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(54) Title: PREPARATION OF INTERMEDIATES OF BOCEPREVIR

(57) Abstract: The present application relates to processes for preparing intermediates of Boceprevir and their use in preparation of Boceprevir or its pharmaceutically acceptable salts thereof.



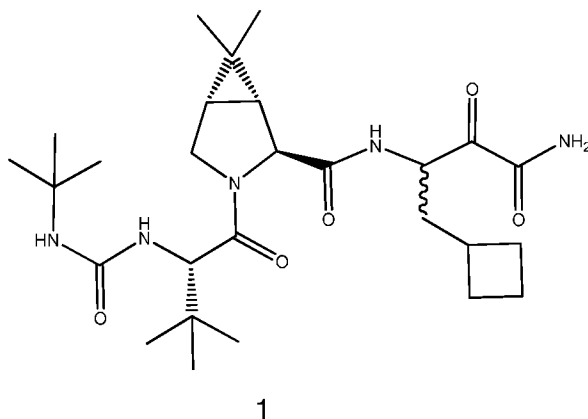
PREPARATION OF INTERMEDIATES OF BOCEPREVIR

INTRODUCTION

Aspects of the present invention relate to processes for preparing intermediates of Boceprevir.

BACKGROUND

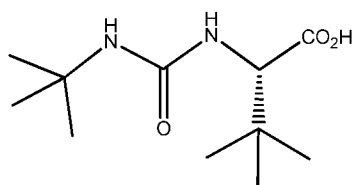
The drug compound having the adopted name "Boceprevir" has chemical name: (1R,5S)-N-[3-amino-1-(cyclobutylmethyl)-2,3-dioxopropyl]-3-[2(S)-[[[(1,1-dimethylethyl)amino]carbonyl]amino]-3,3-dimethyl-1-oxobutyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2(S)-carboxamide; and is represented by structure formula (1).



The commercial pharmaceutical product VICTRELISTM capsules contain boceprevir as the active ingredient. Boceprevir is a hepatitis C virus (HCV) NS3/4A protease inhibitor indicated for the treatment of chronic hepatitis C (CHC) genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients (18 years and older) with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy.

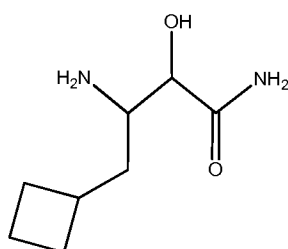
The following compounds of formulae 2, 3 and 4 are the key intermediates useful in the preparation of boceprevir.

(S)-2-(3-tert-butyl-ureido)-3,3-dimethyl-butyric acid having the following structure of formula (2):



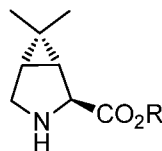
2

3-(amino)-3-cyclobutylmethyl-2-hydroxy-propionamide having the following structure of formula (3):



3

alkyl (1R,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate having the following structure of formula (4):



4

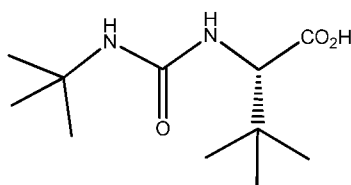
U.S. Patent No. 7,012,066 discloses boceprevir and its pharmaceutically acceptable salts. Processes for the preparation of boceprevir, its intermediates and its salts have been disclosed in U.S. Patent Nos. 7,326,795, 7,528,263 and U.S. Patent Application Publication No. 2010/0145013 A1.

There remains a need for methods of synthesizing compounds which are useful in the preparation of the hepatitis C virus ("HCV") protease inhibitors.

In view of the importance of hepatitis C virus ("HCV") protease inhibitors, new, cost-effective, novel methods of making such antagonists are always of interest.

SUMMARY

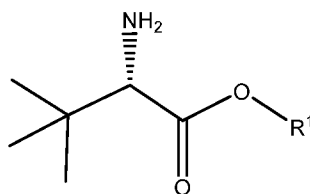
In first aspect, the present application provides process for preparing a compound of formula (2) or a salt thereof,



2

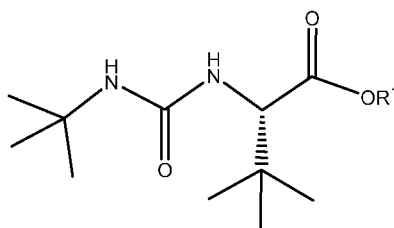
which comprises:

(a) reacting a compound of formula (5) or a pharmaceutically acceptable salt thereof,



5

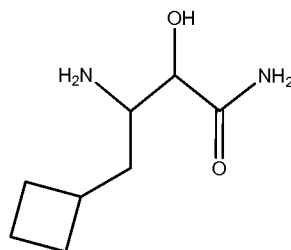
wherein R¹ represents hydrogen, an alkyl group, substituted alkyl group or an aryl group; with a reagent and tertiary butyl amine, or a compound derived there from to provide a compound of formula (6),



6

(b) optionally, converting a compound of formula (6) to a compound of formula (2) or a salt thereof.

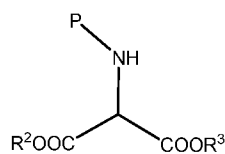
In second aspect, the present application provides process for preparing 3-amino-3-cyclobutylmethyl-2-hydroxy-propionamide having the following structure of formula (3) or salts thereof:



3

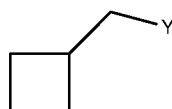
which comprises:

- (a) reacting a compound of formula (7),



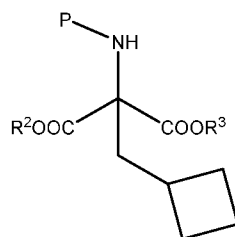
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wherein R^2 or R^3 represents an alkyl group; P represents a protecting group; with a compound of formula (8),



8

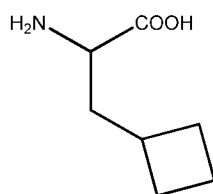
wherein Y represents halo group; to provide a compound of formula (9),



9

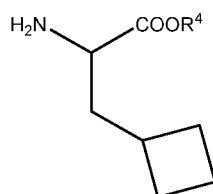
wherein R^2 , R^3 and P are as described previously;

- (b) reacting a compound of formula (9) with a reagent to provide a compound of formula (10) or salts thereof,



