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(71) **Applicant**: **RANBAXY LABORATORIES LIMITED** [IN/IN]; Head Office: 12th Floor, Devika Tower, 06 Nehru Place, New Delhi, Delhi 110019 (IN).

(72) **Inventors**: **KUMAR, Satish**; House No. 148, Sawan Vihar, Nr. Kanwla Gurudwara, P.O. Model Town, Ambala City, Haryana 134003 (IN). **DURVASULA, Venugopa,l Venkatarama**; Door No. 23-8-8, Velturi Vari Street, Vizianagaram, Andhra Pradesh 535002 (IN). **RATHOD, Parendu, Dhirajlal**; 1372A, Maruti Vihar, Chakkarpur, Gurgaon, Haryana 122002 (IN). **ARYAN, Ram, Chander**; 1066, Sector-A, Pocket-A, Vasant Kunj, New Delhi, Delhi 110070 (IN).

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(54) **Title**: PROCESS FOR THE PREPARATION OF TELAPREVIR AND ITS INTERMEDIATES

(57) **Abstract**: The present invention provides a process for the preparation of telaprevir and its intermediates.

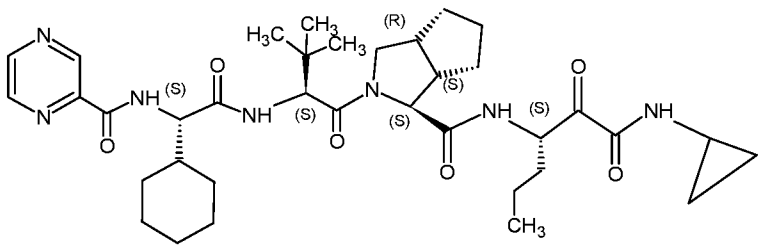
PROCESS FOR THE PREPARATION OF TELAPREVIR AND ITS INTERMEDIATES

Field of the Invention

The present invention provides a process for the preparation of telaprevir and its intermediates.

Background of the Invention

Telaprevir is a serine protease inhibitor disclosed in U.S. Patent No. 7,820,671. It is chemically designated as (1*S*,3a*R*,6a*S*)-2-[(2*S*)-2-({(2*S*)-2-cyclohexyl-2-[(pyrazin-2-ylcarbonyl)amino]acetyl}amino)-3,3-dimethylbutanoyl]-*N*-[(3*S*)-1-(cyclopropylamino)-1,2-dioxohexan-3-yl]-3,3a,4,5,6,6a-hexahydro-1H-cyclopenta[c]pyrrole-1-carboxamide, and has the structure depicted by Formula I.



Formula I

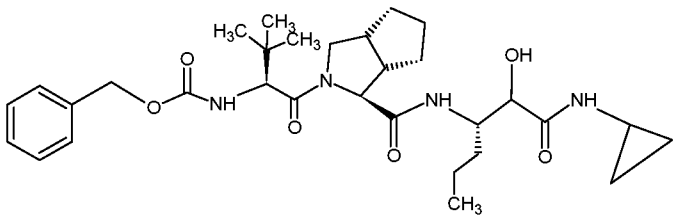
Telaprevir is marketed in the United States under the brand name Incivek® and is used for the treatment of hepatitis C, in combination with peginterferon alpha and ribavirin.

Processes for the preparation of telaprevir are disclosed in U.S. Patent No. 7,776,887; U.S. Publication No. 2010/0298568; PCT Publication Nos. WO 02/18369, WO 2008/090819, and WO 2011/153423; and Chemical Communications, 46(42), p. 7918-7920 (2010).

Summary of the Invention

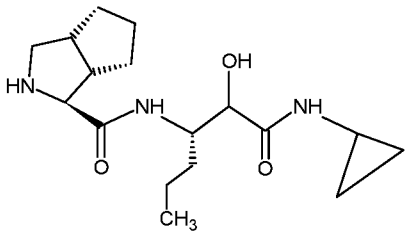
The present invention provides an alternate, industrially advantageous, efficient, and economical process for the preparation of telaprevir.

A first aspect of the present invention provides a process for the preparation of benzyl {(2S)-1-[(1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrol-2(1H)-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate of Formula II,

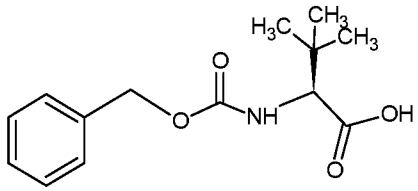


Formula II

comprising condensing (1S,3aR,6aS)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide of Formula III with N-[(benzyloxy)carbonyl]-3-methyl-L-valine of Formula IV.

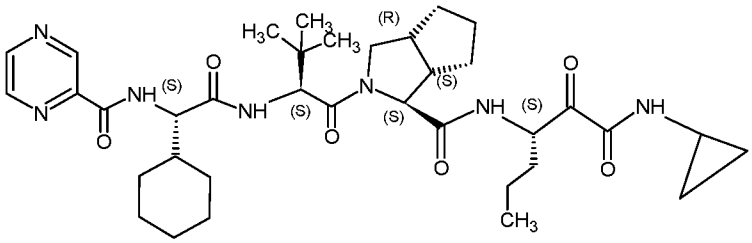


Formula III



Formula IV

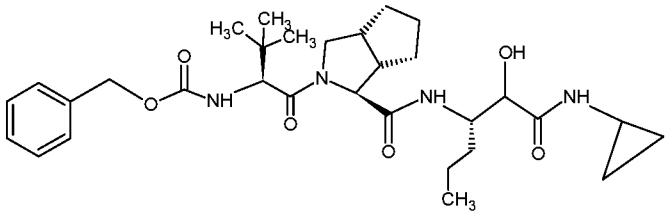
A second aspect of the present invention provides a process for the preparation of telaprevir of Formula I,



