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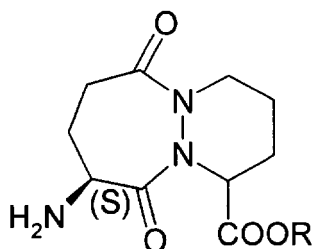
PROCESS FOR THE PREPARATION OF BICYCLIC COMPOUNDS AND THE USE
OF THIS PROCESS FOR THE PREPARATION OF AN ICE INHIBITOR
COMPOUND.

5 A subject of the present invention is a novel process
for the preparation of bicyclic compounds and the use of this
process as an intermediate stage in the preparation of a
compound which inhibits the interleukin-1 beta converting
enzyme (ICE).

10 The compound of formula (I) as defined below, in which R
represents a terbutyl radical and the amine is protected in
the form of phthalimido, is described in the Patent EP 94095.
This compound of formula (I) is also used for the preparation
of the compound of formula (V) having an inhibitory activity
15 on the interleukin-1 beta converting enzyme described in the
International Application WO 97/22619.

One of the objectives of the invention is to find a
novel process of obtaining the compounds of formula (I).

Therefore a subject of the invention is a process for
20 the preparation of the compounds of formula (I)

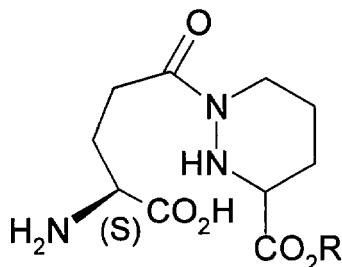


(I)

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in which R represents a hydrogen atom, an alkyl, aryl or
aralkyl radical containing up to 18 carbon atoms and the
amine function can be free or protected,

30 starting from a compound of formula (IA)



(IA)

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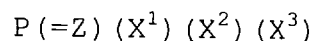
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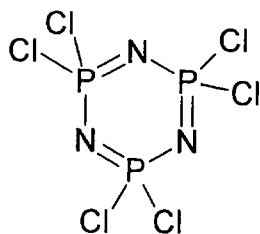
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in which R has the same meaning as previously and the amine function can be free or protected, characterized in that the cyclization is carried out in a basic medium and in the presence:

- 5 - of a derivative of phosphonic acid of formula (P1):



in which Z is a sulphur or oxygen atom, X^1 represents a halogen atom, X^2 and X^3 , identical or different, represent a halogen atom, an alkyloxy radical containing 1 to 6 carbon atoms, an aryloxy radical containing 6 to 12 carbon atoms or an arylalkyloxy radical containing 7 to 15 carbon atoms,
 10 - or of a trimer of formula (P2)



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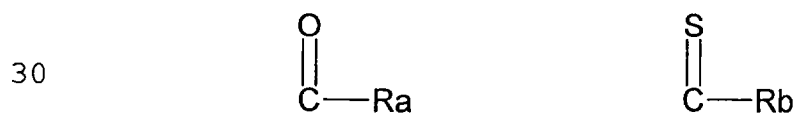
R preferably represents a hydrogen atom, a methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tertbutyl, benzyl, phenyl or naphthyl radical and quite particularly methyl, ethyl and tertbutyl.

When the amine function is protected, the protection can be done according to the standard methods known to a person skilled in the art.

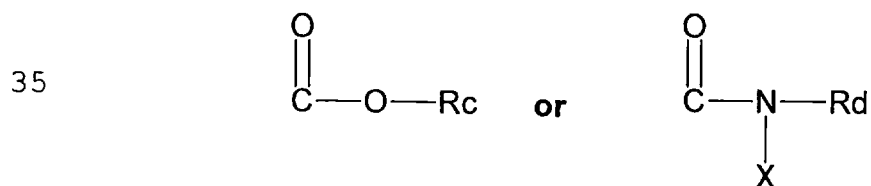
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The amine function can be protected in the form of an - NR^1R^2 radical in which

- either R^1 represents a



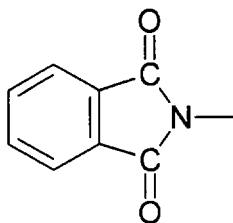
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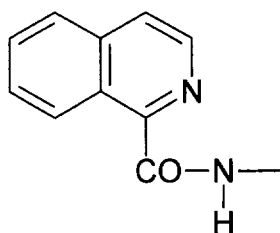
radical, Ra, Rb, Rc and Rd representing an alkyl or aryl radical containing up to 18 carbon atoms or a mono or polycyclic radical containing one or more heteroatoms, X
 5 representing a hydrogen atom, an alkyl radical containing up to 8 carbon atoms or an aryl radical containing up to 14 carbon atoms, and R² represents a hydrogen atom,
 - or R¹ and R² together form a mono or polycyclic radical containing 1 or more heteroatoms. The amine can thus be
 10 protected in the form of a phthalimido

15



or also in the form of the

20



25 radical.

