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(54) Title: A PROCESS FOR THE SYNTHESIS OF 2-AMINO-5-PROTECTED AMINO-3-HYDROXY-1, 6-DIPHENYLHEX-
ANE OR A SALT THEREOF - AN INTERMEDIATE FOR ANTIVIRAL DRUGS

(57) Abstract: The present invention relates to an improved process for preparing 2-amino-5-protected-amino-3-hydroxy-1,6-
diphenylhexane compounds or acid addition salts thereof, which can be useful intermediates for preparing compounds with an-
tiviral activity. The present invention further provides a process for preparing HIV protease inhibitors, lopinavir and ritonavir.



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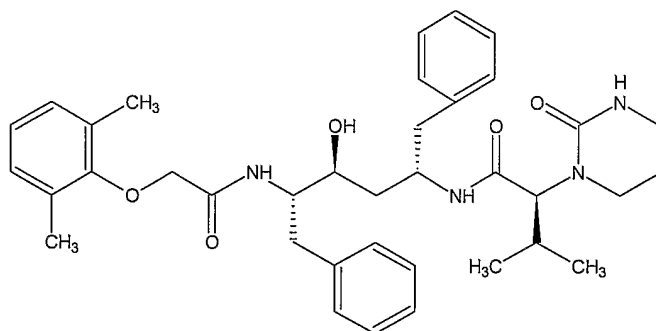
A PROCESS FOR THE SYNTHESIS OF 2-AMINO-5-PROTECTED AMINO-3-HYDROXY-1,6-DIPHENYLHEXANE OR A SALT THEREOF - AN INTERMEDIATE FOR ANTIVIRAL DRUGS

Field of the Invention

5 The present invention relates to an improved process for preparing 2-amino-5-protected-amino-3-hydroxy-1,6-diphenylhexane compounds or acid addition salts thereof, which can be useful intermediates for preparing compounds with antiviral activity. The present invention further provides a process for preparing HIV protease inhibitors, lopinavir and ritonavir

Background of the Invention

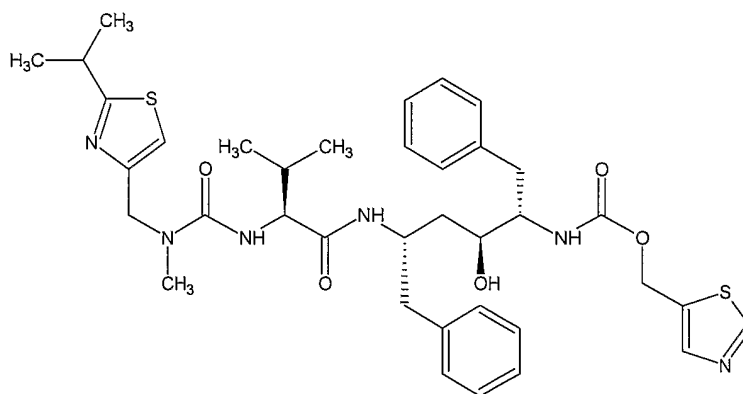
Lopinavir (Formula I below) is chemically [1S-[1R*,(R*),3R*,4R*]]-N-[4-[(2,6-dimethyl-phenoxy)acetyl]amino]-3-hydroxy-5-phenyl-1-(phenylmethyl)pentyl]tetrahydro-alpha-(1-methylethyl)-2-oxo-1(2H)-pyrimidineacetamide.



15 Formula I

Ritonavir (Formula II below) is chemically, [5S-(5R*,8R*,10R*,11R*)]-10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester.

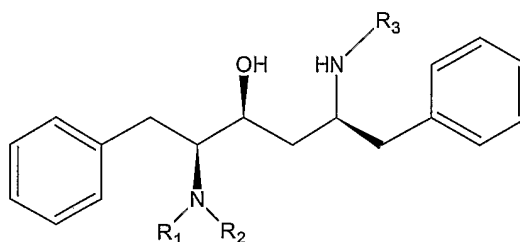
- 2 -



Formula II

Lopinavir and Ritonavir are indicated in combination with other anti-retroviral agents for the treatment of HIV-infection.

- 5 Compounds of Formula III or an acid addition salt thereof, wherein R_1 , R_2 are hydrogen and R_3 is an amino protecting group is useful intermediate for preparing compounds with antiviral activity such as lopinavir and ritonavir.



Formula III

- 10 U.S. Patent No. 5,914,332 discloses a process for preparation of succinic acid salt of compound of Formula III, wherein R_1 and R_2 are hydrogen and R_3 is *t*-butoxy carbonyl in four steps starting from (2*S*)-5-amino-2-(*N,N*-dibenzylamino)-3-oxo-1,6-diphenylhex-4-ene. The steps involve reduction of keto functionality and double bond, protection of the 2-amino group with butyloxycarbonyl group, debenzylation of the 5-dibenzylamino group and finally forming an acid addition salt with succinic acid. After
- 15 every step however, the intermediates are isolated. The intermediate of Formula III as its succinate salt is further converted to lopinavir.

- 20 WO 94/14436 provides a process for the preparation of compound of Formula III wherein R_1 and R_2 are hydrogen and R_3 is tert-butyloxycarbonyl, providing a free base of a compound of Formula III.

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WO 95/11224 also provides a process for preparation of succinic acid salt of compound of Formula III wherein R_1 and R_2 are hydrogen and R_3 is tert-butyloxycarbonyl.

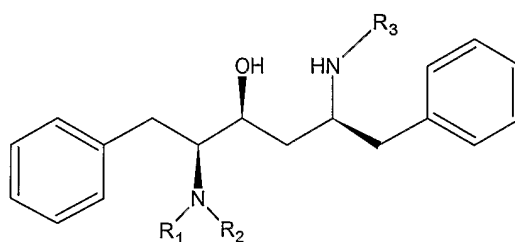
However, there remains a need for novel improved processes for preparing compounds of Formula III.

5

Summary of the Invention

In one aspect, provided are processes for preparation of 2-amino-5-protected-amino-3-hydroxy-1,6-diphenylhexane compounds of Formula III, or acid addition salts thereof, wherein the entire reaction sequence is carried out *in-situ*. Such processes avoid time consuming isolation of intermediates after every step resulting in improved yield
10 without affecting the purity and quality of the product.

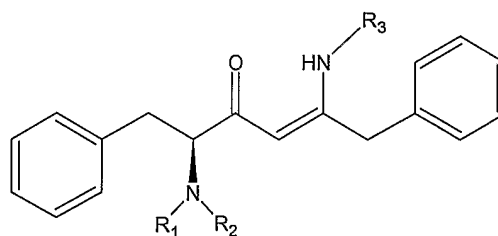
Thus one aspect provides for processes for preparing a compound of Formula III or an acid addition salt thereof,



Formula III

15 wherein R_1 and R_2 are hydrogen and R_3 is an acid labile amino protecting group, comprising the steps of:

a) reducing a compound of Formula IV

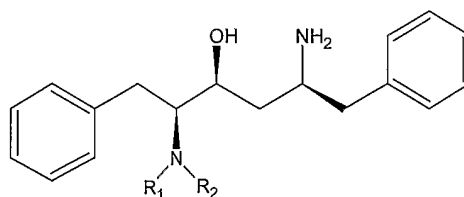


Formula IV

20

wherein R_1 and R_2 are non-acid labile amino protecting groups and R_3 is hydrogen, in presence of one or more reducing agents and one or more acids to form a compound of Formula V,

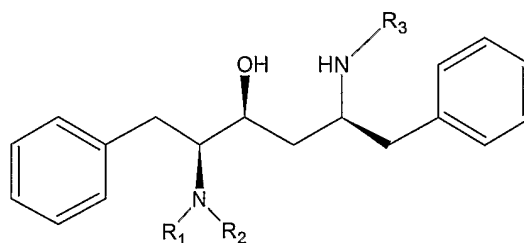
- 4 -



Formula V

wherein R_1 and R_2 are non-acid labile amino protecting groups;

- 5 b) reacting the compound of Formula V with one or more acid labile amino protecting reagents to form a compound of Formula VI,



Formula VI

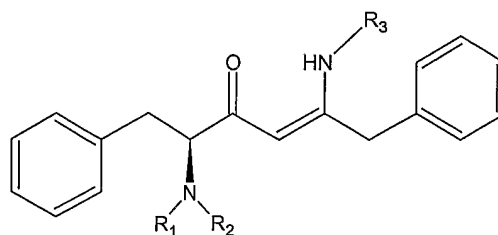
wherein R_1 and R_2 are non-acid labile amino protecting groups and R_3 is an acid labile amino protecting group;

- 10 c) deprotecting the compound of Formula VI to form a compound of Formula III; and
- d) optionally converting the compound of Formula III to an acid addition salt,

wherein the entire process is carried out *in-situ*.