Formula I

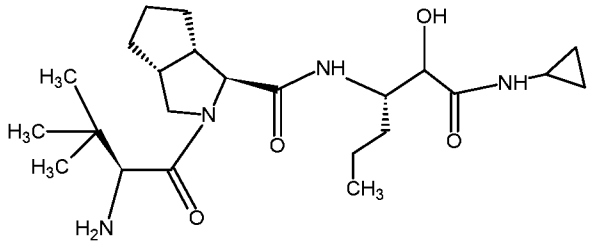
comprising the steps of:

a) deprotecting benzyl {(2S)-1-[(1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrol-2(1H)-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate of Formula II



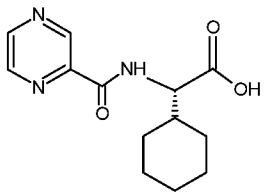
Formula II

to obtain (1S,3aR,6aS)-2-[(2S)-2-amino-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta [c]pyrrole-1-carboxamide of Formula V;



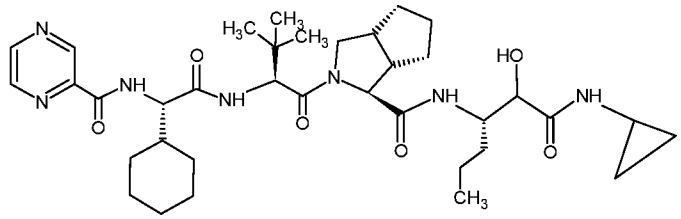
Formula V

b) condensing (1S,3aR,6aS)-2-[(2S)-2-amino-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide of Formula V with (2S)-cyclohexyl[(pyrazin-2-ylcarbonyl)amino]ethanoic acid of Formula VI



Formula VI

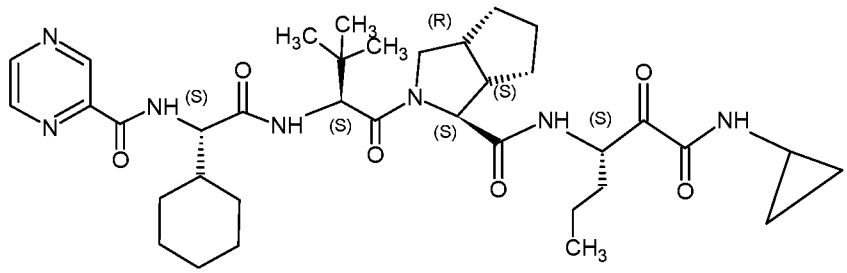
to obtain hydroxy telaprevir of Formula VII; and



Formula VII

c) oxidizing the hydroxy telaprevir of Formula VII to obtain telaprevir of Formula I.

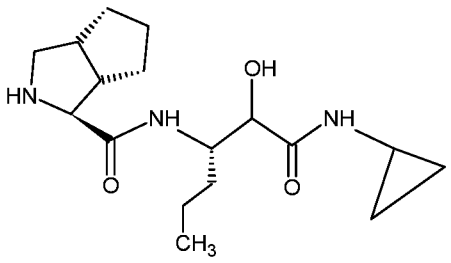
A third aspect of the present invention provides a process for the preparation of telaprevir of Formula I,



Formula I

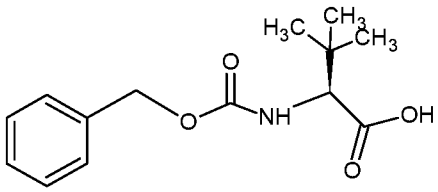
comprising the steps of :

a) condensing (1S,3aR,6aS)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide of Formula III



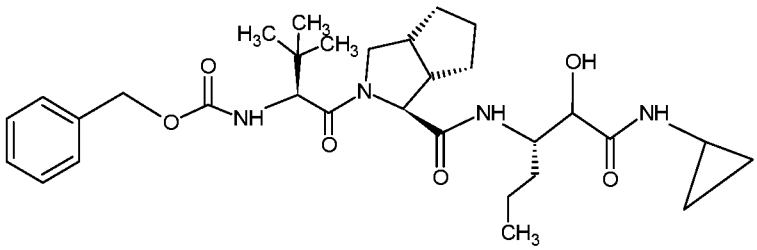
Formula III

with N-[(benzyloxy)carbonyl]-3-methyl-L-valine of Formula IV



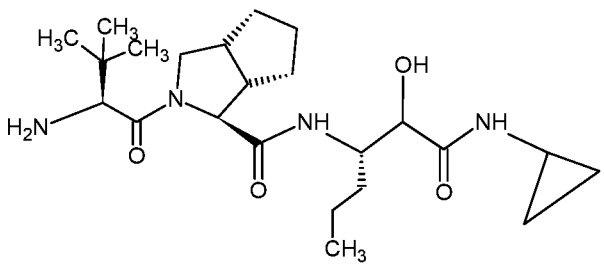
Formula IV

to obtain benzyl {(2S)-1-[(1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrol-2(1H)-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate of Formula II;



Formula II

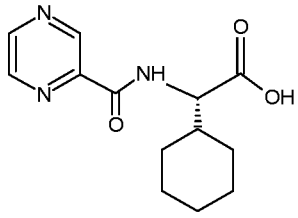
b) deprotecting benzyl {(2S)-1-[(1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrol-2(1H)-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate of Formula II to obtain (1S,3aR,6aS)-2-[(2S)-2-amino-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c] pyrrole-1-carboxamide of Formula V;



Formula V

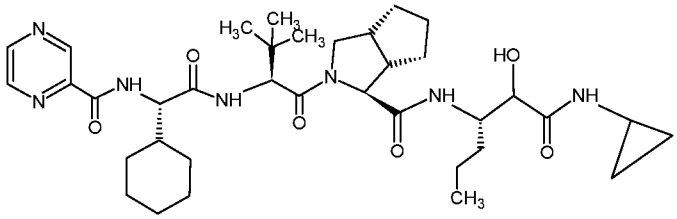
c) condensing (1S,3aR,6aS)-2-[(2S)-2-amino-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]

pyrrole-1-carboxamide of Formula V with (2S)-cyclohexyl[(pyrazin-2-ylcarbonyl)amino]ethanoic acid of Formula VI