Preferably, the amine is protected in the form of a phthalimido.

Among the derivatives of phosphonic acid of formula $P(=Z)(X^1)(X^2)(X^3)$, it is in particular the following
 30 derivatives:

$(Cl)P(O)(Ph)_2$, $(Cl)_2P(O)(OPh)_2$, $(Cl)P(O)(OEt)_2$,
 $(Cl)_2P(O)(OEt)_2$, $POCl_3$, $POBr_3$ and $P(S)Cl_3$.

The cyclization reaction is preferably carried out in the presence of $POCl_3$ or $POBr_3$ and the base is in particular
 35 an organic base, for example triethylamine, pyridine or 2,6-lutidine.

A more particular subject of the invention is the process as described previously in which the trihalogenophosphonic acid is POCl_3 .

A more particular subject of the invention is the
5 process as described previously in which the trihalogenophosphonic acid is POBr_3 .

A more particular subject of the invention is the process as described previously in which the base is chosen from pyridine or 2,6-lutidine.

10 A more particular subject of the invention is the process as defined previously characterized in that the cyclization temperature is comprised between 70 and 80°C.

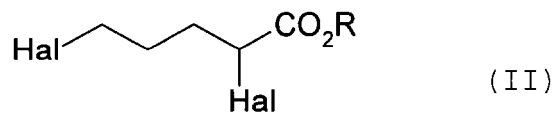
A more particular subject of the invention is the process as defined previously characterized in that the
15 solvent is dichloroethane.

The compound of formula (IA) is in the form of a mixture of SS and SR diastereoisomers or in the form of the SR diastereoisomer.

The compound of formula (I) is in the form of a mixture
20 of SS and SR diastereoisomers or in the form of the SR diastereoisomer.

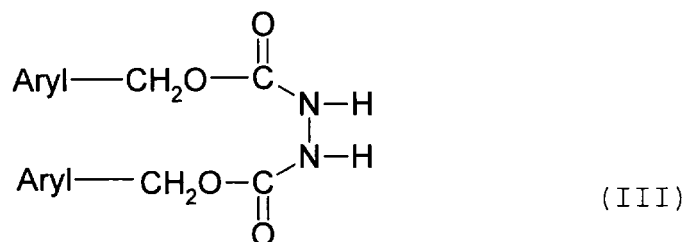
A subject of the invention is also a process for the preparation of the compound of formula (I) in racemic or optically active (Iopt) form, comprising the cyclization
25 process as described above, and characterized in that it comprises the following successive stages:

a) A compound of formula (II)



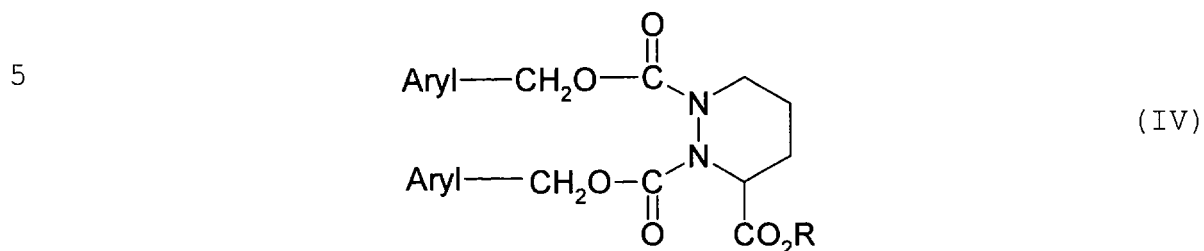
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in which R is as defined previously and Hal represents a halogen atom, is subjected to the action of a compound of formula (III)



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in which Aryl represents an aryl radical containing up to 14 carbon atoms, in order to obtain the compound of formula (IV)



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in the form of a mixture of S and R stereoisomers,

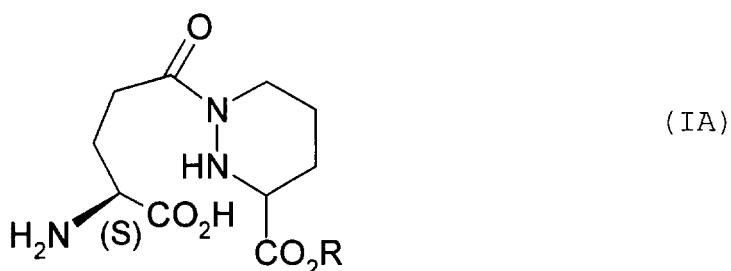
b) the compound of formula (IV) is subjected to the action of an anhydride of formula (F)

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20 the amine function being in protected or non-protected form, while carrying out a deprotection by hydrogenolysis, in order to obtain the compound of formula (IA)

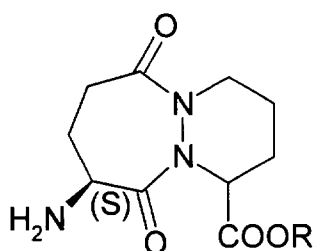
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30 as defined above,

c) the compound of formula (IA) is subjected to the action of a derivative of phosphonic acid (P1) or (P2) as defined above, in the presence of a base, in order to obtain the compound of formula (I) as defined above

