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- (71) **Applicant:** RANBAXY LABORATORIES LIMITED
[IN/IN]; Head Office: 12th Floor, Devika Tower, 06 Nehru
Place, New Delhi 110 019, Delhi (IN).
- (72) **Inventors:** KUMAR, Satish; House No. 148, Sawan Vi-
har, Nr. Kanwla Gurudwara, P.O. Model Town, Ambala
City 134 003, Haryana (IN). DURVASULA, Venugopal
Venkatarama; Door No. 23-8-8, Velturi Vari Street, Viz-
ianagaram 535 002, Andhra Pradesh (IN). RATHOD, Par-
endu Dhirajlal; 1372A, Maruti Vihar, Chakkarpur, Gur-
gaon 122 002, Haryana (IN). ARYAN, Ram Chander;
1066, Sector-A, Pocket-A, Vasant Kunj, New Delhi 110
070, Delhi (IN).

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

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



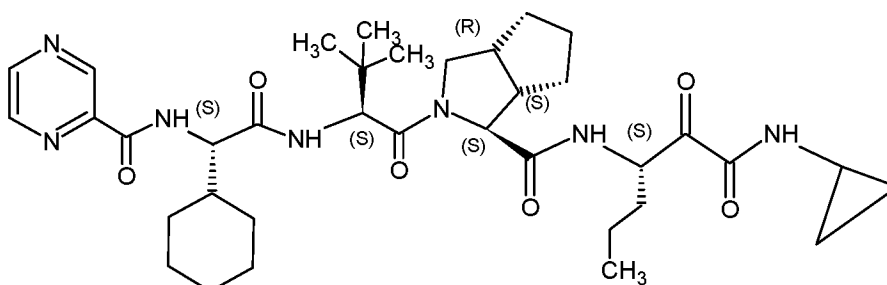
PROCESS FOR THE PREPARATION OF TELAPREVIR AND INTERMEDIATES THEREOF

Field of the Invention

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

Background of the Invention

Telaprevir is a serine protease inhibitor known from U.S. Patent No. 7,820,671. It is chemically designated as (1*S*,3*aR*,6*aS*)-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]-3,3*a*,4,5,6,6*a*-hexahydro-1*H*-cyclopenta[*c*]pyrrole-1-carboxamide and has the structure depicted by Formula I:



Formula I

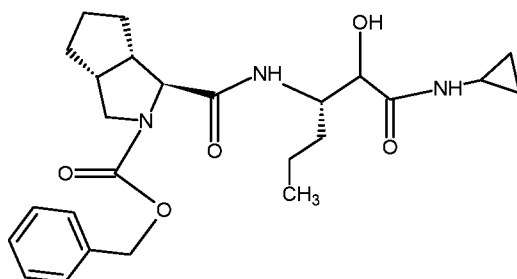
Telaprevir is marketed in the United States under the brand name Incivek[®] and is used for the treatment of hepatitis C in combination with peginterferon alpha and ribavirin.

15 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):7918-7920 (2010).

20 In view of the growing demand for compounds useful for the treatment of hepatitis C, there exists a need for the development of an alternative, cost effective, industrially advantageous, and simple process for the preparation of telaprevir.

Summary of the Invention

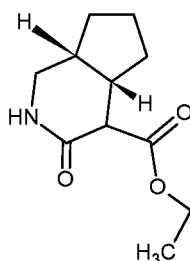
A first aspect of the present invention provides a process for the preparation of benzyl (1*S*,3*aR*,6*aS*)-1-{[(3*S*)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[*c*]pyrrole-2-(1*H*)carboxylate of Formula II



Formula II

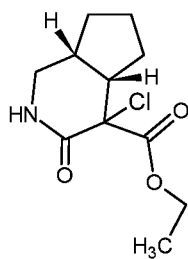
5 comprising the steps of:

- a) chlorinating the ethyl 3-oxo-octahydro-1*H*-cyclopenta[*c*]pyridine-4-carboxylate intermediate of Formula III



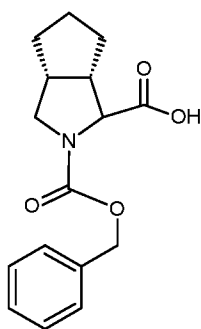
Formula III

to obtain the ethyl 4-chloro-3-oxooctahydro-1*H*-cyclopenta[*c*]pyridine-4-carboxylate intermediate of Formula IV;



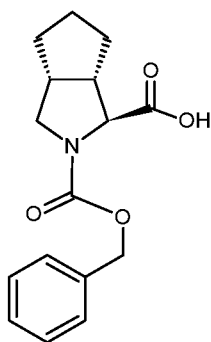
Formula IV

- b) treating the intermediate of Formula IV with hydrochloric acid and sodium hydroxide followed by condensation with benzyl chloroformate to obtain the (3aR,6aS)-2-[(benzyloxy)carbonyl]octahydrocyclopenta[c]pyrrole-1-carboxylic acid intermediate of Formula V;



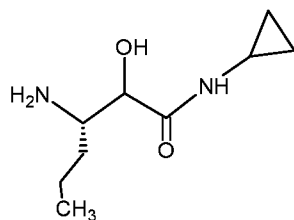
Formula V

- 5 c) resolving the intermediate of Formula V to obtain the (1S,3aR,6aS)-2-[(benzyloxy)carbonyl]octahydrocyclopenta[c]pyrrole-1-carboxylic acid intermediate of Formula VI; and



Formula VI

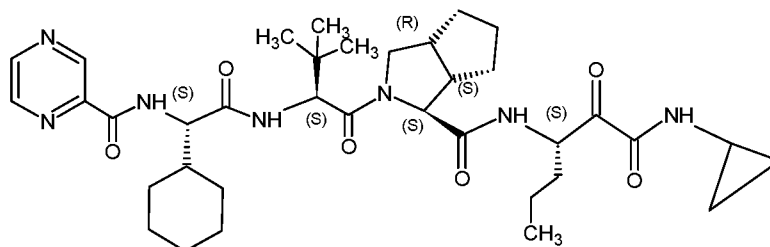
- d) condensing the intermediate of Formula VI with the (3S)-3-amino-N-cyclopropyl-2-hydroxyhexanamide intermediate of Formula VII



Formula VII

to obtain benzyl (1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrole-2-(1H)carboxylate of Formula II.