Formula VI

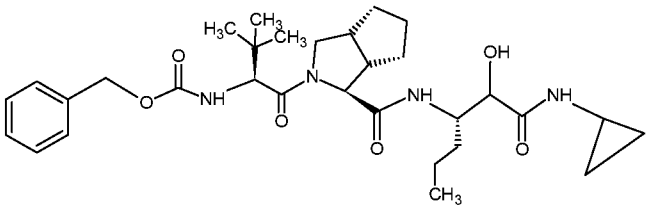
to obtain hydroxy telaprevir of Formula VII; and



Formula VII

d) oxidizing the hydroxy telaprevir of Formula VII to obtain telaprevir of Formula I.

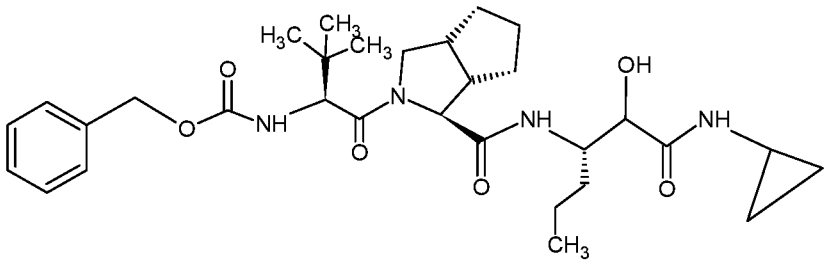
A fourth aspect of the present invention provides the use of benzyl {(2S)-1-[(1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrol-2(1H)-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate of Formula II



Formula II

for the preparation of telaprevir of Formula I.

A fifth aspect of the present invention provides benzyl {(2S)-1-[(1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrol-2(1H)-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate of Formula II.



Formula II

Detailed Description of the Invention

The following abbreviations are used in the present invention:

HATU	2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphatemethanaminium
HBTU	O-Benzotriazole-N,N,N',N'-tetramethyl-uronium-hexafluoro-phosphate
HDBTU	2-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HOTU	*O*-[(Ethoxycarbonyl)cyanomethylenamino]-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HOBT	*N*-Hydroxybenzotriazole
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EDC.HCl	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride
BOP	(Benzotriazol-1-yl-oxy)tris(dimethylamino)phosphonium hexafluorophosphate
PyBOP	(Benzotriazol-1-yloxy)-tripyrrolidinophosphoniumhexafluorophosphate
DEPBT	3-(Diethoxy-phosphoryloxy)-3H-benzo[d][1,2,3] triazin-4-one
Oxyma	Ethyl (hydroxyimino)cyanoacetate
COMU	(1-Cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate
TNTU	2-(endo-5-norborene-2,3-dicarboxyamido)-1,1,3,3-tetramethyluroniumtetrafluoroborate

TPTDP	*S*-(1-oxo-2-pyridyl)thio-1,3-dimethylpropyleneuronium tetrafluoroborate
TPTU	*O*-[1,2-dihydro-2-oxo-pyridyl]-*N,N, N',N'*-tetramethyluronium tetrafluoroborate
TBTU	*O*-(Benzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium tetrafluoroborate
DIC	*N,N'*-diisopropylcarbodiimide
DCC	*N,N'*-Dicyclohexylcarbodiimide
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
TPAP	Tetrapropylammonium perruthenate

Various embodiments and variants of the present invention are described hereinafter.

The term "about", as used herein, refers to any value which lies within a range defined by a number up to ±10% of the value.

N-[(Benzyloxy)carbonyl]-3-methyl-L-valine of Formula IV, to be used as an intermediate in the process of the present invention, may be prepared according to the process disclosed in WO 2007/022459, which is incorporated herein by reference.

(2S)-Cyclohexyl[(pyrazin-2-ylcarbonyl)amino]ethanoic acid of Formula VI, to be used as an intermediate in the process of the present invention, may be prepared according to the process disclosed in Chemical Communications, 46(42), p. 7918-7920 (2010).

The condensation of the intermediate of Formula III with the intermediate of Formula IV to obtain the intermediate of Formula II is carried out in the presence of a coupling agent, a base, and a solvent at a temperature of about 0°C to about 40°C for about 12 hours to about 2 days. Examples of coupling agents include HATU, HBTU, HDBTU, HOTU, HOBT, EDC, EDC.HCl, BOP, PyBOP, DEPBT, Oxyma, COMU, TNTU, TPTDP, TPTU, TBTU, DIC, DCC, or mixtures thereof. The base may be selected from organic or inorganic bases. Examples of organic bases include N,N-diisopropylethylamine, triethylamine, triisopropylamine, N,N-2-trimethyl-2-propanamine, N-methylmorpholine, 4-dimethylaminopyridine,2,6-di-tert-butyl-4-dimethylaminopyridine, 1,4-diazabicyclo[2.2.2]-octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or mixtures thereof. Examples of inorganic bases include sodium bicarbonate, potassium bicarbonate, or mixtures thereof. The solvent may be selected from nitriles, chlorinated hydrocarbons, amides, dialkylsulfoxides, or mixtures thereof. Examples of

nitriles include acetonitrile, propionitrile, butyronitrile, and valeronitrile. Examples of chlorinated hydrocarbons include dichloromethane, dichloroethane, chlorobenzene, and chloroform. Examples of amides include dimethylformamide, dimethylacetamide, and N-methyl formamide. Examples of dialkylsulfoxides include dimethylsulfoxide, diethylsulfoxide, and dibutylsulfoxide.