10

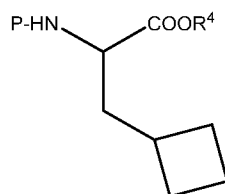
(c) converting a compound of formula (10) or salts thereof to a compound of formula (11),



11

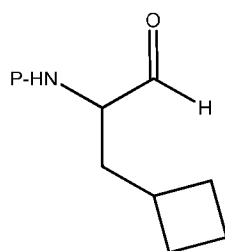
wherein R^4 is same as either R^2 or R^3 and are described previously;

(d) protecting the compound of formula (11) to provide a compound of formula (12),



12

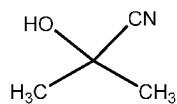
(e) reducing the compound of formula (12) to provide a compound of formula (13),



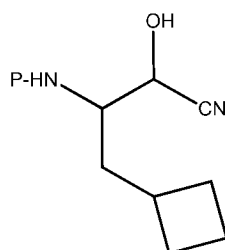
13

wherein P is a protecting group.

(f) reacting the compound of formula (13) with

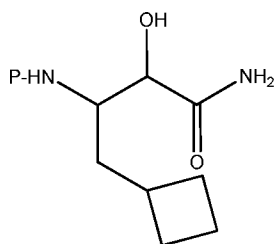


to provide a compound of formula (14),



14

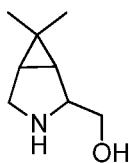
(g) converting the compound of formula (14) to provide a compound of formula (15),



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(h) deprotecting the compound of formula (15) to provide a compound of formula (3) or salts thereof.

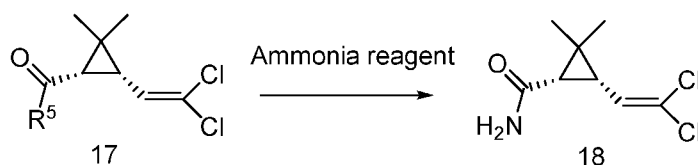
In third aspect, the present application provides process for preparing amine alcohol of formula (16) or its stereo isomers and its pharmaceutically acceptable salts thereof



16

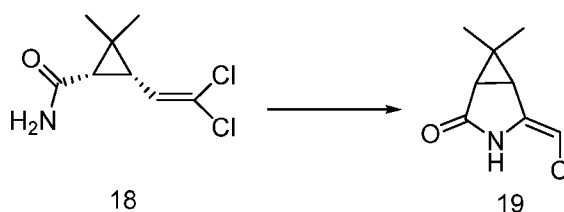
which comprises:

(a) reacting a compound of formula (17) with a reagent of ammonia in a suitable solvent to provide a compound of formula (18)

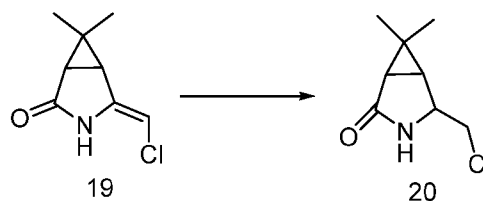


wherein R^5 = hydroxyl; halogen selected from a group of chloro, bromo and iodo; OR^6 ; and R^6 is C_1 - C_8 alkyl

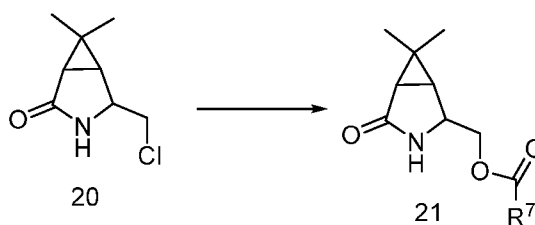
(b) converting a compound of formula (18) to a chloro compound of formula (19)



(c) converting chloro compound of formula (19) to chloro amide of formula (20).

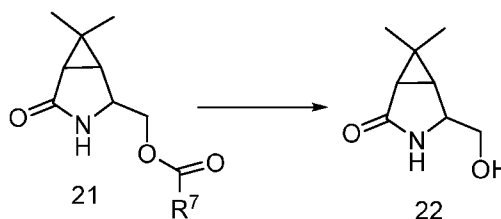


(d) converting chloro amide of formula (20) to ester of formula (21)



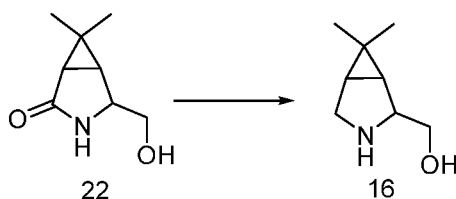
wherein R^7 = alkyl or aryl

(e) converting ester of formula (21) to amide alcohol of formula (22).

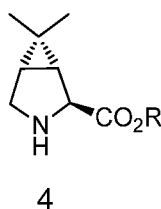


wherein R^7 = alkyl or aryl

(f) reduction of amide alcohol of formula (22) to amine alcohol of formula (16).



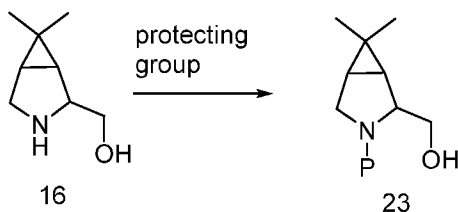
In fourth aspect, the present application provides process for preparing compound having the following structure of formula (4) or its stereoisomers and their pharmaceutically acceptable salts thereof:



wherein R= C₁-C₈ alkyl

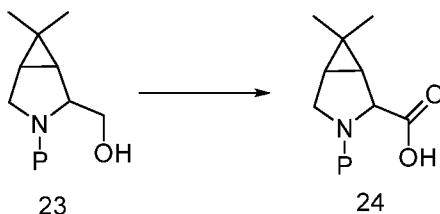
which comprises:

- (a) reacting amine alcohol of formula (16) with a nitrogen protecting reagent to provide nitrogen protected alcohol of formula (23),

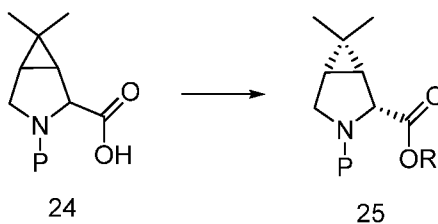


wherein P= amine protecting group

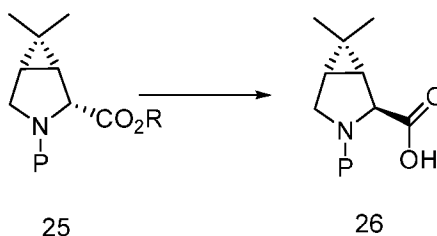
- (b) oxidation of nitrogen protected alcohol of formula (23) to an acid of formula (24),



