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

(57) **Abstract:** The present application relates to novel processes for preparation of (1S,3a R,6a S)-octahydrocyclopenta[c]pyrrole-1-carboxylic acid and its derivatives; and their use in preparation of Telaprevir.

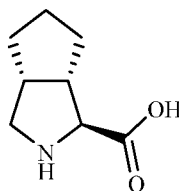


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PROCESS FOR PREPARATION OF INTERMEDIATES OF TELAPREVIR

FIELD OF THE INVENTION

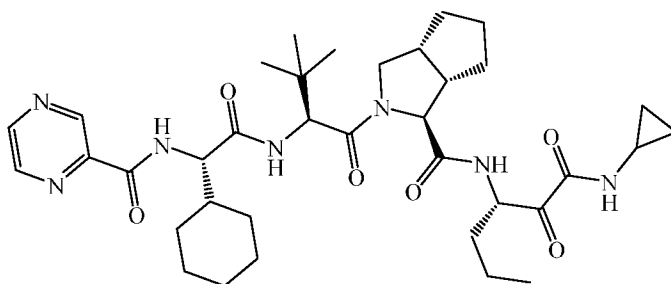
The present application relates to novel processes for preparation of (1S,3aR,6aS)-octahydrocyclopenta[c]pyrrole-1-carboxylic acid of formula (VIIb) and its derivatives; and their use in preparation of Telaprevir.



Formula VIIb

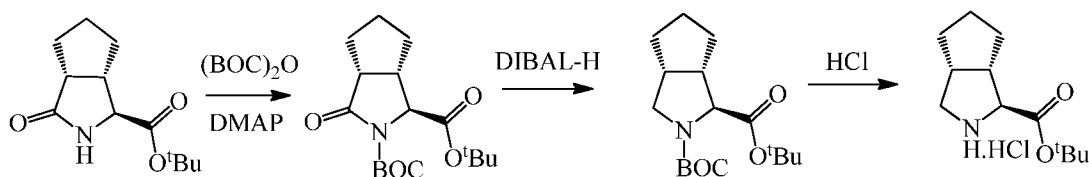
BACKGROUND OF THE INVENTION

(1S,3aR,6aS)-octahydrocyclopenta[c]pyrrole-1-carboxylic acid of formula (VIIb) and its derivatives are important intermediates for chemical synthesis of hepatitis C virus (HCV) protease inhibitor telaprevir of formula I.



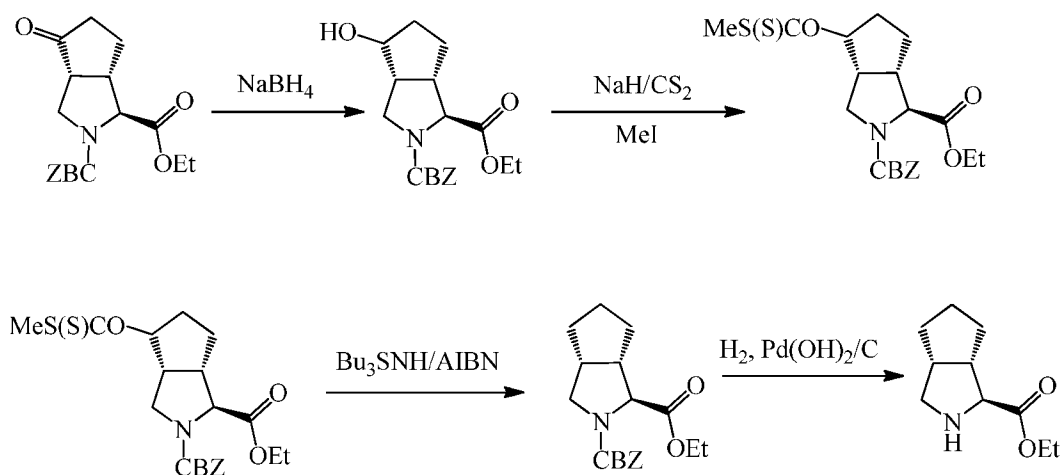
Formula I

International patent application publication WO 2002018369 (WO '369) discloses a process for preparation of (1S,3aR,6aS)-tert-butyloctahydrocyclopenta[c]pyrrole-1-carboxylate (tert-butyl ester of compound of formula VIIb), in which (1S,3aR,6aS)-tert-butyl 3-oxooctahydrocyclopenta[c]pyrrole-1-carboxylate is protected with tert-butyloxycarbonyl (boc) and the boc protected compound is reduced with DIBAL-H and subsequent deprotection yielded (1S,3aR,6aS)-tert-butyl-3-oxooctahydrocyclopenta[c]pyrrole-1-carboxylate hydrochloride. The process disclosed in WO '369 is schematically represented in scheme-I.



Scheme-I

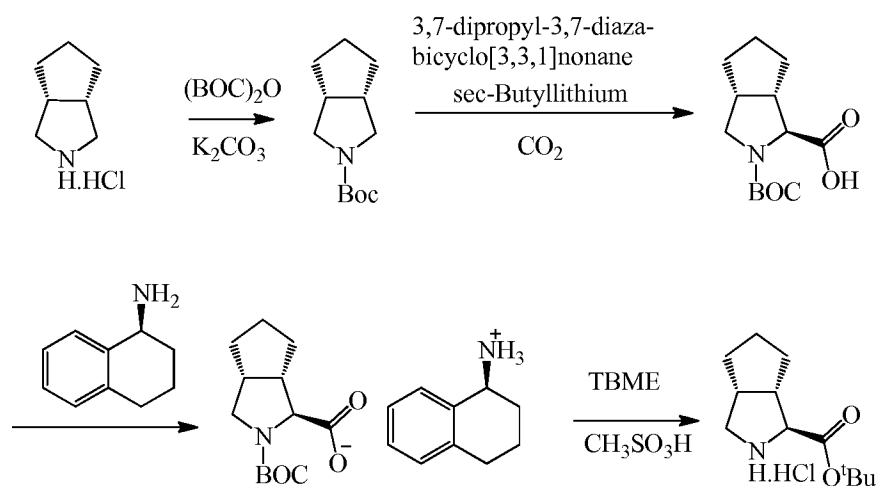
WO '369 also discloses another process for preparation of (1S,3aR,6aS)-ethyloctahydrocyclopenta[c]pyrrole-1-carboxylate (ethyl ester of compound of formula VIIb), in which (1S,3aR,6aS)-2-benzyl 1-ethyl-4-oxohexahydrocyclopenta[c]pyrrole-1,2(1H)-dicarboxylate is reduced using sodiumborohydride to form (1S,3aR,6aS)-2-benzyl-1-ethyl-4-hydroxyhexahydrocyclopenta[c]pyrrole-1,2(1H)-dicarboxylate. The hydroxy compound is treated with sodium hydride in presence of carbon disulfide and methyl iodide to form (1S,3aR,4S,6aS)-2-benzyl-1-ethyl-4-(((methylthio)carbonothioyl)oxy)hexahydro cyclopenta[c]pyrrole-1,2(1H)-dicarboxylate and subsequent reduction and deprotection yielded (1S,3aR,6aS)-ethyloctahydrocyclopenta[c]pyrrole-1-carboxylate. The process is schematically represented in scheme-II.



Scheme-II

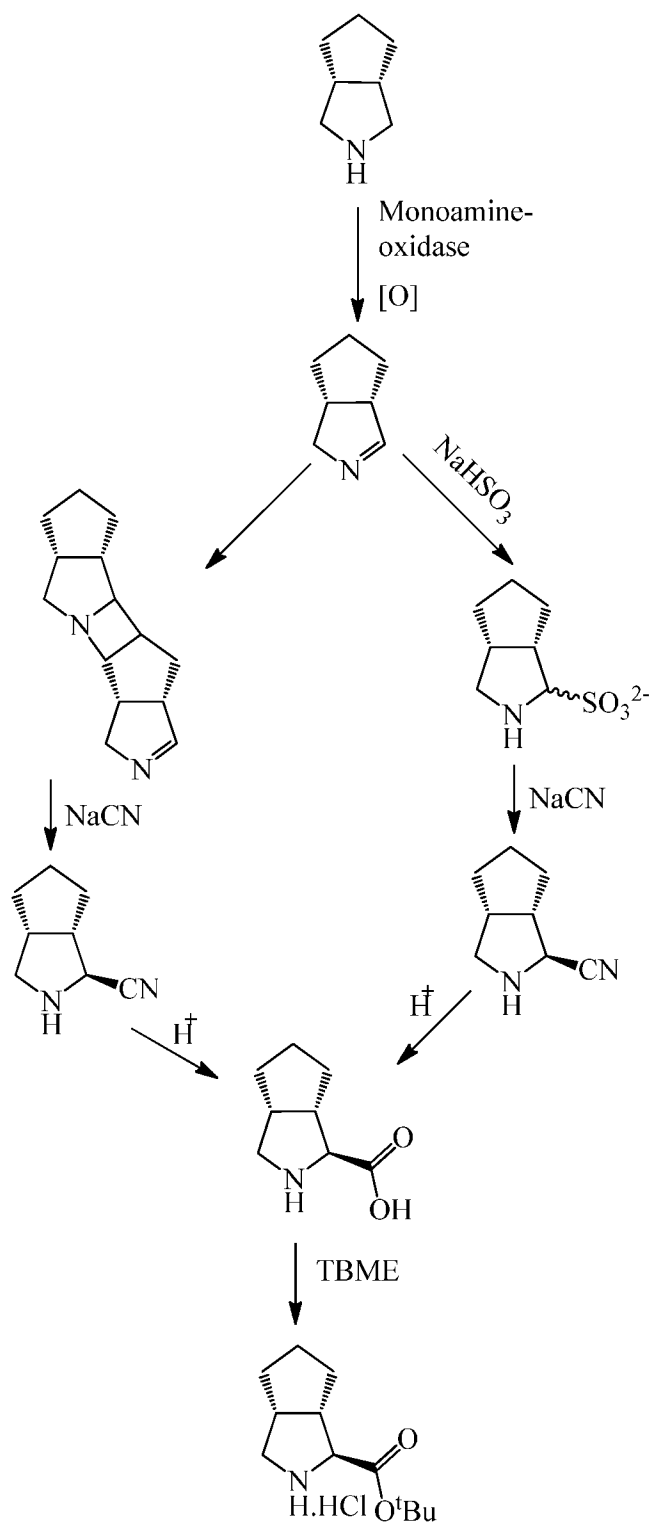
International patent application publication WO 2007022459 (WO '459) discloses a process for preparation of (1S,3aR,6aS)-tert-butyloctahydrocyclopenta[c]pyrrole-1-carboxylate, in which (3aR,6aS)-tert-butyl hexahydrocyclopenta[c]pyrrole-2(1H)-carboxylate is treated with carbon dioxide in the presence of 3,7-dipropyl-3,7-diazabicyclo[3,3,1]nonane and sec-butyllithium to form enriched (1S,3aR,6aS)-

octahydrocyclopenta[c]pyrrole-1-carboxylic acid. Subsequent resolution of the acid using a chiral base such as (S)-1,2,3,4-tetrahydronaphthalen-1-amine, and tert-butyl ester formation yielded (1S,3aR,6aS)-tert-butyloctahydrocyclopenta[c]pyrrole-1-carboxylate. The process disclosed in WO '459 is schematically represented in scheme-III.



Scheme-III

International patent application publication WO 2010008828 (WO '828) discloses a process for preparation of (1S,3aR,6aS)-tert-butyloctahydrocyclopenta[c]pyrrole-1-carboxylate, in which (3aR,6aS)-octahydrocyclopenta[c]pyrrole is treated with monoamine oxidase enzyme to yield (3aS,6aR)-1,3a,4,5,6,6a-hexahydrocyclopenta[c]pyrrole. The (3aS,6aR)-1,3a,4,5,6,6a-hexahydrocyclopenta[c]pyrrole exists in the form a dimer or a trimer and is treated with sodium cyanide to form (1S,3aR,6aS)-octahydrocyclopenta[c]pyrrole-1-carbonitrile. Subsequent hydrolysis of the nitrile and ester formation using tert-butylmethyl ether yielded (1S,3aR,6aS)-tert-butyloctahydrocyclopenta[c]pyrrole-1-carboxylate. The process disclosed in WO '828 is schematically represented in scheme-IV.



Scheme-IV

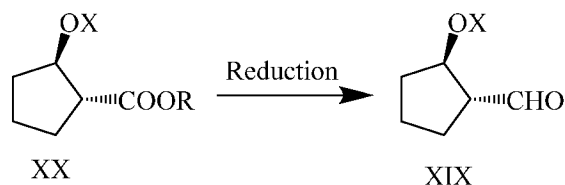
The prior-art processes herein described above suffer from drawbacks such as low yield and purity. Hence there is a continuing need to develop simplified and improved processes for preparing the compound of formula VIIb which processes are suitable for commercial manufacturing in high purity and yield.

SUMMARY OF THE INVENTION

The object of the present application is to provide novel and industrially advantageous processes for preparation of the (1S,3aR,6aS)-octahydrocyclopenta[c]pyrrole-1-carboxylic acid of formula (VIIb).

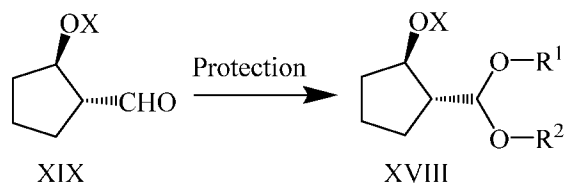
In an aspect, the application provides a process for preparation of (1S,3aR,6aS)-octahydrocyclopenta[c]pyrrole-1-carboxylic acid of formula (VIIb), comprising:

(a) reducing a compound of formula XX with a suitable reducing agent to form a compound of formula XIX



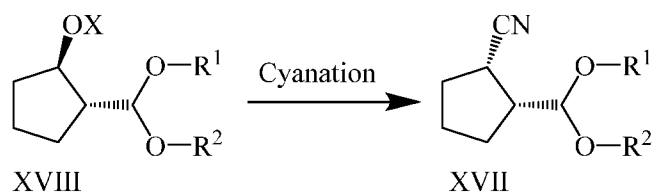
wherein X is hydrogen or a leaving group such as mesyl, tosyl, acetyl or trifluoroacetyl; R is hydrogen or C₁-C₄ alkyl or C₅-C₁₂ aralkyl,

(b) protecting the aldehyde functionality of the compound of formula XIX to form a compound of formula XVIII.

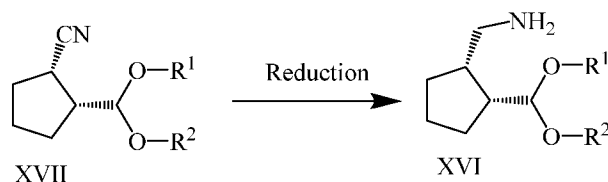


wherein R¹ and R² are C₁-C₅ alkyl or both form a cyclic ring,

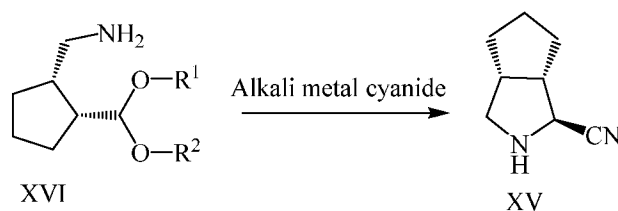
(c) cyanating the compound of formula XVIII with a suitable cyanating agent to form compound of formula XVII



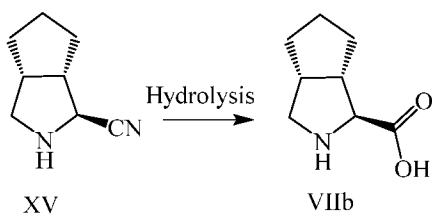
(d) reducing the compound of formula XVII in the presence of a suitable catalyst to obtain compound of formula XVI,



(e) treating the compound of formula XVI with an acid and an alkali metal cyanide to form compound of formula XV, and

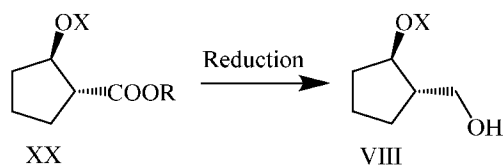


(f) hydrolyzing the compound of formula XV to form compound of formula VIIb or its acid addition salt



In another aspect, the application provides a process for preparation of a compound of formula VIIb, comprising:

(a) reducing the compound of formula XX with a suitable reducing agent to form a compound of formula VIII



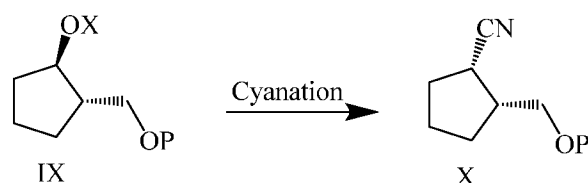
wherein X is hydrogen or a leaving group such as mesyl, tosyl, acetyl or trifluoroacetyl;
R is hydrogen or C₁-C₄ alkyl or C₅-C₁₂ aralkyl,

(b) protecting the primary hydroxyl group of compound of formula VIII to get compound of formula IX,

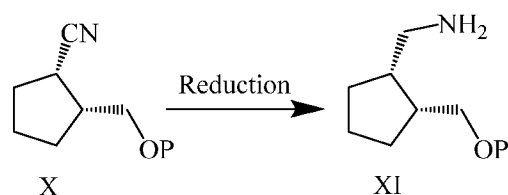


wherein P is a protecting group,

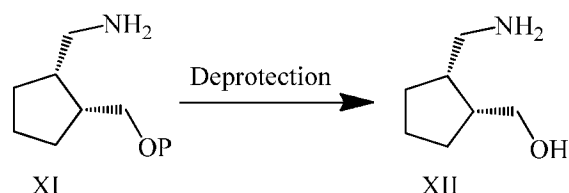
(c) cyanating the compound of formula IX with a suitable cyanating agent to form compound of formula X



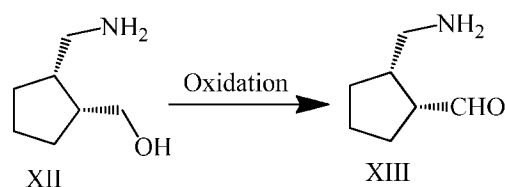
(d) reducing the compound of formula X in the presence of a suitable catalyst to obtain compound of formula XI,



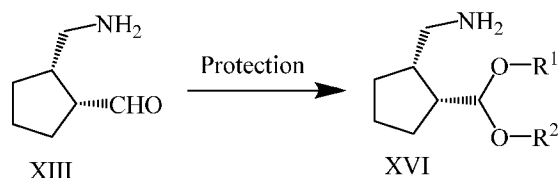
(e) optionally, deprotecting the compound of formula XI to form compound of formula XII,



(f) oxidizing the compound of formula XII to form compound of formula XIII,

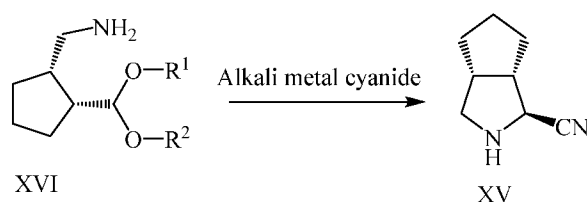


(g) optionally, protecting the aldehyde of the compound of formula XIII to form a compound of formula XVI.

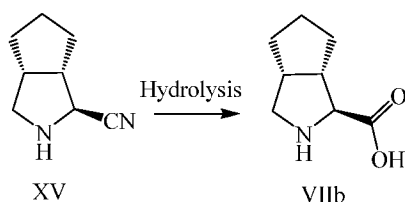


R^1 and R^2 are C_1 - C_5 alkyl or both form a cyclic ring,

(h) treating the compound of formula XIII or the compound of formula XVI with an alkali metal cyanide to form a compound of formula XV, and

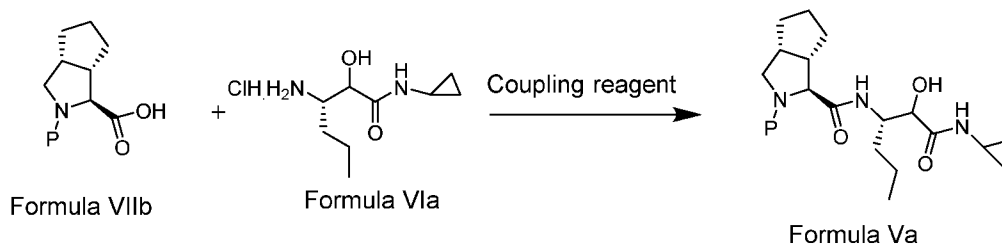


(i) hydrolyzing the compound of formula XV to form compound of formula VIIb or its acid addition salt



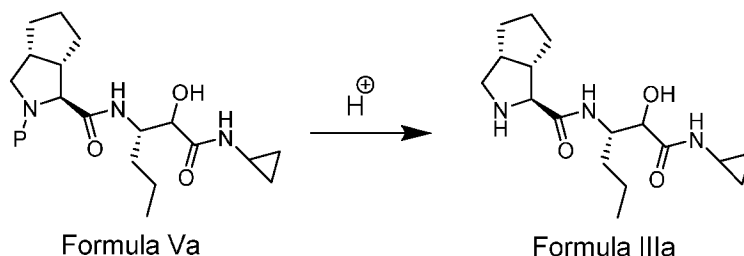
In another aspect, the present application provides use of compound of formula VIIb prepared by the processes disclosed in the present application in the preparation of telaprevir comprising,

(a) reacting compound of formula VIIb or a protected form of formula VIIb with a compound of formula VIa or its salt in the presence of a suitable coupling reagent to form compound of formula Va or its salt,

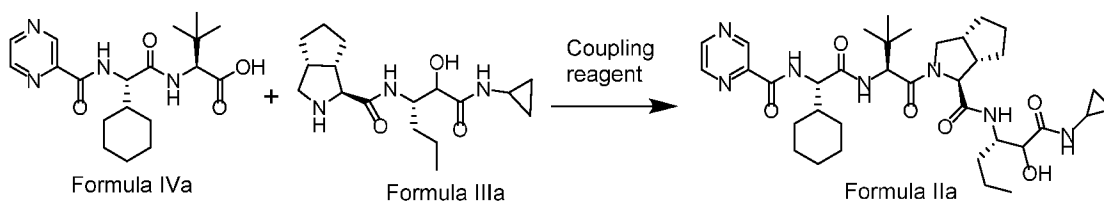


wherein P is an amine protecting group;

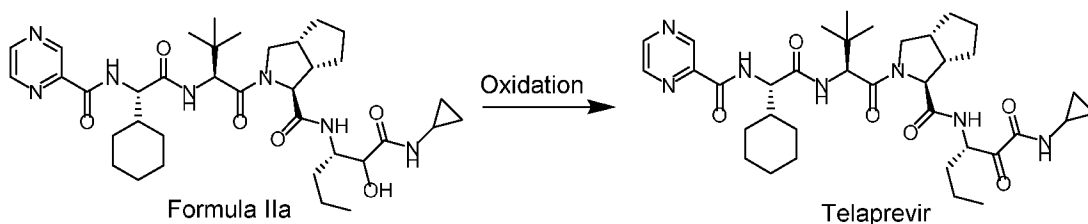
(b) deprotecting the compound of formula Va or its salt using an acid to form compound of formula IIIa or a salt thereof.



(c) reacting a compound of formula IIIa or a salt thereof with a compound of formula IVa or a salt thereof in the presence of a suitable coupling reagent to form a compound of formula IIa,



(d) oxidizing the compound of Formula IIa using a suitable oxidizing reagent to form telaprevir.



In another aspect, the application provides new intermediates and starting materials in the process according to the present invention.

In another aspect, the present application provides Telaprevir having purity greater than about 99.5 area % as measured by HPLC.

In another aspect, the present application provides Telaprevir having purity greater than about 99.8 area % as measured by HPLC.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is an illustrative example of an XRPD pattern of crystalline telaprevir, prepared in Example 24.

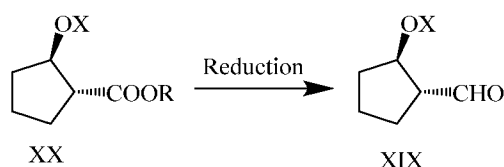
Fig. 2 is an illustrative example of an XRPD pattern of crystalline compound of formula IVa, prepared in Example 8.

DETAILED DESCRIPTION OF THE INVENTION

The present application provides novel processes for preparation of (1S,3aR,6aS)-octahydrocyclopenta[c]pyrrole-1-carboxylic acid of formula (VIIb) and its use in preparation of telaprevir.