In the preferred embodiments of the present invention, the coupling agent is selected from HOBT, HATU, HBTU, TBTU, EDC, EDC.HCl, or mixtures thereof; the base is selected from N,N-diisopropylethylamine, 4-dimethylaminopyridine, triethyl amine, or N,N-2-trimethyl-2-propanamine; and the solvent is selected from dichloromethane, acetonitrile, dimethylformamide, or mixtures thereof.

The deprotection of benzyl {(2S)-1-[(1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrol-2(1H)-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate of Formula II to obtain the intermediate of Formula V is carried out in the presence of a metal catalyst, hydrogen gas, and a solvent at a temperature of about 0°C to about 40°C for about 5 minutes to about 20 hours. The metal catalyst may be selected from palladium supported on carbon, palladium black, palladium in the presence of barium sulphate, platinum supported on carbon, or raney nickel. The solvent may be selected from alcohols, nitriles, aromatic hydrocarbons, chlorinated hydrocarbons, dialkylsulfoxides, water, or mixtures thereof. Examples of alcohols include methanol, ethanol, n-propanol, isopropanol, n-butanol, and 2-methyl-1-pentanol. Examples of nitriles include acetonitrile, propionitrile, butyronitrile, and valeronitrile. Examples of aromatic hydrocarbons include toluene and xylene. Examples of chlorinated hydrocarbons include dichloromethane, dichloroethane, chlorobenzene, and chloroform. Examples of dialkylsulfoxides include dimethylsulfoxide, diethylsulfoxide, and dibutylsulfoxide.

In a preferred embodiment of the present invention, the deprotection of benzyl {(2S)-1-[(1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrol-2(1H)-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate of Formula II is carried out in the presence of methanol at about 10°C to about 30°C for about 1 hour to about 10 hours.

The condensation of (1S,3aR,6aS)-2-[(2S)-2-amino-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-

1-carboxamide of Formula V with the intermediate of Formula VI is carried out in the presence of a coupling agent, a base, and a solvent at a temperature of about 0°C to about 40°C for about 10 hours to about 20 hours. Examples of coupling agents include HATU, HBTU, HDBTU, HOTU, HOBT, EDC, EDC.HCl, BOP, PyBOP, DEPBT, Oxyma, COMU, TNTU, TPTDP, TPTU, TBTU, DIC, DCC, or mixtures thereof. The base may be selected from organic or inorganic bases. Examples of organic bases include N,N-diisopropylethylamine, triethylamine, triisopropylamine, N,N-2-trimethyl-2-propanamine, N-methylmorpholine, 4-dimethylaminopyridine, 2,6-di-tert-butyl-4-dimethylaminopyridine, 1,4-diazabicyclo[2.2.2] octane, 1,8-diazabicyclo[5.4.0]undec-7-ene, or mixtures thereof. Examples of inorganic bases include sodium bicarbonate, potassium bicarbonate, or a mixture thereof. The solvent may be selected from nitriles, chlorinated hydrocarbons, amides, dialkylsulfoxides, or mixtures thereof. Examples of nitriles include acetonitrile, propionitrile, butyronitrile, and valeronitrile. Examples of chlorinated hydrocarbons include dichloromethane, dichloroethane, chlorobenzene, and chloroform. Examples of amides include dimethylformamide, dimethylacetamide, and N-methyl formamide. Examples of dialkylsulfoxides include dimethylsulfoxide, diethylsulfoxide, and dibutylsulfoxide.

In the preferred embodiments of the present invention, the coupling agent is selected from HOBT, HATU, HBTU, TBTU, EDC, EDC.HCl, or mixtures thereof; the base is selected from N,N-diisopropylethylamine, 4-dimethylaminopyridine, triethyl amine, or N,N-2-trimethyl-2-propanamine; and the solvent is selected from dichloromethane, acetonitrile, dimethylformamide, or mixtures thereof.

The oxidation of the hydroxy telaprevir of Formula VII to obtain telaprevir of Formula I is carried out in the presence of an oxidizing agent and a solvent. The oxidation is carried out at a temperature of about 0°C to about 20°C for about 1 hour to about 15 hours. Examples of oxidizing agents include Dess-Martin periodinane, oxalyl chloride, chromium trioxide, potassium permanganate, or mixtures thereof. A catalytic amount of TEMPO or TPAP may also be added for facilitating the oxidation reaction. The solvent may be selected from nitriles, aromatic hydrocarbons, chlorinated hydrocarbons, dialkylsulfoxides, water, or mixtures thereof. Examples of nitriles include acetonitrile, propionitrile, butyronitrile, and valeronitrile. Examples of aromatic hydrocarbons include toluene and xylene. Examples of chlorinated hydrocarbons include dichloromethane,

dichloroethane, chlorobenzene, and chloroform. Examples of dialkylsulfoxides include dimethylsulfoxide, diethylsulfoxide, and dibutylsulfoxide.

In a preferred embodiment of the present invention, the oxidation of the intermediate of Formula VII is carried out in the presence of Dess-Martin periodinane and dichloromethane at a temperature of about 0°C to about 10°C for about 1 hour to about 5 hours.

The isolation of telaprevir and its intermediates may be carried out by filtration, concentration, decantation, or a combination thereof. In the preferred embodiments of the present invention, the isolation of telaprevir and its intermediates is carried out by concentration.

In the foregoing section, embodiments are described by way of examples to illustrate the processes of invention. However, these are not intended in any way to limit the scope of the present invention. Variants of the examples that would be evident to persons ordinarily skilled in the art are within the scope of the present invention.

EXAMPLES

Example 1: Preparation of (1S,3aR,6aS)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide (Formula III)

Step A:

In a round bottom flask flushed with nitrogen gas, ethyl-3-oxo-octahydro-1*H*-cyclopenta[*c*]pyridine-4-carboxylate (225 g) was dissolved in dichloromethane (3 mL). A solution of sulfuryl chloride (151.2 g in 375 mL of dichloromethane) was added over 30 minutes at 25°C to 30°C. The reaction mixture was stirred for 2 hours. The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, the reaction mixture was concentrated under reduced pressure to obtain ethyl 4-chloro-3-oxooctahydro-1H-cyclopenta[c]pyridine-4-carboxylate.