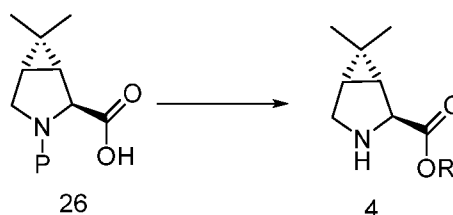
- (c) esterification of acid of formula (24) to provide ester of formula (25)



(d) epimerization of ester of formula (25) to provide acid of formula (26),

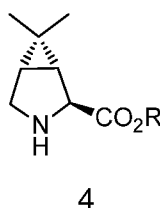


(e) deprotection and esterification of acid of formula (26) to provide a compound of formula (4) or its stereoisomers and their pharmaceutically acceptable salts thereof



wherein R= C₁-C₈ alkyl

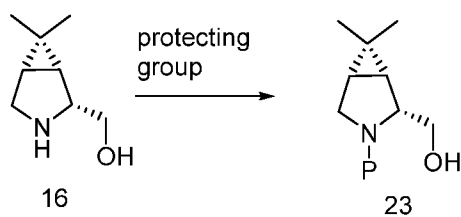
In fifth aspect, the present application provides process for preparing compound having the following structure of formula (4) or its stereoisomers and their pharmaceutically acceptable salts thereof:



wherein R= C₁-C₈ alkyl

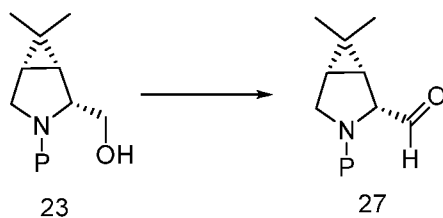
which comprises:

(a) reacting amine alcohol of formula (16) with a nitrogen protecting reagent to provide nitrogen protected alcohol of formula (23),

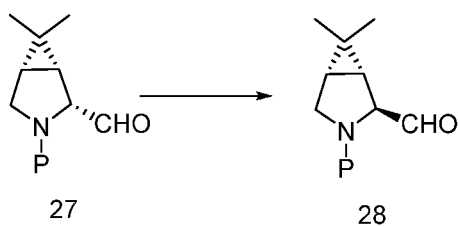


wherein P= amine protecting group

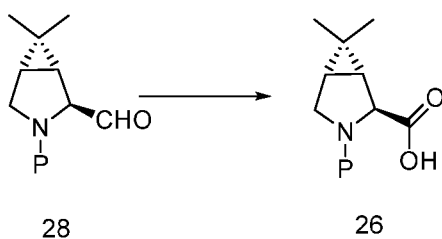
(b) oxidation of nitrogen protected alcohol of formula (23) to an aldehyde of formula (27),



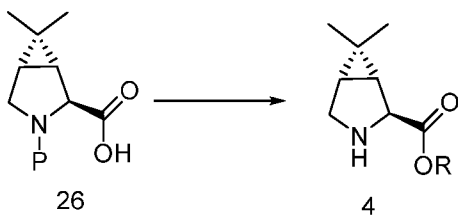
(c) epimerization of aldehyde of formula (27) to provide compound of formula (28)



(d) oxidation of aldehyde of formula (28) to provide acid of formula (26),

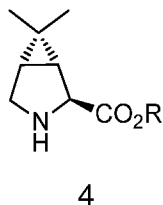


(e) deprotection and esterification of acid of formula (26) to provide a compound of formula (4) or its stereoisomers and their pharmaceutically acceptable salts thereof



wherein R= C₁-C₈ alkyl

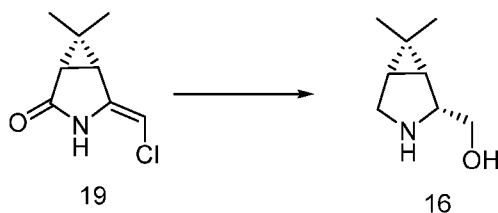
In sixth aspect, the present application provides process for preparing compound having the following structure of formula (4) or its stereoisomers and their pharmaceutically acceptable salts thereof:



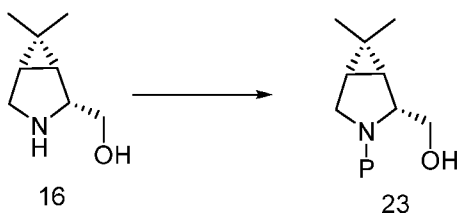
wherein R= C₁-C₈ alkyl

which comprises:

- (a) conversion of chloro compound of formula (19) to amine alcohol of formula (16),

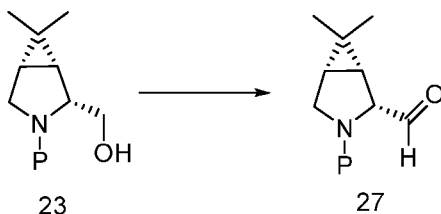


- (b) reacting amine alcohol of formula (16) with a nitrogen protecting reagent to provide nitrogen protected alcohol of formula (23),

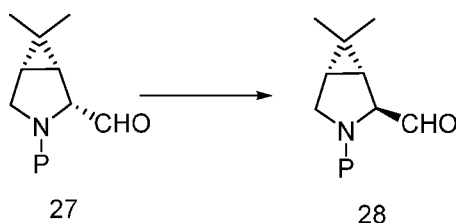


wherein P= amine protecting group

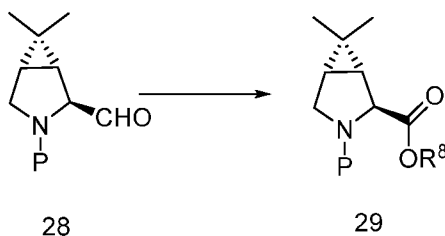
- (c) oxidation of nitrogen protected alcohol of formula (23) to an aldehyde of formula (27),