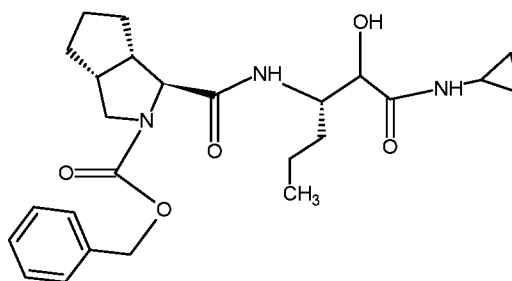
A second aspect of the present invention provides a process for the preparation of
5 telaprevir of Formula I



Formula I

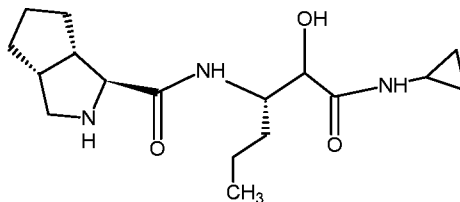
comprising the steps of:

- a) deprotecting the benzyl (1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrole-2-(1H)carboxylate intermediate of Formula II



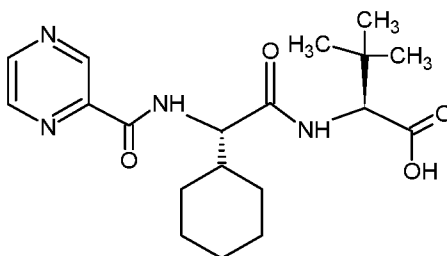
Formula II

10 to obtain the (1S,3aR,6aS)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide intermediate of Formula VIII;



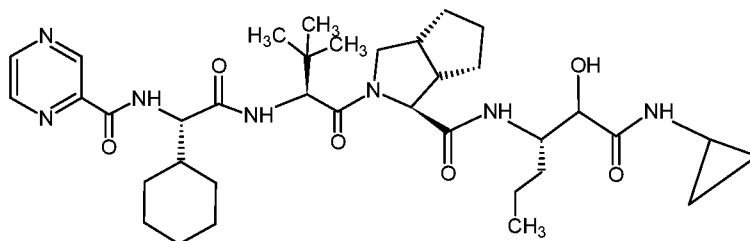
Formula VIII

- b) condensing the intermediate of Formula VIII with the N-{(2S)-2-cyclohexyl-2-[(pyrazin-2-yl-carbonyl)amino]acetyl}-3-methyl-L-valine intermediate of Formula IX



Formula IX

to obtain the hydroxy telaprevir intermediate of Formula X; and

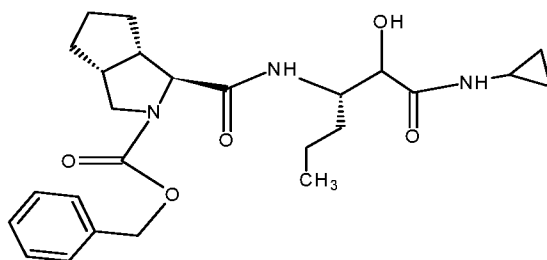


Formula X

- 5 c) oxidizing the hydroxy telaprevir intermediate of Formula X to obtain telaprevir of Formula I.

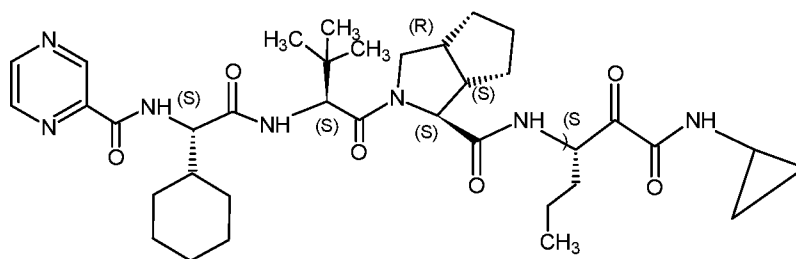
A third aspect of the present invention provides the use of the benzyl (1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c] pyrrole-2-(1H)carboxylate intermediate of Formula

10 II for the preparation of telaprevir of Formula I.



Formula II

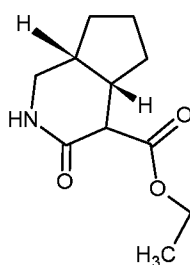
A fourth aspect of the present invention provides a process for the preparation of telaprevir of Formula I



Formula I

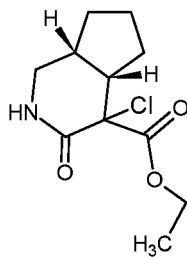
comprising the steps of:

- 5 a) chlorinating the ethyl 3-oxo-octahydro-1*H*-cyclopenta[*c*]pyridine-4-carboxylate intermediate of Formula III



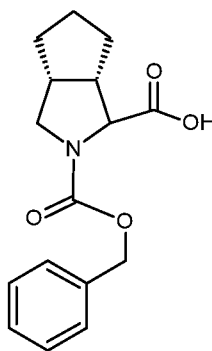
Formula III

to obtain the ethyl 4-chloro-3-oxooctahydro-1*H*-cyclopenta[*c*]pyridine-4-carboxylate intermediate of Formula IV;



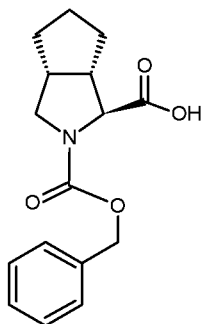
Formula IV

- b) treating the intermediate of Formula IV with hydrochloric acid and sodium hydroxide followed by condensation with benzyl chloroformate to obtain the (3aR,6aS)-2-[(benzyloxy)carbonyl]octahydrocyclopenta[c]pyrrole-1-carboxylic acid intermediate of Formula V;



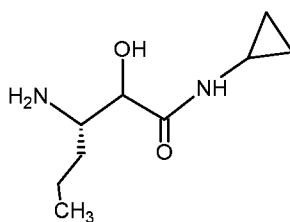
Formula V

- 5 c) resolving the intermediate of Formula V to obtain the (1S,3aR,6aS)-2-[(benzyloxy)carbonyl]octahydrocyclopenta[c]pyrrole-1-carboxylic acid intermediate of Formula VI;



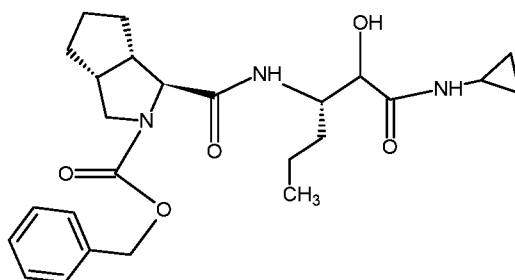
Formula VI

- d) condensing the intermediate of Formula VI with the (3S)-3-amino-N-cyclopropyl-2-hydroxyhexanamide intermediate of Formula VII



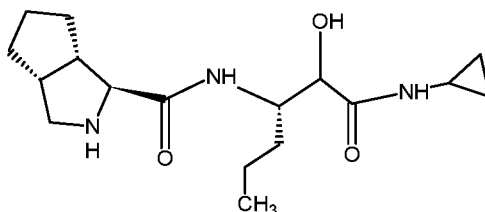
Formula VII

to obtain the benzyl (1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrole-2-(1H)carboxylate intermediate of Formula II;