Yield: 99%

Step B:

In a round bottom flask, ethyl 4-chloro-3-oxooctahydro-1H-cyclopenta[c]pyridine-4-carboxylate (182 g) was treated with concentrated hydrochloric acid (294 mL). The reaction mixture was heated at 85°C to 90°C for 6 hours. To the reaction mixture,

aqueous sodium hydroxide solution (191 g in 200 mL of water) was added at 30°C to 35°C. The reaction mixture was stirred for 24 hours and cooled to 5°C to 10°C. Benzylchloroformate dissolved in toluene (50% w/v, 250 mL) was added to the reaction mixture over 30 minutes. The reaction mixture was heated to 20°C to 25°C and stirred for 24 hours. The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, the organic layer was extracted with water (2 x 2000 mL) and washed with dichloromethane (800 mL). The aqueous layer was acidified with concentrated hydrochloric acid (142 mL) and extracted with dichloromethane (1000 mL). The combined dichloromethane layer was concentrated under reduced pressure to obtain an oil (165.2 g). The oil (66 g) was dissolved in ethyl acetate (330 mL) to obtain a solution. (S)-Phenyl ethyl amine (27.6 g) was added to the solution at 20°C to 25°C and the reaction mixture was stirred for 24 hours to 30 hours. The reaction mixture was filtered, and the filtrate was concentrated under reduced pressure to obtain an oil. The oil was dissolved in dichloromethane (400 mL) and washed with aqueous hydrochloric acid (40 mL concentrated hydrochloric acid in 400 mL of water). The organic layer was concentrated to provide an oil. The oil (26.5 g) was dissolved in isopropyl acetate (106 mL) to obtain a solution and (S)-1,2,3,4-tetrahydronapthylamine (13.5 g) was added to the solution at 18°C to 25°C. The reaction mixture was stirred for 24 hours. A solid adduct of (3aR,6aS)-2-[(benzyloxy)carbonyl]octahydrocyclopenta[c]pyrrole-1-carboxylic acid with (S)-1,2,3,4-tetrahydronapthylamine was formed. The solid adduct was filtered and washed with isopropyl acetate (26.5 mL). The adduct (1 g) was dissolved in isopropyl acetate (10 mL) and heated to a temperature of 60°C to 65°C to obtain a clear solution. The solution was cooled to 55°C to 60°C. A seed crystal of the solid adduct (0.1 g) was added to the reaction mixture followed by cooling to 35°C for 1 hour. The solution was stirred for 2 hours, filtered, washed with isopropyl acetate (5 mL), and dried. The dried solid was dissolved in dichloromethane (10 mL) and washed with 1N hydrochloric acid (10 mL). The organic layer was concentrated under reduced pressure to obtain (3a*R*,6a*S*)-2-[(benzyloxy)carbonyl]octahydrocyclopenta-[c]pyrrole-1-carboxylic acid.

Yield: 90%

Step C:

In a round bottom flask,(3a*R*,6a*S*)-2-[(benzyloxy)carbonyl]octahydrocyclopenta-[c]pyrrole-1-carboxylic acid (16 g) was dissolved in dichloromethane (200 mL). To this

solution, TBTU (20 g) was added at 10°C. The reaction mixture was stirred for 10 minutes. (3*S*)-3-Amino-N-cyclopropyl-2-hydroxyhexanamide (10 g) and N,N-diisopropylethylamine (10 mL) were added to the solution at 0°C to 5°C. The reaction mixture was stirred for 4 hours at 20°C to 25°C. The reaction mixture was washed with hydrochloric acid (1N, 2 x 100 mL), sodium bicarbonate solution (5%, 100 mL), and water (100 mL) sequentially. The dichloromethane layer was concentrated at 35°C to 40°C under reduced pressure to obtain a solid residue. The solid residue was slurry-washed with hexane (200 mL), and dried to obtain benzyl (1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta [c]pyrrole-2-(1H)-carboxylate (19.6 g).

The benzyl (1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate (9 g) was dissolved in methanol (108 mL). To this solution, palladium supported on carbon (0.9 g) was added and a hydrogen pressure of 1.5 bars was applied for 4 hours at a temperature of 20°C to 25°C. The reaction mixture was filtered through a Hyflo® bed and concentrated under reduced pressure to obtain (1S,3aR,6aS)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide.

Yield: 95.89%

Example 2: Preparation of benzyl {(2S)-1-[(1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrol-2(1H)-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate (Formula II)

In a round bottom flask, N-[(benzyloxy)carbonyl]-3-methyl-L-valine (Formula IV; 1.7 g) was dissolved in dichloromethane (60 mL). To this solution, HOBT (0.85 g) and EDC.HCl (1.4 g) were added and the reaction mixture was stirred for 15 minutes. The solution was cooled to 0°C. (1S,3aR,6aS)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide (Formula III; 2.0 g) and N,N-diisopropylethylamine (1.08 mL) were added to the reaction mixture at 0°C to 5°C. The reaction mixture was stirred for 24 hours at 20°C to 25°C. The reaction mixture was sequentially washed with hydrochloric acid (1N, 2 x 60 mL), sodium bicarbonate solution (5%, 60 mL), and water (60 mL). The dichloromethane layer was concentrated to obtain benzyl {(2S)-1-[(1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-

yl]carbamoyl}hexahydrocyclopenta[c]pyrrol-2(1H)-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate.

