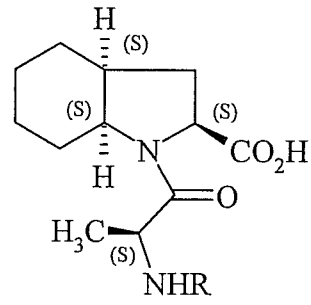
NEW PROCESS FOR THE SYNTHESIS OF (2S,3aS,7aS)-1-[(S)-ALANYL]-OCTAHYDRO-1*H*-INDOLE-2-CARBOXYLIC ACID COMPOUNDS AND APPLICATION IN THE SYNTHESIS OF PERINDOPRIL

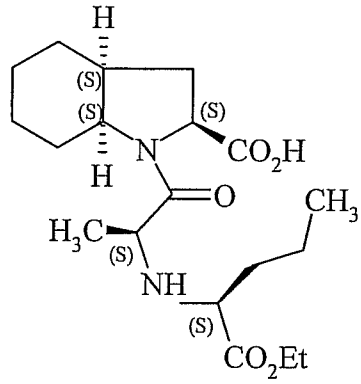
The present invention relates to a process for the synthesis of compounds of formula (I) :



(I),

wherein R represents a hydrogen atom or a protecting group for the amino function,

and to their application in the synthesis of perindopril of formula (II) :



(II)

and pharmaceutically acceptable salts thereof.

Perindopril and its pharmaceutically acceptable salts, and more especially its tert-butylamine salt, have valuable pharmacological properties.

Their principal property is that of inhibiting angiotensin I converting enzyme (or kininase II), which allows, on the one hand, prevention of the conversion of the decapeptide angiotensin I to the octapeptide angiotensin II (a vasoconstrictor) and, on the other hand, prevention of the degradation of bradykinin (a vasodilator) to an inactive peptide.

Those two actions contribute to the beneficial effects of perindopril in cardiovascular diseases, more especially in arterial hypertension and heart failure.

Perindopril, its preparation and its use in therapeutics have been described in European patent specification EP 0 049 658.

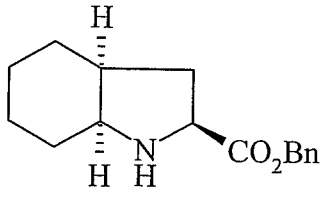
In view of the pharmaceutical value of this compound, it has been important to be able to obtain it by an effective synthesis process, readily transposable to an industrial scale, that leads to perindopril in a good yield and with excellent purity.

Patent specification EP 0 308 341 describes the industrial synthesis of perindopril by the coupling of (2*S*,3a*S*,7a*S*)-octahydroindole-2-carboxylic acid benzyl ester with N-[(*S*)-1-carboxybutyl]-(*S*)-alanine ethyl ester in the presence of dicyclohexylcarbodiimide, followed by deprotection of the carboxylic group of the heterocycle by catalytic hydrogenation.

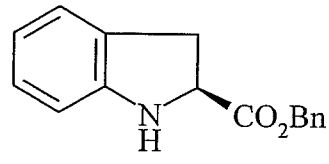
That process has disadvantages related to use of the dicyclohexylcarbodiimide.

The Applicant has developed a process for the synthesis of perindopril that uses other coupling agents.

More specifically, the present invention relates to a process for the synthesis of perindopril, which process is characterised in that the benzyl ester of formula (IIIa) or (IIIb) :



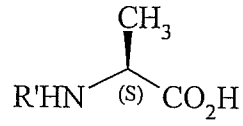
(IIIa)



(IIIb)

or an addition salt of the ester of formula (IIIa) or (IIIb) with a mineral acid or organic acid is reacted

with the alanine compound of formula (IV) :



(IV),

wherein R' represents a protecting group for the amino function,

in the presence of a coupling agent selected from the following reagents and pairs of reagents :