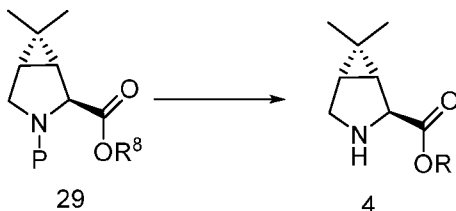
(d) epimerization of aldehyde of formula (27) to provide compound of formula (28)



(e) oxidation of aldehyde of formula (28) to provide ester of formula (29),



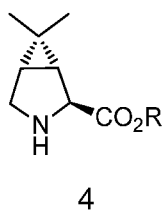
(f) deprotection of ester of formula (29) to provide a compound of formula (4) or its stereoisomers and their pharmaceutically acceptable salts,



wherein R^8 =alkyl or aryl

wherein $R^8=R=C_1$ - C_8 alkyl

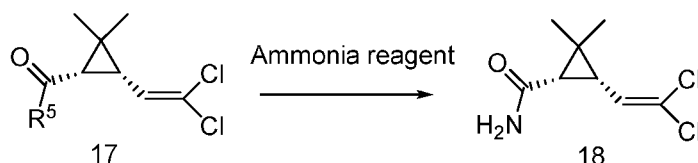
In seventh aspect, the present application provides process for preparing compound having the following structure of formula (4) or its stereoisomers and their pharmaceutically acceptable salts thereof:



wherein $R=C_1$ - C_8 alkyl

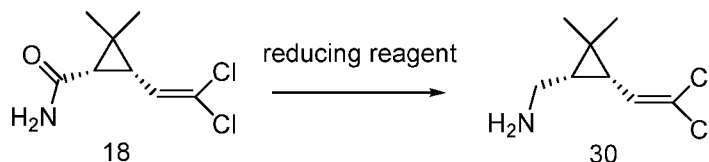
which comprises:

(a) reacting a compound of formula (17) with a reagent of ammonia in a suitable solvent to provide a compound of formula (18)

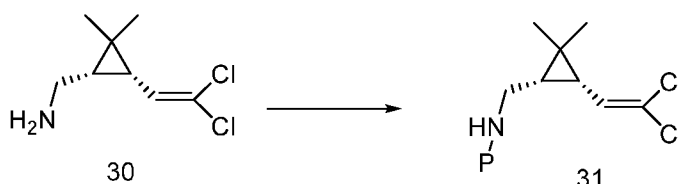


wherein R^5 = hydroxyl; halogen selected from a group of chloro, bromo and iodo; OR^6 ; and R^6 is C_1 - C_8 alkyl

(b) reacting a compound of formula (18) with a reducing agent in a suitable solvent to provide a compound of formula (30)

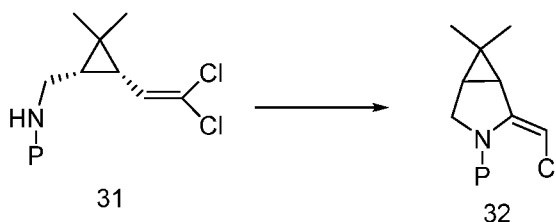


(c) converting a compound of formula (30) to an amino protected compound of formula (31)

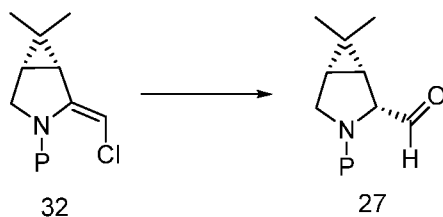


wherein P = amine protecting group

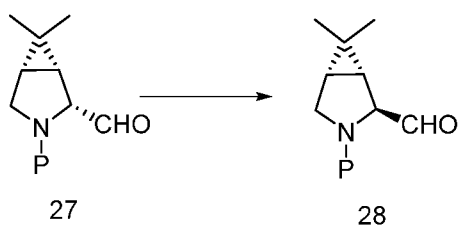
(d) converting amino protected compound of formula (31) to a chloro compound of formula (32)



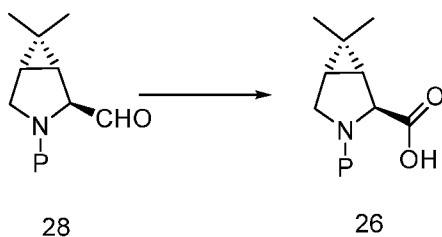
(e) oxidation of chloro compound of formula (32) to an aldehyde of formula (27),



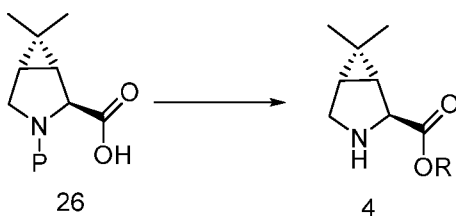
(f) epimerization of aldehyde of formula (27) to provide compound of formula (28)



(g) oxidation of aldehyde of formula (28) to provide acid of formula (26),

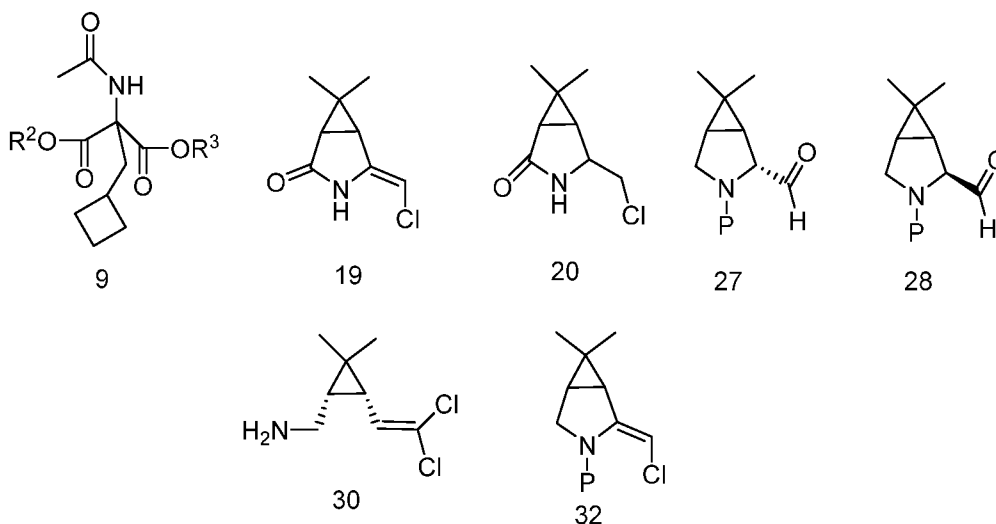


(h) deprotection and esterification of acid of formula (26) to provide a compound of formula (4) or its stereoisomers and their pharmaceutically acceptable salts thereof



wherein R= C₁-C₈ alkyl, P=amine protecting group

Eighth aspect of the present application provides novel intermediate compounds which are suitable for the preparation of boceprevir, its intermediates or their pharmaceutically acceptable salts.