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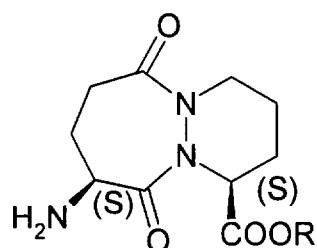


(I)

d) if appropriate, the amine function is deprotected in order to obtain the compound of formula (I) in which the amine function is not protected,

e) if appropriate, the compound of formula (I) in the SS + SR or SR form is subjected to the action of a deracemization and/or epimerization agent in order to obtain the compound of formula (Iopt) corresponding to the SS diastereoisomer,

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(Iopt)

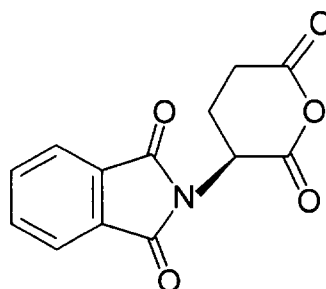
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f) if appropriate, the amine function is deprotected in order to obtain the compound of formula (Iopt) in which the amine function is not protected.

25 In a preferred embodiment:

- Hal represents a chlorine atom;
- R represents an alkyl radical containing 1 to 4 carbon atoms;
- Aryl represents a phenyl or naphthyl radical,
- 30 - Compound (F) is N-phthaloyl-L-glutamic anhydride

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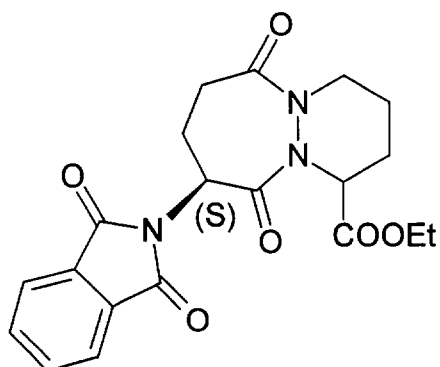
- The amine function of the compounds of formulae (IA), (I) or (Iopt) is in protected form and in particular in phthalimido form;
- The reaction between the compounds of formula (II) and the compounds of formula (III) takes place in the presence of a base for example in the presence of an alkaline carbonate such as potassium carbonate;
- The deprotection by hydrogenolysis is carried out according to standard conditions known to a person skilled in the art, for example the hydrogenolysis agent is hydrogen in the presence of palladium on carbon;
- The deracemization and/or epimerization agent is a base, more especially a strong base, for example an alkaline or alkaline-earth alcoholate such as sodium or potassium methylate, sodium or potassium *tert*butylate or a lithiated amine such as LDA;
- The action of a deprotection agent of the amine can be carried out in particular by the action of a hydrazine.

A quite particular subject of the invention is the process as defined previously in which (F) is the anhydride of phthaloyl glutamic acid.

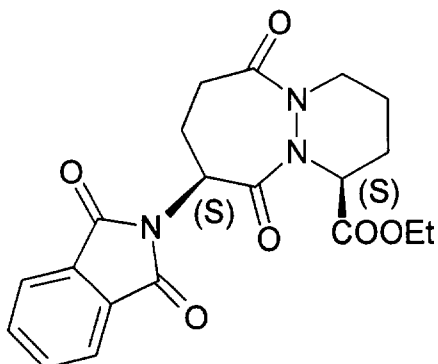
A quite particular subject of the invention is the process as defined previously in which the amine function of the compounds of formulae (IA), (I) or (Iopt) is protected in the form of a phthalimido group.

A quite particular subject of the invention is the process as defined previously in which, within the compounds of formula (II), (IV), (IA), (I) and (Iopt), R is a methyl, ethyl or *tert*butyl radical.

A quite particular subject of the invention is the process as defined previously in which the compound of formula (I) is ethyl 9-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-3,4,7,8,9,10-hexahydro-6,10-dioxo-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylate:

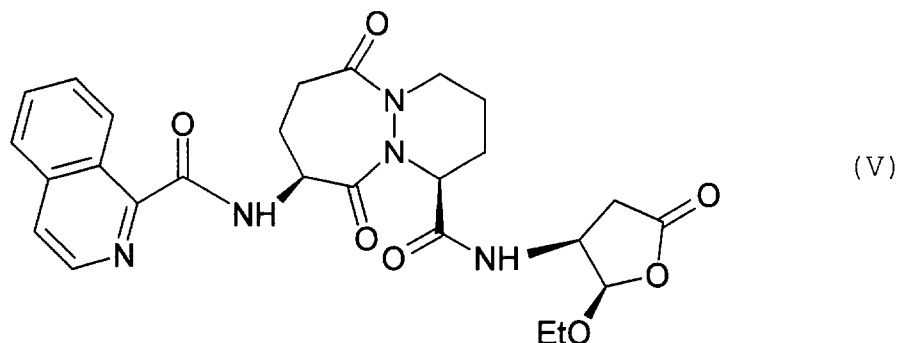


A quite particular subject of the invention is the process as defined previously in which the compound of formula (Iopt) is ethyl -(1S-cis)-9-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-3,4,7,8,9,10-hexahydro-6,10-dioxo-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylate:



The compounds of formula (I) can in general be used for the synthesis of medicaments as indicated in the Patent EP 94095. The compounds of formulae (II) and (III) and (F) are known and can be prepared according to the experimental method described below.