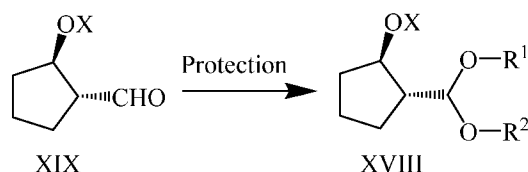
In one aspect, the application provides a process for preparation of (1S,3aR,6aS)-octahydrocyclopenta[c]pyrrole-1-carboxylic acid of formula (VIIb), comprising:

(a) reducing a compound of formula XX with a suitable reducing agent to form a compound of formula XIX



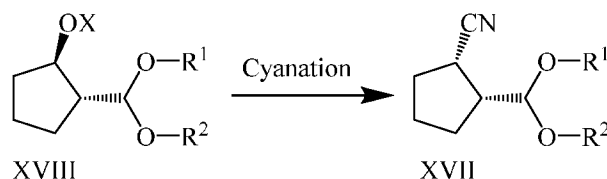
wherein X is hydrogen or a leaving group such as mesyl, tosyl, acetyl or trifluoroacetyl; R is hydrogen or C₁-C₄ alkyl or C₅-C₁₂ aralkyl,

(b) protecting the aldehyde functionality of the compound of formula XIX to form a compound of formula XVIII.

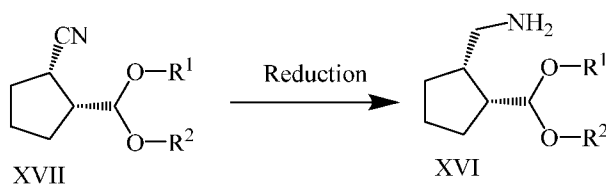


wherein R¹ and R² are C₁-C₅ alkyl or both form a cyclic ring,

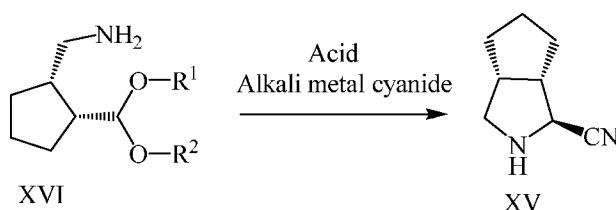
(c) cyanating the compound of formula XVIII with a suitable cyanating agent to form compound of formula XVII



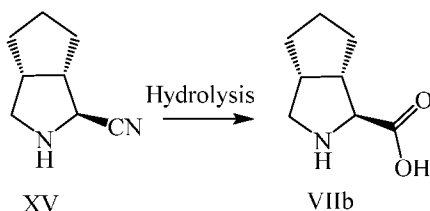
(d) reducing the compound of formula XVII in the presence of a suitable catalyst to obtain compound of formula XVI,



(e) treating the compound of formula XVI with an alkali metal cyanide to form compound of formula XV, and



(f) hydrolyzing the compound of formula XV to form compound of formula VIIb or its acid addition salt



The step (a) of the process involves reduction of compound of formula XX with a suitable reducing agent to form a compound of formula XIX. The reduction is carried out using a suitable reducing agent in presence of a suitable solvent.

Compound of Formula XX may be obtained by any process including processes described in the art, or by a process described in this application.

The suitable reducing agent is selected from the group comprising of diisobutyl aluminum hydride (DIBAL-H), sodium bis (2-methoxyethoxy)aluminum hydride (Red-Al) triisobutyl aluminum (TIBAL), potassium diisobutyl-tert-butoxyaluminium hydride (PDBBA), lithium diisobutyl-tert-butoxyaluminium hydride (LDBBA), sodium diisobutyl-tert-butoxyaluminium hydride (SDBBA), diisobutyl aluminum butylated oxytoulene (DIBAL-BOT), sodium aluminum hydride (SAH), lithium aluminum hydride (LAH), bis(4-methyl-1-piperazinyl) aluminum hydride (BMAH). In one embodiment the reducing agent is diisobutyl aluminum hydride (DIBAL-H). In another embodiment the reducing agent is sodium-bis-(2-methoxyethoxy)aluminum hydride (Red-Al).

The reducing agent may be used in the form of a solution in a suitable solvent. The quantity of reducing agent may range from about 1 to about 4 moles. In one embodiment the quantity of the reducing agent is about 1 to about 2 moles, per mole of compound of Formula XX.

Suitable solvents that can be used for the reaction include, but are not limited to: ethers such as diethyl ether, methyl tert-butyl ether, tetrahydrofuran, toluene, 1,4-Dioxane, 2-Methyltetrahydrofuran and the like; hydrocarbons such as toluene, xylene, n-hexane, n-heptane, cyclohexane, and the like; and any mixtures thereof. In one embodiment the solvent used in step (a) is ether such as diethyl ether, methyl tert-butyl ether, tetrahydrofuran and the like. In another embodiment the solvent is hydrocarbons such as toluene, xylene, n-hexane, n-heptane, cyclohexane, and the like.

The process of step (a) is suitably carried out at temperatures ranging from about -100°C to about 50°C. In one embodiment the reduction is carried out at temperatures ranging from about -80°C to about 30°C.

After completion of the reaction the reaction mixture is quenched with aqueous ammonium chloride or Rochelle's salt, and the salt by-product is removed by filtration. The organic layer containing the product may be distilled completely to produce a residue, or it may be used directly in the next reaction step.

The step (b) of the process involves protection of the aldehyde of the compound of formula XIX with a suitable protecting group in presence of a suitable solvent to form a compound of formula XVIII.

The suitable protecting group is selected from the group comprising of trimethylorthoformate, triethylorthoformate, ethylene glycol, propylene glycol, acetic anhydride and propionic anhydride.

The quantity of the protecting group may range from about 1 to about 20 moles. In one embodiment the quantity of the reducing agent is about 1 to about 10 moles, per mole of compound of Formula XIX.

The protection may be carried out in the presence of an acid and a suitable solvent. The solvent that can be used for the reaction include, but are not limited to: alcohols such as methanol, ethanol, isopropanol (IPA), n-butanol, tert-butanol, and the like; ethers such as diethyl ether, methyl tert-butyl ether, tetrahydrofuran and the like;

halogenated hydrocarbons such as dichloromethane (DCM), ethylene dichloride, chloroform, and the like; hydrocarbons such as toluene, xylene, n-hexane, n-heptane, cyclohexane, and the like; esters such as ethyl acetate, propyl acetate, and the like; and any mixtures thereof. In one embodiment the solvent used in step (b) is an alcohol such as methanol, ethanol, isopropanol (IPA), n-butanol, tert-butanol, and the like. In another embodiment the solvent used in step (b) is hydrocarbons such as toluene, xylene, n-hexane, n-heptane, cyclohexane, and the like;

The process of step (b) is suitably carried out at temperatures ranging from about -30°C to about 80°C. In one embodiment the reduction is carried out at temperatures ranging from about 0°C to about 50°C.

After completion of the reaction, the reaction mixture is diluted with aq. Base such as sodium carbonate or sodium bicarbonate, and the solution is extracted with a suitable water immiscible solvent. The organic layer containing the product may be distilled completely to produce a residue, or it may be used directly in the next reaction step.

The step (c) of the process involves cyanation of the protected aldehyde of the compound of formula XVIII with a suitable cyanating agent in a suitable solvent.

The suitable cyanating agent is selected from the group comprising of Copper cyanide, Sodium cyanide, Potassium cyanide, Zinc cyanide and potassium hexacyanoferrate ($K_4Fe(CN)_6$). In one embodiment the cyanating agent is Sodium cyanide.

The quantity of the cyanating agent may range from about 1 to about 5 moles. In one embodiment the quantity of the cyanating agent is about 1 to about 3 moles per mole of compound of Formula XVIII.

The suitable solvent that can be used for cyanation include, but are not limited to: polar aprotic solvents such as Dimethylformamide, Dimethylsulfoxide, Dimethyl acetamide, acetonitrile and the like; ethers such as diethyl ether, methyl tert-butyl ether, tetrahydrofuran and the like; hydrocarbons such as toluene, xylene, n-hexane, n-heptane, cyclohexane, and the like; and any mixtures thereof. In one embodiment the solvent used in cyanation is a polar aprotic solvent such as Dimethylformamide, Dimethylsulfoxide, Dimethyl acetamide, acetonitrile and the like;

The process of cyanation is suitably carried out at temperatures ranging from about 0°C to about 100°C. In one embodiment the cyanation is carried out at temperatures ranging from about 20°C to about 80°C.

After completion of the reaction, the reaction mixture may be diluted with water and the solution is extracted with a suitable water immiscible solvent. The organic layer containing the product may be distilled completely to produce a residue, or it may be used directly in the next reaction step.

The step (d) of the process involves reduction of the cyanide of the compound of formula XVII in presence of a suitable catalyst, hydrogen gas, and a suitable solvent.

The suitable catalyst is selected from the group comprising of Raney Nickel, Palladium, Platinum, Rhodium, and Ruthenium. In one embodiment the hydrogenation catalyst is Raney-Nickel.

The quantity of the catalyst may range from about 0.01 to about 5 moles. In one embodiment the quantity of the catalyst is about 0.1 to about 1 mole per mole of compound of Formula XVII.

The suitable solvent that can be used for the catalytic hydrogenation include, but are not limited to: alcohols such as methanol, ethanol, isopropanol (IPA), n-butanol, tert-butanol, and the like; ethers such as diethyl ether, methyl tert-butyl ether, tetrahydrofuran and the like; hydrocarbons such as toluene, xylene, n-hexane, n-heptane, cyclohexane, and the like; esters such as ethyl acetate, propyl acetate, and the like; water, formic acid, acetic acid and any mixtures thereof. In one embodiment the solvent used in the catalytic hydrogenation is an alcohol such as methanol, ethanol, isopropanol (IPA), n-butanol, tert-butanol, and the like;

The process of catalytic hydrogenation is suitably carried out at temperatures ranging from about 0°C to about 100°C. In one embodiment the catalytic hydrogenation is carried out at temperatures ranging from about 30°C to about 80°C.

After completion of the hydrogenation, the catalyst is isolated from the reaction mixture by way of filtration. The filtrate containing the product may be distilled completely to produce a residue, or it may be used directly in the next reaction step.

The compound of formula XVI may optionally be protected with and an amine protecting group.

The step (e) of the process involves treatment of the amine of the compound of formula XVI or the protected amine with a cyanide to form compound of formula XV.

If the compound of formula XVI is protected one, before reacting it with cyanide the compound is treated with a suitable acid to deprotect the amine. The suitable acid used in the process of step (e) is selected from the group comprising of hydrochloric acid, hydrobromic acid, sulfuric acid, formic acid and acetic acid. In one embodiment the acid used in the process of step (e) is hydrochloric acid.

The acid concentration may vary from about 0.1N to about 10N. In one embodiment the acid concentration is 1N.

The suitable cyanide used in the process of step (e) is selected from the group comprising of Copper cyanide, Sodium cyanide, Potassium cyanide, Zinc cyanide. In one embodiment the cyanide is Potassium cyanide.

The quantity of the cyanide used in the process of step (e) may vary from about 1 to about 10 moles. In one embodiment the quantity of the cyanide is about 1 to about 5 moles per mole of compound of Formula XVI.

The process of step (e) is suitably carried out at temperatures ranging from about 0°C to about 80°C. In one embodiment the reaction is carried out at temperatures ranging from about 10°C to about 50°C.

After completion of the reaction, the reaction mixture is diluted with water and may be treated with a base. The resulted solution is extracted with a suitable water immiscible solvent. The solvent containing the product may be distilled completely to produce a residue, or it may be used directly in the next reaction step.

The step (f) of the process involves hydrolysis of the cyanide of the compound of formula XV in presence of a mineral acid to form compound of formula VIIb.

The mineral acid used in the hydrolysis is selected from the group comprising of Hydrochloric acid, Hydrobromic acid, Hydroiodic acid and Sulfuric acid. In one embodiment the mineral acid used in the hydrolysis is Hydrochloric acid.

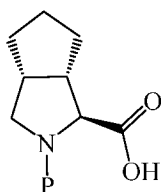
The mineral acid may be used in the form of a solution having a concentration of about 0.1N to about 10N. In one embodiment the acid concentration is 1N.

The solvent used for the preparation of the mineral acid solution include, but are not limited to: alcohols such as methanol, ethanol, isopropanol (IPA), n-butanol, tert-

butanol, and the like; ethers such as diethyl ether, methyl tert-butyl ether, tetrahydrofuran and the like; esters such as ethyl acetate, propyl acetate, and the like; water, and any mixtures thereof. In one embodiment the solvent used in the preparation of the mineral acid solution is an alcohol such as methanol, ethanol, isopropanol (IPA), n-butanol, tert-butanol, and the like. In another embodiment the solvent used in the preparation of the mineral acid solution is water.

After completion of the reaction, the reaction mixture is concentrated and the compound of formula VIIb is isolated. In one embodiment the compound of formula VIIb is isolated as an acid addition salt.

The compound of formula VIIb or its acid addition salt may be protected to form compound of formula VIIa or an acid addition salt.



VIIa

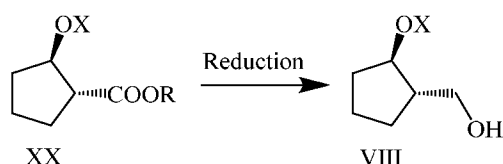
wherein P is an amine protecting group.

The suitable amine protecting group is selected from the group comprising of 9-Fluorenylmethyloxy carbonyl (Fmoc), tert-butyloxycarbonyl (BOC), benzyloxy carbonyl (CBZ), acetyl, trifluoroacetyl, benzyl, triphenylmethyl, and p-toluenesulfonyl. In one embodiment the amine protecting group is tert-butyloxycarbonyl.

Protection of the amine functionality of the compound of formula VIIb is suitably carried out using any process including processes described in the art, or by a process described in this application.

In another aspect, the application provides a process for preparation of a compound of formula VIIb, comprising:

(a) reducing the compound of formula XX with a suitable reducing agent to form a compound of formula XIX



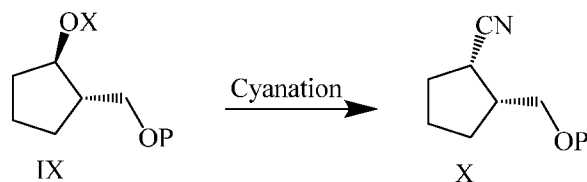
wherein X is hydrogen or a leaving group such as mesyl, tosyl, acetyl or trifluoroacetyl;
R is hydrogen or C₁-C₄ alkyl or C₅-C₁₂ aralkyl,

(b) protecting the primary hydroxyl group of compound of formula VIII to get compound of formula IX,

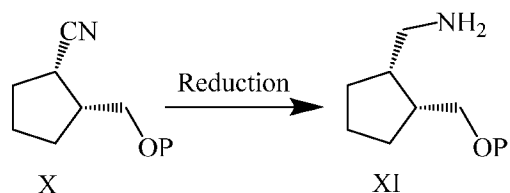


wherein X is a protecting group,

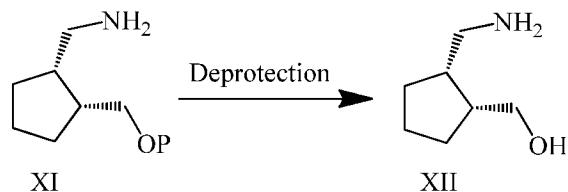
(c) cyanating the compound of formula IX with a suitable cyanating agent to form compound of formula X



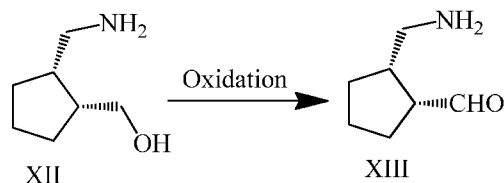
(d) reducing the compound of formula X in the presence of a suitable catalyst to obtain compound of formula XI,



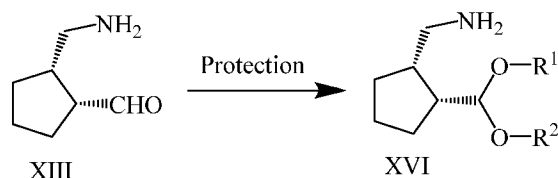
(e) deprotecting the compound of formula XI to form compound of formula XII,



(f) oxidizing the compound of formula XII to form compound of formula XIII,

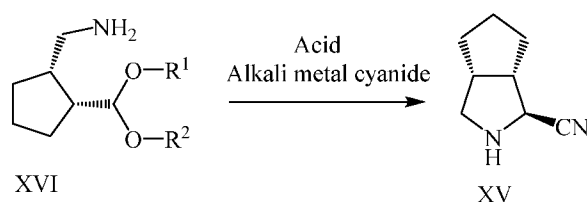


(g) optionally, protecting the aldehyde of the compound of formula XIII to form a compound of formula XVI.

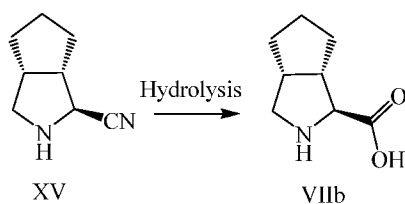


R^1 and R^2 are C_1 - C_5 alkyl or both form a cyclic ring,

(h) treating the compound of formula XIII or the compound of formula XVI with an alkali metal cyanide to form a compound of formula XV, and



(i) hydrolyzing the compound of formula XV to form compound of formula VIIb or its acid addition salt



The step (a) of the process involves reduction of compound of formula XX with a suitable reducing agent to form a compound of formula VIII. The reduction is carried out in presence of a suitable solvent.

Compound of Formula XX may be obtained by any process including processes described in the art, or by a process described in this application.

The suitable reducing agent is selected from the group comprising of sodium aluminum hydride, sodium borohydride, lithium aluminum hydride, sodium bis (2-methoxyethoxy)aluminumhydride (Red-Al) and bis(4-methyl-1-piperaziny) aluminum hydride (BMAH). In one embodiment the reducing agent is lithium aluminum hydride (LAH). In another embodiment the reducing agent is sodium bis (2-methoxyethoxy)aluminumhydride (Red-Al).

The quantity of reducing agent may range from about 1 to about 4 moles. In one embodiment the quantity of the reducing agent is about 1 to about 2 moles, per mole of compound of Formula XX.

Suitable solvents that can be used for the reaction include, but are not limited to: ethers such as diethyl ether, methyl tert-butyl ether, tetrahydrofuran and the like; hydrocarbons such as toluene, xylene, n-hexane, n-heptane, cyclohexane, and the like; and any mixtures thereof. In one embodiment the solvent used in step (a) is ether such as diethyl ether, methyl tert-butyl ether, tetrahydrofuran and the like.

The process of step (a) is suitably carried out at temperatures ranging from about -30°C to about 50°C. In one embodiment the reduction is carried out at temperatures ranging from about -10°C to about 30°C.

After completion of the reaction, the reaction mixture may be diluted and the salt by-product can be removed by filtration. The organic layer containing the product may be distilled completely to produce a residue, or it may be used directly in the next reaction step.

The step (b) of the process involves protection of primary hydroxyl functionality of the compound of formula VIII with a suitable hydroxyl protecting group in presence of a suitable solvent to form a compound of formula IX.

The primary hydroxyl protection is suitably carried out using known methods. See e.g., T. W. Green and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley and Sons, Inc. (1999).

In one embodiment the hydroxyl protecting group is silyl group such as trimethylsilyl, triethylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, t-butyldimethylsilyl, t-butyldiphenylsilyl, triisopropylsilyl and the like. In another embodiment the hydroxyl protecting group is t-butyldiphenylsilyl (TBDPS).

The step (c) of the process involves cyanation of the compound of formula IX with a suitable cyanating agent in a suitable solvent to form compound of formula X.

The suitable cyanating agent is selected from the group comprising of Copper cyanide, Sodium cyanide, Potassium cyanide and Zinc cyanide. In one embodiment the cyanating agent is Sodium cyanide.

The quantity of the cyanating agent may range from about 1 to about 10 moles. In one embodiment the quantity of the cyanating agent is about 1 to about 3 moles per mole of compound of Formula IX.

The suitable solvent that can be used for cyanation include, but are not limited to: polar aprotic solvents such as Dimethylformamide, Dimethylsulfoxide, Dimethyl acetamide, acetonitrile and the like; ethers such as diethyl ether, methyl tert-butyl ether, tetrahydrofuran and the like; hydrocarbons such as toluene, xylene, n-hexane, n-heptane, cyclohexane, and the like; and any mixtures thereof. In one embodiment the solvent used in cyanation is a polar aprotic solvent such as Dimethylformamide, Dimethylsulfoxide, Dimethyl acetamide, acetonitrile and the like;

The process of cyanation is suitably carried out at temperatures ranging from about 0°C to about 100°C. In one embodiment the cyanation is carried out at temperatures ranging from about 20°C to about 80°C.

After completion of the reaction, the reaction mixture may be diluted with water and the solution is extracted with a suitable water immiscible solvent. The organic layer containing the product may be distilled completely to produce a residue, or it may be used directly in the next reaction step.

The step (d) of the process involves reduction of the cyanide of the compound of formula X in presence of a suitable catalyst, hydrogen gas and a suitable solvent.

The suitable catalyst is selected from the group comprising of Raney Nickel, Palladium, Platinum, Rhodium, and Ruthenium. In one embodiment the hydrogenation catalyst is Raney-Nickel.

The quantity of the catalyst may range from about 0.01 to about 5 moles. In one embodiment the quantity of the catalyst is about 0.1 to about 1 mole per mole of compound of Formula X.

The suitable solvent that can be used for the catalytic hydrogenation include, but are not limited to: alcohols such as methanol, ethanol, isopropanol (IPA), n-butanol, tert-butanol, and the like; ethers such as diethyl ether, methyl tert-butyl ether, tetrahydrofuran and the like; esters such as ethyl acetate, propyl acetate, and the like; water, formic acid, acetic acid and any mixtures thereof. In one embodiment the solvent

used in the catalytic hydrogenation is an alcohol such as methanol, ethanol, isopropanol (IPA), n-butanol, tert-butanol, and the like;

The process of catalytic hydrogenation is suitably carried out at temperatures ranging from about 0°C to about 100°C. In one embodiment the catalytic hydrogenation is carried out at temperatures ranging from about 10°C to about 50°C.

After completion of the hydrogenation, the catalyst is isolated from the reaction mixture by way of filtration. The filtrate containing the product may be distilled completely to produce a residue, or it may be used directly in the next reaction step.

The step (e) of the process involves deprotection of compound of formula XI using a suitable acid to form a compound of formula XII.

The suitable acid that can be used for the deprotection is selected from the group comprising of hydrochloric acid, hydrofluoric acid, hydroiodic acid, hydrobromic acid, tetrabutylammonium fluoride, tetrabutylammonium bromide, acetic acid, and sulfuric acid. In one embodiment the acid used for deprotection of the compound of formula XI is hydrochloric acid.

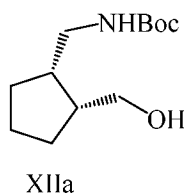
The acid may be used in the form of a solution having a concentration of about 0.1N to about 10N. The solvent used for the preparation of the acid solution include, but are not limited to: alcohols such as methanol, ethanol, isopropanol (IPA), n-butanol, tert-butanol, and the like; ethers such as diethyl ether, methyl tert-butyl ether, tetrahydrofuran and the like; esters such as ethyl acetate, propyl acetate, and the like; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone (MIBK), and the like; water, and any mixtures thereof. In one embodiment the solvent used in the preparation of the mineral acid solution is an alcohol such as methanol, ethanol, isopropanol (IPA), n-butanol, tert-butanol, and the like.

After completion of the deprotection, the reaction mixture may be concentrated completely to produce a residue, and the crude may be purified or may be used directly in the next reaction step.

The amine functionality of the compound of formula XII may be protected using a suitable protecting group.

The amine protection is suitably carried out using known methods. See e.g., T. W. Green and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, 3rd edition, John Wiley and Sons, Inc. (1999).

In one embodiment the amine functionality of the compound of formula XII may be protected using tert-butyloxycarbonyl (BOC) protecting group to form compound of formula XIIa.



The step (f) of the process involves oxidation of compound of formula XII or compound of formula XIIa using a suitable oxidizing agent and a suitable solvent to form a compound of formula XIII.

The suitable oxidizing agent is selected from the group comprising of Pyridinium chlorochromate (PCC), Pyridinium dichromate (PDC), Dess-Martin periodinane (DMP), (2,2,6,6-Tetramethylpiperidin-1-yl)oxyl (TEMPO), Aluminum isopropoxide, o-iodoxybenzoic acid (IBX), 2-Iodoxybenzenesulfonic acid and diisopropyl azodicarboxylate (DIAD). In one embodiment the oxidizing agent is Dess-Martin periodinane.

The quantity of the oxidizing agent may range from about 0.1 to about 10 moles. In one embodiment the quantity of the catalyst is about 0.5 to about 3 moles per mole of compound of Formula XII.

The process of step (f) is suitably carried out at temperatures ranging from about -30°C to about 100°C. In one embodiment the oxidation is carried out at temperatures ranging from about 0°C to about 50°C.

After completion of the oxidation, the reaction mixture is concentrated completely to produce a residue and the residue is dissolved in another solvent or it may be used directly in the next reaction step.