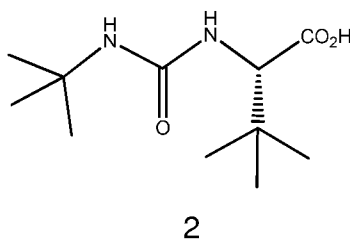
wherein P= amine protecting group

Ninth aspect of the present application provides a process for the preparation of boceprevir of formula (1) or its pharmaceutically acceptable salts using the compound of formula (2), (3) and (4) or their stereoisomers and their pharmaceutically acceptable salts prepared according to process of the present application.

Tenth aspect of the present application provides pharmaceutical compositions comprising boceprevir of formula (1) or its pharmaceutically acceptable salts by using compounds of formula (2), (3) and (4) or their stereoisomers and their pharmaceutically acceptable salts prepared according to process of the present application together with one or more pharmaceutically acceptable excipient, carrier and diluents.

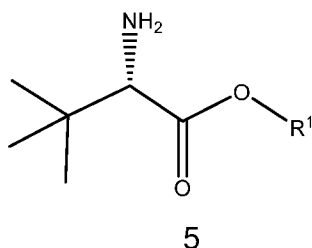
DETAILED DESCRIPTION

In first aspect, the present application provides process for preparing a compound of formula (2) or a salt thereof,

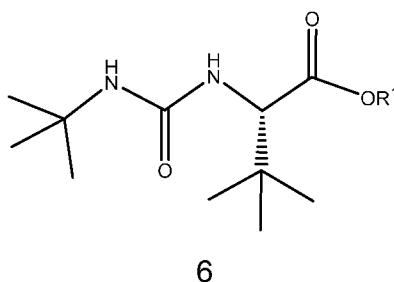


which comprises:

(a) reacting a compound of formula 5 or a pharmaceutically acceptable salt thereof,



wherein R^1 represents hydrogen, an alkyl group, substituted alkyl group or an aryl group; with a reagent and tertiary butyl amine, or a compound derived there from to provide a compound of formula (6),



(b) optionally, converting a compound of formula (6) to a compound of formula (2) or a salt thereof.

Step (a) involves reacting a compound of formula (5) or a pharmaceutically acceptable salt thereof, with a reagent and tertiary butyl amine.

In one variant, step (a) may be carried out by reacting a compound of formula (5) or a pharmaceutically acceptable salt thereof, with a reagent and tertiary butyl amine to provide a compound of formula (6).

In another variant, step (a) may be carried out by reacting a compound of formula 5 or a pharmaceutically acceptable salt thereof, with a compound derived from a reagent and tertiary butyl amine.

Suitable reagents that may be used in step (a) include, N, N'-carbonyldiimidazole (CDI), alkyl chloroformate (e.g. ethyl chloroformate, isobutyl chloroformate or the like), dialkyl carbonate or any other suitable reagent.

Step (a) may be carried out in the presence of one or more suitable bases. Suitable bases that may be used in step (a) include, but are not limited to, organic bases, such as, for example, triethylamine, tributylamine, N-methylmorpholine, N,N-

diisopropylethylamine, N-methylpyrrolidine, pyridine, 4-(N,N-dimethyl amino)pyridine, morpholine, imidazole, 2-methylimidazole, 4-methylimidazole, 1,4-diazabicyclo[2.2.2]octane ("DABCO"), 1,8-diazabicyclo[5.4.0]undec-7-ene ("DBU"), or the like; ion exchange resins including resins bound to ions, such as, for example, sodium, potassium, lithium, calcium, magnesium, substituted or unsubstituted ammonium, or the like; or mixtures thereof.

Step (a) may be carried out in one or more suitable solvents. Suitable solvents that may be used in step (a) include, but are not limited to, ether solvents, such as, for example, diethyl ether, diisopropyl ether, tert-butyl methyl ether, dibutyl ether, tetrahydrofuran, 1,2-dimethoxyethane, 2-methoxyethanol, 2-ethoxyethanol, anisole, 1,4-dioxane, or the like; aliphatic or alicyclic hydrocarbon solvents, such as, for example, hexane, heptane, pentane, cyclohexane, methylcyclohexane, or the like; halogenated hydrocarbon solvents, such as, for example, dichloromethane, chloroform, 1,1,2-trichloroethane, 1,2-dichloroethene, or the like; aromatic hydrocarbon solvents, such as, for example, toluene, xylene, chlorobenzene, tetralin, or the like; nitrile solvents, such as, for example, acetonitrile, propionitrile, or the like; polar aprotic solvents, such as, for example, N,N-dimethyl formamide, N,N-dimethyl acetamide, N-methyl pyrrolidone, pyridine, dimethyl sulphoxide, sulpholane, formamide, acetamide, propanamide, nitromethane, or the like; or mixtures thereof.

Suitable temperatures for the reaction of step (a) may be less than about 100°C, less than about 80°C, less than about 60°C, less than about 40°C, less than about 30°C, less than about 20°C, less than about 10°C, or less than about 5°C, or any other suitable temperatures.

Step (b) optionally, involves converting a compound of formula (6) to (S)-2-(3-tert-butyl-ureido)-3-3-dimethyl-butyric acid of formula (2).