- 15 In another aspect, provided are processes for preparing lopinavir comprising the steps of:

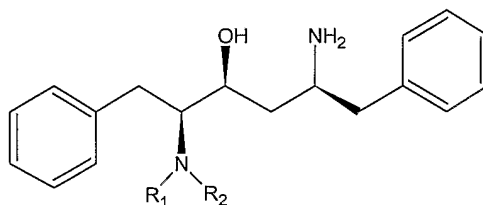
- a) reducing a compound of Formula IV



Formula IV

- 5 -

wherein R_1 and R_2 are non-acid labile amino protecting groups and R_3 is hydrogen, in presence of one or more reducing agents and one or more acids to form a compound of Formula V,

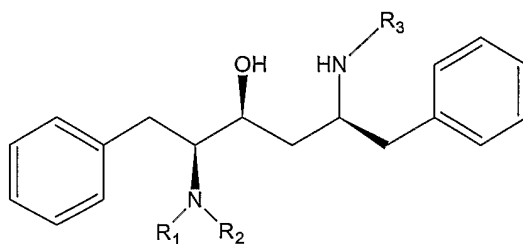


5

Formula V

wherein R_1 and R_2 are non-acid labile amino protecting groups,

- b) reacting the compound of Formula V with one or more acid labile amino protecting reagents to form a compound of Formula VI,

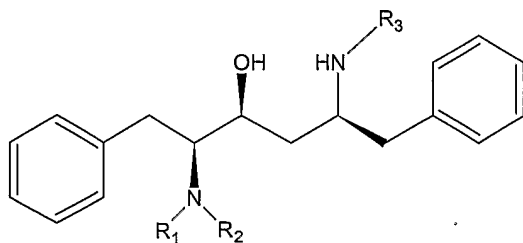


10

Formula VI

wherein R_1 and R_2 are non-acid labile amino protecting groups and R_3 is acid labile amino protecting group,

- c) deprotecting the compound of Formula VI to form a compound of Formula III,



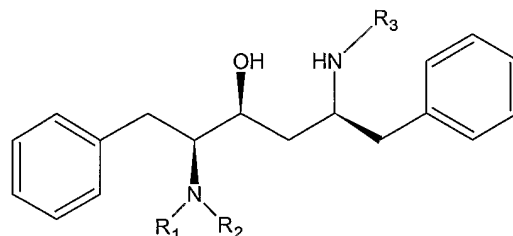
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Formula III

wherein R_1 and R_2 are hydrogen and R_3 is an acid labile amino protecting group,

- 6 -

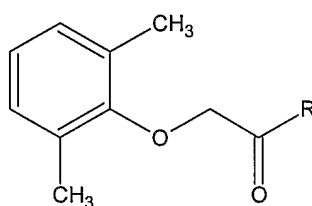
- d) converting the compound of Formula III to form an acid addition salt of the compound of Formula III,



Formula III

- 5 wherein R_1 and R_2 are hydrogen and R_3 is an acid labile amino protecting group,

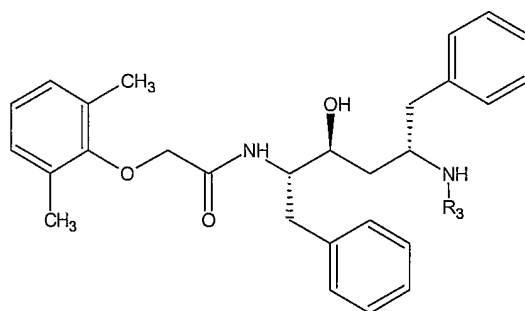
- e) coupling the acid addition salt of the compound of Formula III with a compound of Formula VII,



Formula VII

10

wherein R is hydrogen or a leaving group, to form a compound of Formula VIII,

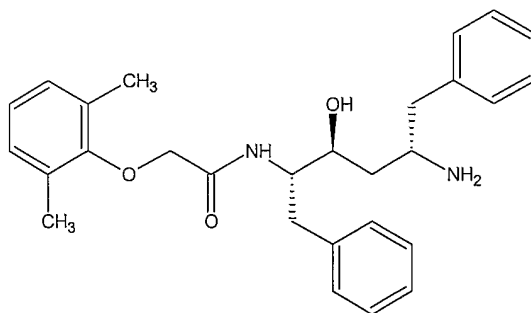


Formula VIII

- 15 wherein R_3 is acid labile amino protecting group,

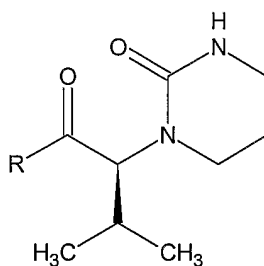
- f) deprotecting the acid labile amino protecting group in the compound of Formula VIII to form a compound of Formula IX, and

- 7 -



Formula IX

g) reacting the compound of Formula IX with a compound of Formula X,



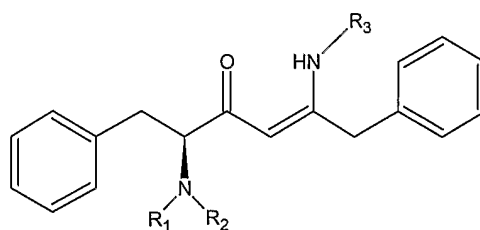
Formula X

5

wherein R is hydrogen or a leaving group, to form lopinavir or salt thereof,
wherein reaction steps a) to d) are carried out *in-situ*.

In another aspect, provided are processes for preparing ritonavir comprising the steps of:

10 a) reducing a compound of Formula IV

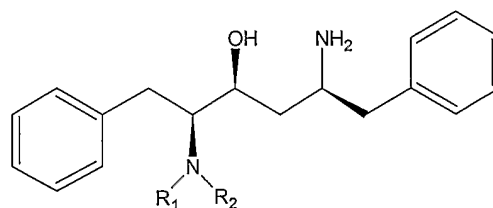


Formula IV

wherein R₁ and R₂ are non-acid labile amino protecting groups and R₃ is hydrogen, in presence of one or more reducing agents and one or more acids to form a compound of Formula V,

15

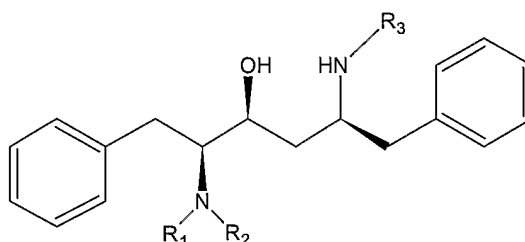
- 8 -



Formula V

wherein R_1 and R_2 are non-acid labile amino protecting groups,

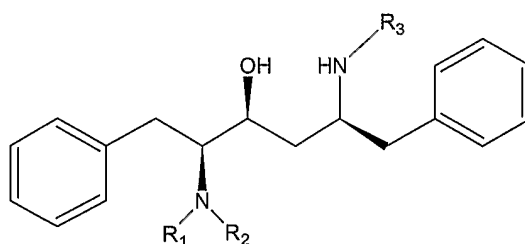
- b) reacting compound of Formula V with acid labile amino protecting reagent to yield a compound of Formula VI



Formula VI

wherein R_1 , R_2 are non-acid labile amino protecting groups and R_3 is acid labile amino protecting group,

- c) deprotecting the compound of Formula VI to obtain a compound of Formula III,

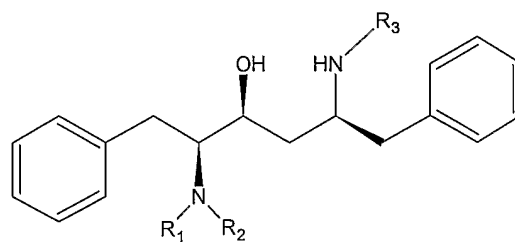


Formula III

wherein R_1 and R_2 are hydrogen and R_3 is an acid labile amino protecting group,

- d) converting a compound of Formula III to form an acid addition salt of the compound of Formula III,

- 9 -



Formula III

wherein R_1 and R_2 are hydrogen and R_3 is an acid labile amino protecting group,

- 5 e) coupling the acid addition salt of the compound of Formula III with 5-(*p*-nitrophenyloxycarbonyloxymethyl) thiazole hydrochloride and treating the resulting product containing (2*S*,3*S*,5*S*)-5-amino-2-(*N*-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxy hexane with a mixed anhydride of *N*-((*N*-methyl-*N*-((2-isopropyl-4-
- 10 thiazolyl)methyl)amino)carbonyl)-*L*-valine to form ritonavir,

wherein steps a) to d) are carried out *in-situ*.