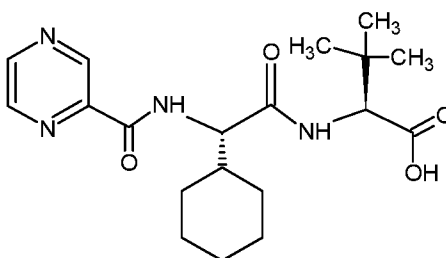
Formula II

- 5 e) deprotecting the intermediate of Formula II to obtain the (1S,3aR,6aS)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide intermediate of Formula VIII;



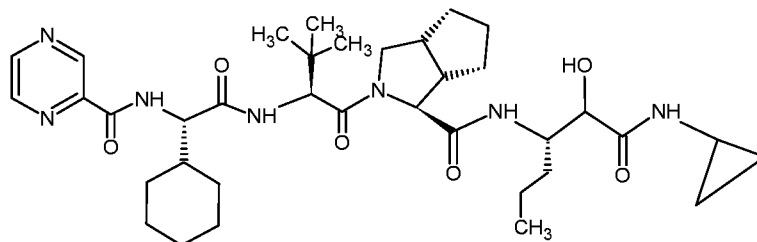
Formula VIII

- 10 f) condensing the intermediate of Formula VIII with the N-{(2S)-2-cyclohexyl-2-[(pyrazin-2-yl-carbonyl)amino]acetyl}-3-methyl-L-valine intermediate of Formula IX



Formula IX

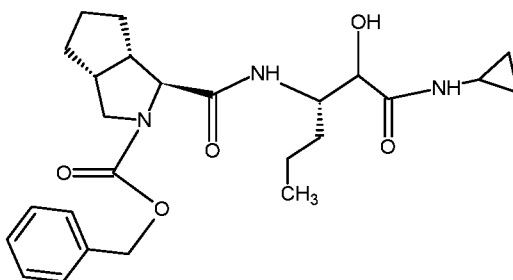
to obtain the hydroxy telaprevir intermediate of Formula X; and



Formula X

- g) oxidizing the hydroxy telaprevir intermediate of Formula X to obtain telaprevir of Formula I.

A fifth aspect of the present invention provides the benzyl (1*S*,3*aR*,6*aS*)-1-{[(3*S*)-
 5 1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[*c*]-
 pyrrole-2-(1*H*)-carboxylate intermediate of Formula II.



Formula II

Detailed Description of the Invention

The following abbreviations are used in the present invention:

HATU	2-(1 <i>H</i> -7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate methanaminium
HBTU	<i>O</i> -Benzotriazole- <i>N,N,N',N'</i> -tetramethyl-uronium-hexafluoro-phosphate
HDBTU	2-(3,4-dihydro-4-oxo-1,2,3-benzotriazin-3-yl)- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate
HOTU	<i>O</i> -[(Ethoxycarbonyl)cyanomethylenamino]- <i>N,N,N',N'</i> -tetramethyluronium hexafluorophosphate

HOBT	<i>N</i> -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-yl-oxy)]-tripyrrolidinophosphonium hexafluorophosphate
DEPBT	3-(Diethoxy-phosphoryloxy)-3H-benzo[d][1,2,3] triazin-4-one
Oxyma	Ethyl (hydroxyimino)cyanoacetate
COMU	(1-Cyano-2-ethoxy-2-oxoethylidenaminoxy)dimethylamino-morpholino-carbenium hexafluorophosphate
TNTU	2-(endo-5-norborene-2,3-dicarboxyamido)-1,1,3,3-tetramethyluronium tetrafluoroborate
TPTDP	<i>S</i> -(1-oxo-2-pyridyl)thio-1,3-dimethylpropyleneuronium tetrafluoroborate
TPTU	<i>O</i> -[1,2-dihydro-2-oxo-pyridyl]- <i>N,N,N',N'</i> -tetramethyluronium tetrafluoroborate
TBTU	<i>O</i> -(Benzotriazol-1-yl)- <i>N,N,N',N'</i> -tetramethyluronium tetrafluoroborate
DIC	<i>N,N</i> -diisopropylcarbodiimide
DCC	<i>N,N'</i> -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
5 defined by a number up to $\pm 10\%$ of the value.

The ethyl 3-oxo-octahydro-1*H*-cyclopenta[*c*]pyridine-4-carboxylate intermediate of Formula III may be prepared according to the process provided in *Zhurnal*

Organicheskoi Khimii, Vol. 5, 1784-1788 (1969), which is incorporated herein by reference.

The (3S)-3-amino-N-cyclopropyl-2-hydroxyhexanamide intermediate of Formula VII may be prepared according to the processes disclosed in PCT Publication Nos. WO 2007/109080, WO 2007/109023, WO 2007/022459, and WO 2010/126881, which are
5 incorporated herein by reference for their disclosure of the preparation of the (3S)-3-amino-N-cyclopropyl-2-hydroxyhexanamide intermediate of Formula VII.

The N-{(2S)-2-cyclohexyl-2-[(pyrazin-2-yl-carbonyl)amino]acetyl}-3-methyl-L-valine intermediate of Formula IX may be prepared according to the process disclosed in
10 PCT Publication No. WO 02/18369, which is incorporated herein by reference for its disclosure of the preparation of the N-{(2S)-2-cyclohexyl-2-[(pyrazin-2-yl-carbonyl)amino]acetyl}-3-methyl-L-valine intermediate of Formula IX.

In the processes of the present invention, the preparation of telaprevir and its intermediates is carried out in an inert atmosphere.

15 The chlorination of the intermediate of Formula III to obtain the intermediate of Formula IV is carried out in the presence of a chlorinating agent selected from sulfuryl chloride or N-chlorosuccinimide, and a solvent at a temperature of about 10°C to 40°C for about 30 minutes to about 10 hours. The solvent may be selected from the group comprising chlorinated hydrocarbons, aromatic hydrocarbons, or mixtures thereof.
20 Examples of chlorinated hydrocarbons include dichloromethane, dichloroethane, chlorobenzene, and chloroform. Examples of aromatic hydrocarbons include toluene and xylene.

In a preferred embodiment of the present invention, the chlorination of the intermediate of Formula III is carried out in dichloromethane at about 20°C to about 30°C
25 for about 2 hours to about 4 hours.

The intermediate of Formula IV is treated with hydrochloric acid at a temperature of about 80°C to about 90°C. The reaction mixture is stirred for about 5 hours to about 10 hours, followed by the addition of aqueous sodium hydroxide solution at a temperature of about 30°C to about 35°C. The reaction mixture is stirred for about 20 hours to about 36
30 hours, cooled to a temperature of about 0°C to about 20°C, and then condensed with benzyl chloroformate to obtain the intermediate of Formula V. The condensation with

benzyl chloroformate is carried out in the presence of a solvent at a temperature of about 0°C to about 40°C for about 15 hours to about 30 hours. The solvent may be selected from the group comprising nitriles, aromatic hydrocarbons, chlorinated hydrocarbons, or mixtures thereof. Examples of nitriles include acetonitrile, propionitrile, butyronitrile, and
5 valeronitrile. Examples of aromatic hydrocarbons include toluene and xylene. Examples of chlorinated hydrocarbons include dichloromethane, dichloroethane, chlorobenzene, and chloroform. In a preferred embodiment of the present invention, toluene is used as the solvent.