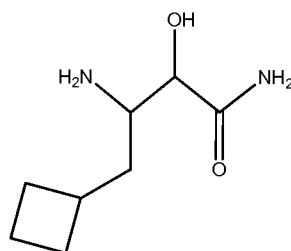
Step (b) may be carried out in one or more inorganic bases, such as, for example, alkali metal hydrides, such as, for example, sodium hydride, potassium hydride, or the like; sodamide; n-butyl lithium; lithium diisopropylamide; alkali metal hydroxides, such as, for example, lithium hydroxide, sodium hydroxide, potassium hydroxide, and cesium hydroxide; alkaline metal hydroxides, such as, for example, barium hydroxide, strontium hydroxide, magnesium hydroxide, calcium hydroxide, or the

like; alkali metal carbonates, such as, for example, sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate, or the like; alkaline earth metal carbonates, such as, for example, magnesium carbonate, calcium carbonate, or the like; alkali metal bicarbonates, such as, for example, sodium bicarbonate, potassium bicarbonate, or the like; ion exchange resins including resins bound to ions, such as, for example, sodium, potassium, lithium, calcium, magnesium, substituted or unsubstituted ammonium, or the like; or mixtures thereof.

Step (b) may be carried out in one or more suitable solvents. Suitable solvents that may be used in step (b) include, but are not limited to, water; alcohol solvents, such as, for example, methanol, ethanol, propanol, 1-propanol, 2-propanol, butanol, pentanol, ethylene glycol, glycerol, or the like; ketone solvents, such as, for example, acetone, butanone, pentanone, methyl isobutyl ketone, or the like; ester solvents, such as, for example, ethyl formate, methyl acetate, ethyl acetate, propyl acetate, butyl acetate, methyl propanoate, ethyl propanoate, methyl butanoate, ethyl butanoate, or the like; ether solvents, such as, for example, diethyl ether, diisopropyl ether, t-butyl methyl ether, dibutyl ether, tetrahydrofuran, 1,2-dimethoxyethane, 2-methoxyethanol, 2-ethoxyethanol, anisole, or the like; aliphatic or alicyclic hydrocarbon solvents, such as, for example, hexane, heptane, pentane, cyclohexane, methylcyclohexane, or the like; halogenated hydrocarbon solvents, such as, for example, dichloromethane, chloroform, 1,1,2-trichloroethane, 1,2-dichloroethene, or the like; aromatic hydrocarbon solvents, such as, for example, toluene, xylene, chlorobenzene, tetralin, or the like; nitrile solvents, such as, for example, acetonitrile, propionitrile, or the like; or any mixtures thereof.

Suitable temperatures that may be used in step (b) may be less than about 200°C, less than about 150°C, less than about 100°C, less than about 80°C, less than about 60°C, less than about 40°C, less than about 30°C, less than about 20°C, less than about 10°C, or any other suitable temperature.

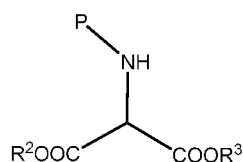
In second aspect, the present application provides process for preparing 3-amino-3-cyclobutylmethyl-2-hydroxy-propionamide having the following structure of formula (3) or salts thereof:



3

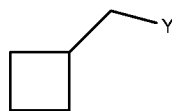
which comprises:

(a) reacting a compound of formula (7),



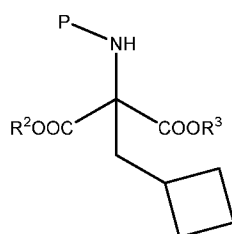
7

wherein R^2 or R^3 represents an alkyl group; P represents a protecting group; with a compound of formula (8),



8

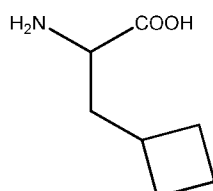
wherein Y represents halo group; to provide a compound of formula (9),



9

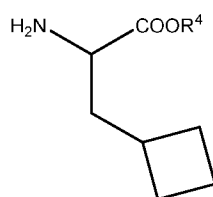
wherein R^2 , R^3 and P are as described previously;

(b) reacting a compound of formula (9) with a reagent to provide a compound of formula (10) or salts thereof,



10

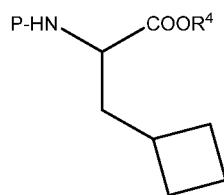
(c) converting a compound of formula (10) or salts thereof, in to a compound of formula (11),



11

wherein R^4 is as described previously;

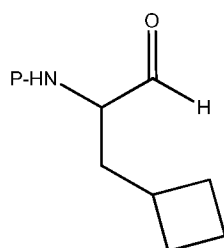
(d) protecting the compound of formula (11) to provide a compound of formula (12),



12

wherein R^4 is same as either R^2 or R^3 and are described previously;

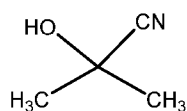
(e) reducing the compound of formula (12) to provide a compound of formula (13),



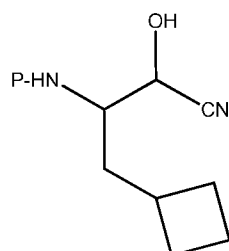
13

wherein P= protecting group

(f) reacting the compound of formula (13) with

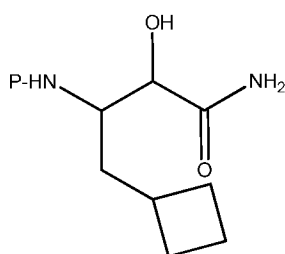


to provide a compound of formula (14),



14

(g) converting the compound of formula (14) to provide a compound of formula (15),



15

(h) deprotecting the compound of formula (15) to provide a compound of formula (3) or salts thereof.

Step (a) involves reacting a compound of formula (7) with a compound of formula (8) to provide a compound of formula (9).

Suitable bases that may be used in step (a) include, but are not limited to, inorganic bases, such as, for example, alkali metal hydrides, such as, for example, sodium hydride, potassium hydride, or the like; sodamide; n-butyl lithium; lithium diisopropylamide; alkali metal hydroxides, such as, for example, lithium hydroxide, sodium hydroxide, potassium hydroxide, and cesium hydroxide; alkaline metal hydroxides, such as, for example, barium hydroxide, strontium hydroxide, magnesium hydroxide, calcium hydroxide, or the like; alkali metal carbonates, such as, for example, sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate, or the like; alkaline earth metal carbonates, such as, for example, magnesium carbonate, calcium carbonate, or the like; alkali metal bicarbonates, such as, for example, sodium bicarbonate, potassium bicarbonate, or the like; ion exchange resins including resins bound to ions, such as, for example, sodium, potassium, lithium, calcium, magnesium, substituted or unsubstituted ammonium, or the like; or mixtures thereof.