Yield: 89.09%

Example 3: Preparation of (1S,3aR,6aS)-2-[(2S)-2-amino-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide (Formula V)

In a Parr apparatus, benzyl {(2S)-1-[(1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino) -2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrol-2(1H)-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate (Formula II; 2.9 g) was dissolved in methanol (45 mL). To this solution, palladium supported on carbon (0.3 g, 10%, 50% wet) was added and hydrogen pressure of 1.5 bars was applied for 4 hours at 20°C to 25°C. The reaction mixture was filtered through a Hyflo® bed and the filtrate was concentrated under reduced pressure to obtain (1S,3aR,6aS)-2-[(2S)-2-amino-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide.

Yield: 97.10%

Example 4: Preparation of hydroxy telaprevir (Formula VII)

In a round bottom flask, (2S)-cyclohexyl[(pyrazin-2-ylcarbonyl)amino]ethanoic acid (Formula VI; 0.42 g) was dissolved in dichloromethane (25 mL). HOBT (0.25 g) and EDC.HCl (0.37 g) were added, followed by the addition of (1S,3aR,6aS)-2-[(2S)-2-amino-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide (Formula V; 0.7 g) and N,N-diisopropylethylamine (0.28 mL) at 5°C to 10°C. The temperature of the reaction mixture was raised to 20°C to 25°C, and the reaction mixture was stirred for 15 hours. The reaction mixture was washed sequentially with 1N hydrochloric acid (2 x 25 mL), 5% sodium bicarbonate (25 mL), and water (25 mL). The dichloromethane layer was concentrated at 35°C to 40°C under reduced pressure to obtain hydroxy telaprevir.

Yield: 86.76%

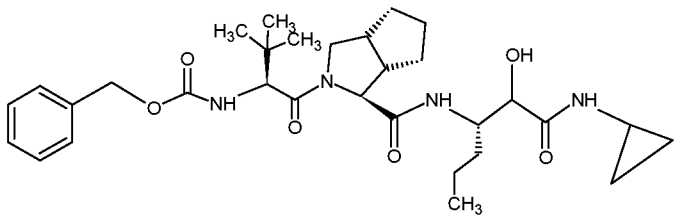
Example 5: Preparation of telaprevir (Formula I)

In a round bottom flask, hydroxy telaprevir (Formula VII; 0.6 g) was dissolved in dichloromethane (15 mL). To the resulting solution, Dess-Martin periodinane (0.72 g) was added at 5°C. The reaction mixture was stirred at 0°C to 5°C for 2 hours. The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, the reaction mixture was quenched with sodium thiosulphate solution (2.4 g in 20 mL water), and washed with sodium bicarbonate solution (1 g in 20 mL water) and water (20 mL). The dichloromethane layer was concentrated under reduced pressure to obtain telaprevir.

Yield: 93.61%

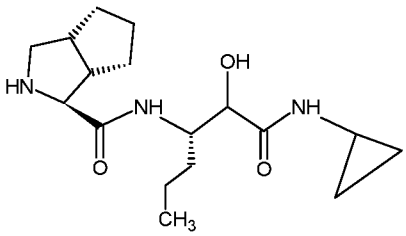
We Claim:

1. A process for the preparation of benzyl {(2S)-1-[(1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrol-2(1H)-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate of Formula II

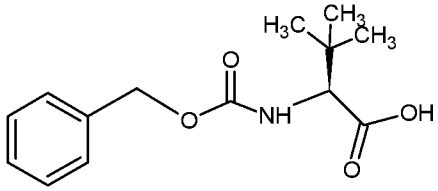


Formula II

comprising condensing (1S,3aR,6aS)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide of Formula III with N-[(benzyloxy)carbonyl]-3-methyl-L-valine of Formula IV.



Formula III



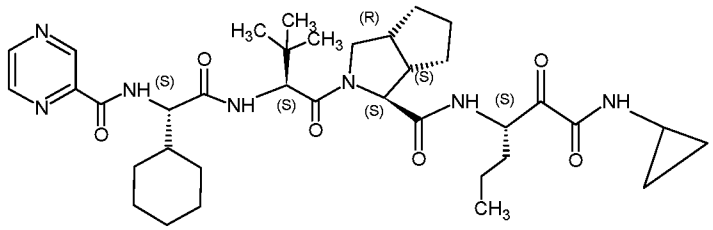
Formula IV

2. The process according to claim 1, wherein the condensation of (1S,3aR,6aS)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide of Formula III with N-[(benzyloxy)carbonyl]-3-methyl-L-valine of Formula IV is carried out in the presence of a coupling agent selected from the group consisting of HOBT, HATU, HBTU, TBTU, EDC, EDC.HCl, or mixtures thereof.

3. The process according to claim 1, wherein the condensation of (1S,3aR,6aS)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide of Formula III with N-[(benzyloxy)carbonyl]-3-methyl-L-valine of Formula IV is carried out in the presence of a base selected from the group consisting of N,N-diisopropylethylamine, 4-dimethylaminopyridine, triethyl amine, N,N-2-trimethyl-2-propanamine, or mixtures thereof.

4. The process according to claim 1, wherein the condensation of (1S,3aR,6aS)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide of Formula III with N-[(benzyloxy)carbonyl]-3-methyl-L-valine of Formula IV is carried out at a temperature of about 0°C to about 40°C.

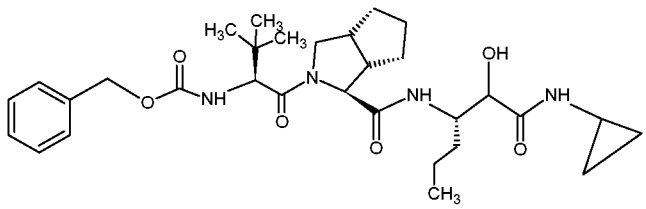
5. A process for the preparation of telaprevir of Formula I,



Formula I

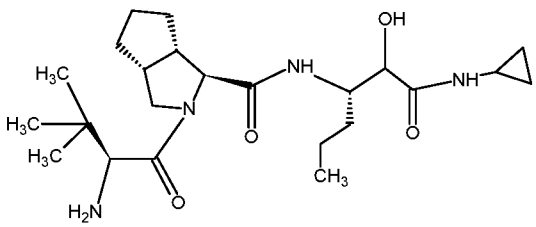
comprising the steps of:

a) deprotecting benzyl {(2S)-1-[(1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrol-2(1H)-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate of Formula II