The resolution of the intermediate of Formula V to obtain the intermediate of
10 Formula VI is carried out using a resolving agent and a solvent at a temperature of about 15°C to about 70°C. The resolving agent may be selected from (S)-mandelic acid, di-butyl tartrate, (S)-phenyl ethyl amine, (S)-1,2,3,4-tetrahydronaphthylamine, or mixtures thereof. The solvent may be selected from the group comprising alcohols, esters, or mixtures thereof. Examples of alcohols include methanol, ethanol, n-propanol,
15 isopropanol, n-butanol, and 2-methyl-1-pentanol. Examples of esters include ethyl acetate, propyl acetate, isopropyl acetate, and butyl acetate.

The resolution of the intermediate of Formula V is facilitated by adding a seed crystal of an adduct of (1S,3aR,6aS)-2-[(benzyloxy)carbonyl]octahydrocyclopenta[c]-pyrrole-1-carboxylic acid of Formula VI with (S)-1,2,3,4-tetrahydro naphthylamine.

20 In one embodiment of the present invention, resolution of the intermediate of Formula V is carried out in ethyl acetate.

In another embodiment of the present invention, resolution of the intermediate of Formula V is carried out in isopropyl acetate.

The condensation of the intermediate of Formula VI with the intermediate of
25 Formula VII 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.

The coupling agent may be selected from HATU, HBTU, HDBTU, HOTU, HOBT, EDC, EDC.HCl, BOP, PyBOP, DEPBT, Oxyma, COMU, TNTU, TPTDP, TPTU, TBTU, DIC, DCC, or mixtures thereof.

30 The base may be selected from the group comprising organic and 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 the group comprising 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 the intermediate of Formula II to obtain the intermediate of Formula VIII 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, and raney nickel.

The solvent may be selected from the group comprising 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, deprotection of the intermediate 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.

5 The condensation of the intermediate of Formula VIII with the intermediate of Formula IX to obtain the intermediate of Formula X 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.

The coupling agent may be selected from HATU, HBTU, HDBTU, HOTU, HOBT, EDC, EDC.HCl, BOP, PyBOP, DEPBT, Oxyma, COMU, TNTU, TPTDP, TPTU, TBTU, DIC, DCC, or mixtures thereof.

10 The base may be selected from the group comprising organic and 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.
15 Examples of inorganic bases include sodium bicarbonate, potassium bicarbonate, or mixtures thereof.

The solvent may be selected from the group comprising nitriles, chlorinated hydrocarbons, amides, dialkylsulfoxides, or mixtures thereof. Examples of nitriles include acetonitrile, propionitrile, butyronitrile, and valeronitrile. Examples of chlorinated
20 hydrocarbons include dichloromethane, dichloroethane, chlorobenzene, and chloroform. Examples of amides include dimethylformamide, dimethylacetamide, and N-methylformamide. Examples of dialkylsulfoxides include dimethylsulfoxide, diethylsulfoxide, and dibutylsulfoxide.

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

30 The oxidation of the intermediate of Formula X to obtain telaprevir of Formula I may be carried out in the presence of an oxidizing agent and a solvent at a temperature of about 0°C to about 20°C for about 1 hour to about 15 hours.

The oxidizing agent may be selected from Dess-Martin periodinane (DMP), oxalyl chloride, chromium trioxide, potassium permanganate, or mixtures thereof. A catalytic amount of TEMPO or TPAP may also be added to the reaction mixture for facilitating the oxidation reaction.

- 5 The solvent may be selected from the group comprising 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.
- 10 Examples of dialkylsulfoxides include dimethylsulfoxide, diethylsulfoxide, and dibutylsulfoxide.

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

- 15 The isolation of telaprevir and intermediates thereof 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 intermediates thereof is carried out by concentration.

- In the foregoing section, embodiments are described by way of examples to
- 20 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

- 25 Example 1: Preparation of ethyl 4-chloro-3-oxooctahydro-1H-cyclopenta[c]pyridine-4-carboxylate (Formula IV)

- In a round bottom flask flushed with nitrogen gas, ethyl-3-oxo-octahydro-1H-cyclopenta[c]pyridine-4-carboxylate (Formula III; 225 g) was dissolved in dichloromethane (300 mL). A solution of sulfuryl chloride (151.2 g in dichloromethane 375 mL) was added over about 30 minutes at about 25°C to about 30°C. The reaction
- 30 mixture was stirred for about 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%

Example 2: Preparation of (3aR,6aS)-2-[(benzyloxy)carbonyl]octahydrocyclopenta[c]pyrrole-1-carboxylic acid (Formula V)

In a round bottom flask, concentrated hydrochloric acid (294 mL) was added to ethyl 4-chloro-3-oxooctahydro-1H-cyclopenta[c]pyridine-4-carboxylate (Formula IV; 182 g). The reaction mixture was heated to between about 85°C and about 90°C for about 6 hours. Aqueous sodium hydroxide solution (191 g in 200 mL water) was added to the reaction mixture at about 30°C to about 35°C. The reaction mixture was stirred for about 24 hours and cooled to about 5°C to about 10°C. Benzyl chloroformate (50% w/w in toluene, 250 mL) was added to the reaction mixture over about 30 minutes. The reaction mixture was heated to about 20°C to about 25°C and stirred for about 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 L) and washed with dichloromethane (800 mL). The aqueous layer was acidified with concentrated hydrochloric acid and extracted with dichloromethane (1 L). The dichloromethane layer was concentrated under reduced pressure to obtain (3aR,6aS)-2-[(benzyloxy)carbonyl]octahydrocyclopenta[c]pyrrole-1-carboxylic acid as an oil.

Yield: 90%

Example 3: Resolution of (3aR,6aS)-2-[(benzyloxy)carbonyl]octahydrocyclopenta[c]pyrrole-1-carboxylic acid (Formula V)

Method A:

In a round bottom flask, (3aR,6aS)-2-[(benzyloxy)carbonyl]octahydrocyclopenta[c]pyrrole-1-carboxylic acid (Formula V; 66 g) was dissolved in ethyl acetate (330 mL). To this solution, (S)-phenyl ethyl amine (27.6 g) was added at a temperature of about 20°C to about 25°C and the reaction mixture was stirred for about 24 hours to about 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 (400 mL). The organic layer was concentrated to obtain an oil. The oil (26.5 g) was dissolved in isopropyl acetate (106 mL) and (S)-1,2,3,4-

tetrahydronaphthylamine (13.5 g) was added at about 18°C to about 25°C. The reaction mixture was stirred for about 24 hours. A solid adduct of (1S,3aR,6aS)-2-[(benzyloxy)carbonyl]octahydrocyclopenta[c]pyrrole-1-carboxylic acid (Formula VI) with (S)-1,2,3,4-tetrahydronaphthylamine was formed. The solid adduct was filtered and
5 washed with isopropyl acetate (26.5 mL). The adduct (1 g) was dissolved in isopropyl acetate (10 mL) and heated to a temperature of about 60°C to about 65°C to obtain a clear solution. The solution was cooled to about 55°C to about 60°C. A seed crystal of the solid adduct (0.1 g) was added to the reaction mixture followed by cooling to about 35°C for about 1 hour. The solution was stirred for about 2 hours, filtered, washed with
10 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 (1S,3aR,6aS)-2-[(benzyloxy)carbonyl]octahydrocyclopenta[c]pyrrole-1-carboxylic acid.