A subject of the invention is also the use of the process as defined above as an intermediary stage for the preparation of a compound of formula (V)



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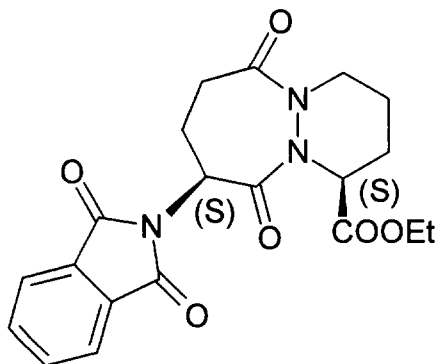
via the compound of formula (Iopt) as defined previously, characterized in that this process comprises the stages of the process for the preparation of the compounds of formula (Iopt) starting from the compounds of formula (II) as defined

15 previously.

A subject of the invention is also the use as defined above, characterized in that the compound of formula (Iopt) is ethyl (1S-cis)-9-(1,3-dihydro-1,3-dioxo-2H-isoindol-2yl)-3,4,7,8,9,10-hexahydro-6,10-dioxo-6H-pyridazino-[1,2-

20 a][1,2]diazepine-1-carboxylate

25



30 A subject of the invention is also the use of the process as defined above as an intermediate stage of the overall preparation process for the compounds of formula (I) and (Iopt) as defined previously.

Finally, a subject of the invention, as an intermediate

35 compound, is the compound of formula (IA) as defined previously.

The following examples illustrate the invention without however limiting it.

Preparation 1**Preparation of bis(phenylmethyl) 1,2-hydrazinecarboxylate**

1.5 litres of methanol and 25 g of hydrazine monohydrate at 80% are placed under nitrogen. The reaction medium is cooled down to 0°C and then 75 g of benzyl chloroformate and a solution of 93 g of sodium carbonate in 1100 ml of demineralized water are introduced. The reaction mixture is maintained at 0°C for 1 hour, followed by separating and washing by displacement with a mixture of 100 ml of methanol and 100 ml of water, then washing by displacement with 500 ml of water at 0°C. After drying 107.6 g of sought product is obtained.

Preparation 2**Preparation of N-phthaloyl-L-glutamic anhydride D (+)**

2-tetrahydro-2,6-dioxo-2H-pyran-3-yl-1H-isoindole-1,3(2H)-dione (R)

Stage a: N-phthaloyl-L-glutamic acid

2-(1,3-dihydro-1,3-dioxo-2H-isoindole-2-yl)-pentanedioic acid (2S)

10 g of L-glutamic acid then 16 g of N-carbethoxyphthalimide (Nefkens reagent, commercial) are added to a solution of 14.4 g of sodium carbonate in 180 ml of water. Agitation is carried out at ambient temperature for 2 hours followed by extraction with ethyl acetate.

The organic phase is evaporated under reduced pressure until a dry extract is obtained and 2.74 g of crude product is obtained. Washing is carried out with sodium bicarbonate, then after returning to the acid and extraction with ethyl acetate, 370 mg of expected product and H₂N-CO₂Et are isolated. Moreover, the aqueous phase is adjusted to pH=2 with 36% hydrochloric acid at a temperature lower than 5°C then extracted with ethyl acetate, washed with a saturated solution of sodium chloride, dried, filtered and concentrated under reduced pressure until 22.7 g of expected product is obtained in the form of an oil.

Mass spectrum (M-H)⁻ = 276⁻

Infrared (Nujol):

1775 cm⁻¹(m), 1720 cm⁻¹ (F, complex): CO

1611 cm^{-1} : Aromatic

Stage b:

160 ml of tetrahydrofuran is added and 18.6 g of DCC (1,3-Dicyclohexyl-carbodiimide) in solution in 55 ml of tetrahydrofuran is added dropwise over 30 minutes to the product obtained in stage a). Agitation is carried out for 1 hour at 15-17°C, followed by filtering, rinsing with tetrahydrofuran, evaporating under reduced pressure until a dry extract is obtained which is taken up in isopropyl oxide. After agitation for 30 minutes, filtering is carried out followed by washing and drying. 14.98 g of expected product is obtained.