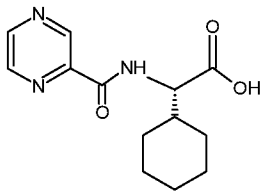
Formula II

to obtain (1S,3aR,6aS)-2-[(2S)-2-amino-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide of Formula V;



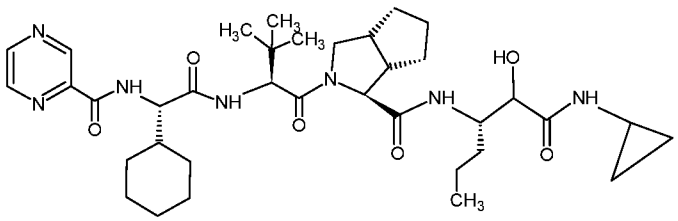
Formula V

b) condensing (1S,3aR,6aS)-2-[(2S)-2-amino-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl] octahydrocyclopenta[c] pyrrole-1-carboxamide of Formula V with (2S)-cyclohexyl[(pyrazin-2-ylcarbonyl)amino]ethanoic acid of Formula VI;



Formula VI

to obtain hydroxy telaprevir of Formula VII; and



Formula VII

c) oxidizing the hydroxy telaprevir of Formula VII to obtain telaprevir of Formula I.

6. The process according to claim 5, wherein the deprotection of benzyl {(2S)-1-[(1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl} hexahydrocyclopenta[c]pyrrol-2(1H)-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate of Formula II in step a) is carried out using a metal catalyst and hydrogen gas.

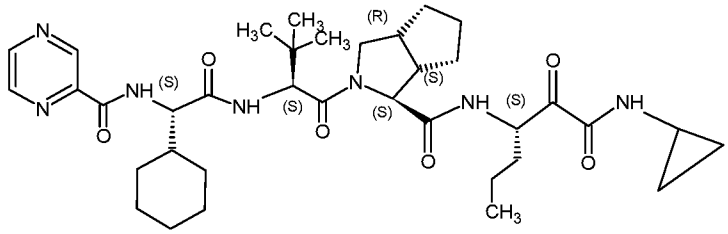
7. The process according to claim 5, wherein the condensation of (1S,3aR,6aS)-2-[(2S)-2-amino-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide of Formula V with (2S)-cyclohexyl[(pyrazin-2-ylcarbonyl)amino]ethanoic acid of Formula VI in step b) is carried out in the presence of a coupling agent selected from the group consisting of HOBT, HATU, HBTU, TBTU, EDC, EDC.HCl, or mixtures thereof.

8. The process according to claim 5, wherein the condensation of (1S,3aR,6aS)-2-[(2S)-2-amino-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide of Formula V with (2S)-cyclohexyl[(pyrazin-2-ylcarbonyl)amino]ethanoic acid of Formula VI in step b) is carried

out in the presence of a base selected from the group consisting of N,N-diisopropylethylamine, 4-dimethylaminopyridine, triethyl amine, N,N-2-trimethyl-2-propanamine, or mixtures thereof.

9. The process according to claim 5, wherein the oxidation of the hydroxy telaprevir in step c) is carried out in the presence of Dess-Martin periodinane.

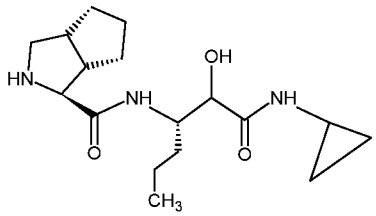
10. A process for the preparation of telaprevir of Formula I,



Formula I

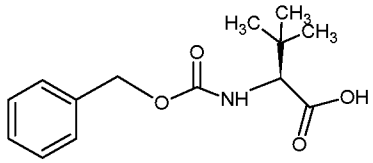
comprising the steps of:

a) condensing (1S,3aR,6aS)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide of Formula III



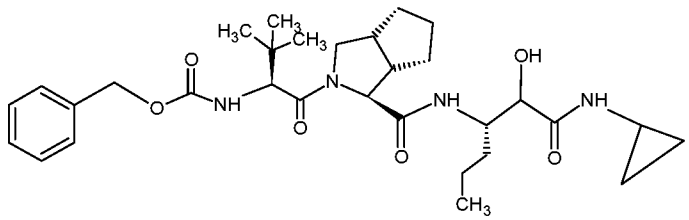
Formula III

with N-[(benzyloxy)carbonyl]-3-methyl-L-valine of Formula IV



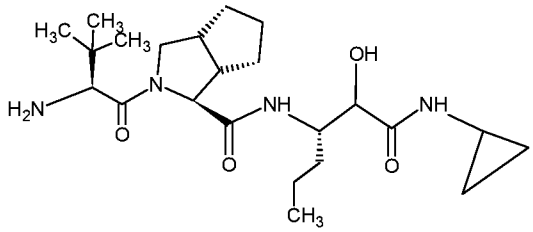
Formula IV

to obtain benzyl {(2S)-1-[(1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrol-2(1H)-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate of Formula II;



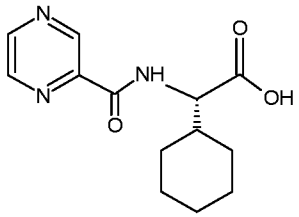
Formula II

b) deprotecting benzyl {(2S)-1-[(1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrol-2(1H)-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate of Formula II to obtain (1S,3aR,6aS)-2-[(2S)-2-amino-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide of Formula V;



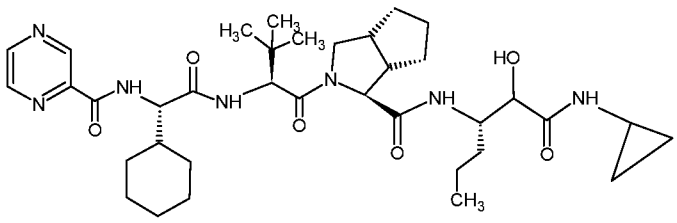
Formula V

c) condensing (1S,3aR,6aS)-2-[(2S)-2-amino-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c] pyrrole-1-carboxamide of Formula V with (2S)-cyclohexyl[(pyrazin-2-ylcarbonyl)amino]ethanoic acid of Formula VI,



Formula VI

to obtain hydroxy telaprevir of Formula VII; and



Formula VII

d) oxidizing the hydroxy telaprevir of Formula VII to obtain telaprevir of Formula I.

