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FULL NAMES OF APPLICANT

71 LES LABORATOIRES SERVIER

FULL NAMES OF INVENTORS

72 1. DUBUFFET, THIERRY
2. LECOUBE, JEAN-PIERRE

EARLIEST PRIORITY CLAIMED

COUNTRY

NUMBER

DATE

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31 03292131.4

32 29 AUG 2003

TITLE OF INVENTION

54 NOVEL METHOD FOR THE SYNTHESIS OF PERINDOPRIL AND THE PHARMACEUTICALLY-ACCEPTABLE SALTS THEREOF

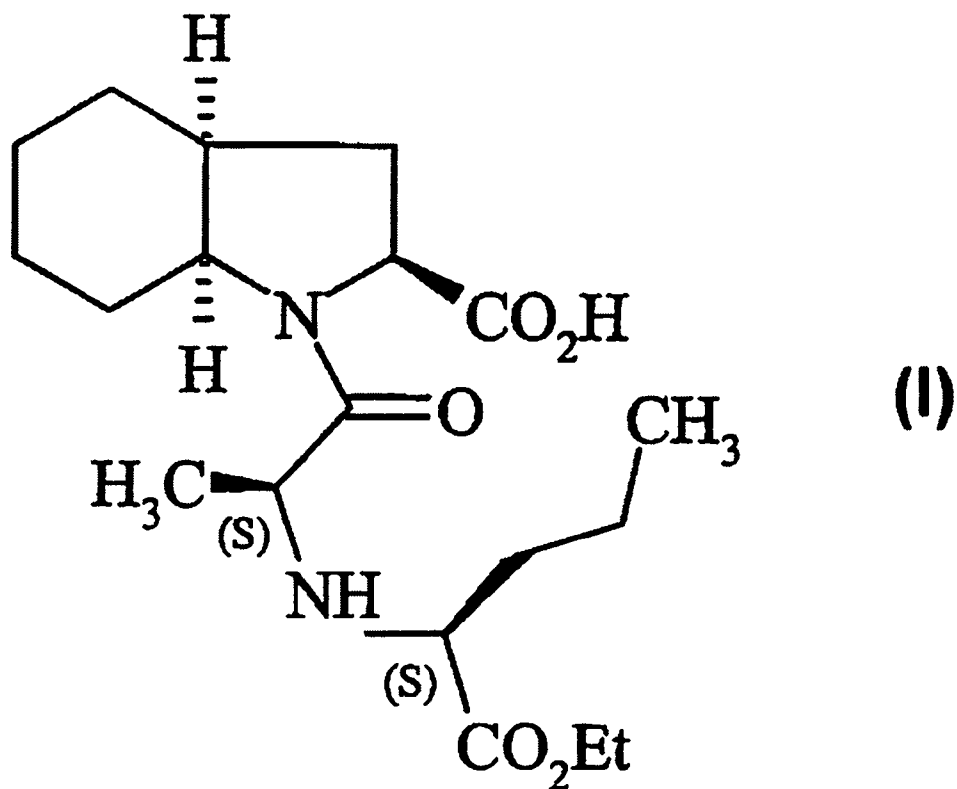
57 ABSTRACT (NOT MORE THAT 150 WORDS)

NUMBER OF SHEETS 16

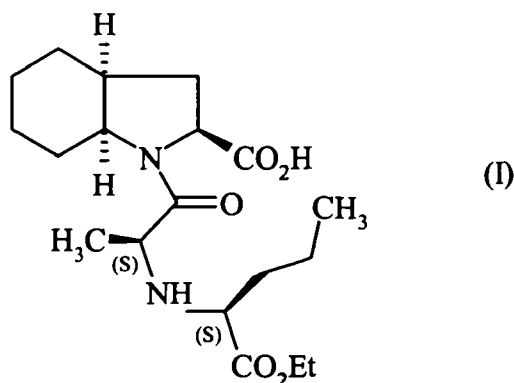
If no classification is finished, Form P.9 should accompany this form.
The figure of the drawing to which the abstract refers is attached.

ABSTRACT

The invention relates to a method for the synthesis of perindopril having formula (I) and the pharmaceutically-acceptable salts thereof.



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



and its pharmaceutically acceptable salts.

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 the European patent specification EP 0 049 658.

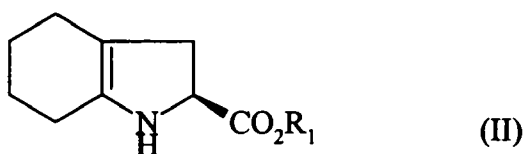
In view of the pharmaceutical value of this compound, it has been important to be able to obtain it by an effective synthesis process, readily transposable to an industrial scale, that leads to perindopril in a good yield and with excellent purity starting from reasonably priced starting materials.

