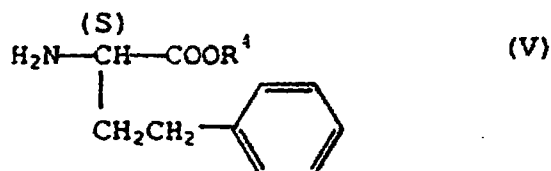


dans laquelle R^3 représente un radical alkyle inférieur ou un radical aryle, pour former un dérivé d'ester d'un acide 3-acyl-2-oxoimidazolidine-4-carboxylique possédant la configuration (S, R), de la formule :

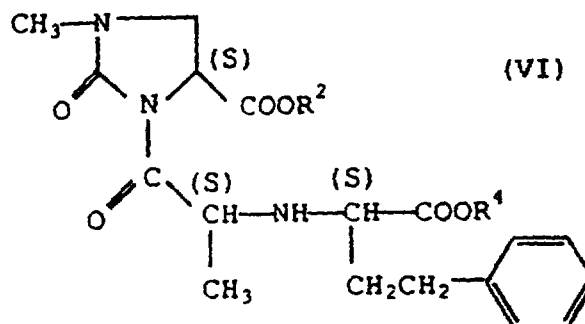


dans laquelle R^2 et R^3 possèdent les mêmes significations que celles qui leur ont été attribuées plus haut,

et on fait réagir le composé (IV) en question avec un ester d'acide aminé possédant la configuration (S) de la formule :



dans laquelle R^4 représente un radical alkyle inférieur ou un radical benzyle, pour former un dérivé de diester 2-oxoimidazolidinique possédant la configuration (S, S, S), de la formule :



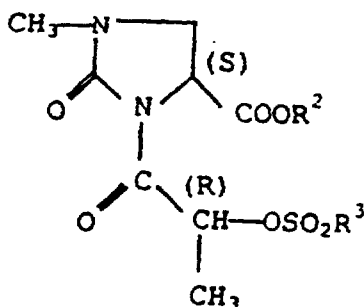
dans laquelle R^2 et R^4 possèdent les mêmes significations que celles qui leur ont été précédemment



attribuées,

et on élimine ensuite R^2 du composé précité et également, lorsque R^4 représente un radical benzyle, on élimine aussi le radical benzyle en question.

2. Procédé suivant la revendication 1, caractérisé en ce que R^3 dans le composé (III) précité est un radical méthyle, éthyle, phényle, ou p-méthylphényle.
3. Procédé suivant la revendication 1, caractérisé en ce que ledit dérivé réactif au radical carboxyle du composé (III) est un ester actif avec le N-hydroxysuccinimide, un chlorure d'acide, ou un bromure d'acide.
4. Procédé suivant la revendication 1, caractérisé en ce que la réaction de condensation du composé (II) et du composé (III) est réalisée en la présence d'un accepteur d'acide choisi parmi le t-butylate de potassium, l'hydroxyde de sodium, ou l'hydroxyde de potassium.
5. Procédé suivant la revendication 1, caractérisé en ce que ladite réaction de condensation du composé (II) et du composé (III) est réalisée en la présence d'un solvant choisi parmi le tétrahydrofuranne, le dioxanne, ou le diméthylformamide.
6. Procédé suivant la revendication 1, caractérisé en ce que ladite réaction de condensation du composé (II) et du composé (III) est réalisée sous refroidissement jusqu'à la température ambiante.
7. Procédé suivant la revendication 1, caractérisé en ce que la réaction de condensation du composé (IV) et du composé (V) est réalisée en la présence d'un accepteur d'acide, choisi parmi le carbonate de potassium, le carbonate de sodium, la triéthylamine, la tributylamine ou la N-méthylmorpholine.
8. Procédé suivant la revendication 1, caractérisé en ce que la réaction de condensation du composé (IV) et du composé (V) est réalisée en la présence d'un solvant choisi parmi le sulfoxyde de diméthyle, l'hexaméthylphosphorylamide ou le diméthylformamide.
9. Procédé suivant la revendication 1, caractérisé en ce que ladite réaction de condensation du composé (IV) et du composé (V) est réalisée depuis la température ambiante jusqu'à une température obtenue sous chauffage.
10. Dérivé d'ester d'un acide 3-acyl-2-oxoimidazolidine-4-carboxylique possédant la configuration (S, R) de la formule

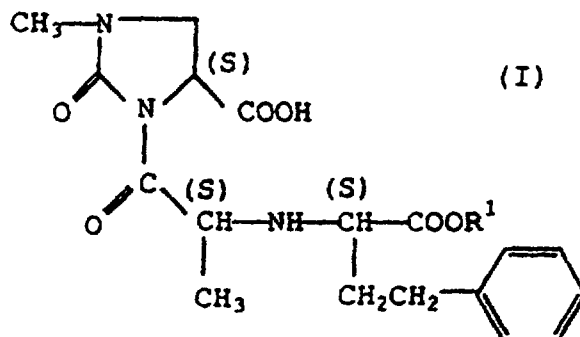


dans laquelle R^2 représente un radical tert-butyle ou un radical benzyle et R^3 représente un radical alkyle inférieur ou un radical aryle.

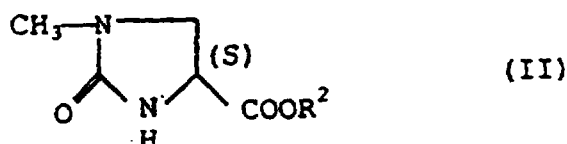


Revendications pour les Etats contractants suivants : ES, GR

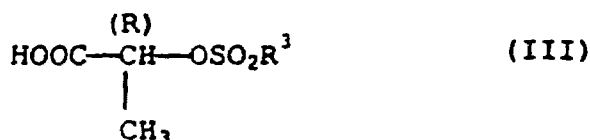
1. Procédé de préparation d'un dérivé de la 2-oxoimidazolidine optiquement actif de la formule :



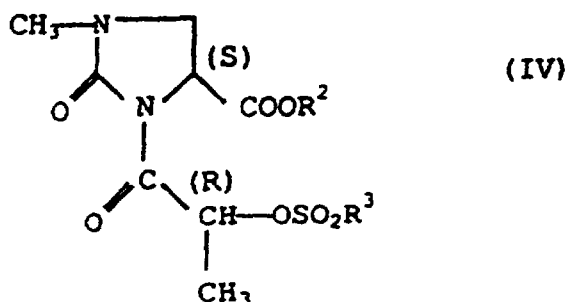
dans laquelle R¹ représente un atome d'hydrogène ou un radical alkyle inférieur, caractérisé en ce que l'on fait réagir un dérivé d'ester de l'acide 2-oxoimidazolidine-4-carboxylique possédant la configuration (S), de la formule :



dans laquelle R² représente un radical tert-butyle ou un radical benzyle, avec un dérivé réactif au groupe carboxyle d'un composé de l'acide propionique possédant la configuration (R), de la formule :



dans laquelle R³ représente un radical alkyle inférieur ou un radical aryle, pour former un dérivé d'ester d'un acide 3-acyl-2-oxoimidazolidine-4-carboxylique possédant la configuration (S, R), de la formule :



dans laquelle R² et R³ possèdent les mêmes significations que celles qui leur ont été attribuées plus

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l'hexaméthylphosphorylamide ou le diméthylformamide.

9. Procédé suivant la revendication 1, caractérisé en ce que ladite réaction de condensation du composé (IV) et du composé (V) est réalisée depuis la température ambiante jusqu'à une température obtenue sous chauffage.

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