$\alpha_D = -52.63$

^1H NMR (DMSO) 2.12 (m, 1H); 2.61 (m, 1H); 2.98 (dm, 1H); 3.16 (ddd, 1H); 5.48 (dd, 1H); 7.82 (m, >4H)

Example 1 : ethyl (1S-cis)-9-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-3,4,7,8,9,10-hexahydro-6,10-dioxo-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylate.

Stage a: preparation of 2,5-dibromopentanoic acid

39 ml of bromine is added to a mixture of 106 g of 5-bromopentanoic acid and 1 ml of phosphorus tribromide. The reaction mixture is taken to 70-80°C for 16 hours 30 minutes. The reaction medium is taken to 100°C for 15 minutes and allowed to return to ambient temperature. 147 g of sought product is obtained.

Stage b: Preparation of ethyl 2,5-dibromopentanoate

24.37 g of oxalyl chloride is added to a mixture containing 50 g of the acid prepared in the previous stage, 15 drops of dimethylformamide and 300 ml of dichloromethane. The reaction mixture is maintained under agitation, at ambient temperature, until the reaction is complete. The reaction mixture is cooled down to 10°C and 50 ml of ethyl alcohol is added. Agitation is carried out for 30 minutes at 10°C, the reaction medium is left to return to ambient temperature and agitation is carried out for 3 hours at ambient temperature, followed by bringing to dryness and the sought product is obtained.

Stage c: Cyclization

Preparation of 3-ethyl-1,2-bis(phenylmethyl) (S)-tetrahydro-1,2,3-pyridazinetricarboxylate and 3-ethyl-1,2-bis(phenylmethyl) (R)-tetrahydro-1,2,3-pyridazine-tricarboxylate.

5 A suspension of 12.1 g of ethyl 2,5-dibromopentanoate (Stage b) in 50 ml of diglyme is introduced at 20-25°C into a suspension containing 10.42 g of bis(phenylmethyl) 1,2-hydrazine-carboxylate (Preparation 1), 65 ml of diglyme and 8.26 g of potassium carbonate. The suspension obtained is
10 heated at 90°C and agitation is maintained for 48 hours, followed by cooling down to 20°C, pouring into a solution containing 50 ml of 2N hydrochloric acid and 150 ml of a mixture of water and ice. Extraction is carried out with ethyl acetate, followed by washing with water, drying,
15 filtering, rinsing with ethyl acetate and drying. Finally, the crude product is purified by chromatography on silica eluting with a heptane/ethyl acetate mixture 40/20 and 10.71 g of sought product is obtained.

Stage d: Acylation and hydrogenolysis

20 **Preparation of (1S)-[3-oxo-3-(tetrahydro-3-ethoxycarbonyl-1(2H)-pyridazinyl)propyl]-1,3-dihydro-1,3-dioxo-2H-isoindole-2-acetic acid α ,**

The mixture constituted by 15 g of 3-ethyl-1,2-bis(phenylmethyl) tetrahydro-1,2,3-pyridazinetricarboxylate
25 in the form of an R + S mixture as prepared in Stage c, 150 ml of tetrahydrofuran, 2.5 g of palladium on carbon (10%) and 9.08 g of phthaloyl glutamic acid anhydride as prepared according to Preparation 2 is placed under hydrogen pressure (1.3 bar) for 24 hours. After filtration, evaporation under
30 reduced pressure is carried out until a dry extract is obtained which is taken up in 100 ml of ethyl acetate and 150 ml of a saturated solution of sodium bicarbonate. Extraction is carried out 3 times and the bicarbonate solution is acidified to pH=3 with 36% hydrochloric acid. Extraction is
35 carried out 3 times with dichloromethane followed by washing with water. 13.16 g of crude product is obtained which is purified by chromatography on silica eluting with a

toluene/ethyl acetate/acetic acid mixture 20/80/1.5 in order to obtain 12.7 g of expected product.

NMR (250Hz, CDCl₃): 1.24 (d, 3H, OCH₂CH₃); 4.12 (q, 2H, OCH₂CH₃); 4.36-4.40 (m, 1H, H1 in position alpha or beta);
 5 4.69-4.92 (m, 1H, H9 in position alpha); 7.70 - 7.86 aromatic H's.

Stage e1: cyclization with POCl₃

ethyl -(1S-cis)-9-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-
 3,4,7,8,9,10-hexahydro-6,10-dioxo-6H-pyridazino-[1,2-
 10 a][1,2]diazepine-1-carboxylate.
 ethyl -(1R-trans)-9-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-
 3,4,7,8,9,10-hexahydro-6,10-dioxo-6H-pyridazino-[1,2-
 a][1,2]diazepine-1-carboxylate.