11. The process according to claim 10, wherein the condensation of (1S,3aR,6aS)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide of Formula III with the N-[(benzyloxy)carbonyl]-3-methyl-L-valine of Formula IV in step a) is carried out in the presence of a coupling agent selected from the group consisting of HOBT, HATU, HBTU, TBTU, EDC, EDC.HCl, or mixtures thereof.

12. The process according to claim 10, wherein the condensation of (1S,3aR,6aS)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide of Formula III with the N-[(benzyloxy)carbonyl]-3-methyl-L-valine of Formula IV in step a) is carried out in the presence of a base selected from the group consisting of N,N-diisopropylethylamine, 4-dimethylaminopyridine, triethyl amine, N,N-2-trimethyl-2-propanamine, or mixtures thereof.

13. The process according to claim 10, wherein the deprotection of benzyl {(2S)-1-[(1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl} hexahydrocyclopenta[c]pyrrol-2(1H)-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate of Formula II in step b) is carried out using a metal catalyst and hydrogen gas.

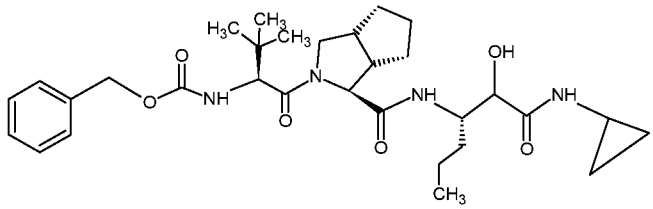
14. The process according to claim 10, wherein the condensation of (1S,3aR,6aS)-2-[(2S)-2-amino-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide of Formula V with (2S)-cyclohexyl[(pyrazin-2-ylcarbonyl)amino]ethanoic acid of Formula VI in step c) is carried out in the presence of a coupling agent selected from the group consisting of HOBT, HATU, HBTU, TBTU, EDC, EDC.HCl, or mixtures thereof.

15. The process according to claim 10, wherein the condensation of (1S,3aR,6aS)-2-[(2S)-2-amino-3,3-dimethylbutanoyl]-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide of Formula V with (2S)-

cyclohexyl[(pyrazin-2-ylcarbonyl)amino]ethanoic acid of Formula VI in step c) is carried out in the presence of a base selected from the group consisting of N,N-diisopropylethylamine, 4-dimethylaminopyridine, triethyl amine, N,N-2-trimethyl-2-propanamine, or mixtures thereof.

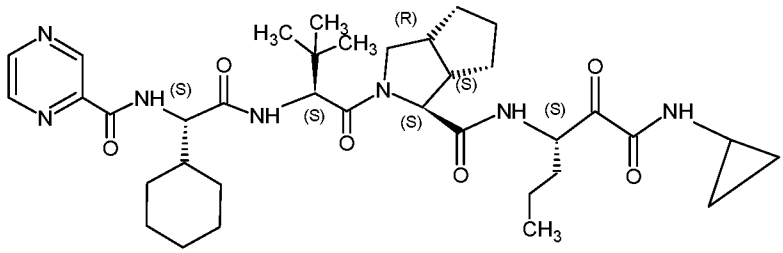
16. The process according to claim 10, wherein the oxidation of the hydroxy telaprevir in step d) is carried out in the presence of Dess-Martin periodinane.

17. The use of benzyl {(2S)-1-[(1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrol-2(1H)-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate of Formula II



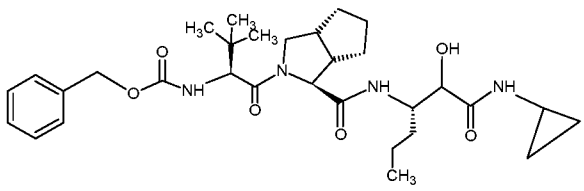
Formula II

for the preparation of telaprevir of Formula I.



Formula I

18. Benzyl {(2S)-1-[(1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrol-2(1H)-yl]-3,3-dimethyl-1-oxobutan-2-yl}carbamate of Formula II



Formula II

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/062496

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D209/52 C07K5/02
ADD.

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)
C07D C07K

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 practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 7 776 887 B2 (TANOURY GERALD J [US] ET AL) 17 August 2010 (2010-08-17) cited in the application scheme V; column 37 - column 40	1-18
A	US 2010/298568 A1 (TANOURY GERALD J [US] ET AL) 25 November 2010 (2010-11-25) cited in the application scheme II; page 7 - page 8	1-18

-/--

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

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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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 August 2014	03/09/2014

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Brandstetter, T

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2014/062496

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WO 2011/153423 A2 (VERTEX PHARMA [US]; TANOURY GERALD J [US]) 8 December 2011 (2011-12-08) cited in the application scheme IV; page 31	1-18
A	ANASS ZNABET ET AL: "A highly efficient synthesis of telaprevir by strategic use of biocatalysis and multicomponent reactions", CHEMICAL COMMUNICATIONS, vol. 46, no. 42, 1 January 2010 (2010-01-01), page 7918, XP055027224, ISSN: 1359-7345, DOI: 10.1039/c0cc02823a schemes 2-4; page 7919	1-18

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