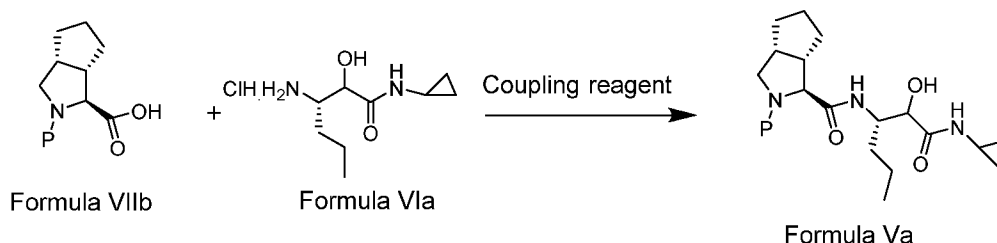
The step (g) of the process involves protection of the aldehyde of the compound of formula XIII with a suitable protecting group in presence of a suitable solvent to form a compound of formula XVI.

The step (h) of the process involves treatment of the amine of the compound of formula XVI with an acid and a cyanide to form compound of formula XV.

The step (i) of the process involves hydrolysis of the cyanide of the compound of formula XV in presence of a suitable acid or suitable base to form compound of formula VIIb. The processes of step (g) to step (i) are suitably carried out using the process as described above in this application.

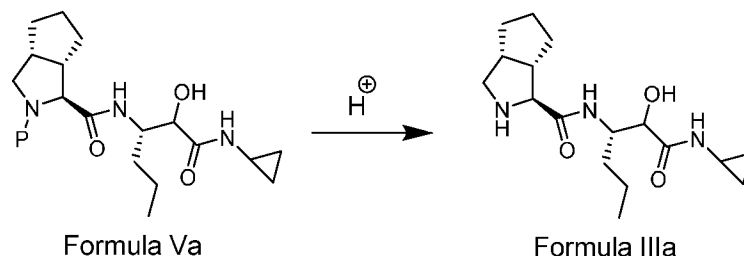
In another aspect the application provides use of the compound of formula VIIb prepared by the processes disclosed in the present application in the preparation of telaprevir comprising:

(a) reacting compound of formula VIIb or a protected form of formula VIIb with a compound of formula VIa or its salt in the presence of a suitable coupling reagent to form compound of formula Va or its salt,

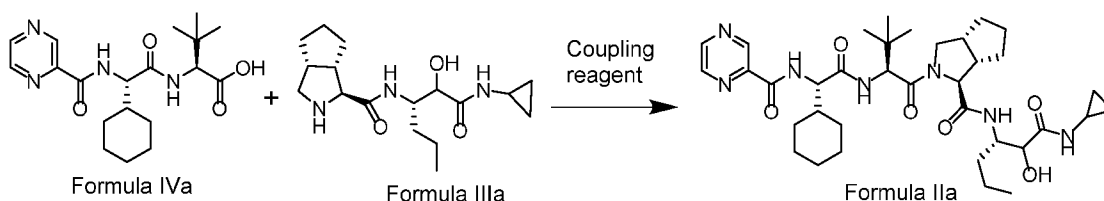


wherein P is an amine protecting group;

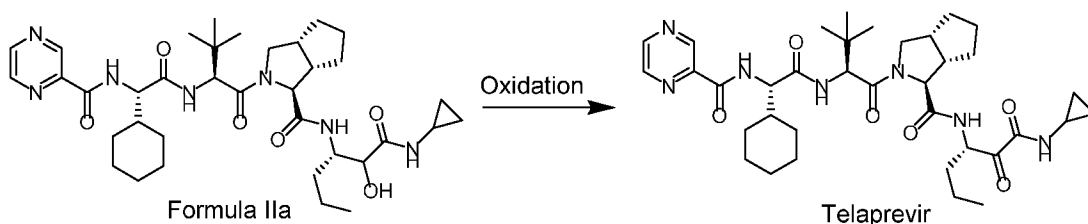
(b) deprotecting the compound of formula Va or its salt using an acid to form compound of formula IIIa or a salt thereof;



(c) reacting a compound of formula IIIa or a salt thereof with a compound of formula IVa or a salt thereof in the presence of a suitable coupling reagent to form a compound of formula IIa;



(d) oxidizing the compound of Formula IIa using a suitable oxidizing reagent to form telaprevir.



The amine protecting group as used herein is known in the art (see, e.g., T. W. Greene & P.G.M Wutz, "Protective groups in Organic Synthesis", 3rd edition, John Wiley & Sons, Inc. (1999), and the earlier editions of this book.

Step (a) of the process involves coupling of a compound of Formula VIIb or a protected form of compound of formula VIIb or its salt with a compound of Formula VIa or its salt in the presence of a suitable coupling reagent to form a compound of formula Va or its salt.

The compound of formula VIa is used as an acid addition salt. The acid addition salt of compound of formula VI is selected from hydrochloride, hydrobromide, acetate, trifluoroacetate, and hemisulphate.

Compounds of formula VIIb and formula VIa or their salts may be obtained by any processes including processes described in the art, or by a process described in this application.

Suitable coupling reagent that may be used is selected from the group comprising 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDC), dicyclohexylcarbodiimide (DCC), diisopropylcarbodiimide (DIC), benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), ((1-H-1,2,3-benzotriazol-1-yloxy)-tris(pyrrolidino)phosphonium tetrafluorophosphate (PyBOP), bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOP-Cl), 1-hydroxybenzotriazole (HOBT), hydroxyazabenzotriazole (HOAT) or mixtures thereof.

Quantities of coupling reagent may range from about 1 to about 4 moles, or about 2 to about 3 moles, per mole of compound of Formula IV.

The reaction is effected in the presence of a solvent. The solvent that can be used, include, but is not limited to, a halogenated hydrocarbon solvent such as dichloromethane, ethylene dichloride, chloroform, or the like; ketone solvents such as acetone, methyl isobutyl ketone (MIBK), or the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), dimethylacetamide (DMA), acetonitrile or the like; or mixtures thereof. Preferably the solvent is N,N-dimethylformamide (DMF). Quantities of solvent used for the process may be from about 1 mL to about 30 mL, per gram of compound of Formula IV.

Optional reagents that may be used in the amide bond forming reaction include ethyl-2-cyano-2-(hydroxyimino)acetate (oxyma) or active ester reagents such as 1-hydroxybenzotriazole (HOBT), hydroxyazabenzotriazole (HOAT), hydroxysuccinimide (HOSu) in amounts ranging from about 0.5 to about 5 equivalents.

The reaction is suitably carried out at temperatures ranging from about 0°C to about 80°C, preferably about 10°C to about 50°C.

The time required for completion of the reaction may also vary widely, depending on many factors, notably the reaction temperature and the nature of the reagents and solvent employed. However, provided that the reaction is effected under the preferred conditions outlined above, a period from about 30 minutes to about 30 hours, preferably from about 3 hours to about 20 hours, is sufficient.

Step (b) of the process involves deprotection of the compound of formula Va to provide compound of formula IIIa. For this step, a suitable method may be selected depending on the N-protective group. For example the protective group capable of being deprotected with an acid such as tert-butoxycarbonyl, benzyloxycarbonyl, the reaction of the process may be attained by acid treatment.

The acid to be used includes, for example, a mineral acid, a sulfonic acid, or a carboxylic acid. The mineral acid is not specifically limited, but includes hydrogen halides such as hydrogen chloride, and hydrogen bromide; sulfuric acid; phosphoric acid. The sulfonic acid is not specifically limited, but includes, for example, methane sulfonic acid, ethane sulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid,

camphorsulfonic acid, and 1-phenylethanesulfonic acid. The carboxylic acid is not specifically limited, but includes, for example, formic acid, acetic acid, trifluoroacetic acid, benzoic acid, and tartaric acid. Among these acids, hydrogen chloride, hydrogen bromide, sulfuric acid, p-toluenesulfonic acid, and benzoic acid that form salts having good crystallinity are preferable; and in particular hydrogen chloride, hydrogen bromide and sulfuric acid are preferable, and hydrogen chloride or sulfuric acid is more preferable.

The amount of the acid to be used may be at least a theoretical amount; but the use thereof in a large amount is not economical. Therefore the lower limit of the amount is generally not less than 1 time by mol, and the higher limit is generally not more than 10 times by mol, preferably not more than 3 times by mol, more preferably not more than 2 times by mol relative to the compound of the formula Va.

The acid may be added directly as it is, or the aqueous solution or the solution in which the acid is previously dissolved in a solvent mentioned below may be used. The concentration of the acid to be added is not specifically limited, but the lower limit is generally 0.1% by weight, preferably 1% by weight, more preferably 5% by weight and the higher limit is 100% by weight.

The reaction is generally carried out in a solvent. The solvent is not specifically limited, but includes alcohols such as methanol, ethanol, isopropanol, n-propanol; ethers such as tetrahydrofuran, diethyl ether, methyl tert-butyl ether, 1,3-dioxolan, 1,2-dimethoxy ethane, diethylene glycol dimethyl ether; aliphatic esters such as ethyl acetate, isopropyl acetate, tert-butyl acetate; and halogenated hydrocarbons such as dichloromethane, 1,2-dichloethane.

In case the protective groups that could not be deprotected by acid, the compound is appropriately deprotected according to the type of the protective group, and then is processed with acid according to the above mentioned process to obtain the compound of formula IIIa.

Step (c) of the process involves coupling o compound of Formula IIIa or its salt with compound of Formula IVa or its salt in the presence of a suitable coupling reagent to form a compound of formula IIa or its salt.

Optionally, the coupling reaction is carried out using an adduct such as copper chloride as taught in International Journal of Peptide and Protein Research **39**, 1992, 237-234.

The coupling reagent and solvent used in the coupling reaction can appropriately be selected from the above mentioned embodiments.

The reaction is suitably carried out at temperatures ranging from about 0°C to about 80°C, preferably about 10°C to about 50°C.

The reaction is monitored by TLC. After completion of the reaction, water is added to the reaction mixture and the compound of formula IIa is isolated by filtration.

Step (d) of the process involves oxidation of the compound of formula IIa or its salt to form telaprevir or its salt. Suitable oxidizing agent is selected from Dess-Martin periodinane (1,1-dihydro-1,1,1-triacetoxy-1,2-benziodoxol-3(1H)-one), chromic acid in acetone, sodium hypochlorite in the presence of (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl (TEMPO) or a TEMPO derivative such as 4-Hydroxy-TEMPO, 4-Amino-TEMPO, 4-Acetamido-TEMPO, 4-(2-Bromoacetamido)-TEMPO, 4-Carboxy-TEMPO, 4-Cyano-TEMPO, 4-Methoxy-TEMPO or 4-Oxo-TEMPO; or potassium permanganate in the presence of TEMPO or a TEMPO derivative.

The oxidation is affected in the presence of a solvent. The solvents that can be used include, but are not limited to, ethers such as diethyl ether, tetrahydrofuran (THF) and the like; halogenated solvent such as dichloromethane, ethylene dichloride, chloroform and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), dimethylacetamide (DMA), acetonitrile and the like; hydrocarbon solvents such as n-hexane, n-heptane, cyclohexane, toluene and the like; esters such as ethyl acetate methyl acetate, isopropyl acetate and the like or mixtures thereof. Preferably the solvent is dichloromethane or ethyl acetate.

The oxidation is carried out at a temperature from about -20°C to about 60°C. Preferably from about 0°C to about 30°C.

The reaction is monitored by TLC. After completion of the reaction, the reaction mixture is quenched with dilute aqueous sodium sulphite solution and the organic layer is concentrated to yield crude telaprevir. The crude telaprevir is purified by recrystallizing it from ethylacetate or dichloromethane or a mixture thereof. Telaprevir

prepared by the processes herein described above is having purity greater than about 99 area % as measured by HPLC.

In another aspect, the present application provides Telaprevir prepared by the processes herein described above is having purity greater than about 99.5 area % as measured by HPLC.

In another aspect, the present application provides Telaprevir prepared by the processes herein described above is having purity greater than about 99.8 area % as measured by HPLC.

In another aspect, the present application provides use of Telaprevir having purity greater than about 99.5 area % as measured by HPLC for the manufacture of a pharmaceutical composition.

In another aspect, the present application provides use of Telaprevir having purity greater than about 99.8 area % as measured by HPLC for the manufacture of a pharmaceutical composition.

DEFINITIONS

The following definitions are used in connection with the present invention unless the context indicates otherwise.

As used herein, the term "vacuum" refers to a reduced pressure of below about 150 mm Hg. In another embodiment, the pressure is below about 50 mm Hg. In another embodiment, the pressure is below about 30 mm Hg. As used herein, the term "reduced pressure" refers to a pressure below 760 mm Hg or 1 atmosphere.

As used herein, the term "room temperature" refers to a temperature of about 20°C to about 35°C, In another embodiment about 20°C to about 25°C and in another embodiment about 25°C.

An "alcohol solvent" is an organic solvent containing a carbon bound to a hydroxyl group. "Alcohol solvents" include, but are not limited to, methanol, ethanol, 2-nitroethanol, 2-fluoroethanol, 2,2,2-trifluoroethanol, hexafluoroisopropyl alcohol, ethylene glycol, 1-propanol, 2-propanol (isopropyl alcohol), 2-methoxyethanol, 1-butanol, 2-butanol, i-butyl alcohol, t-butyl alcohol, 2-ethoxyethanol, diethylene glycol, 1-, 2-, or 3-pentanol, neo-pentyl alcohol, t-pentyl alcohol, diethylene glycol monomethyl

ether, diethylene glycol monoethyl ether, cyclohexanol, benzyl alcohol, phenol, glycerol, C₁₋₆alcohols, or the like.

An “aliphatic or alicyclic hydrocarbon solvent” refers to a liquid, non-aromatic, hydrocarbon, which may be linear, branched, or cyclic. It is capable of dissolving a solute to form a uniformly dispersed solution. Examples of a hydrocarbon solvents include, but are not limited to, n-pentane, isopentane, neopentane, n-hexane, isohexane, 3-methylpentane, 2,3-dimethylbutane, neohexane, n-heptane, isohexane, 3-methylhexane, neoheptane, 2,3-dimethylpentane, 2,4-dimethylpentane, 3,3-dimethylpentane, 3-ethylpentane, 2,2,3-trimethylbutane, n-octane, isooctane, 3-methylheptane, neooctane, cyclohexane, methylcyclohexane, cycloheptane, C₅₋₈aliphatic hydrocarbons, petroleum ethers, or mixtures thereof.

“Aromatic hydrocarbon solvent” refers to a liquid, unsaturated, cyclic, hydrocarbon containing one or more rings which has at least one 6-carbon ring containing three double bonds. It is capable of dissolving a solute to form a uniformly dispersed solution. Examples of aromatic hydrocarbon solvents include, but are not limited to, benzene toluene, ethylbenzene, m-xylene, o-xylene, p-xylene, indane, naphthalene, tetralin, trimethylbenzene, chlorobenzene, fluorobenzene, trifluorotoluene, anisole, C₆-C₁₀aromatic hydrocarbons, or mixtures thereof.

An “ester solvent” is an organic solvent containing a carboxyl group -(C=O)-O- bonded to two other carbon atoms. “Ester solvents” include, but are not limited to, ethyl acetate, n-propyl acetate, n-butyl acetate, isobutyl acetate, t-butyl acetate, ethyl formate, methyl acetate, methyl propanoate, ethyl propanoate, methyl butanoate, ethyl butanoate, C₃₋₆esters, or the like.

A “halogenated hydrocarbon solvent” is an organic solvent containing a carbon bound to a halogen. “Halogenated hydrocarbon solvents” include, but are not limited to, dichloromethane, 1,2-dichloroethane, trichloroethylene, perchloroethylene, 1,1,1-trichloroethane, 1,1,2-trichloroethane, chloroform, carbon tetrachloride, or the like.

A “ketone solvent” is an organic solvent containing a carbonyl group -(C=O)- bonded to two other carbon atoms. “Ketone solvents” include, but are not limited to, acetone, ethyl methyl ketone, diethyl ketone, methyl isobutyl ketone, C₃₋₆ketones, 4-methyl-pentane-2-one or the like.

A “polar aprotic solvent” has a dielectric constant greater than 15 and is at least one selected from the group consisting of amide-based organic solvents, such as N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMA), N-methylpyrrolidone (NMP), formamide, acetamide, propanamide, hexamethyl phosphoramidate (HMPA), and hexamethyl phosphorus triamide (HMPT); nitro-based organic solvents, such as nitromethane, nitroethane, nitropropane, and nitrobenzene; pyridine-based organic solvents, such as pyridine and picoline; sulfone-based solvents, such as dimethylsulfone, diethylsulfone, diisopropylsulfone, 2-methylsulfolane, 3-methylsulfolane, 2,4-dimethylsulfolane, 3,4-dimethylsulfolane, 3-sulfolene, and sulfolane; and sulfoxide-based solvents such as dimethylsulfoxide (DMSO).

An “ether solvent” is an organic solvent containing an oxygen atom –O– bonded to two other carbon atoms. “Ether solvents” include, but are not limited to, diethyl ether, diisopropyl ether, methyl t-butyl ether, glyme, diglyme, tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, dibutyl ether, dimethylfuran, 2-methoxyethanol, 2-ethoxyethanol, anisole, C₂₋₆ethers, or the like.

The term “oxidizing agent” (also called an oxidant, oxidizer) refers to a chemical compound that readily transfers oxygen atoms or a substance that gains electrons in a chemical reaction.

The term “coupling reagent” refers to a chemical compound that react with amino acids to form activated amino acid intermediates which in turn react with the N-terminal amine of the peptide to form the elongated peptide.

“Leaving group” refers to an atom or group (charged or uncharged) that becomes detached from an atom in what is considered to be the residual or main part of the substrate in a specified reaction. For example, in the heterolytic solvolysis of benzyl bromide in acetic acid: the leaving group is bromide. In the reaction of N,N,N-trimethyl-1-phenylmethanaminium ion with methanethiolate, the leaving group is trimethylamine. In the electrophilic nitration of benzene, it is H⁺. The term has meaning only in relation to a specified reaction. Examples of leaving groups include, for example, carboxylates (*i.e.* CH₃COO[–], CF₃CO₂[–], or (CH₃)₂CH₂COO[–]), F[–], water, Cl[–], Br[–], I[–], N₃[–], SCN[–], trichloroacetimidate, thiopyridyl, tertiary amines (*i.e.* trimethylamine), phenoxides (*i.e.* o-nitrophenoxide), and sulfonates (*i.e.* tosylate, mesylate, or triflate).

Powder X-ray Diffraction (PXRD) was performed on an X-ray Powder Diffractometer, equipped with a Cu-anode ($\lambda=1.54$ Angstrom), X-ray source operated at 45 kV, 40 mA, and a Ni filter is used to strip K-beta radiation. Two theta calibration is performed using an NIST SRM 640c Si standard. The sample was analyzed using the following instrument parameters: measuring range= 2-50° 2 θ , step width=0.017°.

Telaprevir and its impurities can be analyzed using HPLC, such as with a liquid chromatograph equipped with a UV detector and the parameters described below:

Column	X-Bridge C18 , 150 mm x 4.6mm x 3.5μ or Equivalent						
Detector Wavelength	210 nm						
Flow rate	1.0 mL/min						
Temperature	55°C						
Mobile phase A: Mixture of Buffer and Methanol in the ratio 850:150 (v/v)							
Mobile phase B: Acetonitrile: Water: Methanol :: 100 : 200 : 700 (v/v)							
Elution gradient Program:							
Time (minutes)	0.01	18	25	38	53	54	60
Vol. % of mobile phase A	65	35	35	10	10	65	65
Vol. % of mobile phase B	35	65	65	90	90	35	35

Separation of R and S isomers at position C* of compounds of the present application by HPLC.

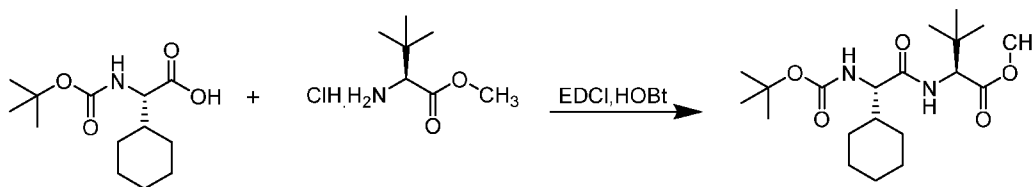
Column	X-Bridge C18 , 150 mm x 4.6mm x 3.5μ or Equivalent						
Detector Wavelength	210 nm						
Flow rate	1.0 mL/min						
Temperature	55°C						
Mobile phase A: Mixture of Buffer and Methanol in the ratio 850:150 (v/v)							
Mobile phase B: Acetonitrile: Water: Methanol :: 100 : 200 : 700 (v/v)							
Elution gradient Program:							
Time (minutes)	0.01	28	30	35	36	40	

Vol. % of mobile phase A	35	35	10	10	35	35	
Vol. % of mobile phase B	65	65	90	90	65	65	

The invention is further defined by reference to the following examples describing in detail the processes of the invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

EXAMPLES

Example 1: Preparation of (S)-methyl-2-((S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetamido)-3, 3-dimethylbutanoate

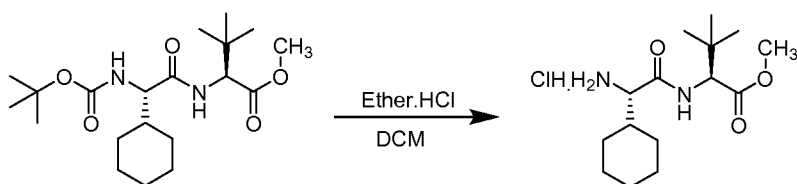


(S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetic acid (50 gm), tetrahydrofuran (500 mL), 1-hydroxybenzotriazole (HOBt, 26.3 gm) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC HCl, 37.2 gm) were charged into a 2000 mL round bottomed flask. The resulted solution was stirred for 30 minutes at 30°C. In another 1000 mL round bottomed flask L-tert-leucine methyl ester (35.3 gm) and tetrahydrofuran (200 mL) were charged, then N,N-dimethylformamide (DMF, 100 mL) and diisopropylethylamine (DIPEA, 50.5 gm) were charged. The resulted solution was stirred for 30 minutes at 30°C and was added to the above (S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetic acid solution at 30°C. The resulted solution was stirred for 20 hours at 30°. The solvent was distilled off completely under vacuum at below 40°C. Water (500 mL) and ethylacetate (500 mL) were added to the crude obtained and the solution was stirred for 15 minutes. The ethyl acetate layer was separated and was washed with 5% aqueous sodium bicarbonate solution (250 mL), 5% aqueous hydrochloric acid solution (250 mL), followed by 5% aqueous sodium chloride solution (250 mL). The ethylacetate layer was concentrated completely under vacuum at 30°C and to the residue n-hexane (500 mL) was added and the resulting

mixture was stirred for 2 hours at 30°C. The precipitate was filtered and washed with n-hexane (50 mL) and dried under vacuum at below 30°C to yield 53.8 gm of title compound.

Purity: 99.82% (by HPLC)

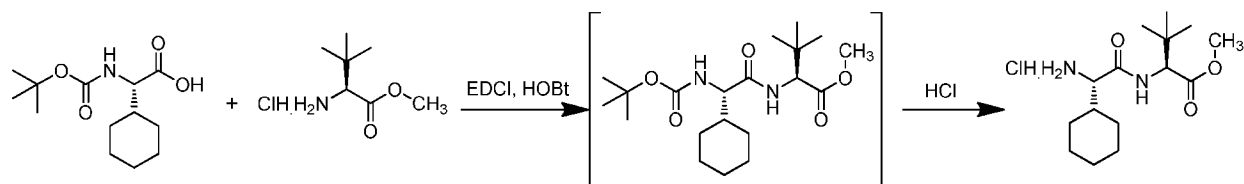
Example 2: Preparation of (S)-methyl 2-((S)-2-amino-2-cyclohexylacetamido)-3,3-dimethylbutanoate hydrochloride



(S)-methyl-2-((S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetamido)-3,3-dimethylbutanoate (5 gm) and dichloromethane (150 mL) were charged into a 500 mL round bottomed flask and the solution was cooled to 0°C. Ethereal hydrochloride (hydrochloride gas dissolved in diethyl ether, 20 mL) was slowly added at 0°C. Temperature raised to 30°C and the mixture was stirred for 15 hours at 30°C. The reaction mixture was concentrated completely under vacuum at 30°C and n-Hexane (40 mL) was added to the residue and the resulting mixture was stirred for 2 hours at 30°C. The precipitate was filtered and wet cake was washed with n-Hexane (10 mL) and the solid dried under vacuum at 30°C to yield 4.0 gm of the title compound.

Purity: 97.61% (by HPLC).