(1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride,
(1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / 1-hydroxybenzotriazole,
(1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / 1-hydroxy-7-azabenzotriazole,
(1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / N-hydroxysuccinimide,
(1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine,
(1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / N-hydroxyphthalimide,
dicyclohexylcarbodiimide / 1-hydroxy-7-azabenzotriazole,
dicyclohexylcarbodiimide / N-hydroxysuccinimide,
dicyclohexylcarbodiimide / 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine,
dicyclohexylcarbodiimide / N-hydroxyphthalimide,
O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate,
O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate,
O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate,
benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate,
benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate,
O-(benzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate,
O-(benzotriazol-1-yl)-1,1,3,3-bis(pentamethylene)uronium hexafluorophosphate,
chloro-tripyrrolidinophosphonium hexafluorophosphate,
chloro-1,1,3,3-bis(tetramethylene)formamidinium hexafluorophosphate,
chloro-1,1,3,3-bis(pentamethylene)formamidinium hexafluorophosphate,
N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline,
O-[(ethoxycarbonyl)-cyanomethyleneamino]-1,1,3,3-tetramethyluronium tetrafluoroborate,

O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate,

O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate / 1-hydroxybenzotriazole,

O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate / N-methylmorpholine,

O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate / collidine,

O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate,

O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate / 1-hydroxybenzotriazole,

O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate,

O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate / 1-hydroxy-benzotriazole,

O-(N-succinimidyl)-1,1,3,3-tetramethyluronium tetrafluoroborate,

O-(N-succinimidyl)-1,1,3,3-bis(tetramethylene)uronium tetrafluoroborate,

O-(N-succinimidyl)-1;1,3,3-bis(tetramethylene)uronium tetrafluoroborate / 1-hydroxy-benzotriazole,

O-(5-norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate,

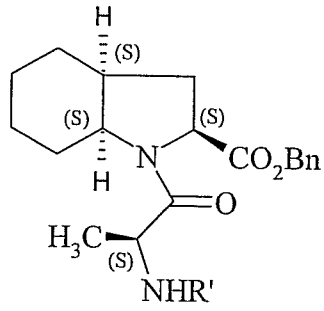
propanephosphonic anhydride,

N-hydroxy-5-norbornene-2,3-dicarboxylic acid imide,

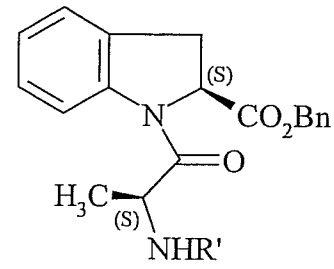
and N-hydroxy-1,2-dihydro-2-oxo-pyridine,

optionally in the presence of a base,

to yield the compound of formula (Va) or (Vb), respectively, depending on whether the compound of formula (IIIa) or (IIIb) is used as starting material :



(Va)



(Vb),

wherein R' is as defined hereinbefore,

which is subjected to a catalytic hydrogenation reaction in the presence of palladium to yield the product of formula (I).

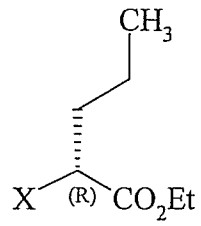
Among the protecting groups for the amino function which can be used in the present invention, there may be mentioned, without implying any limitation, the tert-butyloxycarbonyl, benzyl and benzyloxycarbonyl groups.

The catalytic hydrogenation of the compound of formula (Va) is preferably carried out under a hydrogen pressure of less than 10 bars.

The catalytic hydrogenation of the compound of formula (Vb) is preferably carried out under a hydrogen pressure of from 10 to 35 bars.

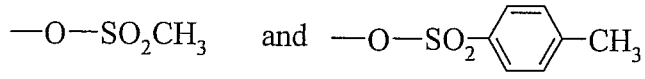
The compound of formula (I) thereby obtained is then subjected, if required, to a reaction deprotecting the amino function, followed by a coupling reaction either with ethyl 2-oxo-pentanoate under conditions of reductive amination

or with a compound of formula (VI) :



(VI),

wherein X represents a leaving group selected from halogen,



to yield optically pure perindopril, which is converted, if desired, into a pharmaceutically acceptable salt such as the tert-butylamine salt.

The Examples hereinbelow illustrate the invention.

Example 1 : ***(2S,3aS,7aS)-1-{(2S)-2-[(tert-Butyloxycarbonyl)-amino]-propionyl}-octahydro-1H-indole-2-carboxylic acid / method 1 :***

Step A : *Benzyl (2S,3aS,7aS)-1-{(2S)-2-[(tert-butyloxycarbonyl)-amino]-propionyl}-octahydro-1H-indole-2-carboxylate :*

200 g of (2*S*,3a*S*,7a*S*)-octahydroindole-2-carboxylic acid benzyl ester para-toluene-sulphonate, 65 ml of triethylamine and 1 litre of ethyl acetate are introduced into a stirred reactor, followed, after stirring for 10 minutes at ambient temperature, by 87 g of N-[tert-butyloxycarbonyl]-(*S*)-alanine and 175 g of O-(benzotriazol-1-yl)-1,1,3,3-bis(tetra-methylene)uronium hexafluorophosphate. The heterogeneous mixture is then heated at 30°C for 3 hours whilst stirring well and is then cooled to 0°C and filtered.
The filtrate is then washed and subsequently evaporated to dryness to yield the expected product.