The following solutions A and B:

15 A: 417 mg of the ester prepared in Stage d in 4 ml of dichloroethane to which 1 ml of a solution of 1.2 ml of 2,6-lutidine in 5 ml of dichloroethane has been added.
 B: 1 ml of a solution of 1.9 ml of POCl₃ in 10 ml of dichloroethane, are added over 3 hours and simultaneously to
 20 a solution of 20 ml of dichloroethane heated beforehand to 75°C, then agitation is carried out for 1 hour at this temperature. The reaction medium is cooled down to 10°C, demineralized water is added, followed by extraction with dichloromethane and evaporation under reduced pressure in
 25 order to obtain a crude product (0.415g) which is purified by chromatography on silica eluting with a heptane/dichloromethane-/ethyl acetate mixture 1/1/1. 161.8 mg of the SS diastereoisomer, 126.7 mg of the SR diastereoisomer and 5.8 mg of an SS + SR mixture are
 30 isolated.

Stage e2: cyclization with POBr₃

ethyl -(1S-cis)-9-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-
 3,4,7,8,9,10-hexahydro-6,10-dioxo-6H-pyridazino-[1,2-
 a][1,2]diazepine-1-carboxylate.
 35 ethyl -(1R-trans)-9-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-
 3,4,7,8,9,10-hexahydro-6,10-dioxo-6H-pyridazino-[1,2-
 a][1,2]diazepine-1-carboxylate.

The following solutions A and B:

A: 417 mg of the ester prepared in Stage d in 4 ml of dichloroethane to which 1 ml of a solution of 2.4 ml of 2,6-lutidine in 10 ml of dichloroethane has been added.

B: 1 ml of a solution of 5.85 g of POBr₃ in 10 ml of dichloroethane, are added over 3 hours and simultaneously to a solution of 20 ml of dichloroethane heated beforehand to 80°C, then agitation is carried out for 1 hour to this temperature. The reaction medium is cooled down 10°C, demineralized water is added, followed by extraction with dichloromethane and evaporation under reduced pressure in order to obtain a crude product (0.419 g) which is purified by chromatography on silica eluting with a heptane/dichloromethane/ethyl acetate mixture 1/1/1. 163 mg of the SS diastereoisomer, 143 mg of the SR diastereoisomer and 6.2 mg of an SS + SR mixture are isolated.

Stage f: deracemization/epimerization

ethyl -(1S-cis)-9-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-3,4,7,8,9,10-hexahydro-6,10-dioxo-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylate.

A solution containing 0.029 g of potassium terbutylate and 0.3 ml of dimethylformamide is introduced at a temperature of -45/-48°C over one hour 30 minutes into a mixture containing 0.194 g of the SS + SR mixture prepared in Stage d, 1.5 ml of dimethylformamide and 0.75 ml of terbutanol. The mixture is maintained under agitation for 1 hour and after cooling down to -50°C, 0.4 g of ammonium chloride in powder form is introduced. Agitation is carried out for 10 minutes at -45°C, 1 ml of ammonium chloride is added at 20°C and agitation is carried out again for 10 minutes. After 5 minutes, 2 ml of demineralized water is added, followed by extraction with ethyl acetate, washing with demineralized water, decanting, concentrating and drying. 0.166 g of the expected SS diastereoisomer is obtained.

$\alpha_D = -75.3^\circ$ (1% in methanol)

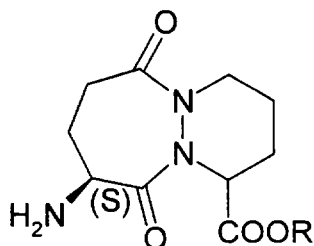
NMR (250Hz, CDCl₃): 1.73 (m, 3H, H-2 α H-3 α H-3 β); 1.24 (d, 3H, OCH₂CH₃); 2.38 (m, 3H, H2 β , H7 α , H8 α); 2.92 (m, 1H, H4 α); 3.39 - 3.44 (m, 1H, H8 β);

3.62(m, 1H, H7beta); 4.23 (m, 2H, OCH₂CH₃); 4.66-4.71 (m, 1H, H4 in position beta); 5.26-5.41 (m, 2H, H1 and H9 in position alpha); 7.72 - 7.88 aromatic H's

CLAIMS

1) Process for the preparation of the compounds of formula (I)

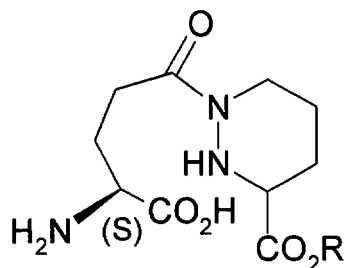
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(I)

10 in which R represents a hydrogen atom, an alkyl, aryl or aralkyl radical containing up to 18 carbon atoms and the amine function can be free or protected, starting from a compound of formula (IA)

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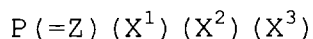


(IA)

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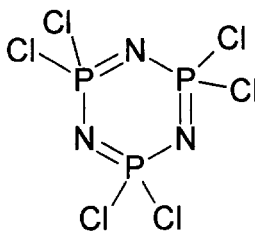
in which R has the same meaning as previously and the amine function can be free or protected, characterized in that the cyclization is carried out in a basic medium and in the presence :