Example 3: Preparation of (S)-methyl-2-((S)-2-amino-2-cyclohexylacetamido)-3,3-dimethylbutanoate hydrochloride

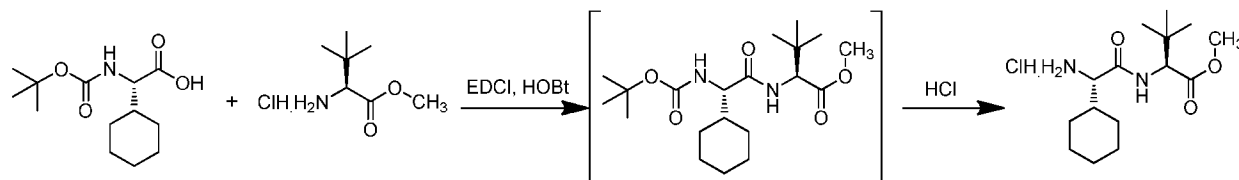


(S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetic acid (10 gm), ethylacetate (100 mL), 1-hydroxybenzotriazole (HOBt, 6.3 gm), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC HCl, 37.2 gm) and L-tert-leucine methyl ester (7 gm)

were charged into a 1000 mL round bottomed flask. The resulted solution was agitated for 20 hours at 28°C. Water (100 mL) was added and the solution was agitated for 10 minutes. Layers were separated and the ethylacetate layer was washed with 5% aqueous hydrochloric acid (50 mL) followed by 5% sodium chloride solution (50 mL). The ethylacetate layer was concentrated to 20 mL and a solution of hydrochloric acid dissolved in ethylacetate (40 mL) was added to the crude. The mixture was agitated for 12 hours at 28°C. The precipitate was filtered and the wet cake was washed with ethylacetate (10 mL) and the solid was dried under vacuum at 40°C to yield 11.3 gm of the title compound.

Purity: 99.93% (by HPLC).

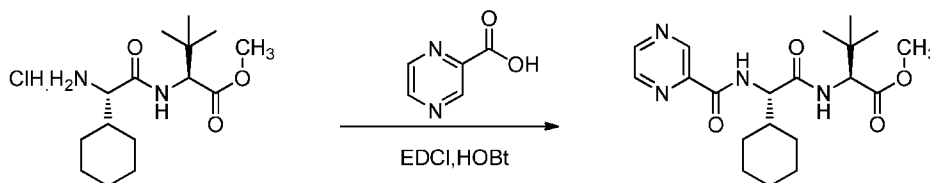
Example 4: Preparation of (S)-methyl-2-((S)-2-amino-2-cyclohexylacetamido)-3,3-dimethylbutanoate hydrochloride



(S)-2-((tert-butoxycarbonyl)amino)-2-cyclohexylacetic acid (10 gm), ethylacetate (100 mL), 1-hydroxybenzotriazole (HOBt, 6.3 gm), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC HCl, 11.2 gm), L-tert-leucine methyl ester hydrochloride (7 gm) and diisopropylethylamine (10 gm) were charged into a 1000 mL round bottomed flask. The resulted solution was agitated for 10 hours at 28°C. Water (100 mL) was added and the solution was agitated for 10 minutes. Layers were separated and the ethylacetate layer was washed with 5% sodium chloride solution (50 mL). The ethylacetate layer was concentrated to 28 mL and a solution of hydrochloric acid dissolved in ethylacetate (40 mL) was added to the crude. The mixture was agitated for 10 hours at 28°C. The precipitate was filtered and the wet cake was washed with ethylacetate (10 mL) and the solid was dried under vacuum at 40°C to yield 11.3 gm of the title compound.

Purity: 99.93% (by HPLC).

Example 5: Preparation of (S)-methyl 2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethyl butanoate.

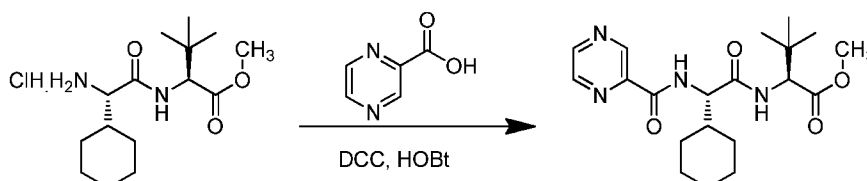


(S)-methyl-2-((S)-2-amino-2-cyclohexylacetamido)-3,3-dimethylbutanoate

hydrochloride (3 gm), tetrahydrofuran (60 mL), 2-Pyrazine carboxylic acid (1.4 gm), 1-hydroxybenzotriazole (HOBt, 1.5 gm) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC HCl, 2.16 gm) were charged into a 500 mL round bottomed flask and the resulted mixture was stirred for 15 minutes at 30°C. Diisopropylethylamine (2.4 gm) was added to the mixture and stirred for 12 hours at 30°C. Water (30 mL) and ethylacetate (50 mL) were added to the reaction mixture and the solution was stirred for 15 minutes. The ethyl acetate layer was separated and was washed with 5% aqueous sodium bicarbonate solution (30 mL X 2), 5% aqueous hydrochloric acid solution (15 mL X 2), followed by 5% aqueous sodium chloride solution (30 mL). The ethylacetate layer was concentrated completely under vacuum at 30°C and to the residue n-hexane (30 mL) was added and the resulted mixture was stirred for 2 hours at 30°C. The precipitation was filtered and washed with n-hexane (5 mL) and dried under vacuum at below 30°C to yield 3 gm of title compound.

Purity: 99.98% (by HPLC).

Example 6: Preparation of (S)-methyl 2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethyl butanoate.



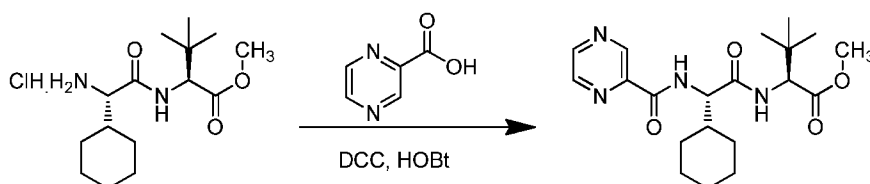
(S)-methyl-2-((S)-2-amino-2-cyclohexylacetamido)-3,3-dimethylbutanoate

hydrochloride (15 gm), ethylacetate (300 mL), 2-Pyrazine carboxylic acid (6.4 gm), 1-hydroxybenzotriazole (HOBt, 6.3 gm), dicyclohexylcarbodiimide (DCC, 14.4 gm) and diisopropylethylamine (DIPEA, 12 gm) were charged into a 1000 mL round bottomed

flask and the resulted mixture was agitated for 5 hours at 28°C. The reaction mass was filtered and the salt was washed with ethylacetate (20 mL). The ethylacetate layer was concentrated completely under vacuum at below 40°C and cyclohexane (75 mL) was added to the residue and the resulted mixture was agitated for 2 hours at 30°C. The precipitate was filtered and the wet cake was washed with cyclohexane (20 mL) and the solid was dried under vacuum at below 40°C to yield 16.6 gm of title compound.

Purity: 99.5% (by HPLC).

Example 7: Preparation of (S)-methyl 2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethyl butanoate.

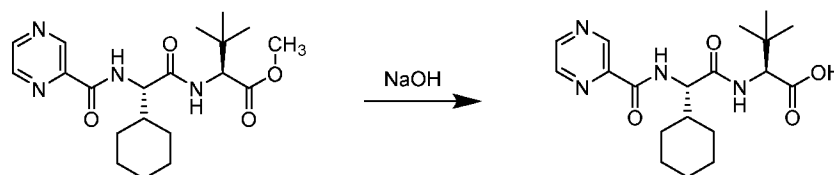


(S)-methyl-2-((S)-2-amino-2-cyclohexylacetamido)-3,3-dimethylbutanoate

hydrochloride (5 gm), ethylacetate (100 mL), 2-Pyrazine carboxylic acid (6.4 gm), 1-hydroxybenzotriazole (HOBt, 2.1 gm), dicyclohexylcarbodiimide (DCC, 3.9 gm) and diisopropylethylamine (DIPEA, 4 gm) were charged into a 500 mL round bottomed flask and the resulting mixture was agitated for 5 hours at 28°C. The reaction mass was filtered and the salt was washed with ethylacetate (10 mL). The ethylacetate layer was washed with 5% aqueous sodium chloride solution and concentrated completely under vacuum at below 40°C. Cyclohexane (25 mL) was added to the residue and the resulting mixture was agitated for 1 hour at 28°C. The precipitate was filtered and the wet cake was washed with cyclohexane (5 mL) and the solid was dried under vacuum at 40°C to yield 5.5 gm of title compound.

Purity: 99.03% (by HPLC).

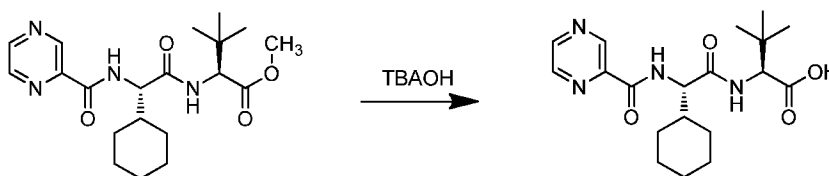
Example 8: Preparation of (S)-2-((R)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoic acid.



(S)-methyl-2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethyl butanoate (30 gm) and *tert*-Butanol (360 mL) were charged into a 1000 mL round bottomed flask and the solution was cooled to 0°C. Aqueous sodium hydroxide solution (6.2 gm of sodium hydroxide was dissolved in 60 mL of water) was added slowly in to the reaction mixture at 0°C. Temperature raised to 30°C and the reaction mixture was stirred for 12 hours at 30°C. *tert*-Butanol was distilled off completely under vacuum at 30°C and water (300 mL) was added to the crude and the resulted solution was cooled to 0°C. 0.5N aqueous hydrochloric acid solution was added slowly until pH reached to 2.5 and the mixture was stirred for 1 hour at 0°C. The precipitate was filtered and the wet cake was washed with water (30 mL) and the solid dried under vacuum at 45°C to yield 26.8 gm of title compound.

Purity: 98.51% (by HPLC).

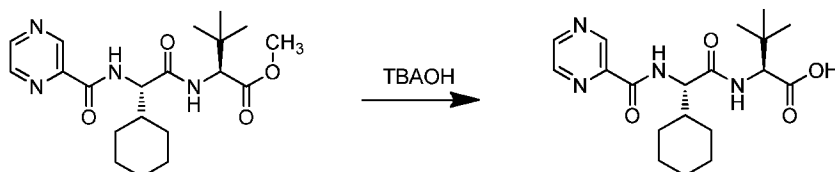
Example 9: Preparation of (S)-2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoic acid.



(S)-methyl-2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethyl butanoate (1 gm), *tert*-Butanol (10 mL) and 20% aqueous tetrabutyl ammonium hydroxide were charged into a 100 mL round bottomed flask and the mixture was agitated for 12 hours at 28°C. *tert*-Butanol was distilled off completely under vacuum at below 40°C and water (20 mL) was added to the crude and the resulted solution was cooled to 0°C. 10% aqueous hydrochloric acid solution was added slowly until pH reached to 2.5 and the mixture was stirred for 1 hour at 0°C. The precipitate was filtered and the solid dried under vacuum at below 45°C to yield 0.86 gm of title compound.

Purity: 99.43% (by HPLC); XRD pattern: Figure 2.

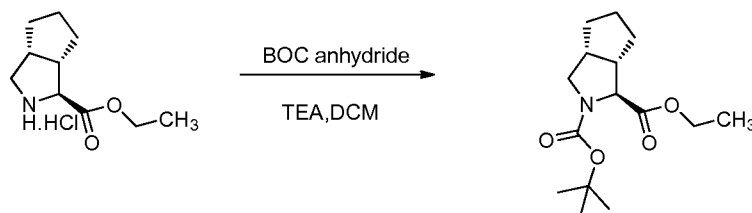
Example 10: Preparation of (S)-2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoic acid.



(S)-methyl-2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethyl butanoate (0.5 gm), *tert*-Butanol (5 mL) and tetrabutyl ammonium hydroxide (3.3 gm) were charged into a 100 mL round bottomed flask and the mixture was agitated for 8 hours at 27°C. *tert*-Butanol was distilled off completely under vacuum at below 40°C and water (10 mL) was added to the crude and the resulted solution was cooled to 0°C. 10% aqueous hydrochloric acid solution was added slowly until pH reached to 2 and the mixture was stirred for 1 hour at 0°C. The precipitate was filtered and the solid dried under vacuum at 45°C to yield 0.45 gm of title compound.

Purity: 99.54% (by HPLC); PXRD pattern: similar to figure 2.

Example 11: Preparation of (1S,3aR,6aS)-2-*tert*-butyl-1-ethyl-hexahydrocyclopenta[c]pyrrole-1,2-(1H)-dicarboxylate.

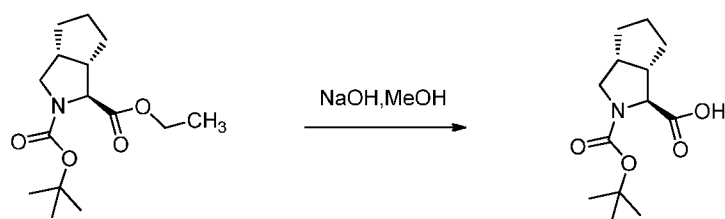


(1S,3aR,6aS)-ethyl octahydrocyclopenta[c]pyrrole-1-carboxylate hydrochloride (5 gm) and dichloromethane (50 mL) were charged into 1000 mL round bottomed flask and the solution was cooled to 0°C. Di-*tert*-butyl dicarbonate (11.6 gm), dimethylaminopyridine (4 gm) and triethylamine (3.45 gm) were added at 0°C. The reaction mixture was maintained for 15 minutes at 0°C and temperature raised slowly to 30°C and the reaction mixture was stirred for 20 hours at 30°C. 5% aqueous sodium bicarbonate solution (50 mL) was added to the reaction mixture and stirred for 15

minutes. Dichloromethane layer was separated and washed with 5% aqueous sodium bicarbonate solution (50 mL), 5% aqueous hydrochloric acid solution (50 mL X 2), followed by 5% aqueous sodium chloride solution (30 mL X 2). The organic layer was concentrated completely under vacuum at 30°C to yield 6 gm of title compound.

Purity: 93.96% (by HPLC)

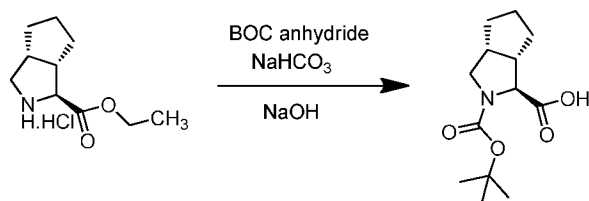
Example 12: Preparation of (1*S*,3*aR*,6*aS*)-2-*tert*-butoxy carbonyl)octahydrocyclopenta [c]pyrrole-1-carboxylic acid



(1*S*,3*aR*,6*aS*)-2-*tert*-butyl-1-ethyl-hexahydrocyclopenta [c]pyrrole-1,2-(1*H*)-dicarboxylate (5 gm) and methanol (50 mL) were charged into a 500 mL round bottomed flask and the solution was cooled to 0°C. Aqueous sodium hydroxide solution (1.5 gm of sodium hydroxide was dissolved in 10 mL of water) was added slowly in to the reaction mixture at 0°C. Temperature was raised to 30°C and the reaction mixture stirred for 20 hours at 30°C. Methanol was distilled off completely under vacuum at 30°C and water (50 mL) added to the crude and the resulted solution was cooled to 0°C. Aqueous hydrochloric acid solution (25%, 8 mL) was added slowly until pH reached to 2.5 and the mixture stirred for 1 hour at 0°C. The precipitate was filtered and the wet cake was washed with water (10 mL) and the solid dried under vacuum at 45°C to yield 3.5 gm of title compound.

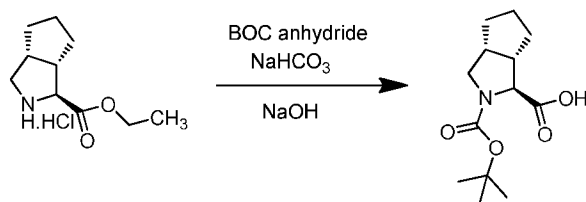
Purity: 100% (by HPLC).

Example 13: Preparation of (1*S*,3*aR*,6*aS*)-2-*tert*-butoxy carbonyl)octahydrocyclopenta [c]pyrrole-1-carboxylic acid.



(1S,3aR,6aS)-ethyl octahydrocyclopenta[c]pyrrole-1-carboxylate hydrochloride (5 gm) and methanol (20 mL), sodium bicarbonate (2.09 gm) and Di-tert-butyl dicarbonate (5.97 gm) were charged into a 200 mL round bottomed flask. The reaction mixture was maintained for 2 hours at 30°C. The reaction mixture was filtered and the salt was washed methanol (10 mL). Aqueous sodium hydroxide solution (2.27 gm of sodium hydroxide was dissolved in 4.72 mL of water) was slowly added to the methanol layer. The mixture was heated to 55°C and agitated for 5 hours. The reaction mass was distilled off completely under vacuum at 50°C and water (25 mL) was added to the crude and the resulted solution was cooled to 0°C. Aqueous hydrochloric acid solution (10% 42 mL) was added slowly until pH reached to 2.5 and the mixture was agitated for 1 hour at 0°C. The precipitate was filtered and the wet cake was washed with water (15 mL) and the solid dried under vacuum at 45°C to yield 5.6 gm of title compound. Purity: 99.57% (by HPLC).

Example 14: Preparation of (1S,3aR,6aS)-2-tert-butoxy carbonyl)octahydrocyclopenta [c]pyrrole-1-carboxylic acid.

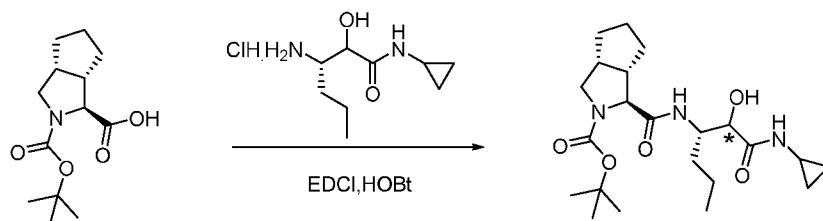


(1S,3aR,6aS)-ethyl octahydrocyclopenta[c]pyrrole-1-carboxylate hydrochloride (5 gm) and methanol (15 mL), sodium bicarbonate (2.48 gm) and Di-tert-butyl dicarbonate (5.97 gm) were charged into a 100 mL round bottomed flask. The reaction mixture was maintained for 2 hours at 28°C. The reaction mixture was filtered and the salt was washed methanol (10 mL). Aqueous sodium hydroxide solution (2.73 gm of sodium hydroxide was dissolved in 5.52 mL of water) was slowly added to the methanol layer. The mixture was heated to 55°C and agitated for 3 hours. The reaction mass was distilled off completely under vacuum at 50°C. Water (25 mL) was added to the crude and the resulted solution was cooled to 0°C. Aqueous hydrochloric acid solution (10% 35 mL) was added slowly until pH reached to 2.5 and the mixture was agitated for 1

hour at 28°C. The precipitate was filtered and the wet cake was washed with water (15 mL) and the solid dried under vacuum at 45°C to yield 5.5 gm of title compound.

Purity: 99.78% (by HPLC).

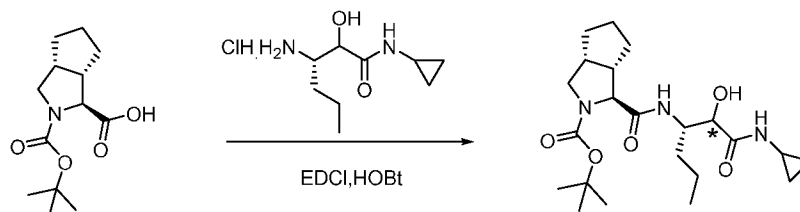
Example 15: Preparation of (1*S*,3*aR*,6*aS*)-2-*tert*-butyl 1-(((3*S*)-1-(cyclopropyl amino)-2-hydroxy-1-oxohexan-3-yl)carbamoyl)hexahydrocyclopenta[*c*]pyrrole-2-(1*H*)carboxylate



(1*S*,3*aR*,6*aS*)-2-*tert*-butoxy carbonyl)octahydrocyclopenta [c]pyrrole-1-carboxylic acid (15 gm) and tetrahydrofuran (300 mL) were charged into a 1000 mL round bottomed flask and the solution was cooled to 0°C. 1-hydroxybenzotriazole (HOBt, 7.93 gm) and 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDC HCl, 12.5 gm) were added and the resulted mixture was stirred for 15 minutes at 0°C. In another 500 mL round bottomed flask tetrahydrofuran (75 mL), (3*S*)-3-amino-*N*-cyclopropyl-2-hydroxyhexanamide hydrochloride (19.62 gm) and *N,N*-Dimethylformamide (30 mL) were charged and mixture was cooled to 5°C. Diisopropylethylamine (19.7 gm) was added and the mixture was added to the above 1000 mL flask at 0°C. Temperature of the resulted mixture was raised to 30°C and stirred for 14 hours. Tetrahydrofuran was distilled off completely under vacuum at 40°C and the mass was cooled to 25°C. Water (100 mL) and ethylacetate (200 mL) were charged and stirred for 30 minutes. The organic layer was washed with 5% aqueous sodium bicarbonate solution (90 mL X 2), 5% aqueous hydrochloric acid solution (90 mL X 2), followed by 5% aqueous sodium chloride solution (90 mL X 2). The organic layer was concentrated completely under vacuum at 40°C to yield 22.1 gm of title compound.

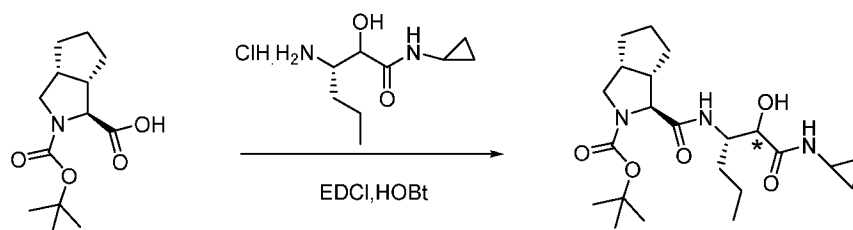
Purity by HPLC : 75.3% (*S*-isomer), 24.32% (*R*-isomer).

Example 16: Preparation of (1*S*,3*aR*,6*aS*)-2-*tert*-butyl 1-(((3*S*)-1-(cyclopropyl amino)-2-hydroxy-1-oxohexan-3-yl)carbamoyl)hexahydrocyclopenta[*c*]pyrrole-2-(1*H*)carboxylate



(1S,3aR,6aS)-2-tert-butoxy carbonyloctahydrocyclopenta [c]pyrrole-1-carboxylic acid (5 gm), ethylacetate (50 mL) 1-hydroxybenzotriazole (HOBT, 2.6 gm), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDC HCl, 4.13 gm), triethylamine (4.35 gm), (3S)-3-amino-N-cyclopropyl-2-hydroxyhexanamide hydrochloride (4.57 gm) and ethylacetate (25 mL) were charged into a 500 mL round bottomed flask and the mixture was agitated for 3 hours. Water (50 mL) and ethylacetate (25 mL) were added and the mixture was heated to 40°C. Layers were separated and the aqueous layer was extracted with ethylacetate (20 mL). Combined organic layer was washed with 2% aqueous hydrochloric acid solution (20 mL) and 2% aqueous sodium bicarbonate solution (20 mL), followed by 5% aqueous sodium chloride solution (20 mL). The organic layer was concentrated completely under vacuum at 40°C and cyclohexane (75 mL) was added to the crude and the mixture was agitated for 30 minutes. The precipitate was filtered and the wet cake was washed with cyclohexane (25 mL) and wet material was dried under vacuum at 40°C to yield 7.5 gm of title compound.

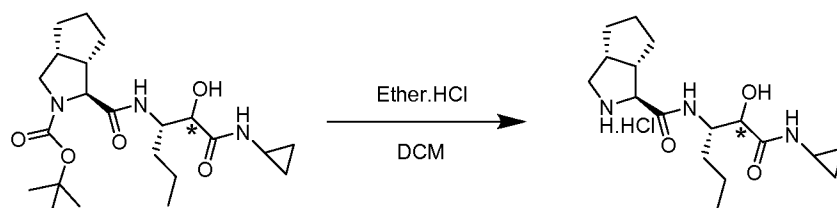
Example 17: Preparation of (1S,3aR,6aS)-2-tert-butyl 1-(((3S)-1-(cyclopropyl amino)-2-hydroxy-1-oxohexan-3-yl)carbamoyl)hexahydrocyclopenta[c]pyrrole-2-(1H)carboxylate



(1S,3aR,6aS)-2-tert-butoxy carbonyloctahydrocyclopenta [c]pyrrole-1-carboxylic acid (10 gm), ethylacetate (150 mL) 1-hydroxybenzotriazole (HOBT, 5.26 gm), 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDC HCl, 11.23 gm), triethylamine (12 mL), (3S)-3-amino-N-cyclopropyl-2-hydroxyhexanamide hydrochloride

(8.7 gm) were charged into a 500 mL round bottomed flask and the mixture was agitated for 5 hours. Water (90 mL) and ethylacetate (150 mL) were added and the mixture was agitated for 10 minutes. Layers were separated and the aqueous layer was extracted with ethylacetate (50 mL). Combined organic layer was washed with 2% aqueous citric acid solution (50 mL) and 2% aqueous sodium bicarbonate solution (50 mL), followed by 5% aqueous sodium chloride solution (50 mL). The organic layer was concentrated to 120 mL and used in the next step.