Step B : *(2S,3aS,7aS)-1-{(2S)-2-[(tert-Butyloxycarbonyl)-amino]-propionyl}-octahydro-1H-indole-2-carboxylic acid :*

The residue obtained in the previous Step (200 g) is dissolved in 200 ml of methylcyclohexane and transferred to a hydrogenator; 26 g of 5 % palladium-on-carbon suspended in 80 ml of methylcyclohexane are then added, followed by 640 ml of water. The mixture is then hydrogenated under a pressure of 0.5 bar at a temperature of from 15 to 30°C, until the theoretical amount of hydrogen has been absorbed.
After filtering off the catalyst, the aqueous phase of the filtrate is washed with methylcyclohexane and then lyophilised to yield the expected product in a yield of 94 %.

Example 2 : (2S,3aS,7aS)-1-{(2S)-2-[(tert-Butyloxycarbonyl)-amino]-propionyl}-octahydro-1H-indole-2-carboxylic acid / method 2 :

Step A : *Benzyl (2S)-1-{(2S)-2-[(tert-butyloxycarbonyl)-amino]-propionyl}-2,3-dihydro-1H-indole-2-carboxylate :*

200 g of benzyl 2,3-dihydro-1*H*-indole-2-carboxylate para-toluenesulphonate, 66 ml of triethylamine and 1 litre of ethyl acetate are introduced into a stirred reactor, followed, after stirring for 10 minutes at ambient temperature, by 89 g of N-[tert-butyloxycarbonyl]-(*S*)-alanine and 151 g of O-(benzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)uronium tetrafluoroborate. The heterogeneous mixture is then heated at 30°C for 3 hours whilst stirring well and is then cooled to 0°C and filtered.
The filtrate is then washed and subsequently evaporated to dryness to yield the expected product.

Step B : *(2S,3aS,7aS)-1-{(2S)-2-[(tert-Butyloxycarbonyl)-amino]-propionyl}-octahydro-1H-indole-2-carboxylic acid :*

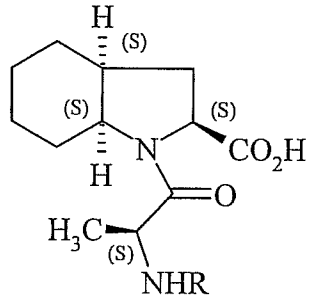
The residue obtained in the previous Step (200 g) is dissolved in 200 ml of methylcyclohexane and transferred to a hydrogenator; 26 g of 5 % palladium-on-carbon suspended in 80 ml of methylcyclohexane are then added, followed by 640 ml of water.

The mixture is then hydrogenated under a pressure of 0.5 bar at a temperature of from 15 to 30°C, until the theoretical amount of hydrogen required for debenzylation has been absorbed; the mixture is then heated to a temperature of from 50 to 100°C and hydrogenated under a pressure of 30 bars until the theoretical amount of hydrogen required for hydrogenation of the ring has been absorbed.

After filtering off the catalyst, the aqueous phase of the filtrate is washed with methylcyclohexane and then lyophilised to yield the expected product.

CLAIMS

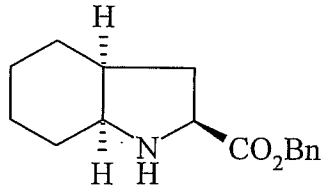
1. Process for the synthesis of compounds of formula (I)



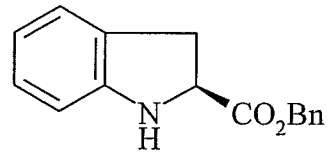
(I),

wherein R represents a hydrogen atom or a protecting group for the amino function,

characterised in that the benzyl ester of formula (IIIa) or (IIIb) :



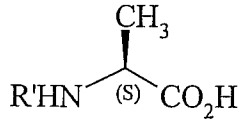
(IIIa)