25 - of a derivative of phosphonic acid of formula (P1):

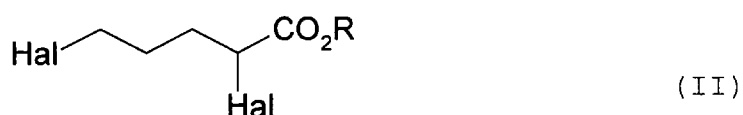


in which Z is a sulphur or oxygen atom, X^1 represents a halogen atom, X^2 and X^3 , identical or different, represent a halogen atom, an alkyloxy radical containing 1 to 6 carbon atoms, an aryloxy radical containing 6 to 12 carbon atoms or an arylalkyloxy radical containing 7 to 15 carbon atoms,
 30 - or of a trimer of formula (P2)

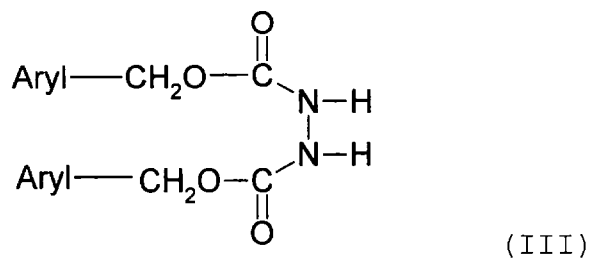
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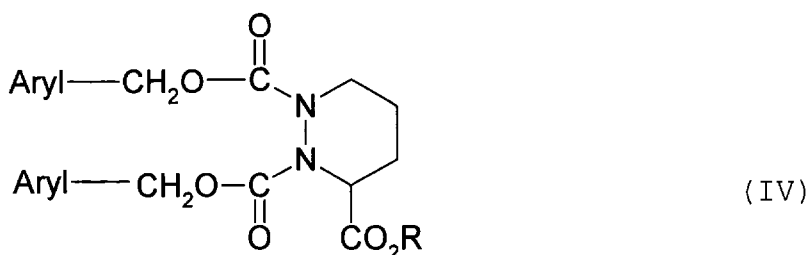
- 2) Process as defined in claim 1 in which (P1) is POCl_3 .
 3) Process as defined in claim 1 in which (P1) is POBr_3 .
 4) Process as defined in any one of claims 1 to 3 in which the base is chosen from pyridine or 2,6-lutidine.
 5) Process as defined in any one of claims 1 to 4 characterized in that the cyclization temperature is comprised between 70 and 80°C.
 6) Process as defined in any one of claims 1 to 4 characterized in that the solvent is dichloroethane.
 7) Process for the preparation of the compound of formula (I) in racemic or optically active (lopt) form, comprising the cyclization process as described in claim 1, and characterized in that it comprises the following successive stages:
 a) A compound of formula (II)



- in which R is as defined in claim 1 and Hal represents a halogen atom, is subjected to the action of a compound of formula (III)

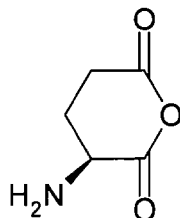


- in which Aryl represents an aryl radical containing up to 14 carbon atoms, in order to obtain the compound of formula (IV)



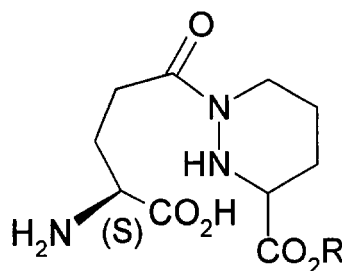
in the form of a mixture of R and S stereoisomers

b) the compound of formula (IV) is subjected to the action of an anhydride of formula (F)



(F)

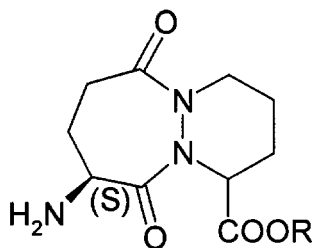
the amine function being in protected or non-protected form, while carrying out a deprotection by hydrogenolysis, in order to obtain the compound of formula (IA)



(IA)

as defined in claim 1,

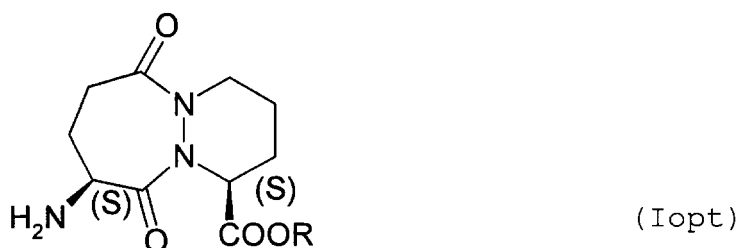
c) according to claim 1, the compound of formula (IA) is subjected to the action of a derivative of phosphonic acid (P1) or (P2) according to claims 1 to 3, in the presence of a base, according to claim 4, in order to obtain the compound of formula (I) as defined in claim 1