Patent specification EP 0 308 341 describes the industrial synthesis of perindopril by the coupling of (2*S*,3*aS*,7*aS*)-octahydroindole-2-carboxylic acid benzyl ester with N-[(*S*)-1-

carboxybutyl]-(*S*)-alanine ethyl ester, followed by deprotection of the carboxylic group of the heterocycle by catalytic hydrogenation.

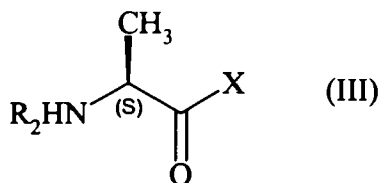
The Applicant has now developed a new process for the synthesis of perindopril.

- 5 More specifically, the present invention relates to a process for the synthesis of perindopril and its pharmaceutically acceptable salts which is characterised in that the compound of formula (II) :



10 wherein R₁ represents a hydrogen atom or a benzyl or linear or branched (C₁-C₆)alkyl group,

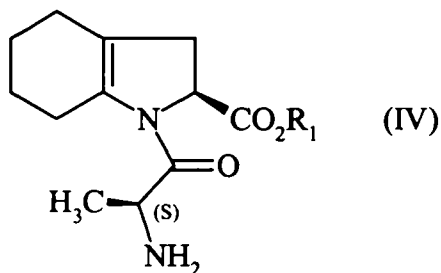
is reacted with a compound of formula (III) having the S configuration :



15 wherein X represents a halogen atom and R₂ represents a protecting group for the amino function,

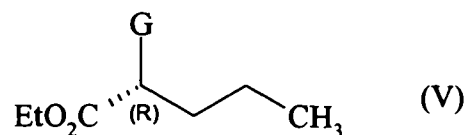
in the presence of a base,

to yield, after deprotection of the amino function, a compound of formula (IV) :



wherein R_1 is as defined hereinbefore,

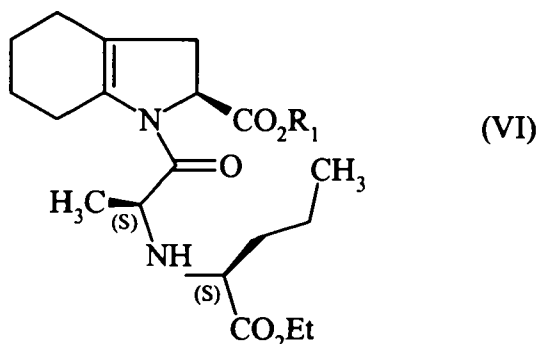
which is reacted with a compound of formula (V) :



wherein G represents a chlorine, bromine or iodine atom or a p-toluenesulphonyloxy,
5 methanesulphonyloxy or trifluoromethanesulphonyloxy group,

in the presence of a base,

to yield a compound of formula (VI) :



wherein R_1 is as defined hereinbefore,

10 which is hydrogenated in the presence of a catalyst such as palladium, platinum, rhodium
or nickel
to yield, after deprotection where necessary, the compound of formula (I).

15 Among the protecting groups for the amino function that can be used in the process of the
present invention, the groups tert-butoxycarbonyl and benzyl may be mentioned without
implying any limitation.

R_1 preferably represents a benzyl group. In that case the protecting group for the amino
function is preferably the tert-butoxycarbonyl group.

Among the bases that can be used in the reaction between the compounds of formulae (II) and (III) or between the compounds of formulae (IV) and (V) there may be mentioned, without implying any limitation, organic amines such as triethylamine, pyridine, N-methylmorpholine or diisopropylethylamine, and mineral bases such as NaOH, KOH, Na₂CO₃, K₂CO₃, NaHCO₃ or KHCO₃.

EXAMPLE 1 : (2S,3aS,7aS)-1-((2S)-2-[(1S)-1-(ethoxycarbonyl)butylamino]-propionyl)-octahydro-1H-indole-2-carboxylic acid tert-butylamine salt

Step A : Benzyl (2S)-1-((2S)-2-[(tert-butoxycarbonyl)amino]propionyl)-2,3,4,5,6,7-hexahydro-1H-indole-2-carboxylate

Introduce 200 g of benzyl (2S)-2,3,4,5,6,7-hexahydro-1H-indole-2-carboxylate and 1.5 litres of dichloromethane into a reactor, then bring the temperature of the reaction mixture to 0°C and add 107 ml of triethylamine and then 162 g of (2S)-2-[(tert-butoxycarbonyl)amino]propionyl chloride. Subsequently, bring the mixture to ambient temperature. After stirring for 1 hour at that temperature, wash the mixture with water and then with a dilute acetic acid solution. The benzyl (2S)-1-((2S)-2-[(tert-butoxycarbonyl)amino]propionyl)-2,3,4,5,6,7-hexahydro-1H-indole-2-carboxylate solution so obtained is used as it is in the following Step.