Yield: 4%

15 **Method B:**

In a round bottom flask, (3aR,6aS)-2-[(benzyloxy)carbonyl]octahydrocyclopenta[c]pyrrole-1-carboxylic acid (Formula V; 21.6 g) was dissolved in isopropyl acetate (108 mL). To this solution, (S)-1,2,3,4-tetrahydro naphthylamine (11 g) was added at a temperature of about 25°C to about 35°C. The reaction mixture was heated to about 55°C
20 to about 60°C. To the reaction mixture, a seed crystal of an adduct of (1S,3aR,6aS)-2-[(benzyloxy)carbonyl]octahydrocyclopenta[c]pyrrole-1-carboxylic acid (Formula VI) with (S)-1,2,3,4-tetrahydro naphthylamine (10.8 g) was added and the reaction mixture was cooled to about 35°C for about 1 hour. The reaction mixture was stirred for 2 hours, filtered, washed with isopropyl acetate (43 mL), and concentrated under reduced pressure
25 to obtain a solid material. The solid material was dissolved in dichloromethane (216 mL) and washed with 1N hydrochloric acid (216 mL). The organic layer was concentrated under reduced pressure to obtain (1S,3aR,6aS)-2-[(benzyloxy)carbonyl]octahydrocyclopenta[c]pyrrole-1-carboxylic acid.

Yield: 10.9%

Example 4: Preparation of benzyl (1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrole-2-(1H)carboxylate (Formula II)

Method A:

5 In a round bottom flask, (1S,3aR,6aS)-2[(benzyloxy)carbonyl]octahydrocyclopenta[c]pyrrole-1-carboxylic acid (Formula VI; 12.4 g) was dissolved in dichloromethane (96 mL) by stirring. To this solution, HOBT (6.6 g) and EDC.HCl (9.8 g) were added. The reaction mixture was cooled to about 0°C and (3S)-3-amino-N-cyclopropyl-2-hydroxyhexanamide (Formula VII; 8.0 g) and N,N-diisopropylethylamine (7.6 mL) were
10 added. The temperature of the reaction mixture was raised to about 30°C and the reaction mixture was stirred for about 16 hours. The reaction mixture was washed with 1N HCl (2 x 80 mL), 5% aqueous sodium bicarbonate solution (80 mL), and water (80 mL). The dichloromethane layer was concentrated under reduced pressure to obtain benzyl (1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrole-2-(1H)carboxylate.
15

Yield: 91.6%

Method B:

In a round bottom flask, (1S,3aR,6aS)-2[(benzyloxy)carbonyl]octahydrocyclopenta[c]pyrrole-1-carboxylic acid (Formula VI; 16 g) was dissolved in dichloromethane (200
20 mL). To this solution, TBTU (20 g) was added at a temperature of about 10°C. The reaction mixture was stirred for about 10 minutes. (3S)-3-Amino-N-cyclopropyl-2-hydroxyhexanamide (Formula VII; 10 g) and N,N-diisopropylethylamine (10 mL) were added at about 0°C. The temperature of the reaction mixture was raised to between about 20°C to about 25°C and stirred for about 4 hours. The reaction mixture was washed with
25 1N HCl (2 x 100 mL), 5% aqueous sodium bicarbonate solution (100 mL), and water (100 mL). The dichloromethane layer was concentrated under reduced pressure to obtain benzyl (1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrole-2-(1H)-carboxylate.

Yield: 79.8%

30

Example 5: Preparation of (1S,3aR,6aS)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide (Formula VIII)

In a round bottom flask, benzyl (1S,3aR,6aS)-1-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrole-2(1H)carboxylate (Formula II; 9.0 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 about 4 hours at a temperature of about 20°C to about 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: 95.8%

Example 6: Preparation of hydroxy telaprevir (Formula X)

Method A:

In a round bottom flask, N-{(2S)-2-cyclohexyl-2-[(pyrazin-2-yl-carbonyl)amino]acetyl}-3-methyl-L-valine (Formula IX; 1.16 g) was dissolved in dichloromethane (30 mL). To this solution, TBTU (1.2 g) was added at about 12°C. (1S,3aR,6aS)-N-(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide (Formula VIII; 1.0 g) and N,N-diisopropylethylamine (0.56 mL) were added at about 0°C to about 5°C. After the addition, the temperature of the reaction mixture was raised to about 23°C to about 25°C and the reaction mixture was stirred for about 7 hours. The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, the reaction mixture was washed with 1N HCl (2 x 20 mL), 5% aqueous sodium bicarbonate solution (20 mL), and water (20 mL). The dichloromethane layer was concentrated under reduced pressure to obtain hydroxy telaprevir.

Yield: 80.6%

Method B:

In a round bottom flask, N-{(2S)-2-cyclohexyl-2-[(pyrazin-2-yl-carbonyl)amino]acetyl}-3-methyl-L-valine (Formula IX; 1.45 g) was dissolved in dichloromethane (25 mL). To this solution, HOBt (0.5 g) and EDC.HCl (0.9 g) were added at a temperature of about 20°C to about 25°C. The solution was cooled to about

0°C to about 5°C followed by the addition of (1S,3aR,6aS)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide (Formula VIII; 1.25 g) and N,N-diisopropylethylamine (1.5 mL). After complete addition, the temperature of the reaction mixture was raised to about 20°C to about 25°C and the reaction mixture was stirred for about 8 hours. The progress of the reaction was monitored by thin layer chromatography. After completion of the reaction, the reaction mixture was washed with 1N HCl (30 mL), 5% aqueous sodium bicarbonate solution (30 mL), and water (30 mL). The dichloromethane layer was concentrated under reduced pressure to obtain hydroxy telaprevir.

Yield: 68.3%

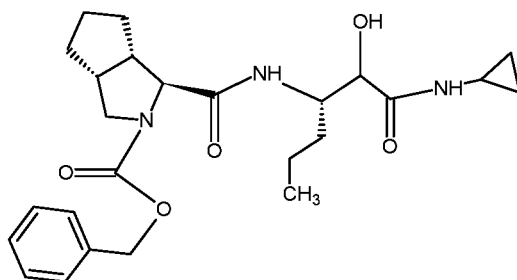
Example 7: Preparation of telaprevir (Formula I)

In a round bottom flask, hydroxy telaprevir (Formula X; 1.05 g) was dissolved in dichloromethane (25 mL). To the resulting solution, Dess-Martin periodinane (1.28 g) was added at about 5°C. The reaction mixture was stirred at about 0°C to about 5°C for about 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 and washed with sodium bicarbonate solution (20 mL). The dichloromethane layer was concentrated under reduced pressure to obtain telaprevir.