(I)

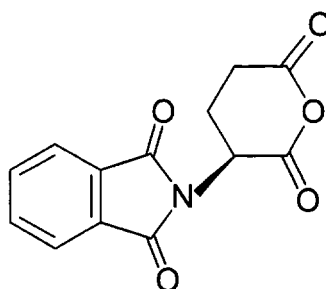
d) if appropriate, the amine function is deprotected in order to obtain the compound of formula (I) in which the amine function is not protected,

e) if appropriate, the compound of formula (I) in the SS + SR or SR form is subjected to the action of a deracemization and/or epimerization agent in order to obtain the compound of formula (Iopt) corresponding to the SS diastereoisomer,



10 f) if appropriate, the amine function is deprotected in order to obtain the compound of formula (Iopt) in which the amine function is not protected.

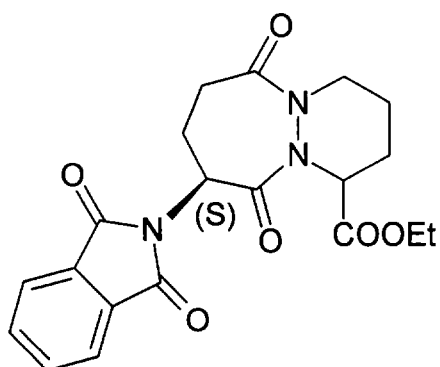
8) Process as defined in claim 7 in which F is N-phthaloyl-L-glutamic anhydride:



9) Process as defined in any one of claims 1 to 8, in which the amine function of the compounds of formulae (IA), (I) and (Iopt) is protected in phthalimido form.

10) Process as defined in any one of claims 1 to 8, in which, within the compounds of formula (II), (IV), (IA), (I) and (Iopt), R is a methyl, ethyl or tertbutyl radical.

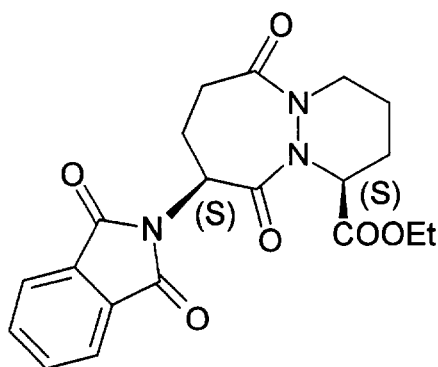
11) Process as defined in any one of the claims 1 to 8 in which the compound of formula (I) is ethyl -9-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-3,4,7,8,9,10-hexahydro-6,10-dioxo-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylate.



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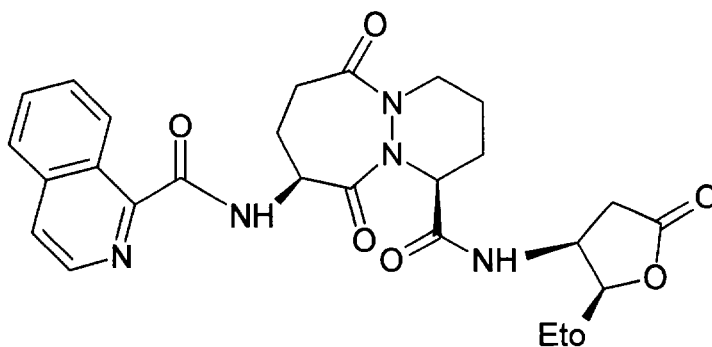
- 12)** Process as defined in any one of the claims 1 to 8 in which the compound of formula (Iopt) is ethyl -(1S-cis)-9-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-3,4,7,8,9,10-hexahydro-6,10-dioxo-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylate:

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- 13)** Use of the process as defined in any one of claims 1 to 12 as an intermediate stage for the preparation of a compound of formula (V)

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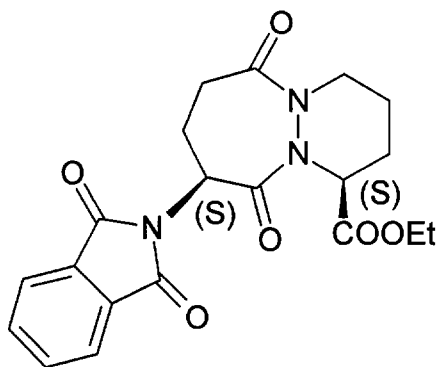
(V)

via the compound of formula (Iopt) as defined in claim 7.

14) Use according to claim 13 characterized in that the compound of formula (Iopt) is ethyl (1S-cis)-9-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-3,4,7,8,9,10-hexahydro-6,10-dioxo-6H-pyridazino-[1,2-a][1,2] diazepine-1-carboxylate.

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15) 15) Use of the process as defined in any one of claims 1 to 6 as an intermediate stage of the overall preparation process for the compounds of formulae (I) and (Iopt) as defined in any one of claims 7 to 14.

16) Compound of formula (IA) as defined in claim 1.