The processes described above can include one or more of the following embodiments. For example, the one or more reducing agents can be selected from borane, borane-tetrahydrofuran, borane-dimethyl sulfide, sodium borohydride, sodium

15 cyanoborohydride, lithium borohydride, potassium borohydride, boron trifluoride-etherate complex, 9-borabicyclo[3.3.1]nonane, (*R*)-*B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane or (*S*)-*B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane or mixtures thereof.

In another embodiment, the one or more acids can be selected from hydrochloric

20 acid, sulphuric acid, phosphoric acid, hydrobromic acid, nitric acid, formic acid, acetic acid, propionic acid, anhydrides of carboxylic acids, methanesulphonic acid, 4-toluenesulphonic acid or mixtures thereof.

In yet another embodiment, the non-acid labile amino protecting group is benzyl. The acid labile amino protecting reagent can be di-*t*-butyldicarbonate and the acid labile

25 amino protecting group is *t*-butyloxycarbonyl.

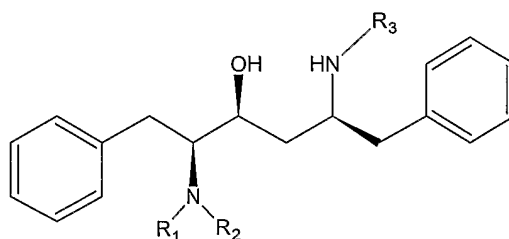
In another embodiment, the compound of Formula IV can be deprotected in the presence of one or more hydrogenating catalysts selected from palladium on carbon,

- 10 -

palladium chloride, rhodium on carbon, platinum oxide, platinum black, ruthenium, or mixtures thereof. In yet another embodiment, the compound of Formula III can be converted to its acid addition salt by contacting the compound of Formula III with an acid. Acid addition salts of compounds of Formula III include its hydrochloride, hydrobromide, sulphate, phosphate, nitrate, formate, acetate, oxalate, maleate, succinate, citrate, tartarate, glutamate, fumarate, adipate, camphoryl, malonate, glutarate, mandelate, nicotinate, glycinate, valinate, p-toluenesulphonate.

Detailed Description of the Invention

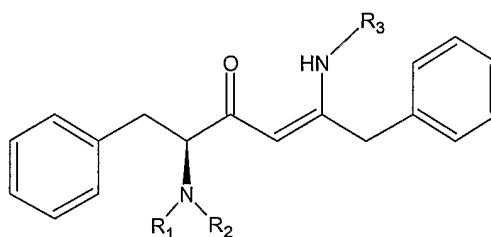
A first aspect of the present invention provides processes for preparing a compound of Formula III or an acid addition salt thereof,



Formula III

wherein R_1 and R_2 are hydrogen and R_3 is an acid labile amino protecting group, comprising the steps of:

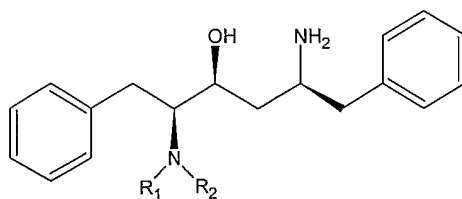
a) reducing a compound of Formula IV



Formula IV

wherein R_1 and R_2 are non-acid labile amino protecting groups and R_3 is hydrogen, in presence of one or more reducing agents and one or more acids to form a compound of Formula V,

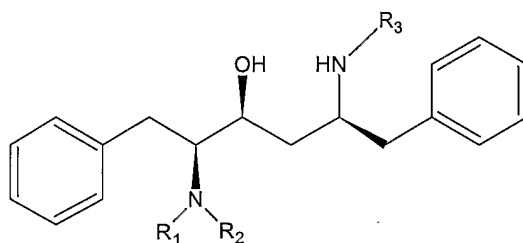
- 11 -



Formula V

wherein R_1 and R_2 are non-acid labile amino protecting groups;

- b) reacting the compound of Formula V with one or more acid labile amino protecting reagents to form a compound of Formula VI,



Formula VI

wherein R_1 and R_2 are non-acid labile amino protecting groups and R_3 is an acid labile amino protecting group;

- c) deprotecting the compound of Formula VI to form a compound of Formula III; and
 d) optionally converting the compound of Formula III to an acid addition salt, wherein the entire process is carried out *in-situ*.

Compounds of Formula IV, wherein R_1 and R_2 are non-acid labile amino protecting groups and R_3 is hydrogen, can be reduced in presence of one or more reducing agents and in the presence of one or more acids. The reduction reaction can be carried out between -10 to 30 °C. The resulting product from this reaction can be used as, for example, a crude oil, in a subsequent reaction step without any further isolation or purification.

Suitable reducing agents include those that are known to one of ordinary skill in the art including, for example, borane, borane-tetrahydrofuran, borane-dimethyl sulfide, sodium borohydride, sodium cyanoborohydride, lithium borohydride, potassium borohydride, boron trifluoride-etherate complex, 9-borabicyclo[3.3.1]nonane, (R)-B-isopinocampheyl-9-borabicyclo[3.3.1]nonane or (S)-B-isopinocampheyl-9-

borabicyclo[3.3.1]nonane and the like, or mixtures thereof. A preferred reducing agent is sodium borohydride.

Suitable acids include those that are known to one of ordinary skill in the art. The acid used can be one or more inorganic acids, for example, hydrochloric acid, sulphuric acid, phosphoric acid, hydrobromic acid, nitric acid and the like or mixtures thereof. The acid can also be one or more organic acids, for example, formic acid, acetic acid, propionic acid, anhydrides of carboxylic acids, methanesulphonic acid, 4-toluenesulphonic acid and the like, or mixtures thereof.

The residue obtained from step a) can be reacted with one or more acid labile amino protecting reagents to form compounds of Formula VI. The reaction can be carried out at room temperature and the resulting product can be used directly in a subsequent reaction step without further purification.

The phrase "non-acid labile amino protecting groups," as used herein, is known to a person of ordinary skill in art.

The phrase "acid labile amino protecting reagent," as used herein, is known to a person of ordinary skill in art.

Non-acid labile amino protecting groups of the residue obtained in step b) can be deprotected by reacting with one or more hydrogenating catalysts at room temperature to form compounds of Formula III. For example, the reaction can be a catalytic transfer hydrogenation carried out in, for example, ammonium formate and methanol. Other typical catalytic transfer hydrogenation reagents known to one of ordinary skill in the art may be used. The reaction mixture can be carried out under reflux temperatures. Suitable hydrogenating catalysts include those known to a person of ordinary skill in art, examples of which include, but are not limited to palladium on carbon, palladium chloride, rhodium on carbon, platinum oxide, platinum black, ruthenium and the like, or mixtures thereof.

Compounds of Formula III can optionally be contacted with an appropriate corresponding acid to convert it to its corresponding acid addition salt. The phrase "acid addition salt," as used herein, includes but is not limited to hydrochloride, hydrobromide, sulphate, phosphate, nitrate, formate, acetate, oxalate, maleate, succinate, citrate, tartarate, glutamate, fumarate, adipate, camphoryl, malonate, glutarate, mandelate, nicotinate, glycinate, valinate, p-toluenesulphonate and the like or mixtures thereof. These salts are

- 13 -

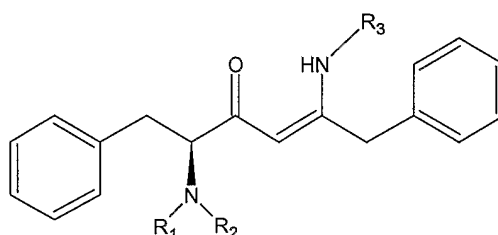
generally prepared by contacting a compound with hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, formic acid, acetic acid, oxalic acid, maleic acid, succinic acid, citric acid, tartaric acid, glutamic acid, fumaric acid, adipic acid, camphoric acid, malonic acid, glutaric acid, mandelic acid, nicotinic acid, glycinic acid, valinic acid,
5 p-toluenesulphonic acid and the like, or mixtures thereof.

The conversion of compounds of Formula III to its acid addition salt can be carried out in one or more solvents, for example, one or more alcohols, *e.g.*, isopropanol. The reaction can also be carried out at temperatures from about 10-70 °C.