(IIIb)

or an addition salt of the ester of formula (IIIa) or (IIIb) with a mineral acid or organic acid is reacted

with the alanine compound of formula (IV) :



(IV),

wherein R' represents a protecting group for the amino function,

in the presence of a coupling agent selected from the following reagents and pairs of reagents :

(1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride,

(1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / 1-hydroxybenzotriazole,

(1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / 1-hydroxy-7-azabenzotriazole,

(1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / N-hydroxysuccinimide,

(1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine,

(1,3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride / N-hydroxyphthalimide,

dicyclohexylcarbodiimide / 1-hydroxy-7-azabenzotriazole,

dicyclohexylcarbodiimide / N-hydroxysuccinimide,

dicyclohexylcarbodiimide / 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine,

dicyclohexylcarbodiimide / N-hydroxyphthalimide,

O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate,

O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate,

O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate,

benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphate,

benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate,

O-(benzotriazol-1-yl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate,

O-(benzotriazol-1-yl)-1,1,3,3-bis(pentamethylene)uronium hexafluorophosphate,

chloro-tripyrrolidinophosphonium hexafluorophosphate,

chloro-1,1,3,3-bis(tetramethylene)formamidinium hexafluorophosphate,

chloro-1,1,3,3-bis(pentamethylene)formamidinium hexafluorophosphate,

N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline,

O-[(ethoxycarbonyl)-cyanomethyleneamino]-1,1,3,3-tetramethyluronium tetrafluoroborate,

O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate,

O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate / 1-hydroxybenzotriazole,

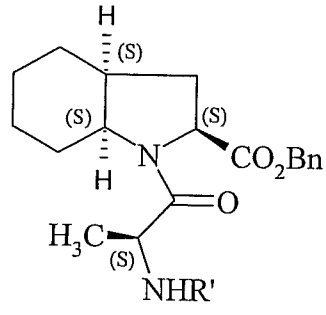
O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate / N-methylmorpholine,

O-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate / collidine,

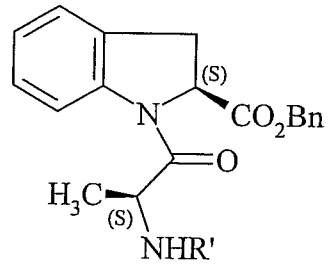
O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate,

O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-tetramethyluronium tetrafluoroborate / 1-hydroxybenzotriazole,
O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate,
O-(1,2-dihydro-2-oxo-1-pyridyl)-1,1,3,3-bis(tetramethylene)uronium hexafluorophosphate / 1-hydroxy-benzotriazole,
O-(N-succinimidyl)-1,1,3,3-tetramethyluronium tetrafluoroborate,
O-(N-succinimidyl)-1,1,3,3-bis(tetramethylene)uronium tetrafluoroborate,
O-(N-succinimidyl)-1,1,3,3-bis(tetramethylene)uronium tetrafluoroborate / 1-hydroxy-benzotriazole,
O-(5-norbornene-2,3-dicarboximido)-1,1,3,3-tetramethyluronium tetrafluoroborate,
propanephosphonic anhydride,
N-hydroxy-5-norbornene-2,3-dicarboxylic acid imide,
and N-hydroxy-1,2-dihydro-2-oxo-pyridine,

optionally in the presence of a base,
to yield the compound of formula (Va) or (Vb), respectively, depending on whether the compound of formula (IIIa) or (IIIb) is used as starting material :



(Va)



(Vb),

wherein R' is as defined hereinbefore,

which is subjected to a catalytic hydrogenation reaction in the presence of palladium to yield the product of formula (I).

2. Process according to claim 1, characterised in that the compound of formula (IIIa) is used as starting material.

3. Process according to claim 1, characterised in that the compound of formula (IIIb) is used as starting material.

4. Process according to claim 2, characterised in that the hydrogenation reaction on the compound of formula (Va) is carried out under a hydrogen pressure of less than 10 bars.

5. Process according to claim 3, characterised in that the hydrogenation reaction on the compound of formula (Vb) is carried out under a hydrogen pressure of from 10 to 35 bars.

6. Process for the synthesis of perindopril or pharmaceutically acceptable salts thereof starting from a compound of formula (I), characterised in that the said compound of formula (I) is obtained by the synthesis process according to any one of claims 1 to 5.