Step B : Benzyl (2S)-1-((2S)-2-aminopropionyl)-2,3,4,5,6,7-hexahydro-1H-indole-2-carboxylate

Introduce the solution obtained in the above Step into a reactor, and then add 133 g of trifluoroacetic acid. After stirring for 1 hour 30 minutes at ambient temperature, wash the mixture with water and then with a saturated solution of sodium hydrogen carbonate and evaporate off the solvents to yield benzyl (2S)-1-((2S)-2-aminopropionyl)-2,3,4,5,6,7-hexahydro-1H-indole-2-carboxylate.

Step C : *Benzyl (2S)-1-[(2S)-2-[(1S)-1-(ethoxycarbonyl)butylamino]propionyl]-2,3,4,5,6,7-hexahydro-1H-indole-2-carboxylate*

Introduce into a reactor 200 g of the compound obtained in the above Step, 106 ml of diisopropylethylamine and 1.5 litres of tetrahydrofuran, and then 183 g of ethyl (2R)-2-p-toluenesulfonyloxy-pentanoate, and subsequently heat at 70°C for 2 hours. After returning to ambient temperature, the mixture is washed with water and then concentrated to dryness. The residue is taken up in dichloromethane. A hydrochloric acid solution (2M) is added until a pH of about 7.5 is obtained. After decanting, the solvents are evaporated off to yield benzyl (2S)-1-[(2S)-2-[(1S)-1-(ethoxycarbonyl)butylamino]propionyl]-2,3,4,5,6,7-hexahydro-1H-indole-2-carboxylate.

Step D : *(2S,3aS,7aS)-1-[(2S)-2-[(1S)-1-(ethoxycarbonyl)butylamino]propionyl]-octahydro-1H-indole-2-carboxylic acid*

Introduce 200 g of the compound obtained in the above Step, in solution in acetic acid, and then 5 g of 10 % Pt/C into a hydrogenation vessel. Hydrogenate under a pressure of 5 bars at from 15 to 30°C until the theoretical amount of hydrogen has been absorbed.

Remove the catalyst by filtration and then cool to from 0 to 5°C and collect the resulting solid by filtration. Wash the cake and dry it to constant weight.

The (2S, 3aS, 7aS)-1-[(2S)-2-[(1S)-1-(ethoxycarbonyl)butylamino]propionyl]octahydro-1H-indole-2-carboxylic acid is thereby obtained in a yield of 85 % and with an enantiomeric purity of 98 %.

Step E : *(2S,3aS,7aS)-1-[(2S)-2-[(1S)-1-(ethoxycarbonyl)butylamino]propionyl]-octahydro-1H-indole-2-carboxylic acid tert-butylamine salt*

The precipitate obtained in the above Step (200 g) is dissolved in 2.8 litres of acetonitrile, and then 40 g of tert-butylamine and 0.4 litres of ethyl acetate are added.

The suspension obtained is then refluxed until dissolution is complete, and the solution obtained is subsequently filtered hot and cooled, with stirring, to a temperature of from 15

to 20°C. The resulting precipitate is then filtered off, made into a paste again with acetonitrile, dried and then recrystallised from ethyl acetate to give the expected product in a yield of 95 % and with an enantiomeric purity of 99 %.

EXAMPLE 2 : (2S,3aS,7aS)-1-((2S)-2-((1S)-1-(ethoxycarbonyl)butylamino)propionyl)-octahydro-1H-indole-2-carboxylic acid tert-butylamine salt

Steps A and B : identical to Steps A and B of Example 1.

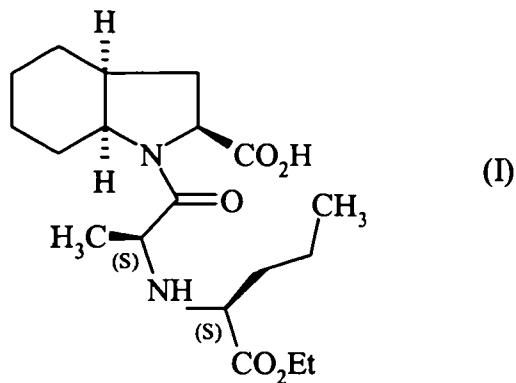
Step C : Benzyl (2S)-1-((2S)-2-((1S)-1-(ethoxycarbonyl)butylamino)propionyl)-2,3,4,5,6,7-hexahydro-1H-indole-2-carboxylate

10 Introduce 200 g of the compound obtained in the above Step, 106 ml of diisopropylethylamine and 1.5 litres of ethyl acetate into a reactor, followed by 165 g of ethyl (2R)-2-chloropentanoate, and then heat at 50°C for 3 hours. After returning to ambient temperature, the mixture is washed with water and then concentrated to dryness. The residue is taken up in dichloromethane. A hydrochloric acid solution (2M) is added
15 until a pH of about 7.5 is obtained. After decanting, the solvents are evaporated off to yield benzyl (2S)-1-((2S)-2-((1S)-1-(ethoxycarbonyl)butylamino)propionyl)-2,3,4,5,6,7-hexahydro-1H-indole-2-carboxylate.