Step (a) may be carried out in one or more suitable solvents. Suitable solvents that may be used in step (a) include, but are not limited to, polar aprotic solvents, such as, for example, N,N-dimethyl formamide, N,N-dimethyl acetamide, N-methyl pyrrolidone, pyridine, dimethyl sulphoxide, sulpholane, formamide, acetamide, propanamide, nitromethane, or the like; or mixtures thereof.

Suitable temperatures for the reaction of step (a) may be less than about 100°C, less than about 80°C, less than about 60°C, less than about 40°C, less than about 30°C, less than about 20°C, less than about 10°C, or less than about 5°C, or any other suitable temperatures.

Step (b) involves reacting a compound of formula (9) with a reagent to provide a compound of formula (10) or salts thereof.

Step (b) may be carried out in the presence of an aqueous solution of acid. Non-limiting examples of acids that can be used in step (b) include, inorganic or organic acids such as, for example, ammonium sulfate, ammonium nitrate, ammonium chloride, citric acid, alkyl sulfonic acid, hydrofluoric acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, periodic acid, sulphuric acid, phosphoric acid, polyphosphoric acid, phosphorous acid, nitric acid, nitrous acid, or the like.

Suitable temperatures for the reaction of step (b) may be less than about 200°C, less than about 150°C, less than about 100°C, less than about 80°C, less than about 60°C, less than about 40°C, less than about 30°C, less than about 20°C, less than about 10°C, or less than about 5°C, or any other suitable temperatures.

Step (c) involves converting a compound of formula (10) or salts thereof to a compound of formula (11).

Step (c) may be carried out in the presence of suitable reagents. Suitable reagents that may be used in step (c) include, but are not limited to, thionyl chloride, or the like.

Suitable solvent that may be used in step (c) include, but are not limited to: alcohol solvents, such as, for example, methanol, ethanol, propanol, 1-propanol, 2-propanol, butanol, pentanol, ethylene glycol, glycerol, or the like; or any mixtures thereof.

Step (d) involves protecting the compound of formula (11) to provide a compound of formula (12).

Step (d) may be carried out in the presence of a suitable protecting group in a suitable solvent.

Step (d) may be optionally carried out in a suitable solvent. Suitable solvents that may be used in step d) include, but are not limited to: ethers such as, for example, diethyl ether, diisopropyl ether, t-butyl methyl ether, tetrahydrofuran, methyl t-butyl ether, cyclopentyl methyl ether, or the like; aliphatic or alicyclic hydrocarbons such as, for example, hexanes, n-heptane, n-pentane, cyclohexane, or the like; halogenated hydrocarbons such as, for example, dichloromethane, chloroform, or the like; aromatic hydrocarbons such as, for example, toluene, xylenes, or the like; nitriles such as, for example, acetonitrile, propionitrile, or the like; or any mixtures thereof.

The term "protecting group" as used herein refers to those groups intended to protect the N-terminus of an amino acid, or to protect an amino group, against undesirable reactions during synthesis procedures. Suitable N-protecting groups that may be used include, but are not limited to: acyl groups such as formyl, acetyl, t-butyl acetyl, pivaloyl, benzoyl, trifluoroacetyl, 4-nitrobenzoyl, and the like; alkyl groups such as benzyl, benzyloxymethyl, and the like; carbamate forming groups such as benzyloxycarbonyl, t-butyloxycarbonyl, fluorenyl-9-methoxycarbonyl, and the like; and any other suitable protecting groups.

Step (d) may be carried out in the presence of a reagent. Suitable reagents that may be used in step (d) include, but are not limited to: Boc anhydride [di-t-butyl dicarbonate or (Boc)₂O]; benzyl chloride and any other suitable reagents.

Step (d) may be carried out in the presence of a base. Suitable bases that may be used in step d) include, but are not limited to: organic bases such as triethylamine, tributylamine, N-methylmorpholine, N,N-diisopropylethylamine, N-methylpyrrolidine, pyridine, 4-(N,N-dimethylamino)pyridine, morpholine, imidazole, 2-methylimidazole, 4-methylimidazole, or the like; inorganic bases such as alkali metal hydrides including sodium hydride, potassium hydride, or the like; sodamide; n-butyl lithium; lithium diisopropylamide; alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide, and cesium hydroxide; alkaline metal hydroxides such as

aluminum hydroxide, magnesium hydroxide, calcium hydroxide, or the like; alkali metal carbonates such as sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate, or the like; alkaline earth metal carbonates such as magnesium carbonate, calcium carbonate or the like; alkali metal bicarbonates such as sodium bicarbonate, potassium bicarbonate, or the like; and ion exchange resins including resins bound to ions such as sodium, potassium, lithium, calcium, and magnesium; substituted or unsubstituted ammonium or the like; or any other suitable bases.

Suitable temperatures that may be used in step d) may be less than about 80°C, less than about 60°C, less than about 40°C, less than about 30°C, less than about 20°C, less than about 10°C, less than about 0°C, less than about -10°C, less than about -20°C, less than about -30°C, or any other suitable temperatures.

Step (e) involves reducing the compound of formula (12) to provide a compound of formula (13).

Suitable reducing agents that may be used in step (e) include, but are not limited to: diisobutylaluminum hydride, or the like. Step (e) may be carried out in a suitable solvent. Suitable solvent that may be used include, but are not limited to: halogenated hydrocarbons such as, for example, dichloromethane, chloroform, or the like.

Step (f) involves reacting the compound of formula (13) with acetone cyanohydrins to provide a compound of formula (14).

Step (f) may be carried out in the presence of suitable base in a suitable solvent.

Suitable bases that may be used in step (f) include, but are not limited to: organic bases such as triethylamine, tributylamine, N-methylmorpholine, N,N-diisopropylethylamine, N-methylpyrrolidine, pyridine, 4-(N,N-dimethylamino)pyridine, morpholine, imidazole, 2-methylimidazole, 4-methylimidazole, or the like.

Suitable solvent that may be used include, but are not limited to: halogenated hydrocarbons such as, for example, dichloromethane, chloroform, or the like.

Step (g) involves conversion of the compound of formula (14) to provide a compound of formula (15).

Suitable reagents that may be used include, but are not limited to: hydrogen peroxide, or the like.

Step (g) may be carried out in the presence of a base. Suitable bases that may be used in step (g) include, but are not limited to: inorganic bases such as alkali metal carbonates such as sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate, or the like; alkaline earth metal carbonates such as magnesium carbonate, calcium carbonate or the like; alkali metal bicarbonates such as sodium bicarbonate, potassium bicarbonate, or the like; or any other suitable bases.