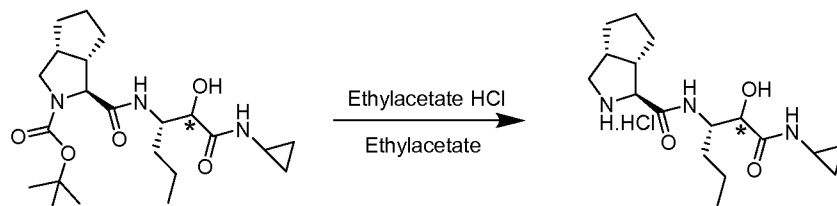
Example 18: Preparation of (1S,3aR,6aS)-N-((3S)-1-(cyclopropyl amino)-2-hydroxy-1-oxohexan-3-yl)carbamoyl)octahydrocyclopenta[c]pyrrole-1-carboxamide hydrochloride



(1S,3aR,6aS)-2-tert-butyl-1-(((3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl)carbamoyl)hexahydrocyclopenta[c]pyrrole-2-(1H)carboxylate (25 gm) and dichloromethane (500 mL) were charged into a 1000 mL round bottomed flask and the solution was cooled to 0°C. Ethereal hydrochloride (hydrochloride gas dissolved in diethyl ether, 100 mL) was slowly added at 0°C. Temperature was raised to 30°C and the mixture was stirred for 12 hours at 30°C. The reaction mixture was concentrated completely under vacuum at 30°C to yield 20.6 gm of the title compound.

Purity by HPLC: 60.5% (S-isomer), 30.9% (R-isomer).

Example 19: Preparation of (1S,3aR,6aS)-N-((3S)-1-(cyclopropyl amino)-2-hydroxy-1-oxohexan-3-yl)carbamoyl)octahydrocyclopenta[c]pyrrole-1-carboxamide hydrochloride

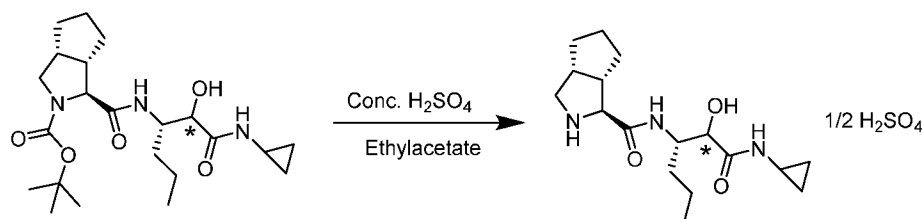


(1S,3aR,6aS)-2-tert-butyl-1-(((3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl)carbamoyl)hexahydrocyclopenta[c]pyrrole-2-(1H)carboxylate (5 gm),

methanol (2 mL) and ethylacetate (15 mL) were charged into a 100 mL round bottomed flask and the solution was cooled to 0°C. Ethylacetate hydrochloride (hydrochloride gas dissolved in ethylacetate, 17 mL) was slowly added at 0°C. The mixture was heated to 30°C and agitated for 4 hours. Ethylacetate (25 mL) was added to the reaction mixture and agitated for 1 hour to 0°C. The mixture was filtered and the wet material was washed with ethylacetate (5 mL). The compound was dried under vacuum at 40°C to yield 4.0 gm of the title compound.

Purity by HPLC: 67.42% (S-isomer): 30.14% (R-isomer)

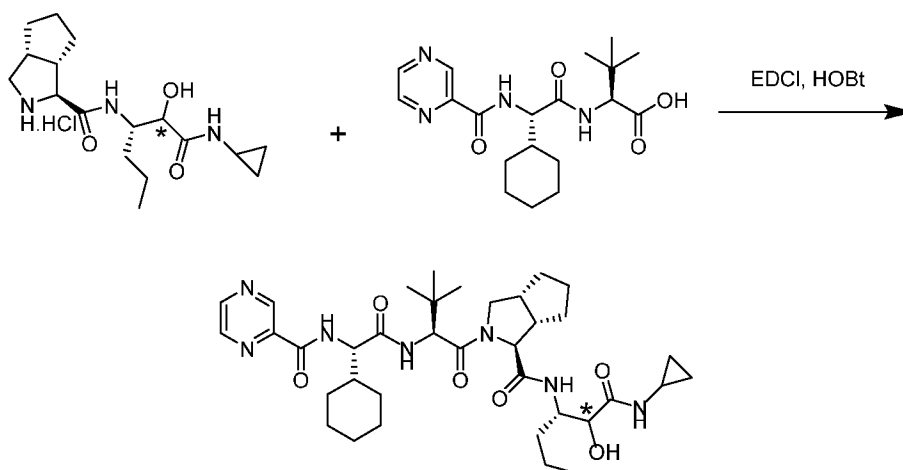
Example 20: Preparation of (1S,3aR,6aS)-N-((3S)-1-(cyclopropyl amino)-2-hydroxy-1-oxohexan-3-yl)carbamoyl)octahydrocyclopenta[c]pyrrole-1-carboxamide hemisulphate



Organic layer obtained from the example 17 (120 mL) and methanol (8.5 mL) were charged into a 500 mL round bottomed flask and the solution was cooled to 0°C. Sulfuric acid (2.5 mL) was slowly added at 0°C. The mixture was heated to 40°C and agitated for 8 hours. Ethylacetate (165 mL) was added to the reaction mixture and agitated for 1 hour to 5°C and the precipitate was filtered. The wet material, ethyl acetate (140 mL) and methanol (7 mL) were charged into a 500 mL round bottomed flask and the mixture was agitated for 1 hour. The precipitate was filtered was washed with ethylacetate (40 mL). The compound was dried under vacuum at 60°C to yield 12.7 gm of the title compound.

Purity by HPLC: 58.46% (S-isomer), 40.54% (R-isomer).

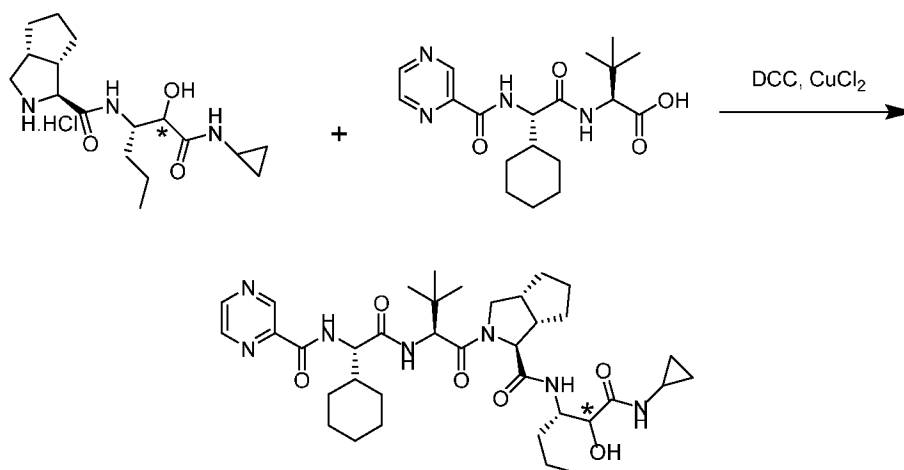
Example 21: Preparation of (1S,3aR,6aS)-2-((S)-2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoyl)-N-((3S)-1-(cyclopropyl amino)-2-hydroxy-1-oxohexan-3-yl)octahydrocyclopenta[c]pyrrole-1-carboxamide



(1S,3aR,6aS)-N-((3S)-1-(cyclopropyl amino)-2-hydroxy-1-oxohexan-3-yl)carbonyl)octahydrocyclopenta[c]pyrrole-1-carboxamide hydrochloride (0.95 gm) and N,N-dimethylformamide (10 mL) were charged into a 250 mL round bottomed flask. 1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride (EDC HCl, 1.0 gm) and dimethylaminopyridine (0.3 gm) were charged and the reaction mixture was stirred for 30 minutes at 28°C. The reaction mixture cooled to 2°C and N,N-dimethylformamide solution of (S)-2-((R)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoic acid (1.0 gm in 10 mL of N,N-dimethylformamide) was added and the reaction mixture was stirred for 3 hours at 5°C. Temperature was raised to 28°C and stirred for 15 hours. The reaction mixture was cooled to 0°C and water (20 mL) added and stirred for 30 minutes at 5°C. The precipitation was filtered and the wet cake was washed with water (5 mL) and dried the compound in vacuum at 30°C to yield 1.1 gm of title compound.

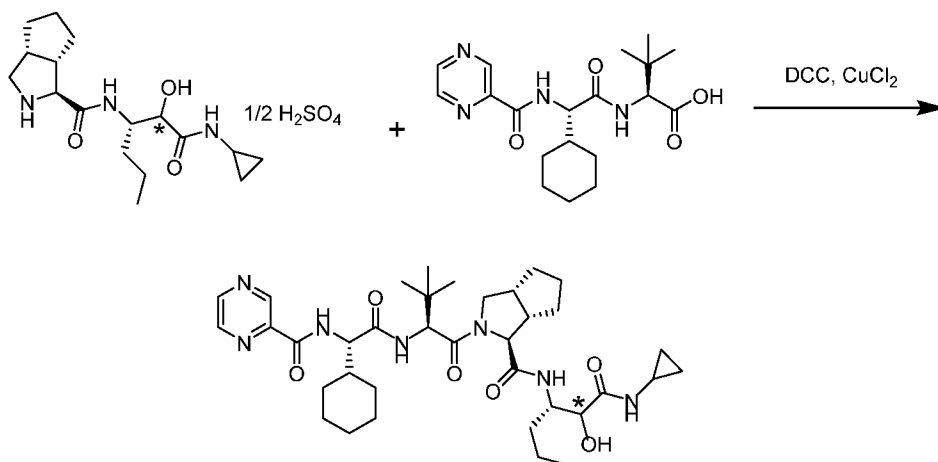
Purity by HPLC: 56.1% (S-isomer), 24.9% (R-isomer).

Example 22: Preparation of (1S,3aR,6aS)-2-((S)-2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoyl)-N-((3S)-1-(cyclopropyl amino)-2-hydroxy-1-oxohexan-3-yl)octahydrocyclopenta[c]pyrrole-1-carboxamide



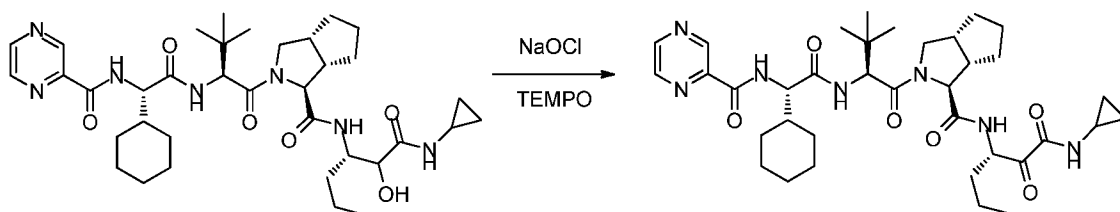
(1S,3aR,6aS)-N-((3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl)carbamoyloctahydrocyclopenta[c]pyrrole-1-carboxamide hydrochloride (10 gm) and N,N-dimethylformamide (60 mL) were charged into a 500 mL round bottomed flask and cooled to 0°C. Copper(II) chloride dihydrate (4.7 gm), dicyclohexylcarbodiimide (6 gm), triethylamine (4.6 mL) and (S)-2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoic acid (11.5 gm) were added and the reaction mixture was agitated for 10 hours at 0°C. Ethylacetate (100 mL) was added to the reaction mixture and heated to 28°C and stirred for 15 minutes. The reaction mixture was filtered and the salt was washed with ethylacetate (100 mL). Water (100 mL) was added to the ethylacetate layer and the resulted solution was agitated for 10 minutes. Layers were separated and the aqueous layer was extracted with ethylacetate (100 mL). The ethylacetate layers were combined and washed with 20% aqueous ammonium chloride (200 mL), 5% aqueous hydrochloric acid solution (100 mL) and 5% aqueous sodium bicarbonate solution (100 mL) followed by 10% aqueous sodium chloride solution (100 mL) and the ethylacetate layer was concentrated under vacuum. Diisopropyl ether (50 mL) was added to the crude and agitated for 30 minutes at 28°C. The precipitation was filtered and the wet cake was washed with diisopropyl ether (30 mL) and dried the compound in vacuum at 30°C to yield 15.4 gm of title compound. Purity by HPLC: 64.57% (S-isomer), 22.49% (R-isomer).

Example 23: Preparation of (1S,3aR,6aS)-2-((S)-2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoyl)-N-((3S)-1-(cyclopropyl amino)-2-hydroxy-1-oxohexan-3-yl)octahydrocyclopenta[c]pyrrole-1-carboxamide



(1S,3aR,6aS)-N-((3S)-1-(cyclopropyl amino)-2-hydroxy-1-oxohexan-3-yl)carbamoyl)octahydrocyclopenta[c]pyrrole-1-carboxamide (5 gm) and dichloromethane (30 mL) were charged into a 500 mL round bottomed flask. Copper(II) chloride dihydrate (1.6 gm) was added and the mixture was cooled to 5°C. Dicyclohexylcarbodiimide (3.1 gm), triethylamine (2.4 mL) and (S)-2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoic acid (5.5 gm) were added and the reaction mixture was agitated for 8 hours at 15°C. The reaction mixture was filtered and the salt was washed with dichloromethane (30 mL). The organic layer was washed with 5% EDTA (2 X 50 mL) and concentrated under vacuum. Methanol (10 mL) and sodium hydroxide (0.5 gm) were added to the crude and agitated for 30 minutes at 28°C and concentrated under vacuum. Ethylacetate (50 mL) was added to the crude and agitated for 10 minutes. Water (50 mL) was added to the crude and agitated for 10 minutes. Layers were separated and the organic layer was washed with 10% aqueous sodium chloride solution (50 mL) and the organic layer was concentrated under vacuum. Diisopropylether (25 mL) was added to the crude and agitated for 30 minutes. The precipitation was filtered and the wet cake was washed with diisopropyl ether (15 mL) and dried the compound in vacuum at 60°C to yield 7.6 gm of title compound. Purity by HPLC: 56.01% (S-isomer), 31.46% (R-isomer)

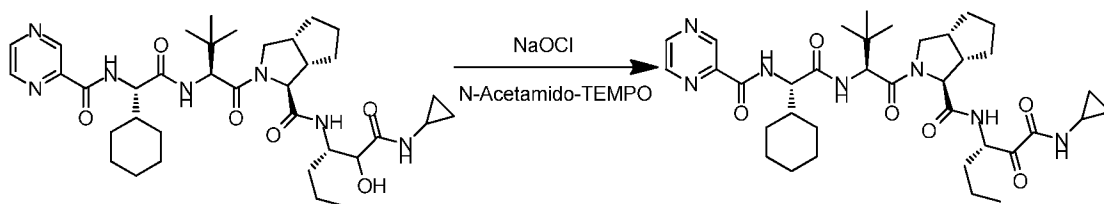
Example 24: Preparation of (1S,3aR,6aS)-2-((S)-2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoyl)-N-((S)-1-(cyclopropyl amino)-1,2-dioxohexan-3-yl)octahydrocyclopenta[c]pyrrole-1-carboxamide (Telaprevir)



(1S,3aR,6aS)-2-((S)-2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoyl)-N-((3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl)-octahydrocyclopenta[c]pyrrole-1-carboxamide (12 gm), dichloromethane (180 mL) and 15% aqueous sodium bromide solution (7.57 mL) were charged into 1000 mL round bottomed flask and 7.5% aqueous sodium bicarbonate solution (30.3 mL) was added to the reaction mixture and the mixture was cooled to 5°C. TEMPO solution (408 mg of TEMPO in 10 mL of dichloromethane) and 12.5% aqueous sodium hypochlorite (11.7 mL) were added to the reaction mixture at 0°C and the reaction mixture was stirred for 2 hours at 5°C. The organic layer was separated and was quenched with 10% aqueous sodium sulphite solution (60 mL) and the resulted mixture was stirred for 15 minutes. The organic layer was separated and washed with water (60 mL) and the organic layer was dried with anhydrous sodium sulphate and concentrated under vacuum completely. Ethyl acetate (100 mL) was charged into the residue and the resulted solution was stirred for 2 hours at 28°C. The precipitate was filtered and the wet cake was washed with ethyl acetate (20 mL) and the solid was dried under vacuum at 30°C to yield 5.2 gm of telaprevir.

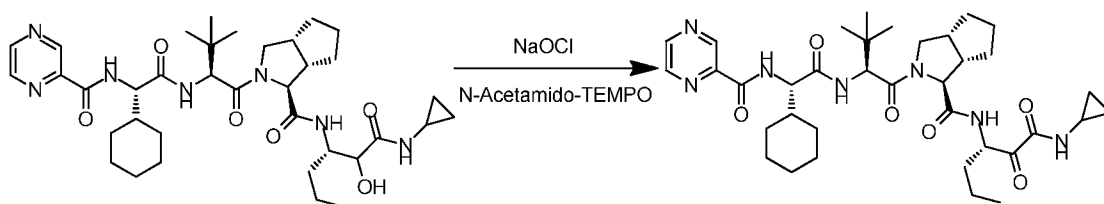
Purity: 96.7 (by HPLC); PXRD pattern: Figure 1.

Example 25: Preparation of (1S,3aR,6aS)-2-((S)-2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoyl)-N-((S)-1-(cyclopropyl amino)-1,2-dioxohexan-3-yl)octahydrocyclopenta[c]pyrrole-1-carboxamide (Telaprevir)



(1S,3aR,6aS)-2-((S)-2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoyl)-N-((3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl)-octahydrocyclopenta[c]pyrrole-1-carboxamide (10 gm) and dichloromethane (100 mL) were charged into a 500 mL round bottomed flask and cooled to 0°C. Potassium bromide (0.34 gm), sodium bicarbonate (9.8 gm) and N-Acetamido-TEMPO (0.31 gm) were added to the reaction mixture and the mixture is agitated for 10 minutes. 10% aqueous sodium hypochlorite (13.1 mL) was slowly added to the reaction mixture at 0°C and the reaction mixture was agitated for 2 hours at 10°C. The reaction mixture was filtered and washed with dichloromethane (30 mL). 10% aqueous hypo solution (100 mL) was added to the organic layer and the solution was agitated for 10 minutes. Layers were separated and the aqueous layer was extracted with dichloromethane (50 mL). Organic layers were combined and washed with 10% aqueous sodium chloride solution (100 mL) and the organic layer was concentrated under vacuum completely. Ethyl acetate (50 mL) was added to the residue and the resulted solution was stirred for 2 hours at 28°C. The precipitate was filtered and the wet cake was washed with ethyl acetate (20 mL) and the solid was dried under vacuum at 30°C to yield 7.0 gm of telaprevir. Purity: 96.5 (by HPLC); XRD pattern: similar to figure 1.

Example 26: Preparation of (1S,3aR,6aS)-2-((S)-2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoyl)-N-((S)-1-(cyclopropyl amino)-1,2-dioxohexan-3-yl)octahydrocyclopenta[c]pyrrole-1-carboxamide (Telaprevir)

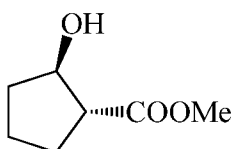


(1S,3aR,6aS)-2-((S)-2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoyl)-N-((3S)-1-(cyclopropylamino)-2-oxohexan-3-yl)-octahydrocyclopenta[c]pyrrole-1-carboxamide (Telaprevir)

hydrocyclopenta[c]pyrrole-1-carboxamide (5 gm) and ethylacetate (50 mL) were charged into a 500 mL round bottomed flask. Potassium bromide (0.18 gm), sodium bicarbonate (3.7 gm) and N-Acetamido-TEMPO (0.15 gm) were added to the reaction mixture and cooled to 0°C and the mixture is agitated for 10 minutes. 10% aqueous sodium hypochlorite (5.5 mL) was slowly added to the reaction mixture at 0°C and the reaction mixture was agitated for 2 hours at 0°C. Water (50 mL) was added to the reaction mixture and the resulted solution was agitated for 10 minutes. Layers were separated and the organic layer was concentrated under vacuum completely. A mixture of acetonitrile and water (9:1, 10 mL) was added to the residue and the resulted solution was stirred for 30 minutes at 28°C. The precipitate was filtered and the wet cake was washed with acetonitrile (5 mL) and the solid was dried under vacuum at 43°C to yield 3.2 gm of telaprevir.

Purity: 96.99% (by HPLC); XRD pattern: similar to Figure 1.

Example 27: Preparation of (1R,2R)-methyl 2-hydroxycyclopentanecarboxylate



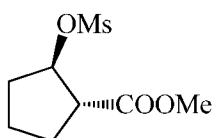
Acetone (375 mL), Bis(2-methylallyl)-(1,5-cyclooctadiene ruthenium (II) (170 mg) and (*R*)-(+)-(1,1'-Binaphthalene-2,2'-diyl)bis(diphenylphosphine) (R-BINAP, 365 mg) are charged into 1000 mL round bottom flask under nitrogen atmosphere. The mixture was sonicated for 20 minutes and cooled to 28°C. 0.2 M methanolic hydrobromide solution (18.9 mL) was added to the mixture at 28°C and the mixture was stirred for 30 minutes. The reaction mixture was concentrated under reduced pressure at 40°C to Ru-BINAP catalyst.

The above freshly prepared Ru-BINAP catalyst, 2-Methoxycarbonyl cyclopentanone (150 g), methanol (1050 mL) are charged into autoclave at 28°C. The autoclave was flushed three times with nitrogen and one time with hydrogen. The vessel was filled with hydrogen pressure at 11 kg/cm², and then heated to 65°C. The reaction mixture was stirred for 5 hours under hydrogen pressure at 65°C. The reaction mixture was cooled to 28°C and unloaded from autoclave. The mixture was concentrated under

reduced pressure at 50°C. The crude was distilled under reduced pressure at 130°C to get 135 g of the title compound as colorless oil.

¹H NMR (400 MHz, CDCl₃) : δ 1.57-1.69 (m, 2H), 1.71-1.81 (m, 2H), 1.92-2.05 (m, 2H), 2.42 (brs, 1H), 2.64 (m, 1H), 3.70 (s, 3H) 3.71 (m, 1H) 4.35 (m, 1H)

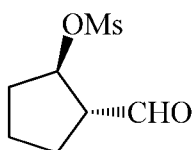
Example 28: Preparation of (1R,2R)-methyl-2-((methanesulfonyl)oxy)cyclopentene carboxylate



(1R,2R)-methyl 2-hydroxycyclopentanecarboxylate (5 g) and Dichloromethane (50 mL) were charged into a 100 mL round bottom flask and mixture was cooled to 0°C. Triethylamine (9.6 mL) was added to the mixture at 0°C over a period of 10 minutes. Methanesulfonylchloride (2.9 mL) was added to the mixture at 0°C over a period of 10 minutes. The mixture was heated to 30°C and stirred for 2 hours. Water (50 mL) was added to the reaction mixture and stirred for 10 minutes. Organic layer was separated and the aqueous layer was extracted with Dichloromethane (2X25 mL). The organic layers were combined and dried with anhydrous sodium sulphate (5 gm) and concentrated completely under vacuum. The resulted residue was purified by column chromatography to yield 5.2 g of the title product as yellow oil.

¹H NMR (400 MHz, CDCl₃): δ 1.73-1.85 (m, 3H), 1.94-2.01 (m, 2H), 2.10-2.18 (m, 2H), 3.01 (s, 3H), 3.05 (m, 1H), 3.72 (s, 3H), 5.27 (m, 1H).

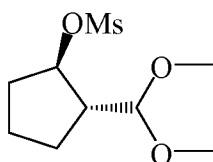
Example 29: Preparation of (1R,2R)-2-formylcyclopentyl methanesulfonate



The compound obtained in Example 28 (1 g) was charged into a 100 mL round bottom flask and Tetrahydrofuran (15 mL) was added under nitrogen atmosphere. The mixture was cooled to -78°C and Diisobutylaluminum hydride (DIBAL-H, 1M in Toluene, 5.4 mL) was added over a period of 20 minutes at -78°C and the reaction mixture was

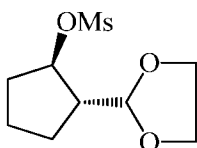
stirred for 3 hours at -78°C . The reaction mixture was quenched with methanol (2 mL) at -78°C and Rochelle salt solution (2M aqueous solution, 5 mL) was slowly added to the resulted solution at -78°C . The resulted solution was slowly heated to 30°C and filtered through a celite bed. Organic layer was separated and the aqueous layer was extracted with ethylacetate (3X15 mL). The organic layers were combined, and washed with water (20 mL) and brine solution (10 mL). The organic layer was dried with anhydrous sodium sulphate (2 gm) and concentrated completely under vacuum to yield 500 mg of the title product. The obtained crude material was taken up for the next reaction without any further purification.