Steps D and E : identical to Steps D and E of Example 1.

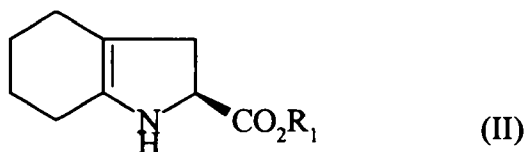
CLAIMS

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



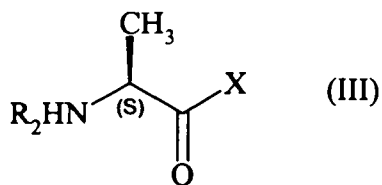
and its pharmaceutically acceptable salts,

5 characterised in that a compound of formula (II) :



wherein R₁ represents a hydrogen atom or a benzyl or linear or branched (C₁-C₆)alkyl group,

is reacted with a compound of formula (III) having the S configuration :

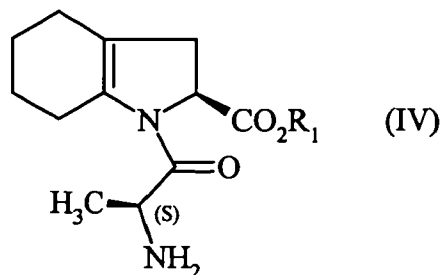


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wherein X represents a halogen atom and R₂ represents a protecting group for the amino function,

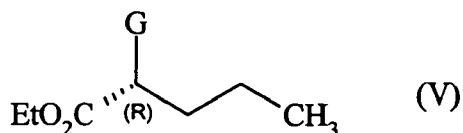
in the presence of a base,

to yield, after deprotection of the amino function, a compound of formula (IV) :



wherein R₁ is as defined hereinbefore,

which is reacted with a compound of formula (V) :

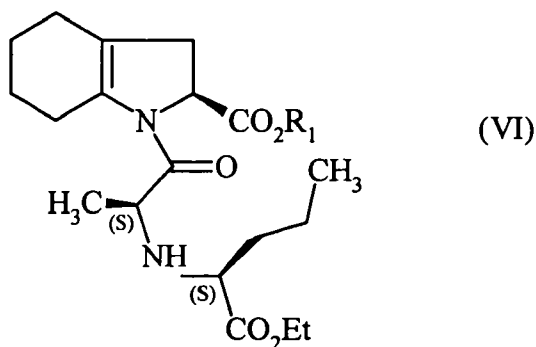


5

wherein G represents a chlorine, bromine or iodine atom or a p-toluenesulphonyloxy, methanesulphonyloxy or trifluoromethanesulphonyloxy group,

in the presence of a base,

to yield a compound of formula (VI) :



10

wherein R₁ is as defined hereinbefore,

which is hydrogenated in the presence of a catalyst

to yield, after deprotection where necessary, the compound of formula (I).

2. Synthesis process according to claim 1, characterised in that the catalyst is selected from palladium, platinum, rhodium or nickel.
3. Synthesis process according to claim 1 or claim 2, characterised in that the protecting
5 group for the amino function is a tert-butoxycarbonyl or benzyl group.
4. Synthesis process according to claim 3, characterised in that R₁ represents a benzyl group, and the protecting group for the amino function is a tert-butoxycarbonyl group.
5. Synthesis process according to any one of claims 1 to 4, characterised in that the base used for the reaction between the compounds of formulae (II) and (III) is an organic
10 amine selected from triethylamine, pyridine, N-methylmorpholine and diisopropylethylamine, or a mineral base.
6. Synthesis process according to claim 5, characterised in that the mineral base is selected from NaOH, KOH, Na₂CO₃, K₂CO₃, NaHCO₃ or KHCO₃.
- 15 7. Synthesis process according to any one of claims 1 to 6, characterised in that the base used for the reaction between the compounds of formulae (IV) and (V) is an organic amine selected from triethylamine, pyridine, N-methylmorpholine and diisopropylethylamine, or a mineral base.
- 20 8. Synthesis process according to claim 7, characterised in that the mineral base is selected from NaOH, KOH, Na₂CO₃, K₂CO₃, NaHCO₃ or KHCO₃.
9. Process according to any one of claims 1 to 8 for the synthesis of perindopril in the form of its tert-butylamine salt.