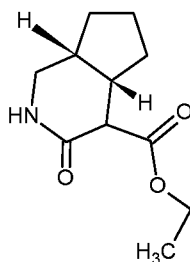
Yield: 66%

We claim:

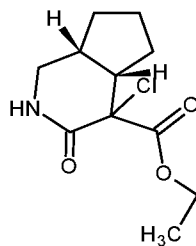
- 1 1. A process for the preparation of benzyl (1S,3aR,6aS)-1-{[(3S)-1-(
 2 (cyclopropylamino)-2-hydroxy-1-oxohexan-3-
 3 yl]carbamoyl}hexahydrocyclopenta[c]pyrrole-2-(1H)carboxylate of Formula II

**Formula II**

- 4 comprising the steps of:
 5 a) chlorinating the ethyl 3-oxo-octahydro-1H-cyclopenta[c]pyridine-4-
 6 carboxylate intermediate of Formula III

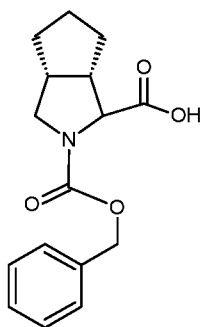
**Formula III**

- 7 to obtain the ethyl 4-chloro-3-oxooctahydro-1H-cyclopenta[c]pyridine-4-
 8 carboxylate intermediate of Formula IV;

**Formula IV**

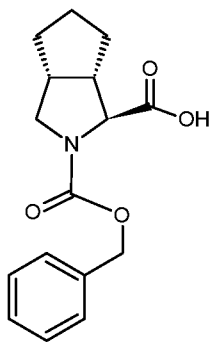
9

- 10 b) treating the intermediate of Formula IV with hydrochloric acid and sodium
11 hydroxide followed by condensation with benzyl chloroformate to obtain the
12 (3aR,6aS)-2-[(benzyloxy)carbonyl]octahydrocyclopenta[c]pyrrole-1-
13 carboxylic acid intermediate of Formula V;



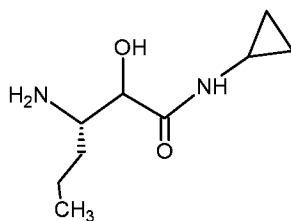
Formula V

- 14 c) resolving the intermediate of Formula V to obtain the (1S,3aR,6aS)-2-
15 [(benzyloxy)carbonyl]octahydrocyclopenta[c]pyrrole-1-carboxylic acid
16 intermediate of Formula VI; and



Formula VI

- 17 d) condensing the intermediate of Formula VI with the (3S)-3-amino-N-
18 cyclopropyl-2-hydroxyhexanamide intermediate of Formula VII



Formula VII

19 to obtain the benzyl (1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-
20 1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrole-2-
21 (1H)carboxylate of Formula II.

1 2. The process according to claim 1, wherein step a) is carried out in the presence of a
2 chlorinating agent selected from sulfonyl chloride or N-chlorosuccinimide.

1 3. The process according to claims 1 or 2, wherein step a) is carried out in a solvent
2 selected from the group comprising chlorinated hydrocarbons, aromatic hydrocarbons, or
3 mixtures thereof.

1 4. The process according to claim 1, wherein the condensation of the intermediate of
2 Formula IV with benzylchloroformate in step b) is carried out in the presence of toluene.

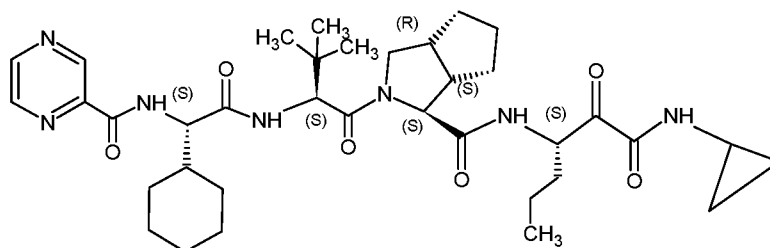
1 5. The process according to claim 1, wherein the resolution of the (3aR,6aS)-2-
2 [(benzyloxy)carbonyl]octahydrocyclopenta[c]pyrrole-1-carboxylic acid intermediate of
3 Formula V in step c) is carried out in the presence of a resolving agent selected from (S)-
4 mandelic acid, di-butyl tartrate, (S)-phenyl ethyl amine, (S)-1,2,3,4-tetrahydronaphthyl
5 amine, or mixtures thereof.

1 6. The process according to claim 1, wherein the resolution of the (3aR,6aS)-2-
2 [(benzyloxy)carbonyl]octahydrocyclopenta[c]pyrrole-1-carboxylic acid intermediate of
3 Formula V in step c) is carried out in the presence of a solvent selected from the group
4 consisting of ethyl acetate and isopropyl acetate.

1 7. The process according to claim 1, wherein the condensation of the intermediate of
2 Formula VI with the intermediate of Formula VII in step d) is carried out in the presence
3 of a coupling agent selected from HOBt, HATU, HBTU, TBTU, EDC, EDC.HCl, or
4 mixtures thereof.

1 8. The process according to claim 1, wherein the condensation of the intermediate of
2 Formula VI with the intermediate of Formula VII in step b) is carried out in the presence
3 of a base selected from the group consisting of N,N-diisopropylethylamine, 4-
4 dimethylaminopyridine, triethyl amine, N,N-2-trimethyl-2-propanamine, or mixtures
5 thereof.

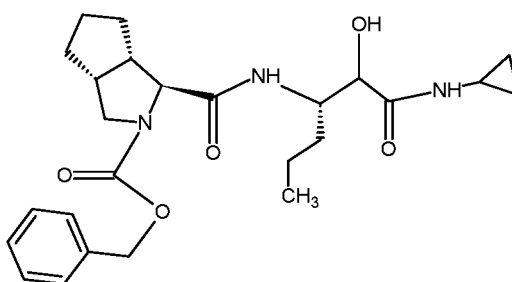
- 1 9. A process for the preparation of telaprevir of Formula I



Formula I

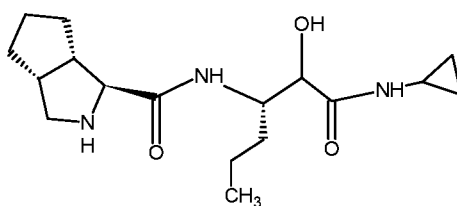
- 2 comprising the steps of:

- 3 a) deprotecting the benzyl (1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-
4 hydroxy-1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrole-2-
5 (1H)carboxylate intermediate of Formula II