Optically pure compounds of Formula III or an acid addition salt thereof can be
10 obtained by the process described herein.

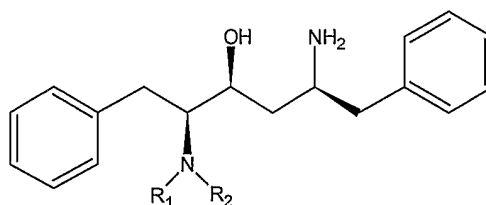
A second aspect of the present invention provides processes for preparing lopinavir comprising the steps of:

a) reducing a compound of Formula IV



15
Formula IV

wherein R₁ and R₂ are non-acid labile amino protecting groups and R₃ is hydrogen, in presence of one or more reducing agents and one or more acids to form a compound of Formula V,

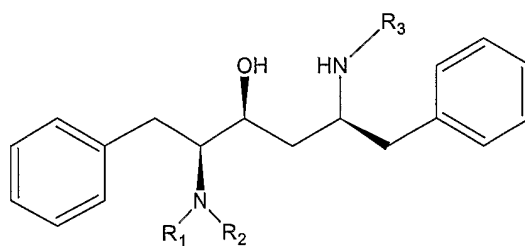


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Formula V

wherein R₁ and R₂ are non-acid labile amino protecting groups,

b) reacting the compound of Formula V with one or more acid labile amino protecting reagents to form a compound of Formula VI,

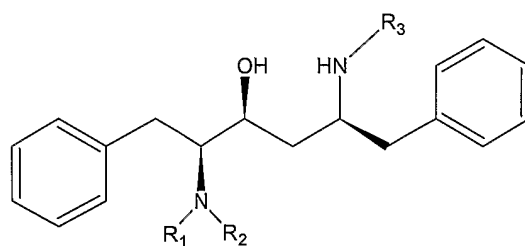
- 14 -



Formula VI

wherein R_1 and R_2 are non-acid labile amino protecting groups and R_3 is acid labile amino protecting group,

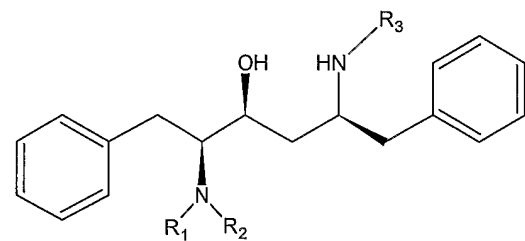
- 5 c) deprotecting the compound of Formula VI to form a compound of Formula III,



Formula III

wherein R_1 and R_2 are hydrogen and R_3 is an acid labile amino protecting group,

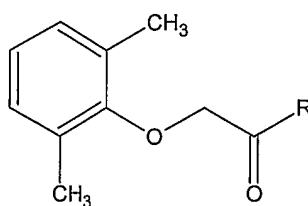
- d) converting the compound of Formula III to form an acid addition salt of the
10 compound of Formula III,



Formula III

wherein R_1 and R_2 are hydrogen and R_3 is an acid labile amino protecting group,

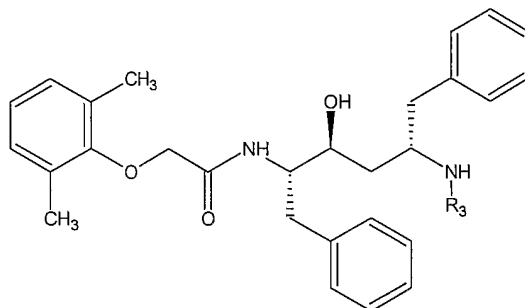
- e) coupling the acid addition salt of the compound of Formula III with a compound of
15 Formula VII,



- 15 -

Formula VII

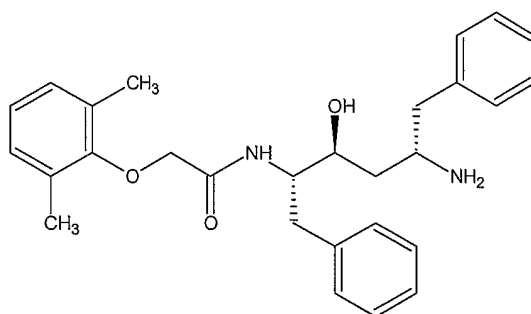
wherein R is hydrogen or a leaving group, to form a compound of Formula VIII,



Formula VIII

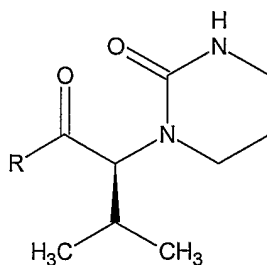
5 wherein R₃ is acid labile amino protecting group,

f) deprotecting the acid labile amino protecting group in the compound of Formula VIII to form a compound of Formula IX, and



Formula IX

10 g) reacting the compound of Formula IX with a compound of Formula X,



Formula X

wherein R is hydrogen or a leaving group, to form lopinavir or salt thereof, wherein reaction steps a) to d) are carried out *in-situ*.

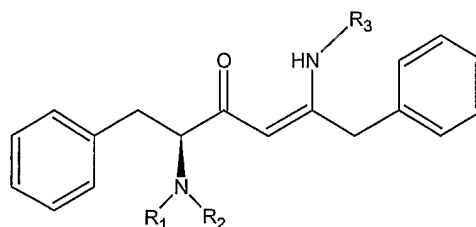
The acid addition salt of a compound of Formula III can be coupled with a compound of Formula VII, wherein R is hydrogen or a leaving group, in the presence of one or more inorganic bases, to form a compound of Formula VIII. Suitable inorganic bases include, but are not limited to, one or more of sodium bicarbonate, sodium carbonate, potassium bicarbonate, potassium carbonate, sodium hydroxide, potassium hydroxide and the like or mixtures thereof. The coupling reaction can also be carried out at about room temperature. The coupling reaction can also be carried out in one or more inert solvents, for example, ethyl acetate/water or isopropyl acetate/water or toluene/water or tetrahydrofuran/water and the like.

Compounds of Formula VIII can be deprotected in the presence of one or more acids, *e.g.* trifluoroacetic acid, acetic acid, methanesulphonic acid, para-toluene sulphonic acid, or mixture thereof, to form compounds of Formula IX. The deprotection reaction can be carried out in one or more organic solvents, for example, halogenated hydrocarbons, *e.g.*, methylene chloride, chloroform, ethylene chloride or mixtures thereof; ethers, *e.g.*, tetrahydrofuran, diisopropyl ether, 1,4-dioxane, diethyl ether, or mixtures thereof.

Compounds of Formula IX can be reacted with compounds of Formula X to form lopinavir in one or more solvents, *e.g.*, ethyl acetate, dimethyl formamide or mixtures thereof.

A third aspect of the present invention provides a process for preparing ritonavir comprising the steps of:

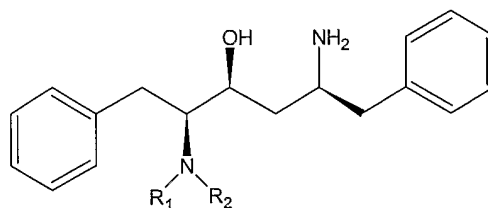
a) reducing a compound of Formula IV



Formula IV

wherein R₁ and R₂ are non-acid labile amino protecting groups and R₃ is hydrogen, in presence of one or more reducing agents and one or more acids to form a compound of Formula V,

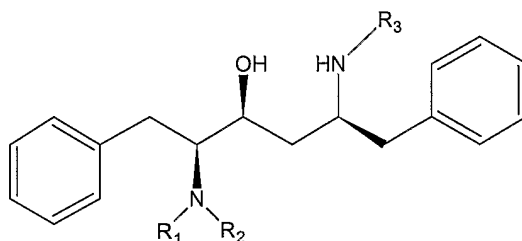
- 17 -



Formula V

wherein R_1 and R_2 are non-acid labile amino protecting groups,

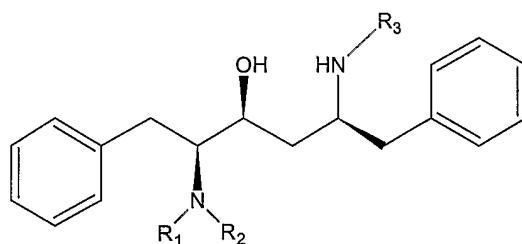
- b) reacting compound of Formula V with acid labile amino protecting reagent to yield
5 a compound of Formula VI



Formula VI

- 10 wherein R_1 , R_2 are non-acid labile amino protecting groups and R_3 is acid labile amino protecting group,