Example 30: Preparation of (1R,2R)-2-(dimethoxymethyl)cyclopentyl methanesulfonate



The compound obtained in Example 29 (150 mg) and Methanol (3 mL) were charged into a 50 mL round bottom flask. Trimethylorthoformate (0.93 mL) and p-Toluene sulfonic acid (5 mg) were added at 30°C and the resulting mixture was stirred for 16 hours at 30°C . Potassium carbonate (50 mg) was added to the reaction mixture and the resulted mixture was concentrated under vacuum at 30°C . Water (5 mL) was added to the residue and the solution was extracted with ethylacetate (2X10 mL). The ethylacetate layers were combined and washed with water (5 mL) and brine solution (5 mL). The organic layer was dried with anhydrous sodium sulphate (1 gm) and concentrated completely under vacuum to yield 90 mg of the title product as dark blue oil.

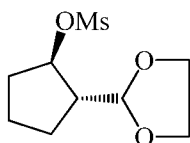
Example 31: Preparation of (1R,2R)-2-(1,3-dioxolan-2-yl)cyclopentyl methanesulfonate



The compound obtained in Example 29 (150 mg) and Toluene (3 mL) were charged into a 50 mL round bottom flask. Ethylene glycol (0.5 mL) and p-Toluene

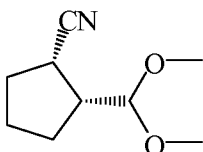
sulfonic acid (5 mg) were added at 30°C and the resulting mixture was stirred for 16 hours at 30°C. Water (5 mL) and ethylacetate (2X10 mL) were added to the reaction mixture and the organic later was separated. The aqueous layer was extracted with ethylacetate (10 mL). The ethylacetate layers were combined and washed with water (10 mL) and brine solution (10 mL). The organic layer was dried with anhydrous sodium sulphate (1 gm) and concentrated completely under vacuum to yield 100 mg of the title product as oil.

Example 32: Preparation of (1R,2R)-2-(1,3-dioxolan-2-yl)cyclopentyl methanesulfonate



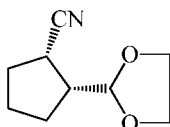
(1R,2R)-methyl-2-((methylsulfonyl)oxy)cyclopentene carboxylate (30 g) was charged into a 1000 mL round bottom flask and Toluene (300 mL) was added under nitrogen atmosphere. The mixture was cooled to -78°C and Diisobutylaluminum hydride (DIBAL-H, 1M in Toluene, 202.5 mL) was added over a period of 3 hours at -78°C and the reaction mixture was stirred for 2 hours at -78°C. The reaction mixture was quenched with methanol (5 mL) at -78°C. Saturated NH₄Cl solution (250 mL) was slowly added to the mixture at -78°C and the resulted solution was slowly heated to 30°C and filtered through a celite bed. The bed was washed with toluene (200 mL). The organic layer was separated and washed with saturated NaHCO₃ solution (500 mL). The organic layer was dried with anhydrous sodium sulphate (20 gm) and the organic layer was charged into a 1000 mL round bottom flask. Ethylene glycol (150 mL) and p-Toluene sulfonic acid (3.4 g) were added at 30°C and the resulting mixture was stirred for 16 hours at 30°C. Water (300 mL) was added to the reaction mixture and the resulted solution was stirred for 10 minutes. The organic later was separated and washed with saturated NaHCO₃ solution (2X250 mL). The organic layer was dried with anhydrous sodium sulphate (20 g) and concentrated completely under vacuum to yield 14 g of the title product as pale yellow syrup.

Example 33: Preparation of (1S,2R)-2-(dimethoxymethyl)cyclopentanecarbonitrile



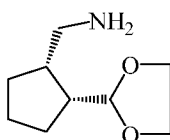
The compound obtained in Example 30 (100 mg) and Dimethylformamide (3 mL) were charged into a 25 mL round bottom flask. Sodium cyanide (103 mg) was added at 30°C. The mixture was heated to 80°C and stirred for 16 hours at 80°C. The reaction mixture was cooled to 30°C and water (20 mL) was added. The resulted solution was extracted with ethylacetate (2X10 mL). The ethylacetate layers were combined and washed with water (10 mL) and brine solution (10 mL). The organic layer was dried with anhydrous sodium sulphate (1 gm) and concentrated completely under vacuum. The crude was purified by column chromatography (10% ethylacetate in hexane) to yield 20 mg of the title product as oil.

Example 34: Preparation of (1S,2R)-2-(1,3-dioxolan-2-yl)cyclopentanecarbonitrile



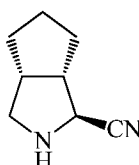
The compound obtained in Example 30 (100 mg) and Dimethylformamide (3 mL) were charged into a 25 mL round bottom flask. Sodium cyanide (102 mg) was added at 30°C. The mixture was heated to 80°C and stirred for 16 hours at 80°C. The reaction mixture was cooled to 30°C and water (20 mL) was added. The resulted solution was extracted with ethylacetate (2X10 mL). The ethylacetate layers were combined and washed with water (10 mL) and brine solution (10 mL). The organic layer was dried with anhydrous sodium sulphate (1 gm) and concentrated completely under vacuum to yield 40 mg of the title product as dark blue oil.

Example 35: Preparation of ((1S,2R)-2-(1,3-dioxolan-2-yl)cyclopentyl)methanamine



The compound obtained in Example 34 (2.5 g) and Methanol (25 mL) were charged into a 100 mL round bottom single neck flask. Raney Nickel (1.5 g) was charged in the mixture under nitrogen atmosphere. Using a balloon hydrogen gas is applied and the reaction mixture is maintained for 16 hours at 27°C. Under nitrogen atmosphere the reaction mixture was filtered through a celite bed and the celite bed was washed with methanol (25 mL). The filtrate was concentrated completely under reduced pressure to get 2.0 g of the title product as pale green syrup.

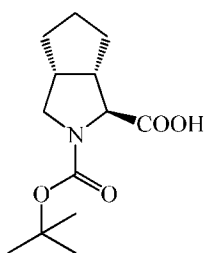
Example 36: Preparation of (1S,3aR,6aS)-octahydrocyclopenta[c]pyrrole-1-carbonitrile



The compound obtained in Example 35 (500 mg), 1N HCl (50 mL) and KCN (760 mg) were charged into a 250 mL round bottom flask at 30°C and the resulting mixture was stirred for 16 hours at 30°C. 30% KOH solution (5 mL) was added to the reaction mixture and extracted with dichloromethane (2X25 mL). The organic layer was dried with anhydrous sodium sulphate (1 gm) and concentrated completely under vacuum. The crude was purified by column chromatography (20% ethylacetate in hexane) to yield 200 mg of the title compound as brown liquid.

¹H NMR (400 MHz, CDCl₃): δ 1.29-1.42 (m, 2H), 1.44-1.51 (m, 1H), 1.61-1.70 (m, 1H), 1.83-1.97 (m, 2H), 2.68 (m, 1H), 2.78 (dd, 1H, *J* = 9.8 Hz, 2 Hz), 3.24 (dd, 1H, *J* = 10 Hz, 7.6 Hz), 3.68 (d, 1H, *J* = 2 Hz).

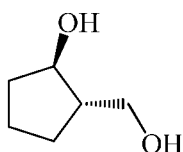
Example 37: Preparation of (1S,3aR,6aS)-2-(tert-butoxycarbonyl)octahydrocyclopenta[c]pyrrole-1-carboxylic acid



The compound obtained in Example 36 (200 mg) and concentrated HCl (2 mL) were charged into a 50 mL round bottom flask at 30°C and the resulting mixture was stirred for 16 hours at 100°C. The reaction mixture was concentrated under vacuum and the obtained crude was dissolved in methanol (2 mL), triethylamine (0.4 mL) and di-tert-butyl dicarbonate (Boc₂O, 400 mg) at 0°C. The resulting mixture was stirred for 2 hours at 30°C and the reaction mixture was concentrated under vacuum and diluted with saturated NaHCO₃ solution (20 mL) and extracted with ethyl acetate (25 mL). The aqueous solution was acidified using citric acid to pH ~5 and the aqueous solution was extracted with ethyl acetate (25 mL). Organic layer was dried with anhydrous sodium sulphate (1 gm) and concentrated completely under vacuum to yield 250 mg of the title compound as a white solid.

¹H NMR (400 MHz, DMSO-d₆): δ 1.33 & 1.38 (2s, 9H), 1.43 (m, 1H), 1.51 (m, 2H), 1.63-1.68 (m, 1H), 1.71 (m, 1H), 1.89 (m, 1H), 2.58 (m, 2H), 3.13 (dd, 1H, *J* = 10.8 Hz, 2.8 Hz), 3.51 (m, 1H), 3.87 (dd, 1H, *J* = 2.8 Hz, 26 Hz); **¹³C NMR** (100 MHz, DMSO-d₆): δ 25.58, 28.35, 28.52, 32.34, 32.44, 33.05, 41.34, 42.29, 47.90, 48.96, 52.88, 53.00, 65.73, 66.01, 79.14, 153.87, 154.28, 174.17, 174.56

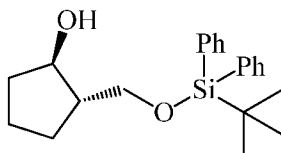
Example 38: Preparation of (1R,2S)-2-(hydroxymethyl)cyclopentanol



Lithium aluminum hydride (7.8 g) and Tetrahydrofuran (200 mL) were charged into a 1000 mL round bottom flask under nitrogen atmosphere and the mixture was cooled to 0°C. The compound obtained in Example 27 (50 g) was dissolved in Tetrahydrofuran (200 mL) and the resulted solution was charged into the reaction mixture at 0°C over a period of 20 minutes. Temperature was raised to 28°C and the reaction mixture was stirred for 2 hours at 28°C. The reaction mixture was quenched with saturated aqueous sodium sulphate (70 mL). The precipitation was filtered and the cake was washed with ethyl acetate (2 X 100 mL). The organic layer was concentrated completely under vacuum to yield 20 g of the title product as colorless oil.

¹H NMR (400 MHz, DMSO-d₆): δ 1.26-1.40 (m, 2H), 1.52-1.88 (m, 5H), 3.20 (dd, 1H, *J* = 10.6 Hz, 6.4 Hz), 3.34 (dd, 1H, *J* = 10.6 Hz, 6.4 Hz), 3.75 (m, 1H), 4.36 (m, 2H).

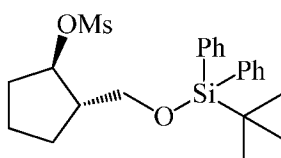
Example 39: Preparation of (1R,2S)-2-(((tert-butyldiphenylsilyl)oxy)methyl)cyclopentanol



The compound obtained in Example 38 (2.5 g) and Dichloromethane (50 mL) were charged into a 250 mL round bottom flask and the resulted solution was cooled to 0°C. Imidazole (3.5 g) and tert-Butylchlorodiphenylsilane (5.9 g) were added at 0°C and the resulting mixture was stirred for 2 hours at 28°C. Water (100 mL) was added to the reaction mixture and the resulted solution was extracted with Dichloromethane (2 X 50 mL). The organic layers were combined and dried with anhydrous sodium sulphate (5 gm) and concentrated completely under vacuum. The crude was purified by column chromatography (20% ethylacetate in hexane) to yield 5.7 g of the title product as colorless oil.

¹H NMR (400 MHz, CDCl₃) : δ 1.05 (s, 9H), 1.15 (m, 1H), 1.60 (m, 2H), 1.73 (m, 2H), 1.94 (m, 1H), 2.02 (m, 1H), 2.46 (brs, 1H), 3.54 (t, 1H, *J* = 9.6 Hz), 3.78 (dd, 1H, *J* = 10.2 Hz, 5.2 Hz), 4.09 (q, 1H), 7.42 (m, 6H), 7.67 (m, 4H).

Example 40: Preparation of (1R,2S)-2-(((tert-butyldiphenylsilyl)oxy)methyl)cyclopentyl methanesulfonate

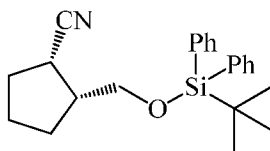


The compound obtained in Example 39 (5 g) and Dichloromethane (100 mL) were charged into a 250 mL round bottom flask and mixture was cooled to 0°C. Triethylamine (4.3 mL) was added to the mixture at 0°C over a period of 10 minutes. Methanesulfonylchloride (1.3 mL) was added to the mixture at 0°C over a period of 20 minutes. The mixture was heated to 28°C and stirred for 2 hours. Water (50 mL) was added to the reaction mixture and stirred for 10 minutes. Organic layer was separated

and the aqueous layer was extracted with Dichloromethane (2 X100 mL). The organic layers were combined and washed with saturated sodium bicarbonate solution (2 X100 mL) followed by washing with brine solution (2 X 50 mL). The organic layer was dried with anhydrous sodium sulphate (10 gm) and concentrated completely under vacuum to yield 5 g of the title product as brown color solid.

¹H NMR (400 MHz, CDCl₃): δ 1.06 (s, 9H), 1.39 (m, 1H), 1.60-1.80 (m, 2H), 1.86-1.98 (m, 3H), 2.36 (m, 1H), 2.92 (s, 3H), 3.50 (dd, 1H, *J* = 10.2 Hz, 6.8 Hz), 3.69 (dd, 1H, *J* = 10.2 Hz, 5.2 Hz), 5.08 (m, 1H), 7.39 (m, 6H), 7.63 (m, 4H)

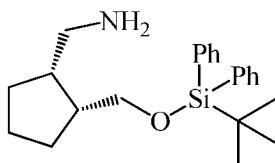
Example 41: Preparation of (1S,2R)-2-(((tert-butylidiphenylsilyl)oxy)methyl)cyclopentanecarbonitrile



The compound obtained in Example 40 (5 g) and Dimethylformamide (50 mL) were charged into a 250 mL round bottom flask. Sodium cyanide (1.13 g) was added at 28°C. The mixture was heated to 60°C and stirred for 16 hours at 60°C. The reaction mixture was cooled to 30°C and water (100 mL) was added. The resulted solution was extracted with ethylacetate (2X100 mL). The ethylacetate layers were combined and washed with water (100 mL). The organic layer was dried with anhydrous sodium sulphate (1 gm) and concentrated completely under vacuum. The crude was purified by column chromatography (10% ethylacetate in hexane) to yield 2.5 g of the title product as colorless oil.

¹H NMR (400 MHz, CDCl₃) : δ 1.07(s, 9H), 1.40-1.52 (m, 1H), 1.65-1.80 (m, 2H), 1.87 (m,1H), 1.95-2.10 (m, 2H), 2.31 (m, 1H), 3.10 (m, 1H), 3.80 (d, 2H, *J* = 7.2 Hz), 7.42 (m, 6H), 7.70 (m, 4H).

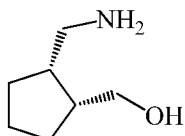
Example 42: Preparation of ((1S,2R)-2-(((tert-butylidiphenylsilyl)oxy)methyl)cyclopentyl)methanamine



The compound obtained in Example 41 (2.5 g) and Ethanol (25 mL) were charged into a 100 mL round bottom single neck flask. Raney Nickel (1 g) was charged in the mixture under nitrogen atmosphere. Using a balloon hydrogen gas is applied and the reaction mixture is maintained for 16 hours at 27°C. Under nitrogen atmosphere the reaction mixture was filtered through a celite bed and the celite bed was washed with ethanol (25 mL). The filtrate was concentrated completely under reduced pressure to get 2.2 g of the title product as yellowish syrup.

¹H NMR (400 MHz, DMSO-d₆): δ 1.02 (s, 9H), 1.23-1.36 (m, 1H), 1.40-1.51 (m, 2H), 1.53-1.72 (m, 3H), 1.91 (m, 1H), 2.18 (m, 1H), 2.41 (dd, 1H, *J* = 12.2 Hz, 8.4 Hz), 2.62 (dd, 1H, *J* = 9.2 Hz, 6 Hz), 3.50 (dd, 1H, *J* = 10.4 Hz, 6.8 Hz), 3.65 (dd, 1H, *J* = 10 Hz, 6.4 Hz), 7.44 (m, 6H), 7.60 (m, 4H).

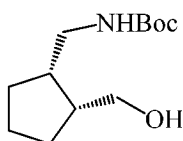
Example 43: Preparation of ((1R,2S)-2-(aminomethyl)cyclopentyl)methanol



The compound obtained in Example 42 (2.2 g) and Methanolic hydrochloride (20 mL) was charged into a 100 mL round bottom flask and the resulted mixture was stirred for 2 hours at 28°C. The reaction mixture was evaporated to dryness under reduced pressure. Diethyl ether (25 mL) was added to the obtained crude and the resulted mixture was concentrated under reduced pressure to yield 650 mg of the title product as yellowish syrup.

¹H NMR (400 MHz, DMSO-d₆): δ 1.26-1.49 (m, 3H), 1.51-1.74 (m, 3H), 2.15 (m, 2H), 2.72 (m, 1H), 2.98 (m, 1H), 3.39 (m, 2H), 7.90 (brs, 3H).

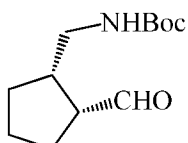
Example 44: Preparation of tert-butyl (((1S,2R)-2-(hydroxymethyl)cyclopentyl)methyl) carbamate



The compound obtained in Example 43 (600 mg) and Methanol (6 mL) were charged into a 50 mL round bottom flask. Triethylamine (0.9 mL) was added the mixture at 0°C. Boc anhydride (1.2 mL) was added at 0°C and the resulted mixture was stirred for 1 hour at 28°C. The reaction mixture was concentrated under reduced pressure. Water (50 mL) was added to the crude and the obtained solution was extracted with Dichloromethane (2X 50 mL). The combined organic layer was dried over anhydrous sodium sulfate (2 g) and concentrated under reduced pressure. The crude was purified by column chromatography (10% ethylacetate in hexane) to yield 400 mg of the title compound as white solid.

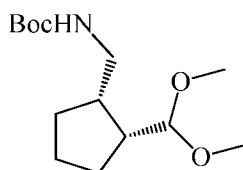
¹H NMR (400 MHz, CDCl₃): δ 1.23-1.42 (m, 2H), 1.44 (s, 9H), 1.48-1.71 (m, 2H), 1.73-2.02 (m, 2H), 2.10-2.24 (m, 2H), 3.14 (d, 1H, *J* = 7.2 Hz), 3.60 (m, 2H).

Example 45: Preparation of tert-butyl (((1S,2R)-2-formylcyclopentyl)methyl)carbamate



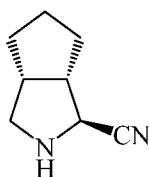
The compound obtained in Example 44 (200 mg) and Dichloromethane (4 mL) were charged into a 25 mL round bottom flask and the mixture was cooled to 0°C. Dess-Martin Periodinane (DMP, 740 mg) was added and the reaction mixture was stirred at 28°C for 2 hours. Dichloromethane was evaporated under Nitrogen atmosphere. To the residue diethyl ether (15 mL) and hexane (25 mL) were charged and the resulted mixture was stirred for 10 minutes. The precipitation was filtered and the filtrate was concentrated under reduced pressure to yield 150 mg of the title product as brownish oil. The obtained crude material was taken up for next reaction without any further purification.

Example 46: Preparation of tert-butyl (((1S,2R)-2-(dimethoxymethyl)cyclopentyl)methyl)carbamate



The compound obtained in Example 45 (700 mg) and Methanol (7 mL) were charged into a 100 mL round bottom flask. Trimethylorthoformate (3.6 mL) and p-Toluene sulfonic acid (10 mg) were added at 30°C and the resulting mixture was stirred for 16 hours at 30°C. Potassium carbonate (50 mg) was added to the reaction mixture and the resulted mixture was concentrated under vacuum at 30°C. Water (25 mL) was added to the residue and the solution was extracted with dichloromethane (2X25 mL). The organic layer was dried with anhydrous sodium sulphate (5 gm) and concentrated completely under vacuum to yield 700 mg of the title product as colorless liquid. The obtained crude compound was taken up for the next reaction without any further purification.

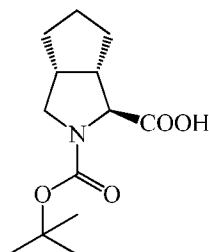
Example 47: Preparation of (1S,3aR,6aS)-octahydrocyclopenta[c]pyrrole-1-carbonitrile



The compound obtained in Example 46 (600 mg), 1N HCl (102 mL) and KCN (570 mg) were charged into a 250 mL round bottom flask at 30°C and the resulting mixture was stirred for 16 hours at 30°C. 30% KOH solution (5 mL) was added to the reaction mixture and extracted with ethyl acetate (2X25 mL). The organic layer was dried with anhydrous sodium sulphate (1 gm) and concentrated completely under vacuum. The crude was purified by column chromatography (20% ethylacetate in hexane) to yield 180 mg of the title compound as brown liquid.

¹H NMR (400 MHz, CDCl₃): δ 1.29-1.42 (m, 2H), 1.44-1.51 (m, 1H), 1.61-1.70 (m, 1H), 1.83-1.97 (m, 2H), 2.68 (m, 1H), 2.78 (dd, 1H, *J* = 9.8 Hz, 2 Hz), 3.24 (dd, 1H, *J* = 10 Hz, 7.6 Hz), 3.68 (d, 1H, *J* = 2 Hz).

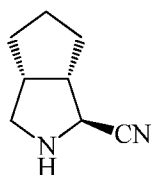
Example 48: Preparation of (1S,3aR,6aS)-2-(tert-butoxycarbonyl)octahydrocyclopenta[c]pyrrole-1-carboxylic acid.



The compound obtained in Example 47 (80 mg) and concentrated HCl (1 mL) were charged into a 25 mL round bottom flask at 30°C and the resulting mixture was stirred for 16 hours at 100°C. The reaction mixture was concentrated under vacuum and crude was triturated with diethyl ether (10 mL). The obtained crude was dissolved in methanol (5 mL), triethylamine (0.15 mL) and Boc₂O (124 mg) at 30°C. The resulting mixture was stirred for 30 min at 30°C and the reaction mixture was diluted with water (10 mL) and extracted with ethyl acetate (2X25 mL). The organic layer was dried with anhydrous sodium sulphate (1 gm) and concentrated completely under vacuum to yield 90 mg of the title compound as a white solid.

¹H NMR (400 MHz, DMSO-d₆): δ 1.33 & 1.38 (2s, 9H), 1.43 (m, 1H), 1.51 (m, 2H), 1.63-1.68 (m, 1H), 1.71 (m, 1H), 1.89 (m, 1H), 2.58 (m, 2H), 3.13 (dd, 1H, *J* = 10.8 Hz, 2.8 Hz), 3.51 (m, 1H), 3.87 (dd, 1H, *J* = 2.8 Hz, 26 Hz); ¹³C NMR (100 MHz, DMSO-d₆): δ 25.58, 28.35, 28.52, 32.34, 32.44, 33.05, 41.34, 42.29, 47.90, 48.96, 52.88, 53.00, 65.73, 66.01, 79.14, 153.87, 154.28, 174.17, 174.56.

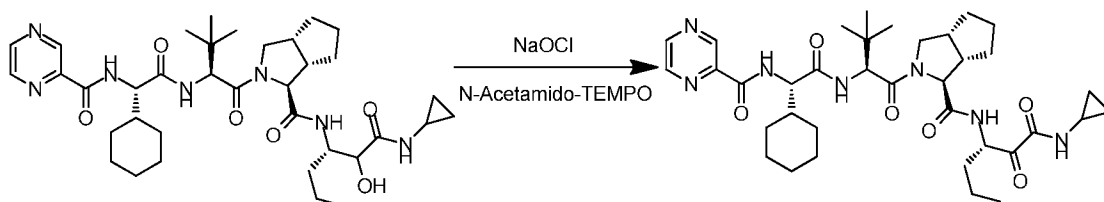
Example 49: Preparation of (1S,3aR,6aS)-octahydrocyclopenta[c]pyrrole-1-carbonitrile



The compound obtained in Example 45 (500 mg), 1N HCl (100 mL) and KCN (520 mg) were charged into a 250 mL round bottom flask at 30°C and the resulting mixture was agitated for 16 hours at 30°C. 30% KOH solution (5 mL) was added to the reaction mixture and extracted with ethyl acetate (2X25 mL). The organic layer was dried with anhydrous sodium sulphate (1 gm) and concentrated completely under vacuum. The

crude was purified by column chromatography (20% ethylacetate in hexane) to yield 150 mg of the title compound as brown liquid.