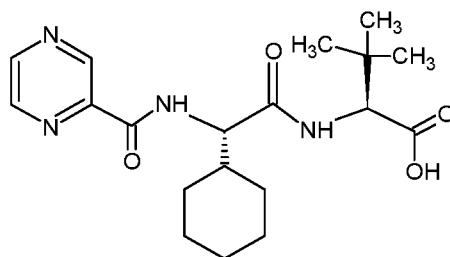
Formula II

- 6 to obtain (1S,3aR,6aS)-N-[(3S)-1-(cyclopropylamino)-2-hydroxy-1-
7 oxohexan-3-yl]octahydrocyclopenta[c]pyrrole-1-carboxamide intermediate
8 of Formula VIII;

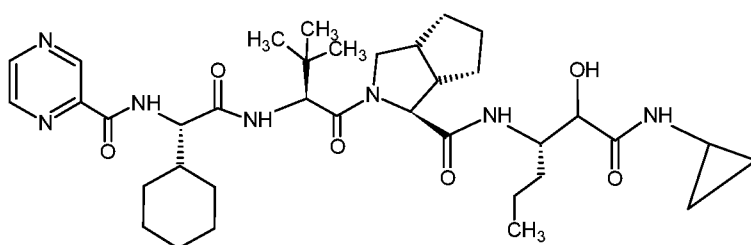


Formula VIII

- 9 b) condensing the intermediate of Formula VIII with the N-{(2S)-2-cyclohexyl-
10 2-[(pyrazin-2-yl-carbonyl)amino]acetyl}-3-methyl-L-valine intermediate of
11 Formula IX

**Formula IX**

12 to obtain the hydroxy telaprevir intermediate of Formula X; and

**Formula X**

13 c) oxidizing the hydroxy telaprevir intermediate of Formula X to obtain
14 telaprevir of Formula I.

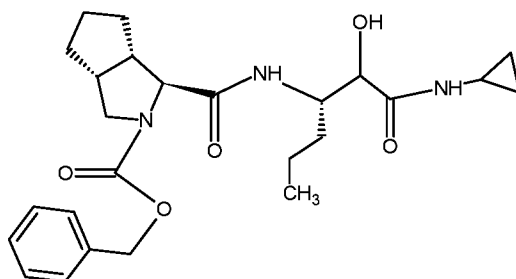
1 10. The process according to claim 9, wherein the deprotection of the intermediate of
2 Formula II in step a) is carried out using a metal catalyst and hydrogen gas.

1 11. The process according to claim 9, wherein the condensation of the intermediate of
2 Formula VIII with the intermediate of Formula IX is carried out in the presence of a
3 coupling agent selected from HOBt, HATU, HBTU, TBTU, EDC, EDC.HCl, or mixtures
4 thereof.

1 12. The process according to claim 9, wherein the condensation of the intermediate of
2 Formula VIII with the intermediate of Formula IX is carried out using a base selected from
3 N,N-diisopropylethylamine, 4-dimethylaminopyridine, triethyl amine, N,N-2-trimethyl-2-
4 propanamine, or mixtures thereof.

1 13. The process according to claim 9, wherein the oxidation of the hydroxy telaprevir
2 of Formula X is carried out in the presence of Dess-Martin periodinane.

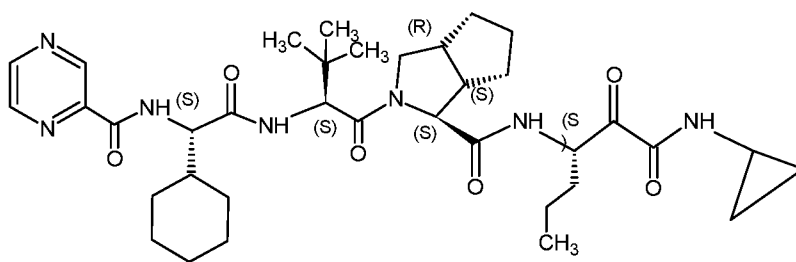
- 1 14. The use of the benzyl (1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-
 2 oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrole-2-(1H)carboxylate of
 3 Formula II



Formula II

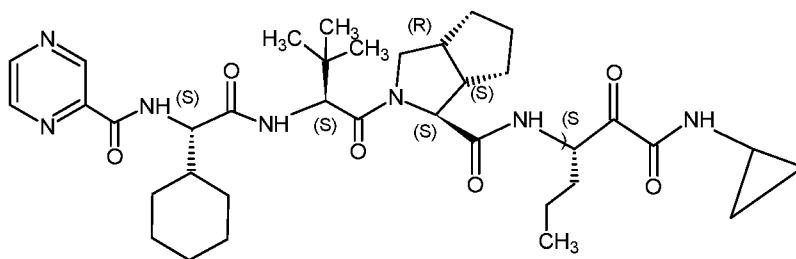
- 4 for the preparation of telaprevir of Formula I.

5



Formula I

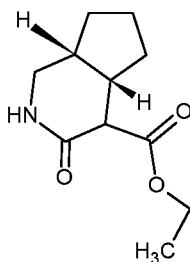
- 1 15. A process for the preparation of telaprevir of Formula I



Formula I

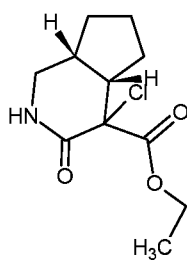
- 2 comprising the steps of:

- 1 a) chlorinating the ethyl 3-oxo-octahydro-1*H*-cyclopenta[*c*]pyridine-4-
2 carboxylate intermediate of Formula III



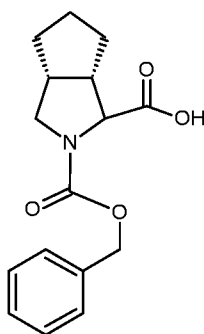
Formula III

- 3 to obtain the ethyl 4-chloro-3-oxooctahydro-1*H*-cyclopenta[*c*]pyridine-4-
4 carboxylate intermediate of Formula IV;



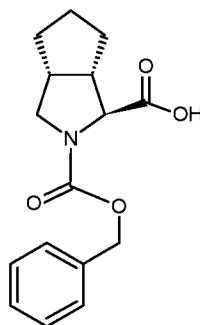
Formula IV

- 5 b) treating the intermediate of Formula IV with hydrochloric acid and sodium
6 hydroxide followed by condensation with benzyl chloroformate to obtain the
7 (3*aR*,6*aS*)-2-[(benzyloxy)carbonyl]octahydrocyclopenta[*c*]pyrrole-1-
8 carboxylic acid intermediate of Formula V;



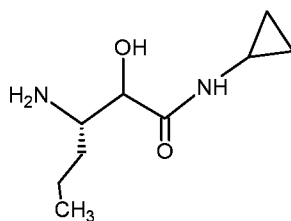
Formula V

- 9 c) resolving the intermediate of Formula V to obtain (1S,3aR,6aS)-2-
 10 [(benzyloxy)carbonyl]octahydrocyclopenta[c]pyrrole-1-carboxylic acid
 11 intermediate of Formula VI;