- c) deprotecting the compound of Formula VI to obtain a compound of Formula III,

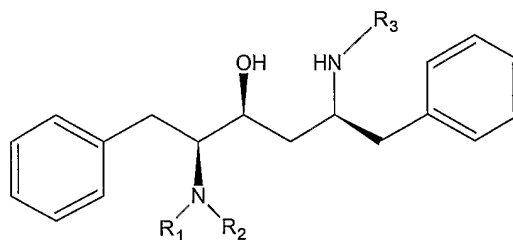


Formula III

- 15 wherein R_1 and R_2 are hydrogen and R_3 is an acid labile amino protecting group,

- d) converting a compound of Formula III to form an acid addition salt of the compound of Formula III,

- 18 -



Formula III

wherein R_1 and R_2 are hydrogen and R_3 is an acid labile amino protecting group,

- e) coupling the acid addition salt of the compound of Formula III with 5-(*p*-nitrophenyloxycarbonyloxymethyl) thiazole hydrochloride and treating the resulting product containing (2*S*,3*S*,5*S*)-5-amino-2-(*N*-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxy hexane with a mixed anhydride of *N*-((*N*-methyl-*N*-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-*L*-valine to form ritonavir,

wherein steps a) to d) are carried out *in-situ*.

- 10 An acid addition salt of a compound of Formula III can be contacted with 5-(*p*-nitrophenyloxycarbonyloxymethyl)thiazole hydrochloride and one or more bases. Suitable bases include inorganic and organic bases known to one of ordinary skill in the art including, for example, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, lithium carbonate, pyridine, triethylamine, ammonia, ethyl 2-hexanoate sodium salt or mixtures thereof. The reaction can also be carried out in one or more organic solvents, for example, chlorinated hydrocarbons, *e.g.*, methylene chloride, chloroform, ethylene chloride, ethylene bromide or mixtures thereof; esters, *e.g.*, ethyl acetate, ethyl formate, methyl formate, methyl acetate, *n*-propyl acetate, isopropyl acetate or mixtures thereof; ethers, tetrahydrofuran, diisopropyl ether, 1,4-dioxane, diethyl ether or mixtures thereof; ketones, *e.g.*, acetone, methyl isobutyl ketone, methyl ethyl ketone or mixtures thereof; lower alcohols, *e.g.*, methanol, ethanol, propanol, isopropanol, butanol or mixtures thereof; or mixtures thereof.

- 25 After reacting the compound of Formula III can be contacted with 5-(*p*-nitrophenyloxycarbonyloxymethyl)thiazole hydrochloride, the resulting product containing (2*S*,3*S*,5*S*)-5-amino-2-(*N*-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxy hexane can be contacted with a mixed anhydride of *N*-((*N*-methyl-*N*-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-*L*-valine to form ritonavir.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention. The examples are provided to illustrate particular aspects of the disclosure and do not limit the scope of the present invention as defined by the claims.

Examples

EXAMPLE 1. PREPARATION OF (2S,3S,5S)-5-AMINO-2-(N,N-DIBENZYLAMINO)-3-HYDROXY-1,6-DIPHENYLHEXANE

Sodium borohydride (6 g) in dimethyl ether (271.2 mL) was cooled to about -5°C and to this mixture a solution of methane sulphonic acid (38.4 g) in dimethyl ether (2.3 mL) was added at -5 to 5°C over 45 minutes. To this resulting mixture, a solution of 2-amino-5S-(N,N-dibenzylamino)-4-oxo-1,6-diphenyl-2-hexene (24.5 g) in a mixture of isopropanol (28 mL) and dimethyl ether (62.6 mL) was added at 0 to 5°C over a period of 30 minutes. The reaction mixture was stirred at 0 to 10°C for 12 hours. Triethanolamine (23.6 g) was added to the resulting mixture at 0°C over about 30 minutes. The mixture was stirred at 0 to 5°C for about 30 minutes. A separate solution of sodium borohydride (5 g) in dimethylacetamide (39.2 mL) was added into the reaction mixture at about 0 to 10°C over a period of about 25 minutes. The solution was stirred at about 15 to 20°C for 2 hours and quenched with water (270 mL) at 10-20°C and to it methyl-*t*-butyl ether (245 mL) was added and stirred for about 10 minutes. The organic layer was separated, washed with aqueous sodium hydroxide (245 mL), ammonium chloride (245 mL) followed by sodium chloride (245 mL). The solvent was evaporated under reduced pressure to yield a residue as an oily mass which was used in the next step without any further purification.

EXAMPLE 2. PREPARATION OF (2S,3S,5S)-2-(N,N-DIBENZYLAMINO)-3-HYDROXY-5-(*t*-BUTYLOXYCARBONYLAMINO)-1,6-DIPHENYLHEXANE

To the residue obtained from the example 1 and potassium carbonate (11.76 g) in a mixture of water (120 mL) and methyl-*t*-butylether (245 mL), was added di-*t*-butyldicarbonate (15.34 g) at 15-20°C over a period of about 20 minutes. The resulting mixture was stirred at room temperature for about 1.5 hours. The organic layer was separated, washed with water (122.5 mL) and then concentrated under reduced pressure to afford a residue as oil which was used directly in the subsequent step.

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EXAMPLE 3. PREPARATION OF (2S,3S,5S)-2-AMINO-3-HYDROXY-5-(*t*-BUTYLOXY-CARBONYLAMINO)-1,6-DIPHENYLHEXANE SUCCINATE SALT

To the residue obtained from example 2 and ammonium formate (19.88g) in methanol (200 mL), was added 10% Palladium-Carbon (30.35 g, 50% wet) at room temperature. The mixture was stirred under reflux for 2 hours. The catalyst was filtered off and washed with methanol (100 mL). The residue obtained after removal of methanol under reduced pressure was taken up in methylene chloride (245 mL) and washed with aqueous sodium hydroxide (122.5 mL) then with sodium chloride solution (122.5 mL). The organic was concentrated to provide a thick oily mass. Isopropanol (588 mL) was added into the residue and stirred to yield a clear solution. Isopropanol (24.5 mL) was removed under reduced pressure at NMT 45°C. To the stirred above solution succinic acid (6.35 g) was added at 20-25°C. The mixture was slowly heated to 40-45°C to dissolve all succinic acid crystals and at about 70°C, a white solid started precipitated out. The mixture was kept stirring at 65-70°C for 1 hour and then at 25-30°C for next 12 hours. The solid was filtered, washed with isopropanol (24.5 mL) and then dried under reduced pressure at 45-50°C for 12 hours to furnish the title compound as a white solid.

Yield: 18.5 g

EXAMPLE 4. PREPARATION OF (2S,3S,5S)-2-(2,6-DIMETHYLPHENOXYACETYL)AMINO-3-HYDROXY-5-(*t*-BUTYLOXYCARBONYLAMINO)-1, 6-DIPHENYLHEXANE

Step 1:

2,6-Dimethylphenyl acetic acid (2.3 g) in ethyl acetate (30 mL), was added thionyl chloride (1.82 g) at room temperature followed by 2 drops of dimethyl formamide. The reaction mixture was stirred at about 50°C for 1.5 hours, cooled to room temperature and concentrated to dryness under reduced pressure. The excess thionyl chloride was further removed azeotropically with ethyl acetate (2 X 30 mL) and the residue was redissolved in ethyl acetate (30 mL) and used immediately to couple with the succinate salt obtained from Example 3.

Step 2:

- 21 -

Succinate salt obtained from example 3 was added portion wise to a vigorously stirred mixture of sodium bicarbonate (4.7 g) in water (40 mL) and ethyl acetate (30 mL) at room temperature over a period of 10 minutes. On stirring at room temperature for 30 minutes, the reaction mixture became almost homogeneous, however suddenly a white solid separated out from the upper ethyl acetate layer. To a cooled at about 15 °C, of the above suspended reaction mixture, a solution of acid chloride in ethyl acetate (from step 1 of example 4) at 15-20°C was slowly added over about 15 minutes. The resulting mixture was stirred at room temperature for 1.5 hours. After 1 hour stirring at room temperature, a white solid again precipitated out from the solution. Ethyl acetate (30 mL) was added and stirred for next 30 minutes. After separating the organic layer, the aqueous layer was extracted with ethyl acetate (20 mL). The combined organic layer was washed successively with aqueous sodium hydroxide (2 X 20 mL), hydrochloric acid (2 X 20 mL), water (1 X 20 mL) and brine (1 X 20 mL). It was then filtered through hyflo bed and dried over sodium sulfate. Concentration of ethyl acetate solution under reduced pressure resulted the title compound as an off-white solid.