Example 50: Preparation of (1S,3aR,6aS)-2-((S)-2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoyl)-N-((S)-1-(cyclopropyl amino)-1,2-dioxohexan-3-yl)octahydrocyclopenta[c]pyrrole-1-carboxamide (Telaprevir)



Ethylacetate (20 mL) and acetic acid (2 mL) were charged into a 100 mL round bottomed flask and the mixture was cooled to 0°C. (1S,3aR,6aS)-2-((S)-2-((S)-2-cyclohexyl-2-(pyrazine-2-carboxamido)acetamido)-3,3-dimethylbutanoyl)-N-((3S)-1-(cyclopropylamino)-2-hydroxy-1-oxohexan-3-yl)-octahydrocyclopenta[c]pyrrole-1-carboxamide (2 g) and N-acetamido-TEMPO (63 mg) and potassium permanganate (1 g) were added at 10°C and the reaction mixture was stirred for 6 hours at 10°C. Water (20 mL) was added to the reaction mixture and the resulted solution was agitated for 10 minutes. Layers were separated and the organic layer was washed with 10% aqueous hydrochloric acid solution, and 5% aqueous sodium sulphate solution followed by 10% aqueous sodium chloride solution. Organic layer was concentrated under vacuum completely and fresh ethyl acetate (10 mL) was added to the residue and the resulted solution was stirred for 30 minutes at 28°C. The precipitation was filtered and the wet cake was washed with ethyl acetate (5 mL) and the solid was dried under vacuum at 43°C to yield 0.52 gm of telaprevir.

Purity: 94.02% (by HPLC); XRD pattern: similar to figure 1.

Example 51: Purification of Telaprevir

Telaprevir (35 gm) and dichloromethane (105 mL) were charged into a 500 mL round bottomed flask and stirred to get clear solution and the solution was filtered. Dichloromethane was distilled out completely under vacuum and fresh dichloromethane (35 mL) was added to the residue. Ethylacetate (350 mL) was added to the mass and

the resulted mixture was stirred for 30 minutes at 28°C. The precipitation was filtered and the wet cake was washed with ethylacetate (35 mL). The wet material was charged into another 500 mL round bottomed flask, dichloromethane (90 mL) was added and stirred to get clear solution. Ethylacetate (300 mL) was added to the clear solution and the resulting mixture was stirred for 30 minutes at 28°C. The precipitation was filtered and the wet cake was washed with ethylacetate (35 mL). The wet material was dried under vacuum at 40°C to yield 28.2 gm of telaprevir.

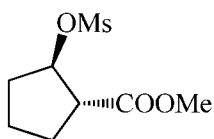
Purity: 99.72% (by HPLC), XRD pattern: similar to figure 1.

Example 52: Purification of Telaprevir

Telaprevir (24 gm) and dichloromethane (72 mL) were charged into a 500 mL round bottomed flask and stirred to get clear solution and the solution was filtered. Dichloromethane was distilled out completely under vacuum and fresh dichloromethane (24 mL) was added to the residue. Ethylacetate (240 mL) was added to the solution and the resulted mixture was stirred for 30 minutes at 28°C. The precipitation was filtered and the wet cake was washed with ethylacetate (24 mL). The wet material was charged into another 500 mL round bottomed flask dichloromethane (72 mL) was added and stirred to get clear solution. Dichloromethane was distilled out completely under vacuum and fresh dichloromethane (24 mL) was added to the residue. Ethylacetate (240 mL) was added to the clear solution and the resulting mixture was stirred for 30 minutes at 28°C. The precipitation was filtered and the wet cake was washed with ethylacetate (24 mL). The wet material was dried under vacuum at 45°C to yield 22.2 gm of telaprevir.

Purity: 99.90% (by HPLC); XRD pattern: similar to figure 1.

Example 53: Preparation of (1R,2R)-methyl-2-((methylsulfonyl)oxy)cyclopentene carboxylate

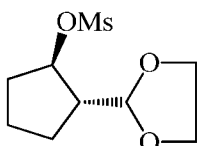


(1R,2R)-methyl-2-hydroxycyclopentanecarboxylate (50 g) and Dichloromethane (1000 mL) were charged into a 3L round bottom flask and the mixture was cooled to

0°C. Triethylamine (96.8 mL) was added to the mixture at 0°C over a period of 10 minutes. Methanesulfonylchloride (29.5 mL) was added to the mixture at 0°C over a period of 10 minutes. The mixture was heated to 30°C and stirred for 2 hours. Water (500 mL) was added to the reaction mixture and stirred for 10 minutes. Organic layer was separated and the aqueous layer was extracted with Dichloromethane (500 mL). The organic layers were combined and washed with saturated sodium bicarbonate solution (3 x 1L) and brine solution (1L). The organic layer was dried with anhydrous sodium sulphate (15 gm) and concentrated completely under vacuum. The resulted residue was purified by column chromatography to yield 69.3 g of the title product as yellow syrup.

¹H NMR (400 MHz, CDCl₃): δ 1.73-1.85 (m, 3H), 1.94-2.01 (m, 2H), 2.10-2.18 (m, 2H), 3.01 (s, 3H), 3.05 (m, 1H), 3.72 (s, 3H), 5.27 (m, 1H).

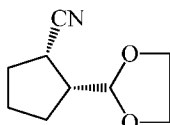
Example 54: Preparation of (1R,2R)-2-(1,3-dioxolan-2-yl)cyclopentyl methanesulfonate



The compound obtained in Example 53 (30 g) was charged into a 1000 mL round bottom flask and Toluene (300 mL) was added under nitrogen atmosphere. The mixture was cooled to -78°C and Diisobutylaluminum hydride (DIBAL-H, 1M in Toluene, 202.5 mL) was added over a period of 30 minutes at -78°C and the reaction mixture was stirred for 2 hours at -78°C. The reaction mixture was quenched with methanol (5 mL) at -78°C and saturated ammonium chloride solution (250 mL) was slowly added to the resulted solution at -78°C. The resulted solution was slowly heated to 30°C and filtered through a celite bed and the bed was washed with Toluene (2 x 100 mL). Organic layer was dried with anhydrous sodium sulphate (10 gm) and charged into a 1000 mL round bottom flask. Ethylene glycol (60 mL) and p-Toluene sulfonic acid (3.4 gm) were added at 30°C and the resulting mixture was stirred for 16 hours at 30°C. Water (300 mL) was added to the reaction mixture and the organic layer was separated. The organic layer was washed with saturated sodium bicarbonate solution (2 x 250 mL) and brine solution (200 mL). The organic layer was dried with anhydrous sodium sulphate (10 gm)

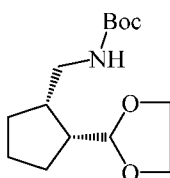
and concentrated completely under vacuum and the residue was purified by column chromatography to yield 14 gm of the title product as yellow syrup.

Example 55: Preparation of (1S,2R)-2-(1,3-dioxolan-2-yl)cyclopentanecarbonitrile



The compound obtained in Example 54 (24 gm) and Dimethylformamide (144 mL) and Sodium cyanide (19.9 gm) were charged into a 500 mL round bottom flask. The mixture was heated to 65°C and stirred for 16 hours. The reaction mixture was cooled to 30°C and water (250 mL) was added. The resulted solution was extracted with ethylacetate (2 x 250 mL). The ethylacetate layers were combined and washed with water (2 x 250 mL) and brine solution (2 x 150 mL). The organic layer was dried with anhydrous sodium sulphate (10 gm) and concentrated completely under vacuum and the residue was purified by column chromatography to yield 13 gm of the title product as yellow syrup.

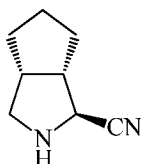
Example 56: Preparation of tert-butyl (((1S,2R)-2-(1,3-dioxolan-2-yl)cyclopentyl)methyl)carbamate



The compound obtained in Example 55 (13 g) and Methanol (260 mL) were charged into a 1L steel vessel. Raney Nickel (3 g) was charged in the mixture under nitrogen atmosphere. The reaction mixture was stirred for 16 hours at 27°C under hydrogen pressure (80 psi) using parr hydrogenator. Under nitrogen atmosphere the reaction mixture was filtered through a celite bed and the celite bed was washed with methanol (200 mL). The filtrate was taken into a 1000 mL round bottom flask, triethylamine (21.6 mL) and boc anhydride (16.9 mL) were added and the resulting mixture was stirred for 2 hours at 28°C. The reaction mass was concentrated completely under reduced pressure and the crude was diluted with water and the

solution was extracted with ethylacetate (2 x 250 mL). The organic layer was washed with 5% citric acid solution to remove excess boc anhydride and washed with brine solution. The organic layer was dried over sodium sulphate (10 g) and concentrated under reduced pressure to get 15.0 g of the title product as pale yellow syrup.

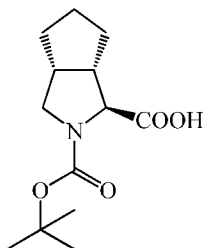
Example 57: Preparation of (1S,3aR,6aS)-octahydrocyclopenta[c]pyrrole-1-carbonitrile



The compound obtained in Example 56 (14 gm), 2N HCl (3L) and KCN (13.4 gm) were charged into a 5L round bottom flask at 30°C and the resulting mixture was stirred for 16 hours at 30°C. 30% KOH solution (1.1L) was added to the reaction mixture and extracted with dichloromethane (2 x 500 mL). The organic layer was dried with anhydrous sodium sulphate (10 gm) and concentrated completely under vacuum to give 4 gm of the title compound as colorless syrup.

¹H NMR (400 MHz, CDCl₃): δ 1.29-1.42 (m, 2H), 1.44-1.51 (m, 1H), 1.61-1.70 (m, 1H), 1.83-1.97 (m, 2H), 2.68 (m, 1H), 2.78 (dd, 1H, *J* = 9.8 Hz, 2 Hz), 3.24 (dd, 1H, *J* = 10 Hz, 7.6 Hz), 3.68 (d, 1H, *J* = 2 Hz).

Example 58: Preparation of (1S,3aR,6aS)-2-(tert-butoxycarbonyl)octahydrocyclopenta[c]pyrrole-1-carboxylic acid



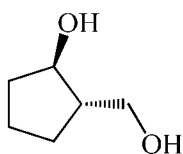
The compound obtained in Example 57 (4 g) and concentrated HCl (28 mL) were charged into a 250 mL round bottom flask at 30°C and the resulting mixture was stirred for 16 hours at 100°C. The reaction mixture was concentrated under vacuum and the obtained crude was triturated with ether and decanted the ether layer and dried under vacuum to give 4 g of crude title product.

To the above crude (4 g), methanol (40 mL), triethylamine (8.17 mL) and di-tert-butyl dicarbonate (Boc_2O , 7.05 mL) were charged at 0°C. The resulting mixture was stirred for 2 hours at 30°C. The reaction mixture was concentrated under vacuum and diluted with saturated NaHCO_3 solution (100 mL) and extracted with ethyl acetate (200 mL). The aqueous solution was acidified using saturated citric acid to pH ~5 and the aqueous solution was extracted with ethyl acetate (200 mL). Organic layer was dried with anhydrous sodium sulphate (5 gm) and concentrated completely. The obtained crude compound was triturated with hexane for 2 hours and the white solid was filtered and dried under vacuum to give 4.48 gm of the title compound as a white solid.

^1H NMR (400 MHz, DMSO-d_6): δ 1.33 & 1.38 (2s, 9H), 1.43 (m, 1H), 1.51 (m, 2H), 1.63-1.68 (m, 1H), 1.71 (m, 1H), 1.89 (m, 1H), 2.58 (m, 2H), 3.13 (dd, 1H, J = 10.8 Hz, 2.8 Hz), 3.51 (m, 1H), 3.87 (dd, 1H, J = 2.8 Hz, 26 Hz); **^{13}C NMR** (100 MHz, DMSO-d_6): δ 25.58, 28.35, 28.52, 32.34, 32.44, 33.05, 41.34, 42.29, 47.90, 48.96, 52.88, 53.00, 65.73, 66.01, 79.14, 153.87, 154.28, 174.17, 174.56.

Chemical purity: 98%, chiral purity: 99.8% by HPLC.

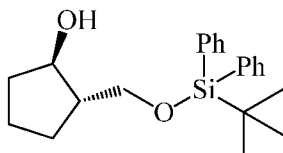
Example 59: Preparation of (1R,2S)-2-(hydroxymethyl)cyclopentanol



Lithium aluminum hydride (33 g) and Tetrahydrofuran (1.7L) were charged into a 3L round bottom flask under nitrogen atmosphere and the mixture was cooled to 0°C. The compound obtained in Example 27 (85 g) was dissolved in Tetrahydrofuran (700 mL) and the resulted solution was added to the reaction mixture at 0°C over a period of 20 minutes. Temperature was raised to 28°C and the reaction mixture was stirred for 5 hours at 28°C. The reaction mixture was cooled to 0°C and quenched with saturated aqueous sodium sulphate (250 mL). The precipitation was filtered and the cake was washed with ethyl acetate (1000 mL). The organic layer dried over sodium sulphate (10 g) and concentrated completely under vacuum to yield 70 g of the title product as colorless oil.

¹H NMR (400 MHz, DMSO-d₆): δ 1.26-1.40 (m, 2H), 1.52-1.88 (m, 5H), 3.20 (dd, 1H, *J* = 10.6 Hz, 6.4 Hz), 3.34 (dd, 1H, *J* = 10.6 Hz, 6.4 Hz), 3.75 (m, 1H), 4.36 (m, 2H).

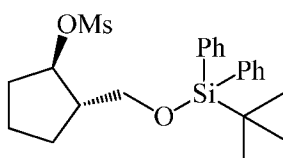
Example 60: Preparation of (1R,2S)-2-(((tert-butyldiphenylsilyl)oxy)methyl)cyclopentanol



The compound obtained in Example 59 (70 g) and Dichloromethane (1.4L) were charged into a 3L round bottom flask and the resulted solution was cooled to 0°C. Imidazole (98 g) and tert-Butylchlorodiphenylsilane (165 g) were added at 0°C and the resulting mixture was stirred for 2 hours at 28°C. Water (1000 mL) was added to the reaction mixture and the resulted solution was extracted with Dichloromethane (2 x 250 mL). The organic layers were combined and washed with brine solution and dried over anhydrous sodium sulphate (5 gm) and concentrated completely under vacuum. The crude was purified by column chromatography (15% ethylacetate in hexane) to yield 160 g of the title product as colorless oil.

¹H NMR (400 MHz, CDCl₃) : δ 1.05 (s, 9H), 1.15 (m, 1H), 1.60 (m, 2H), 1.73 (m, 2H), 1.94 (m, 1H), 2.02 (m, 1H), 2.46 (brs, 1H), 3.54 (t, 1H, *J* = 9.6 Hz), 3.78 (dd, 1H, *J* = 10.2 Hz, 5.2 Hz), 4.09 (q, 1H), 7.42 (m, 6H), 7.67 (m, 4H).

Example 61: Preparation of (1R,2S)-2-(((tert-butyldiphenylsilyl)oxy)methyl)cyclopentyl methanesulfonate

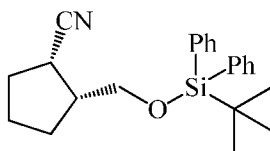


The compound obtained in Example 60 (160 g) and Dichloromethane (3.2L) were charged into a 5L round bottom flask and mixture was cooled to 0°C. Triethylamine (125 mL) and Methanesulfonylchloride (38 mL) were added to the mixture at 0°C. The mixture was heated to 28°C and stirred for 2 hours. Water (2L) was added to the reaction mixture and stirred for 10 minutes. Organic layer was separated and the aqueous layer was extracted with Dichloromethane (3 x 500 mL). The organic layers

were combined and washed with saturated sodium bicarbonate solution (2 x 1L) followed by washing with brine solution (2 x 1L). The organic layer was dried with anhydrous sodium sulphate (20 gm) and concentrated completely under vacuum to yield 195 g of the title product as white solid.

¹H NMR (400 MHz, CDCl₃): δ 1.06 (s, 9H), 1.39 (m, 1H), 1.60-1.80 (m, 2H), 1.86-1.98 (m, 3H), 2.36 (m, 1H), 2.92 (s, 3H), 3.50 (dd, 1H, *J* = 10.2 Hz, 6.8 Hz), 3.69 (dd, 1H, *J* = 10.2 Hz, 5.2 Hz), 5.08 (m, 1H), 7.39 (m, 6H), 7.63 (m, 4H)

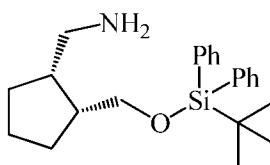
Example 62: Preparation of ((1S,2R)-2-(((tert-butyldiphenylsilyl)oxy)methyl)cyclopentanecarbonitrile



The compound obtained in Example 61 (160 g), Dimethylformamide (960 mL) and Sodium cyanide (72 g) were charged into a 3L round bottom flask. The mixture was heated to 65°C and stirred for 48 hours at 65°C. The reaction mixture was cooled to 30°C and water (1.5L) was added. The resulted solution was extracted with ethylacetate (3 x 500 mL). The organic layer was dried with anhydrous sodium sulphate (20 gm) and concentrated completely under vacuum. The crude was purified by column chromatography (7% ethylacetate in hexane) to yield 70 g of the title product as colorless oil.

¹H NMR (400 MHz, CDCl₃) : δ 1.07(s, 9H), 1.40-1.52 (m, 1H), 1.65-1.80 (m, 2H), 1.87 (m, 1H), 1.95-2.10 (m, 2H), 2.31 (m, 1H), 3.10 (m, 1H), 3.80 (d, 2H, *J* = 7.2 Hz), 7.42 (m, 6H), 7.70 (m, 4H).

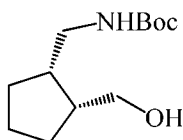
Example 63: Preparation of ((1S,2R)-2-(((tert-butyldiphenylsilyl)oxy)methyl)cyclopentyl)methanamine



The compound obtained in Example 62 (70 g), Methanol (700 mL) and Raney Nickel (1 g) were charged into a 2L steel vessel under nitrogen atmosphere. the reaction mixture was stirred for 16 hours at 27°C under hydrogen pressure (80 psi) using parr hydrogenator. The reaction mixture was filtered through a celite bed and the celite bed was washed with Methanol (500 mL). The filtrate was concentrated completely under reduced pressure to get 65 g of the title product as yellowish syrup.

¹H NMR (400 MHz, DMSO-d₆): δ 1.02 (s, 9H), 1.23-1.36 (m, 1H), 1.40-1.51 (m, 2H), 1.53-1.72 (m, 3H), 1.91 (m, 1H), 2.18 (m, 1H), 2.41 (dd, 1H, *J* = 12.2 Hz, 8.4 Hz), 2.62 (dd, 1H, *J* = 9.2 Hz, 6 Hz), 3.50 (dd, 1H, *J* = 10.4 Hz, 6.8 Hz), 3.65 (dd, 1H, *J* = 10 Hz, 6.4 Hz), 7.44 (m, 6H), 7.60 (m, 4H).

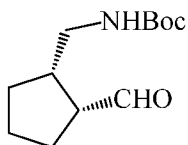
Example 64: Preparation of tert-butyl (((1S,2R)-2-(hydroxymethyl)cyclopentyl)methyl) carbamate



The compound obtained in Example 63 (65g) and Methanol (650 mL) were charged into a 2L round bottom flask. HCl gas was passed in to reaction mixture for 4 hours at 0°C. The reaction mixture was basified using Triethylamine (47 mL). Boc anhydride (45 mL) was added at 0°C and the resulted mixture was stirred for 2 hours at 28°C. The reaction mixture was concentrated under reduced pressure. Water (500 mL) was added to the crude and the obtained solution was extracted with Dichloromethane (2 x 500 mL). The combined organic layer was dried over anhydrous sodium sulfate (10 g) and concentrated under reduced pressure. The crude was purified by column chromatography (7% ethylacetate in hexane) to yield 20 mg of the title compound as white solid. Purity: 72.7% by HPLC.

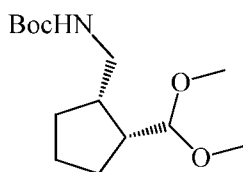
¹H NMR (400 MHz, CDCl₃): δ 1.23-1.42 (m, 2H), 1.44 (s, 9H), 1.48-1.71 (m, 2H), 1.73-2.02 (m, 2H), 2.10-2.24 (m, 2H), 3.14 (d, 1H, *J* = 7.2 Hz), 3.60 (m, 2H).

Example 65: Preparation of tert-butyl (((1S,2R)-2-formylcyclopentyl)methyl)carbamate



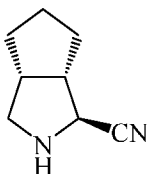
The compound obtained in Example 64 (20 g) and Dichloromethane (400 mL) were charged into a 2L round bottom flask and the mixture was cooled to 0°C. Dess-Martin Periodinane (DMP, 74 g) was added and the reaction mixture was stirred at 28°C for 2 hours. Dichloromethane was evaporated under Nitrogen atmosphere. To the residue diethyl ether (450 mL) and hexane (1L) were charged and the resulted mixture was stirred for 10 minutes. The resulting solution was filtered through a celite and the filtrate was concentrated under reduced pressure to yield 18 mg of the title product as pale yellow syrup. The obtained crude material was taken up for next reaction without any further purification.

Example 66: Preparation of tert-butyl (((1S,2R)-2-(dimethoxymethyl)cyclopentyl)methyl) carbamate



The compound obtained in Example 65 (18 g), Trimethylorthoformate (93 mL), p-Toluene sulfonic acid (180 mg) and Methanol (180 mL) were charged at 30°C and the resulting mixture was stirred for 16 hours at 30°C. Potassium carbonate (10 g) was added to the reaction mixture to adjust pH 9.5 and the resulted mixture was concentrated under vacuum at 30°C. Water (500 mL) was added to the residue and the solution was extracted with dichloromethane (2 x 250 mL). The organic layer was dried with anhydrous sodium sulphate (5 gm) and concentrated completely under vacuum to yield 18 g of the title product as yellow liquid. The obtained crude compound was taken up for the next reaction without any further purification.

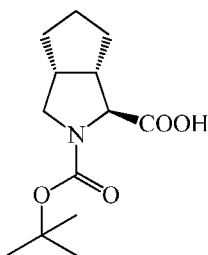
Example 67: Preparation of (1S,3aR,6aS)-octahydrocyclopenta[c]pyrrole-1-carbonitrile



The compound obtained in Example 66 (18 g), 1N HCl (3L) and KCN (17 g) were charged into a 5L round bottom flask at 30°C and the resulting mixture was stirred for 16 hours at 30°C. pH was adjusted to 14 with 30% KOH solution (700 mL) and extracted with dichloromethane (2 x 500 mL). The organic layer was dried with anhydrous sodium sulphate (5 gm) and concentrated completely under vacuum. The crude was purified by column chromatography (20% ethylacetate in hexane) to yield 5 g of the title compound as yellow liquid.

¹H NMR (400 MHz, CDCl₃): δ 1.29-1.42 (m, 2H), 1.44-1.51 (m, 1H), 1.61-1.70 (m, 1H), 1.83-1.97 (m, 2H), 2.68 (m, 1H), 2.78 (dd, 1H, *J* = 9.8 Hz, 2 Hz), 3.24 (dd, 1H, *J* = 10 Hz, 7.6 Hz), 3.68 (d, 1H, *J* = 2 Hz).

Example 68: Preparation of (1S,3aR,6aS)-2-(tert-butoxycarbonyl)octahydrocyclopenta[c]pyrrole-1-carboxylic acid.



The compound obtained in Example 67 (5 g) and concentrated HCl (25 mL) were charged into a 250 mL round bottom flask at 30°C and the resulting mixture was stirred for 16 hours at 100°C. The reaction mixture was concentrated under vacuum and crude was triturated with diethyl ether (10 mL). The obtained crude was dissolved in methanol (50 mL), triethylamine (10.2 mL) and Boc₂O (9.79 mL) at 0°C. The resulting mixture was stirred for 2 hours at 30°C. The reaction mixture was concentrated under vacuum and diluted with saturated sodium bicarbonate solution (100 mL) and extracted with ethyl acetate (250 mL). The aqueous layer was acidified using saturated citric acid (pH 4.5) and extracted with ethyl acetate (250 mL). The organic layer was dried with anhydrous

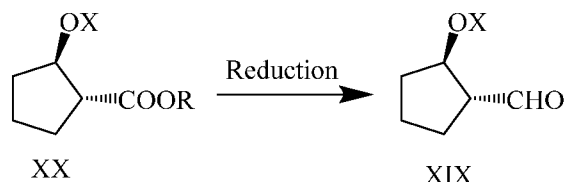
sodium sulphate (5 gm) and concentrated completely under vacuum to yield 5 g of the title compound as a white solid. Chemical purity: 99.31%, chiral purity: 99.79% by HPLC.

¹H NMR (400 MHz, DMSO-d₆): δ 1.33 & 1.38 (2s, 9H), 1.43 (m, 1H), 1.51 (m, 2H), 1.63-1.68 (m, 1H), 1.71 (m, 1H), 1.89 (m, 1H), 2.58 (m, 2H), 3.13 (dd, 1H, *J* = 10.8 Hz, 2.8 Hz), 3.51 (m, 1H), 3.87 (dd, 1H, *J* = 2.8 Hz, 26 Hz); **¹³C NMR** (100 MHz, DMSO-d₆): δ 25.58, 28.35, 28.52, 32.34, 32.44, 33.05, 41.34, 42.29, 47.90, 48.96, 52.88, 53.00, 65.73, 66.01, 79.14, 153.87, 154.28, 174.17, 174.56.