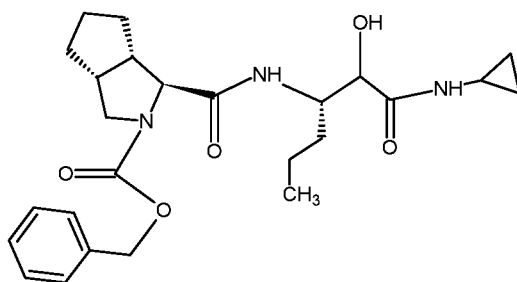
Formula VI

- 12 d) condensing the intermediate of Formula VI with the (3S)-3-amino-N-
 13 cyclopropyl-2-hydroxyhexanamide intermediate of Formula VII



Formula VII

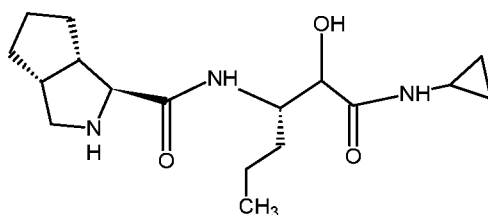
- 14 to obtain the benzyl (1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-
 15 1-oxohexan-3-yl]carbamoyl}hexahydrocyclopenta[c]pyrrole-2-
 16 (1H)carboxylate intermediate of Formula II;



Formula II

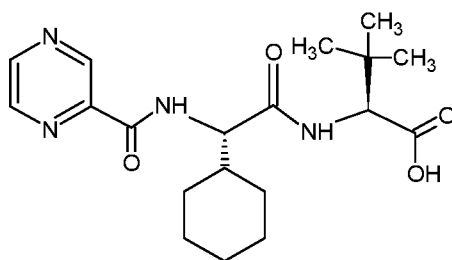
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- 18 e) deprotecting the intermediate of Formula II to obtain the (1*S*,3*aR*,6*aS*)-*N*-
 19 [(3*S*)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-
 20 yl]octahydrocyclopenta[*c*]pyrrole-1-carboxamide intermediate of Formula
 21 VIII;



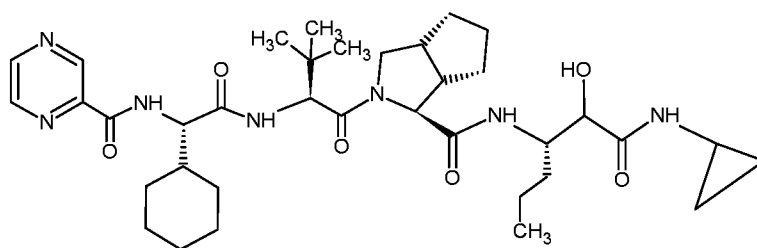
Formula VIII

- 22 f) condensing the intermediate of Formula VIII with the *N*-{(2*S*)-2-cyclohexyl-
 23 2-[(pyrazin-2-yl-carbonyl)amino]acetyl}-3-methyl-L-valine intermediate of
 24 Formula IX



Formula IX

- 25 to obtain the hydroxy telaprevir intermediate of Formula X; and



Formula X

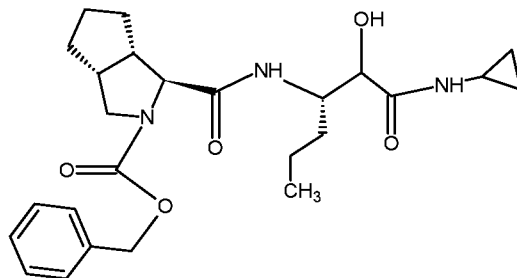
- 26 g) oxidizing the hydroxy telaprevir intermediate of Formula X to obtain
 27 telaprevir of Formula I.

- 1 16. The process according to claim 15, wherein the chlorination of the intermediate of
2 Formula III in step a) is carried out in the presence of a chlorinating agent selected from
3 the group consisting of sulfonyl chloride and N-chlorosuccinimide.
- 1 17. The process according to claim 15, wherein the condensation of the intermediate of
2 Formula IV with benzylchloroformate in step b) is carried out in the presence of toluene.
- 1 18. The process according to claim 15, wherein the resolution of the intermediate of
2 Formula V in step c) is carried out in the presence of a resolving agent selected from the
3 group consisting of (S)-mandelic acid, di-butyl tartrate, (S)-phenyl ethyl amine, (S)-
4 1,2,3,4-tetrahydronaphthyl amine, or mixtures thereof.
- 1 19. The process according to claim 15, wherein the resolution of the intermediate of
2 Formula V in step c) is carried out in the presence of a solvent selected from ethyl acetate
3 and isopropyl acetate.
- 1 20. The process according to claim 15, wherein the condensation of the intermediate of
2 Formula VI with the intermediate of Formula VII in step d) is carried out in the presence
3 of a coupling agent selected from the group consisting of HOBt, HATU, HBTU, TBTU,
4 EDC, EDC.HCl, or mixtures thereof.
- 1 21. The process according to claim 15, wherein the condensation of the intermediate of
2 Formula VI with the intermediate of Formula VII in step d) is carried out in the presence
3 of a base selected from the group consisting of N,N-diisopropylethylamine, 4-
4 dimethylaminopyridine, triethyl amine, N,N-2-trimethyl-2-propanamine, or mixtures
5 thereof.
- 1 22. The process according to claim 15, wherein the deprotection of the intermediate of
2 Formula II in step e) is carried out using a metal catalyst and hydrogen gas.
- 1 23. The process according to claim 15, wherein the condensation of the intermediate of
2 Formula VIII with the intermediate of Formula IX in step f) is carried out in the presence
3 of a coupling agent selected from the group consisting of HOBt, HATU, HBTU, TBTU,
4 EDC, EDC.HCl, or mixtures thereof.
- 1 24. The process according to claim 15, wherein the condensation of the intermediate of
2 Formula VIII with the intermediate of Formula IX in step f) is carried out using a base
3 selected from N,N-diisopropylethylamine, 4-dimethylaminopyridine, triethyl amine, N,N-

4 2-trimethyl-2-propanamine, or mixtures thereof.

1 25. The process according to claim 15, wherein the oxidation of the hydroxy telaprevir
2 of Formula X in step g) is carried out in the presence of Dess-Martin periodinane.

1 26. Benzyl (1S,3aR,6aS)-1-{[(3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-
2 yl]carbamoyl}hexahydrocyclopenta[c]pyrrole-2-(1H)carboxylate of Formula II.



Formula II

INTERNATIONAL SEARCH REPORT

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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

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Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents :

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"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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Date of the actual completion of the international search

11 August 2014

Date of mailing of the international search report

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Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040,
 Fax: (+31-70) 340-3016

Authorized officer

Brandstetter, T

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International application No

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