Yield: 5.6 g

EXAMPLE 5. PREPARATION OF (2S,3S,5S)-2-(2,6-DIMETHYLPHENOXYACETYL)AMINO-3-HYDROXY-5-[2S-(1-TETRAHYDRO-PYRIMID-2-ONYL)-3-METHYL-BUTANOYL]AMINO-1,6-DIPHENYLHEXANE

Step 1:

To a stirred mixture of 2S-(1-tetrahydro-pyrimid-2-onyl)-3-methylbutanoic acid cooled to about 0°C, (2.1 g) in tetrahydrofuran (42 mL) was added thionyl chloride (1.56 g) at about 0 to +5°C over about 5 minutes. The reaction mixture was warmed to room temperature and stirred at this temperature for 1.5 hours. The solution became homogeneous on warming to room temperature. The reaction mixture was concentrated to dryness under reduced pressure. Excess thionyl chloride was further removed azeotropically with heptane (2 X 20 mL). The residue was dissolved in dimethyl formamide (15 mL) at 35-40 °C, cooled down to room temperature and reacted immediately to couple with the compound obtained from Example 4.

Step 2:

To a stirred solution of (2S,3S,5S)-2-(2,6-dimethylphenoxyacetyl)amino-3-hydroxy-5-(*t*-butyloxycarbonylamino)-1,6-diphenylhexane (5.1 g) in methylene chloride (50 mL) was added trifluoroacetic acid (10.65 g) at room temperature over a period of 20 minutes. The reaction mixture was stirred at room temperature for 3 hours. The solvent
5 was removed under reduced pressure and then water (100 mL) was added followed by methylene chloride (100 mL). To the cooled at about 10-15°C biphasic mixture, solid sodium bicarbonate (12 g) was added portionwise, and finally its pH was adjusted to about 8.5 with aqueous sodium hydroxide. The organic layer was separated and washed with water (50 mL). Concentration of methylene chloride layer provided a residue as thick oil.
10 Ethyl acetate (50 mL) was added into the above residue and stirred to yield a clear solution. To the stirred solution imidazole (2.1 g) was added at room temperature. The mixture was cooled to 0°C. To the cold reaction mixture a suspension of acid chloride in dimethyl formamide (from step 1 of Example 5) was slowly added at about 0 to 5°C during 30 minutes. The reaction mixture was stirred at 0 to 5°C for next 30 minutes, then
15 warmed to room temperature and stirred at room temperature for 12 hours. The reaction mixture was cooled down to 10°C and quenched with aqueous hydrochloric acid (100 mL) at 10-15°C. Ethyl acetate (50 mL) was added to the mixture and stirred at room temperature for 30 minutes. The organic layer was separated and washed with aqueous sodium bicarbonate (50 mL) followed by water (2 X 50 mL). Evaporation of the solvent
20 under reduced pressure afforded crude material as an off-white solid which was dissolved in ethyl acetate (28 mL) at 45-50°C and then heptane (28 mL) was slowly added at 50-45°C. The resulting clear solution was slowly allowed to cooled to room temperature and stirred at room temperature for 12 hours. A white solid, precipitated out from the solution was filtered and washed with 1:1 mixture of ethyl acetate and heptane (5 mL). The solid
25 was dried under vacuum at 50-60°C for 12 hours to yield the title compound as a white solid.

Yield: 3.5 g

EXAMPLE 6. PREPARATION OF (2S,3S,5S)-5-AMINO-2-(N-((5-THIAZOLYL)METHOXYCARBONYL)AMINO)-1,6-DIPHENYL-3-HYDROXY HEXANE

30 To a stirred mixture of succinate salt obtained from example 3 (3.8 g) in ethylacetate solution (45 mL) was added 5-(*p*-nitrophenyloxycarbonyl-oxymethyl)thiazole hydrochloride (3.0 g) and sodium bicarbonate (4.0 g). Water (40 mL) was charged to the

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resultant mixture and stirred of two hours at room temperature. The organic layer was separated and heated at 60°C for 7 hours. The solution was cooled to about 30°C and 28% aqueous ammonia (0.41 g) was added. After stirring for two hours, the reaction mixture was washed thrice with 10% potassium carbonate solution (40 mL). Concentrated hydrochloric acid (2.7ml) was added to the organic layer and resultant slurry was stirred at 50°C for three hours. The solid obtained was filtered and washed with ethyl acetate (10ml) twice. The wet solid was taken in ethyl acetate (35 mL) and the mixture was treated with dilute ammonia water (9 mL). The organic layer was separated and concentrated to yield desired oil residue.

Yield: 3.3 g

EXAMPLE 7. PREPARATION OF (2S,3S,5S)-5-(N-(N-((N-METHYL-N-((2-ISOPROPYL-4-THIAZOLYL)METHYL) AMINO)CARBONYL)-L-VALINYL)AMINO)-2-(N-((5-THIAZOLYL)METHOXY CARBONYL)AMINO)-1,6-DIPHENYL-3-HYDROXY HEXANE

Step 1:

N-((N-Methyl-N-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-L-valine (2.5 g) in ethyl acetate (35 mL) was added N-methyl morpholine (1.35 g). The resultant mixture was cooled to about -18°C and isobutylchloroformate (1.15 g) in ethylacetate (5.3 mL) was added drop wise maintaining the temperature between -18 to -15°C. The reaction mixture was stirred for 45 minutes at -15°C and then N-hydroxysuccinimide (1.0 g) was added. The stirring was continued and the reaction mixture was allowed to attain 0°C at which the mixture was stirred for another 90 minutes.

Step 2:

A pre-cooled mixture at about 0°C of residue (3.2 g) obtained from example 6 in ethyl acetate (12 mL) was added to the mixture obtained from step 1 of example 7 and the resultant combined mixture was warmed to ambient temperature and stirred for 18 hours. The reaction mixture was washed successively twice with 10% potassium carbonate solution (30 mL), thrice with 10% citric acid solution (45 mL) and thrice with water (25 mL). The solvent was stripped off under vacuum and the residue obtained as oil was taken in ethyl acetate solution (28 mL). The solution was heated at 60°C and hexane (21 mL) was added to the hot solution. The resultant mixture was brought to 25°C and stirred

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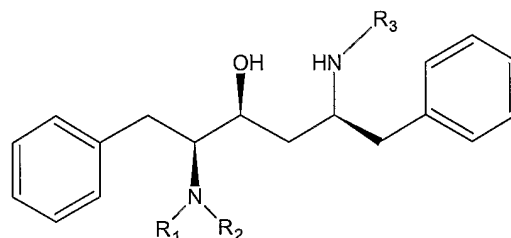
for 24 hours. The solid material was filtered, washed twice with ethyl acetate and hexane mixture (1:1, 10 mL) and dried under vacuum at 55°C for overnight.

Yield: 2.6 g.

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We claim:

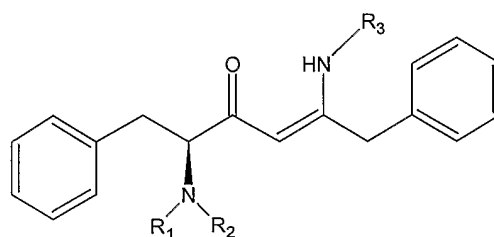
1. A process for preparing a compound of Formula III or an acid addition salt thereof,



Formula III

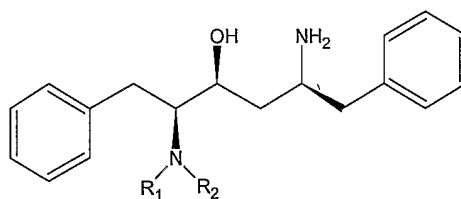
- wherein R_1 and R_2 are hydrogen and R_3 is an acid labile amino protecting group,
comprising the steps of:

- a) reducing a compound of Formula IV



Formula IV

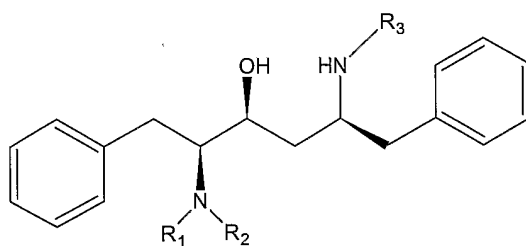
- wherein R_1 and R_2 are non-acid labile amino protecting groups and R_3 is hydrogen, in presence of one or more reducing agents and one or more acids to form a compound of Formula V,



Formula V

- wherein R_1 and R_2 are non-acid labile amino protecting groups;
b) reacting the compound of Formula V with one or more acid labile amino protecting reagents to form a compound of Formula VI,

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Formula VI

wherein R_1 and R_2 are non-acid labile amino protecting groups and R_3 is an acid labile amino protecting group;

c) deprotecting the compound of Formula VI to form a compound of Formula III; and

d) optionally converting the compound of Formula III to an acid addition salt,

wherein the entire process is carried out *in-situ*.