CLAIMS

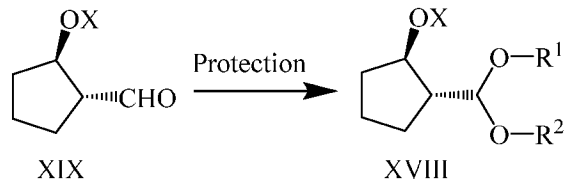
1. A process for preparation of (1S,3aR,6aS)-octahydrocyclopenta[c]pyrrole-1-carboxylic acid of formula (VIIb), comprising:

(a) reducing a compound of formula XX with a suitable reducing agent to form a compound of formula XIX



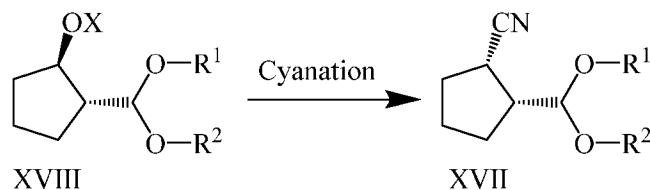
wherein X is hydrogen or a leaving group such as mesyl, tosyl, acetyl or trifluoroacetyl;
R is hydrogen or C₁-C₄ alkyl or C₅-C₁₂ aralkyl,

(b) protecting the aldehyde functionality of the compound of formula XIX to form a compound of formula XVIII.

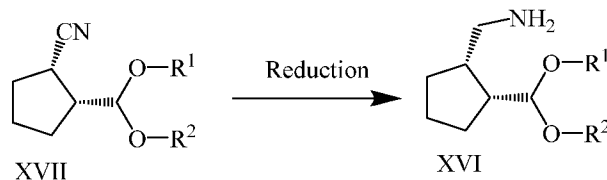


wherein R¹ and R² are C₁-C₅ alkyl or both form a cyclic ring,

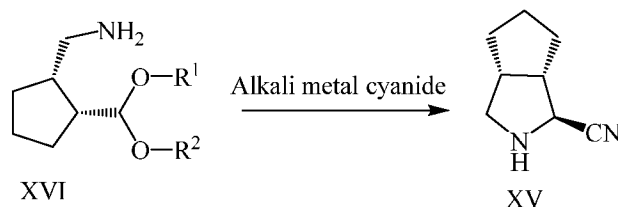
(c) cyanating the compound of formula XVIII with a suitable cyanating agent to form compound of formula XVII



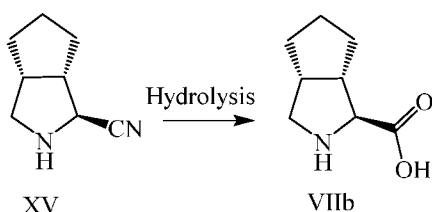
(d) reducing the compound of formula XVII in the presence of a suitable catalyst to obtain compound of formula XVI,



(e) treating the compound of formula XVI with an acid and an alkali metal cyanide to form compound of formula XV, and

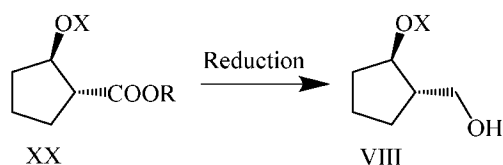


(f) hydrolyzing the compound of formula XV to form compound of formula VIIb or its acid addition salt



2. A process for preparation of a compound of formula VIIb, comprising:

(a) reducing the compound of formula XX with a suitable reducing agent to form a compound of formula VIII



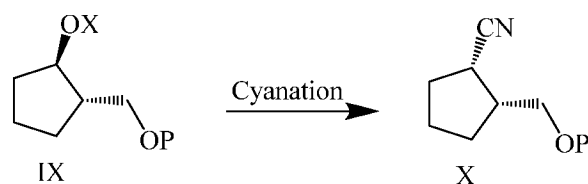
wherein X is hydrogen or a leaving group such as mesyl, tosyl, acetyl or trifluoroacetyl;
R is hydrogen or C₁-C₄ alkyl or C₅-C₁₂ aralkyl,

(b) protecting the primary hydroxyl group of compound of formula VIII to get compound of formula IX,

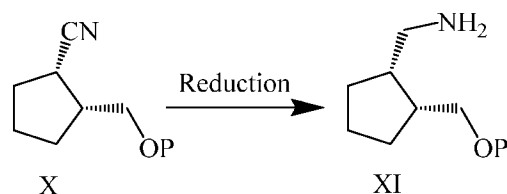


wherein P is a protecting group,

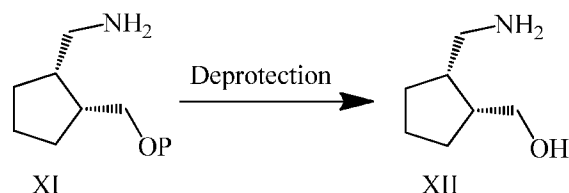
(c) cyanating the compound of formula IX with a suitable cyanating agent to form compound of formula X



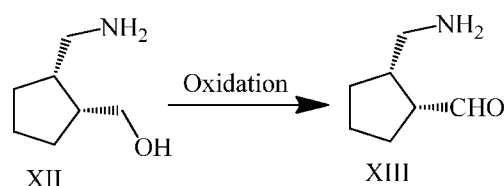
(d) reducing the compound of formula X in the presence of a suitable catalyst to obtain compound of formula XI,



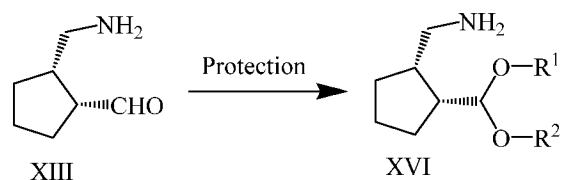
(e) optionally, deprotecting the compound of formula XI to form compound of formula XII,



(f) oxidizing the compound of formula XII to form compound of formula XIII,

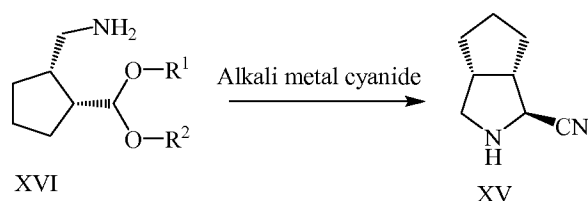


(g) optionally, protecting the aldehyde of the compound of formula XIII to form a compound of formula XVI.

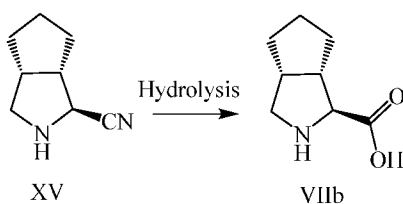


R¹ and R² are C₁-C₅ alkyl or both form a cyclic ring,

(h) treating the compound of formula XIII or the compound of formula XVI with an alkali metal cyanide to form a compound of formula XV, and

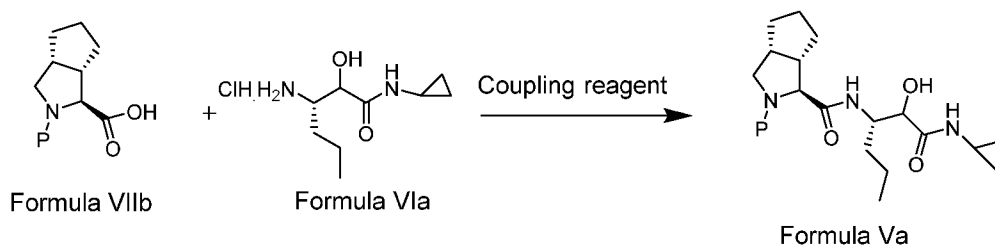


(i) hydrolyzing the compound of formula XV to form compound of formula VIIb or its acid addition salt



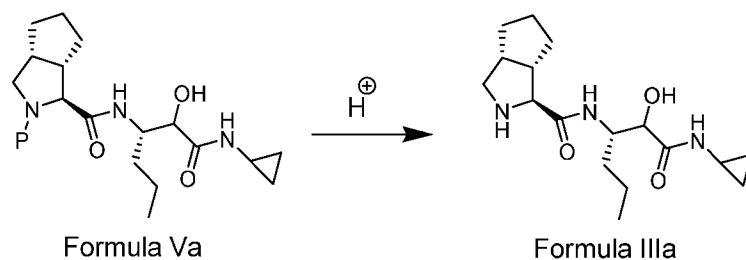
3. The process according to claim 1 or claim 2 further comprises:

(a) reacting the compound of formula VIIb or protected form of formula VIIb with a compound of formula VIa or its salt in the presence of a suitable coupling reagent to form compound of formula Va or its salt,

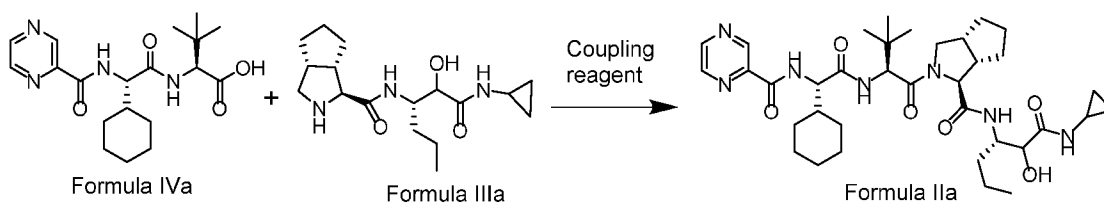


wherein P is an amine protecting group;

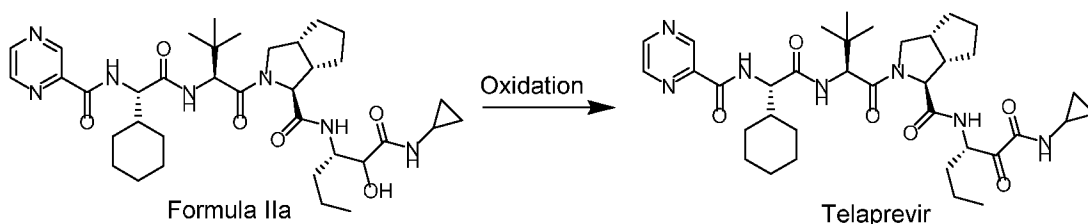
(b) deprotecting the compound of formula Va or its salt using an acid to form compound of formula IIIa or a salt thereof.



(c) reacting a compound of formula IIIa or a salt thereof with a compound of formula IVa or a salt thereof in the presence of a suitable coupling reagent to form a compound of formula IIa,



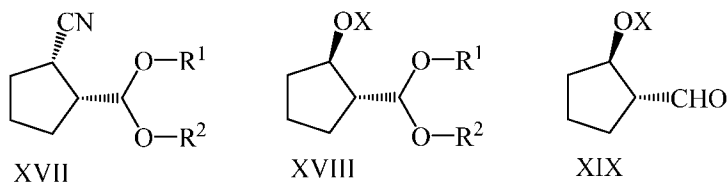
(d) oxidizing the compound of Formula IIa using a suitable oxidizing reagent to form telaprevir.



4. The process according to claim 3, wherein the oxidizing reagent of step (c) is selected from the group comprising 1,1-dihydro-1,1,1-triacetoxy-1,2-benziodoxol-3(1H)-one, chromic acid in acetone, sodium hypochlorite in the presence of (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl, sodium hypochlorite in the presence of (4-Acetamido-2,2,6,6-tetramethyl-piperidin-1-yl)oxyl, potassium permanganate in the presence of (4-Acetamido-2,2,6,6-tetramethyl-piperidin-1-yl)oxyl.

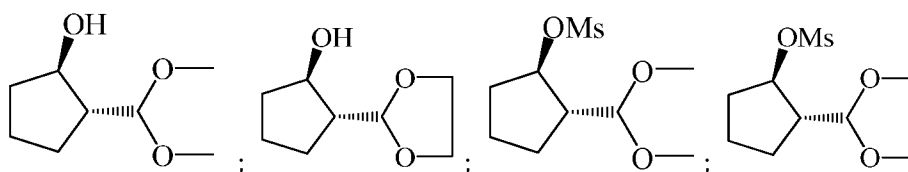
5. The process according to claim 3, wherein the oxidizing reagent is sodium hypochlorite in the presence of (4-Acetamido-2,2,6,6-tetramethyl-piperidin-1-yl)oxyl.

6. Compounds of formula XVII. Formula VIII and formula XIX and isomers thereof

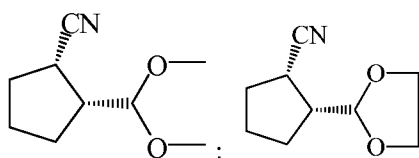


wherein X is hydrogen or a leaving group such as mesyl, tosyl, acetyl or trifluoroacetyl; R^1 and R^2 are C_1 - C_5 alkyl or together with the atoms to which they are attached may form a cyclic ring.

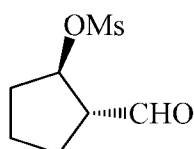
7. The compound of formula XVIII according to claim 6 selected from the group consisting of:



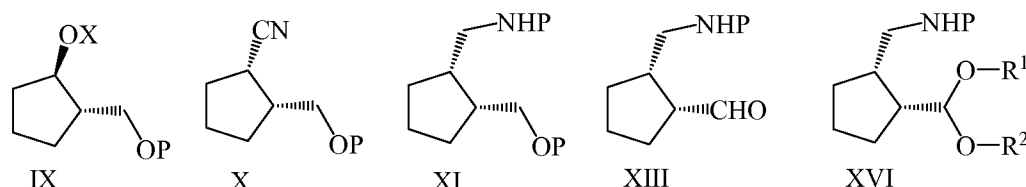
8. The compound of formula XVII according to claim 6 selected from the group consisting of:



9. The compound of formula XIX according to claim 6 is:

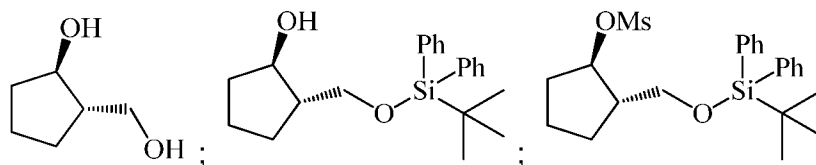


10. Compounds of formula IX to formula XVI and isomers thereof

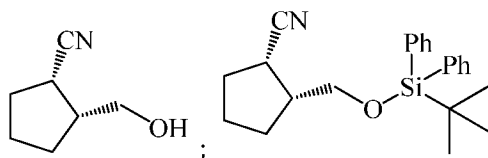


wherein X is hydrogen or a leaving group such as mesyl, tosyl, acetyl or trifluoroacetyl; R^1 and R^2 are C_1 - C_5 alkyl or together with the atoms to which they are attached may form a cyclic ring, P is hydrogen or a protecting group.

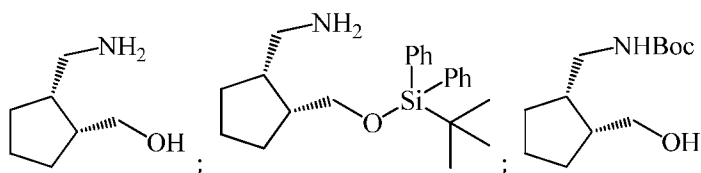
11. The compound of formula IX according to claim 10 is selected from the group consisting of:



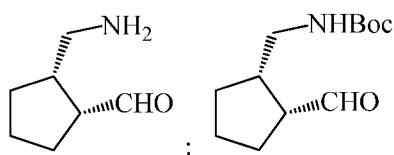
12. The compound of formula X according to claim 10 is selected from the group consisting of:



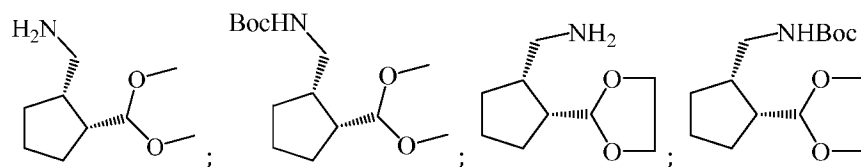
13. The compound of formula XI according to claim 10 is selected from the group consisting of:



14. The compound of formula XIII according to claim 10 is selected from the group consisting of:

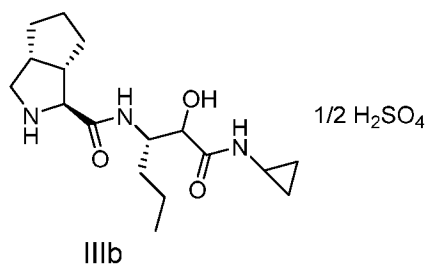


15. The compound of formula XVI according to claim 10 is selected from the group consisting of:



16. Use of the compounds according to claim 6 or claim 15 in the preparation of compound of formula VIIb or protected form of compound of formula VIIb or pharmaceutically acceptable salts thereof.

17. Compound of formula IIIb



18. The compound of formula IIIb according to claim 17 is (1S,3aR,6aS)-N-((3S)-1-(cyclopropyl amino)-2-hydroxy-1-oxohexan-3-yl)carbamoyl)octahydrocyclopenta[c]pyrrole-1-carboxamide hemisulphate.
19. Use of the compound of formula IIIb in preparation of telaprevir.

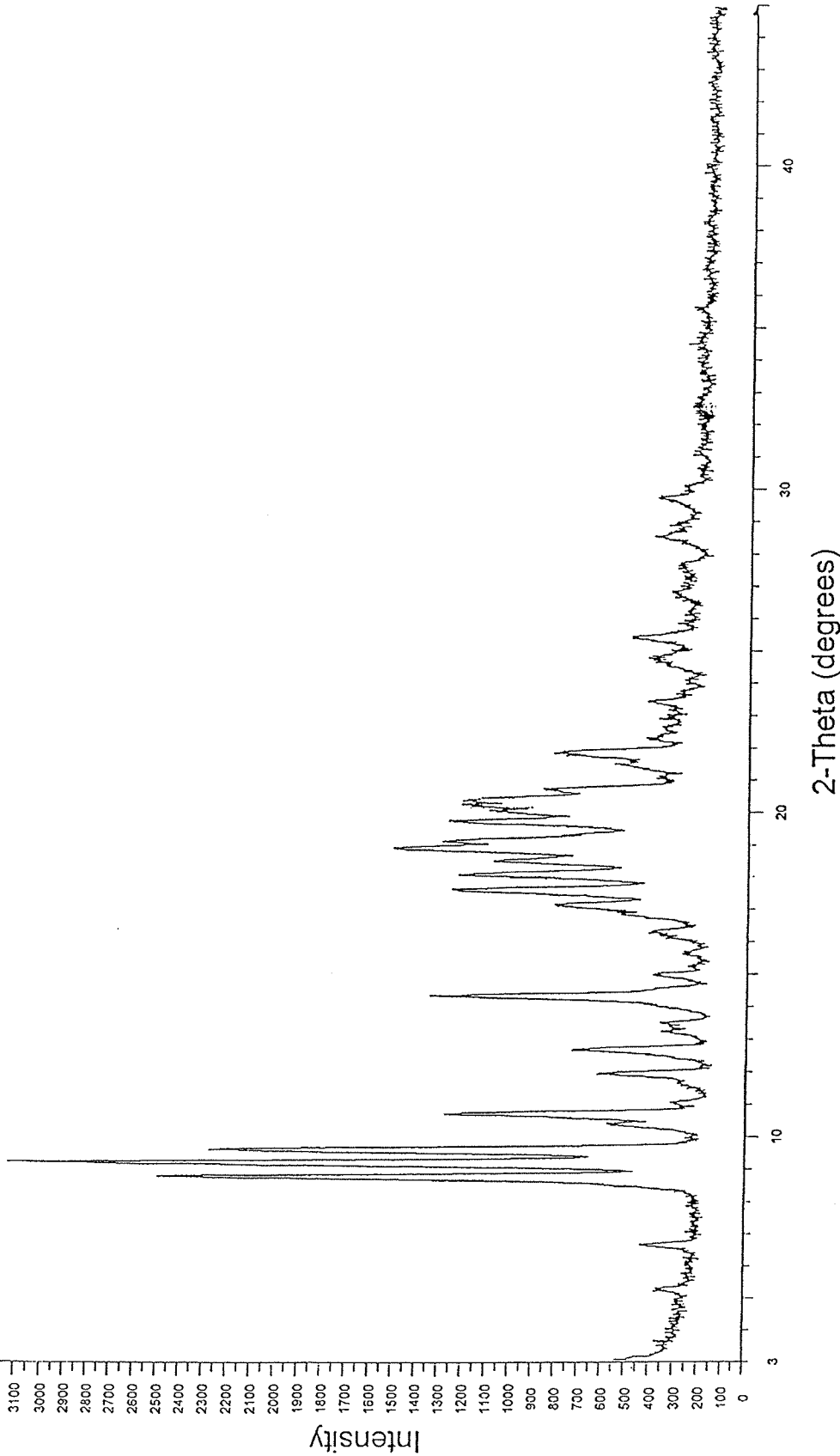


Fig. 1

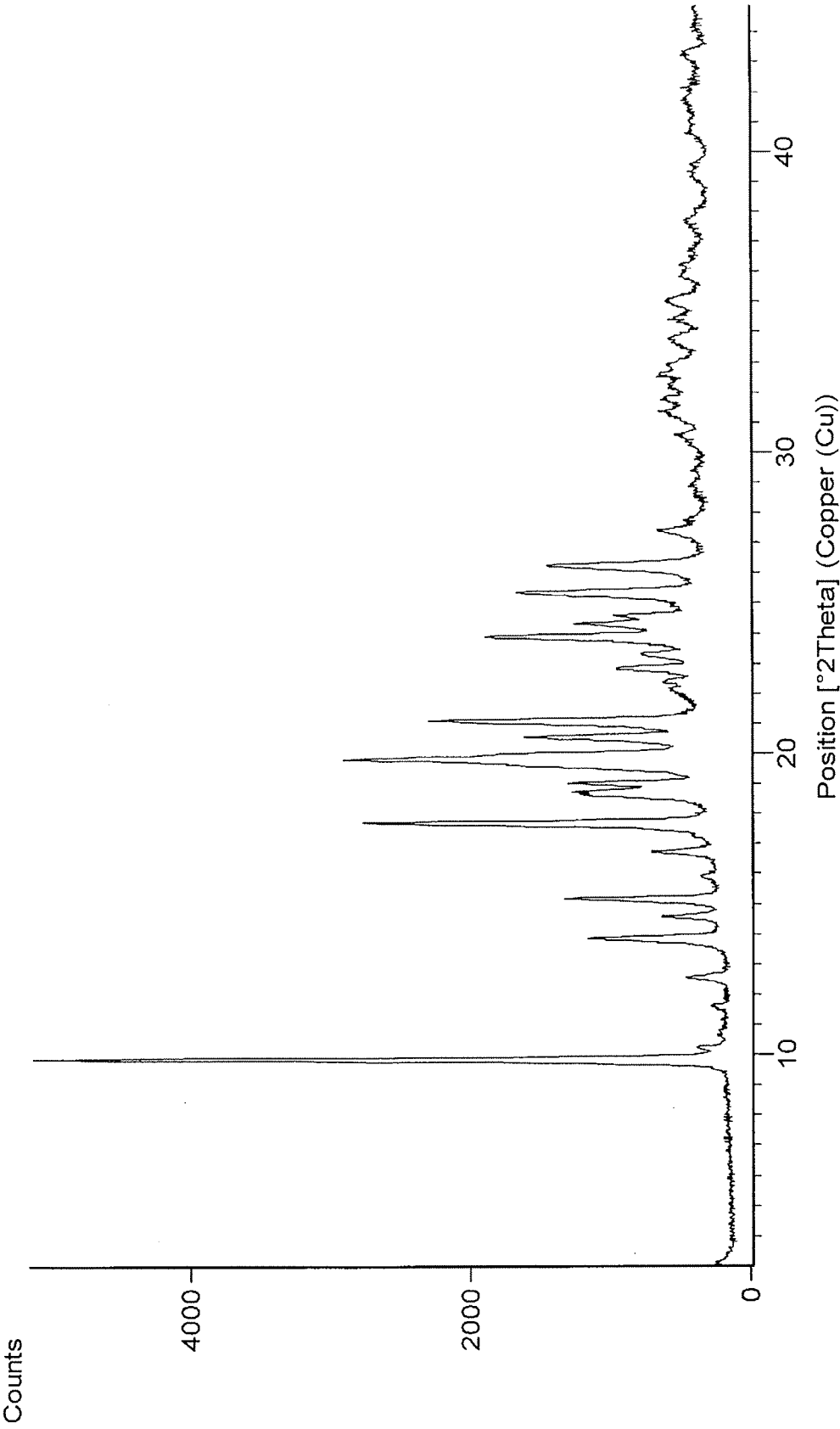


Fig. 2