2. The process of claim 1, wherein the one or more reducing agents are selected from borane, borane-tetrahydrofuran, borane-dimethyl sulfide, sodium borohydride, sodium cyanoborohydride, lithium borohydride, potassium borohydride, boron trifluoride-etherate complex, 9-borabicyclo[3.3.1]nonane, (R)-B-isopinocampheyl-9-borabicyclo[3.3.1]nonane or (S)-B-isopinocampheyl-9-borabicyclo[3.3.1]nonane or mixtures thereof.

3. The process of claim 1, wherein the one or more acids are selected from hydrochloric acid, sulphuric acid, phosphoric acid, hydrobromic acid, nitric acid, formic acid, acetic acid, propionic acid, anhydrides of carboxylic acids, methanesulphonic acid, 4-toluenesulphonic acid or mixtures thereof.

4. The process of claim 1, wherein the non-acid labile amino protecting group is benzyl.

5. The process of claim 1, wherein acid labile amino protecting reagent is di-*t*-butyldicarbonate and the acid labile amino protecting group is *t*-butyloxycarbonyl.

6. The process of claim 1, wherein the compound of Formula IV is deprotected in the presence of one or more hydrogenating catalysts selected from palladium on carbon, palladium chloride, rhodium on carbon, platinum oxide, platinum black, ruthenium, or mixtures thereof.

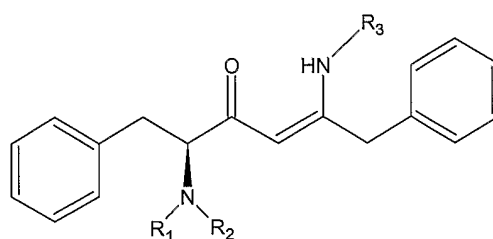
- 27 -

7. The process of claim 1, wherein the compound of Formula III is converted to its acid addition salt by contacting the compound of Formula III with an acid.

8. The process of claim 7, wherein the acid addition salt is a hydrochloride, hydrobromide, sulphate, phosphate, nitrate, formate, acetate, oxalate, maleate, succinate, citrate, tartarate, glutamate, fumarate, adipate, camphoryl, malonate, glutarate, mandelate, nicotinate, glycinate, valinate, p-toluenesulphonate.

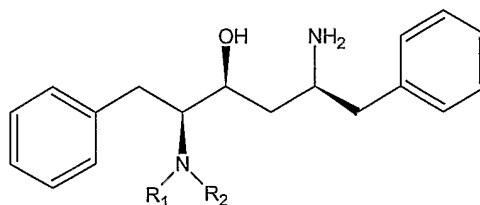
9. A process for preparing lopinavir comprising the steps of:

a) reducing a compound of Formula IV



Formula IV

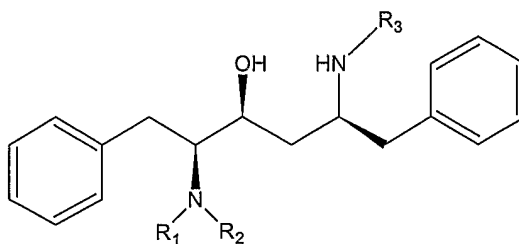
wherein R_1 and R_2 are non-acid labile amino protecting groups and R_3 is hydrogen, in presence of one or more reducing agents and one or more acids to form a compound of Formula V,



Formula V

wherein R_1 and R_2 are non-acid labile amino protecting groups,

b) reacting the compound of Formula V with one or more acid labile amino protecting reagents to form a compound of Formula VI,

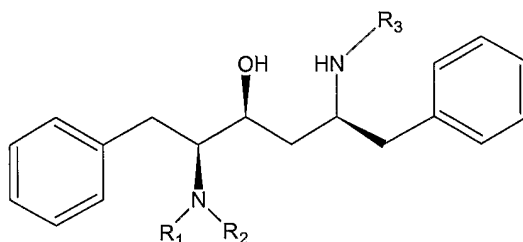


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Formula VI

wherein R_1 and R_2 are non-acid labile amino protecting groups and R_3 is acid labile amino protecting group,

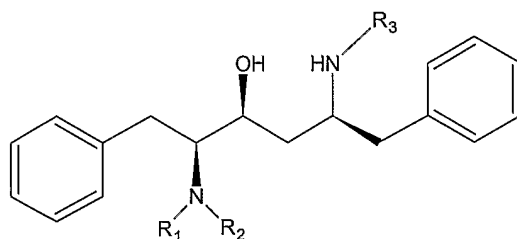
c) deprotecting the compound of Formula VI to form a compound of Formula III,



Formula III

wherein R_1 and R_2 are hydrogen and R_3 is an acid labile amino protecting group,

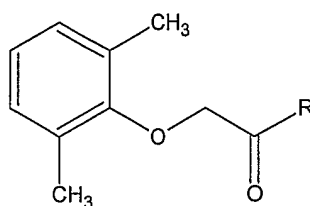
d) converting the compound of Formula III to form an acid addition salt of the compound of Formula III,



Formula III

wherein R_1 and R_2 are hydrogen and R_3 is an acid labile amino protecting group,

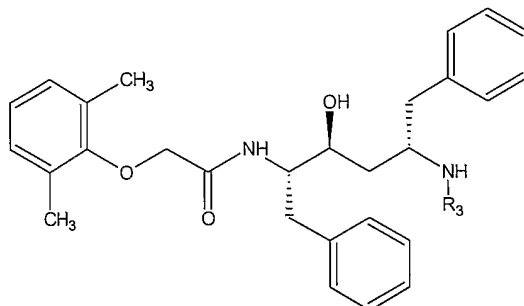
e) coupling the acid addition salt of the compound of Formula III with a compound of Formula VII,



Formula VII

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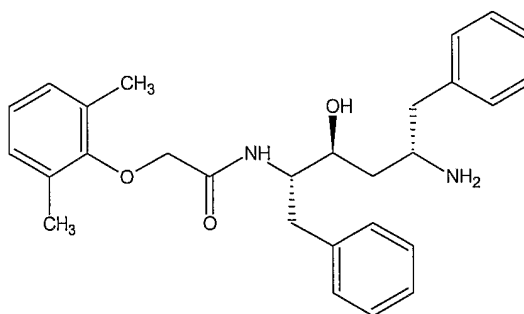
wherein R is hydrogen or a leaving group, to form a compound of Formula VIII,



Formula VIII

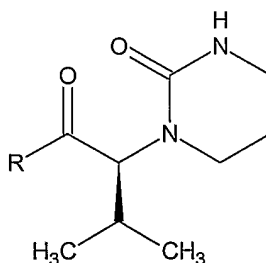
wherein R₃ is acid labile amino protecting group,

f) deprotecting the acid labile amino protecting group in the compound of Formula VIII to form a compound of Formula IX, and



Formula IX

g) reacting the compound of Formula IX with a compound of Formula X,



Formula X

wherein R is hydrogen or a leaving group, to form lopinavir or salt thereof, wherein reaction steps a) to d) are carried out *in-situ*.

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1 10. The process of claim 9, wherein the one or more reducing agents are selected from
2 borane, borane-tetrahydrofuran, borane-dimethyl sulfide, sodium borohydride, sodium
3 cyanoborohydride, lithium borohydride, potassium borohydride, boron trifluoride-etherate
4 complex, 9-borabicyclo[3.3.1]nonane, (R)-B-isopinocampheyl-9-
5 borabicyclo[3.3.1]nonane or (S)-B-isopinocampheyl-9-borabicyclo[3.3.1]nonane or
6 mixtures thereof; and the one or more acids are selected from hydrochloric acid, sulphuric
7 acid, phosphoric acid, hydrobromic acid, nitric acid, formic acid, acetic acid, propionic
8 acid, anhydrides of carboxylic acids, methanesulphonic acid, 4-toluenesulphonic acid or
9 mixtures thereof.

1 11. The process of claim 9, wherein acid labile amino protecting reagent is di-*t*-
2 butyldicarbonate and the acid labile amino protecting group is *t*-butyloxycarbonyl.

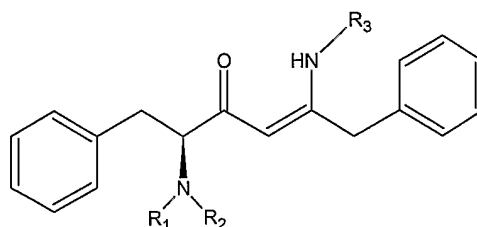
1 12. The process of claim 9, wherein the compound of Formula IV is deprotected in the
2 presence of one or more hydrogenating catalysts selected from palladium on carbon,
3 palladium chloride, rhodium on carbon, platinum oxide, platinum black, ruthenium, or
4 mixtures thereof.

1 13. The process of claim 9, wherein the compound of Formula III is converted to its
2 acid addition salt by contacting the compound of Formula III with an acid.

1 14. The process of claim 13, wherein the acid addition salt is a hydrochloride,
2 hydrobromide, sulphate, phosphate, nitrate, formate, acetate, oxalate, maleate, succinate,
3 citrate, tartarate, glutamate, fumarate, adipate, camphoryl, malonate, glutarate, mandelate,
4 nicotinate, glycinate, valinate, p-toluenesulphonate.

1 15. A process for preparing ritonavir comprising the steps of:

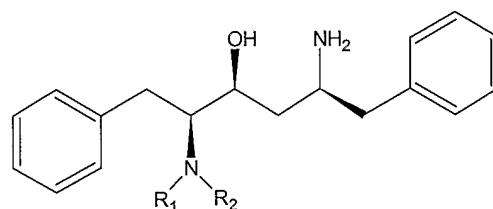
2 a) reducing a compound of Formula IV



Formula IV

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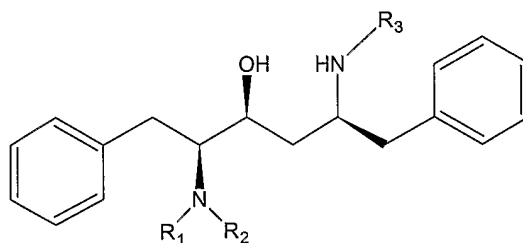
wherein R_1 and R_2 are non-acid labile amino protecting groups and R_3 is hydrogen, in presence of one or more reducing agents and one or more acids to form a compound of Formula V,



Formula V

wherein R_1 and R_2 are non-acid labile amino protecting groups,

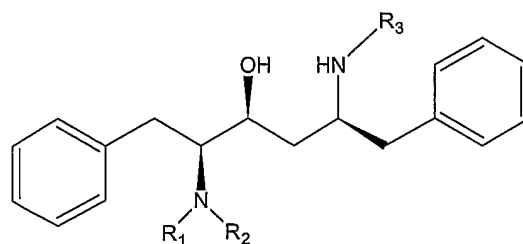
b) reacting compound of Formula V with acid labile amino protecting reagent to yield a compound of Formula VI



Formula VI

wherein R_1 , R_2 are non-acid labile amino protecting groups and R_3 is acid labile amino protecting group,

c) deprotecting the compound of Formula VI to obtain a compound of Formula III,

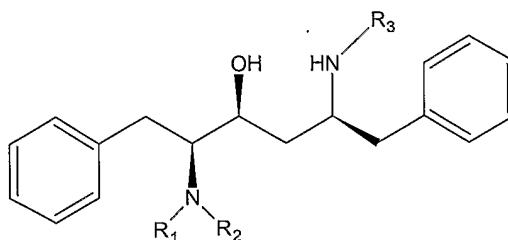


Formula III

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wherein R_1 and R_2 are hydrogen and R_3 is an acid labile amino protecting group,

d) converting a compound of Formula III to form an acid addition salt of the compound of Formula III,



Formula III

wherein R_1 and R_2 are hydrogen and R_3 is an acid labile amino protecting group,

e) coupling the acid addition salt of the compound of Formula III with 5-(*p*-nitrophenyloxycarbonyloxymethyl) thiazole hydrochloride and treating the resulting product containing (2*S*,3*S*,5*S*)-5-amino-2-(*N*-((5-thiazolyl) methoxycarbonyl)amino)-1,6-diphenyl-3-hydroxy hexane with a mixed anhydride of *N*-((*N*-methyl-*N*-((2-isopropyl-4-thiazolyl)methyl)amino)carbonyl)-*L*-valine to form ritonavir,

wherein steps a) to d) are carried out *in-situ*.

16. The process of claim 15, wherein the one or more reducing agents are selected from borane, borane-tetrahydrofuran, borane-dimethyl sulfide, sodium borohydride, sodium cyanoborohydride, lithium borohydride, potassium borohydride, boron trifluoride-etherate complex, 9-borabicyclo[3.3.1]nonane, (*R*)-*B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane or (*S*)-*B*-isopinocampheyl-9-borabicyclo[3.3.1]nonane or mixtures thereof; and the one or more acids are selected from hydrochloric acid, sulphuric acid, phosphoric acid, hydrobromic acid, nitric acid, formic acid, acetic acid, propionic acid, anhydrides of carboxylic acids, methanesulphonic acid, 4-toluenesulphonic acid or mixtures thereof.

17. The process of claim 15, wherein acid labile amino protecting reagent is di-*t*-butyldicarbonate and the acid labile amino protecting group is *t*-butyloxycarbonyl.

1 18. The process of claim 15, wherein the compound of Formula IV is deprotected in
2 the presence of one or more hydrogenating catalysts selected from palladium on carbon,
3 palladium chloride, rhodium on carbon, platinum oxide, platinum black, ruthenium, or
4 mixtures thereof.

1 19. The process of claim 15, wherein the compound of Formula III is converted to its
2 acid addition salt by contacting the compound of Formula III with an acid.

1 20. The process of claim 19, wherein the acid addition salt is a hydrochloride,
2 hydrobromide, sulphate, phosphate, nitrate, formate, acetate, oxalate, maleate, succinate,
3 citrate, tartarate, glutamate, fumarate, adipate, camphoryl, malonate, glutarate, mandelate,
4 nicotinate, glycinate, valinate, p-toluenesulphonate.

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2006/000417

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C271/20 C07C213/00 C07C269/04 C07D239/10 C07D277/28

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BEILSTEIN Data, WPI Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 914 332 A (SHAM ET AL) 22 June 1999 (1999-06-22) cited in the application	1-14
Y	examples 1,24	15-20
Y	----- WO 95/09614 A (ABBOTT LABORATORIES) 13 April 1995 (1995-04-13) examples 20-24	15-20
X	----- WO 95/11224 A (ABBOTT LABORATORIES) 27 April 1995 (1995-04-27) cited in the application examples 5a,7,8a,8b	1-8



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search

29 May 2006

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07/06/2006

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2006/000417

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 5914332	A	22-06-1999	ZA 9610475 A	31-07-1997
WO 9509614	A	13-04-1995	AT 200023 T	15-04-2001
			AU 685509 B2	22-01-1998
			AU 7722994 A	01-05-1995
			CA 2167413 A1	13-04-1995
			DE 69426984 D1	03-05-2001
			DE 69426984 T2	22-11-2001
			DK 721330 T3	25-06-2001
			EP 0721330 A1	17-07-1996
			ES 2156904 T3	01-08-2001
			GR 3036091 T3	28-09-2001
			IL 110915 A	22-12-1999
			JP 9503501 T	08-04-1997
			PT 721330 T	28-09-2001
WO 9511224	A	27-04-1995	AT 183993 T	15-09-1999
			AT 238983 T	15-05-2003
			CA 2174000 A1	27-04-1995
			DE 69420421 D1	07-10-1999
			DE 69420421 T2	04-05-2000
			DE 69432611 D1	05-06-2003
			DE 69432611 T2	18-03-2004
			DK 724563 T3	20-03-2000
			EP 0724563 A1	07-08-1996
			ES 2138667 T3	16-01-2000
			ES 2198094 T3	16-01-2004
			GR 3031939 T3	31-03-2000
			HK 1011677 A1	16-06-2000
			JP 9504024 T	22-04-1997
			PT 916646 T	30-09-2003
			US 5508409 A	16-04-1996
			US 5565604 A	15-10-1996
			US 5541328 A	30-07-1996
			US 5543549 A	06-08-1996
			US 5616776 A	01-04-1997
			US 5569777 A	29-10-1996
			US 5625092 A	29-04-1997
			US 5543551 A	06-08-1996
			US 5543552 A	06-08-1996