Step (g) may be carried out in one or more suitable solvents. Suitable solvents that may be used in step (g) include, but are not limited to, ketone solvents, such as, for example, acetone, butanone, pentanone, methyl isobutyl ketone, or the like; halogenated hydrocarbon solvents, such as, for example, dichloromethane, chloroform, 1,1,2-trichloroethane, 1,2-dichloroethene, or the like; aromatic hydrocarbon solvents, such as, for example, toluene, xylene, chlorobenzene, tetralin, or the like; nitrile solvents, such as, for example, acetonitrile, propionitrile, or the like; polar aprotic solvents, such as, for example, N,N-dimethyl formamide, N,N-dimethyl acetamide, N-methyl pyrrolidone, pyridine, dimethyl sulphoxide, sulfolane, formamide, acetamide, propanamide, nitromethane, or the like; or mixtures thereof.

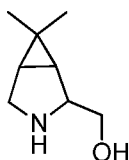
Step (h) involves deprotecting the compound of formula (15) to provide a compound of formula (3) or salts thereof.

Step (h) may be carried out in the presence of a suitable acid in a suitable solvent.

Non-limiting examples of acids that can be used in step (h) include, inorganic or organic acids such as, for example, ammonium sulfate, ammonium nitrate, ammonium chloride, citric acid, alkyl sulfonic acid, hydrofluoric acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, periodic acid, sulphuric acid, phosphoric acid, polyphosphoric acid, phosphorous acid, nitric acid, nitrous acid, or the like.

Suitable solvents that may be used in step (h) include, but are not limited to, water; alcohol solvents, such as, for example, methanol, ethanol, propanol, 1-propanol, 2-propanol, butanol, pentanol, ethylene glycol, glycerol, or the like.

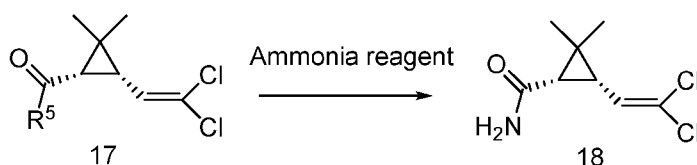
In third aspect, the present application provides process for preparing amine alcohol of formula (16) or its stereo isomers and its pharmaceutically acceptable salts thereof



16

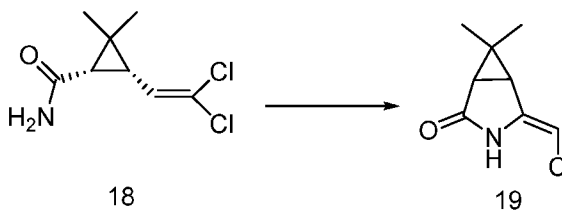
which comprises:

(a) reacting a compound of formula (17) with a reagent of ammonia in a suitable solvent to provide a compound of formula (18)

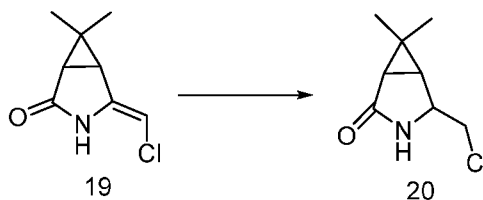


wherein R^5 = hydroxyl; halogen selected from a group of chloro, bromo and iodo; OR^6 ; and R^6 is C_1 - C_8 alkyl

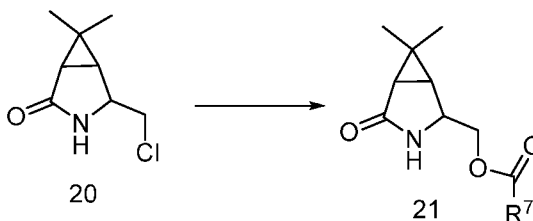
(b) converting a compound of formula (18) to a chloro compound of formula (19)



(c) converting chloro compound of formula (19) to chloro amide of formula (20).

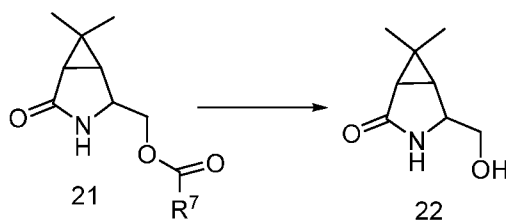


(d) converting chloro amide of formula (20) to ester of formula (21)



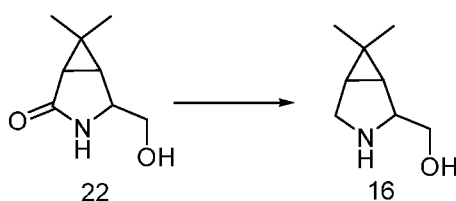
wherein R^7 = alkyl or aryl

(e) converting ester of formula (21) to amide alcohol of formula (22).



wherein R^7 = alkyl or aryl

(f) reduction of amide alcohol of formula (22) to amine alcohol of formula (16).



Cis-Cypermenthric acid resolution can be carried out chemically or enzymatically. In the chemical resolution, suitable chiral reagent include, but are not limited to, phenylethyl amine or the like. In case of Cis-Cypermenthric acid, the acid is converted to acid halides by processes known in art

In the step (a), suitable source of ammonia include, but are not limited to, ammonia gas; aqueous ammonia solution; alcohol solvent saturated with ammonia wherein the suitable alcohol solvent is methanol, ethanol, iso-propanol, tert-butanol and amyl alcohol; masked ammonia such as ammonium carbonate; or any other sources of ammonia.

Step (a) may be carried out in one or more suitable solvents. Suitable solvents that may be used in step (a) include, but are not limited to, ether solvents, such as, for example, diethyl ether, diisopropyl ether, tert-butyl methyl ether, dibutyl ether, tetrahydrofuran, 1,2-dimethoxyethane, 2-methoxyethanol, 2-ethoxyethanol, anisole, 1,4-dioxane, or the like; aliphatic or alicyclic hydrocarbon solvents, such as, for example, hexane, heptane, pentane, cyclohexane, methylcyclohexane, or the like; halogenated hydrocarbon solvents, such as, for example, dichloromethane, chloroform, 1,1,2-trichloroethane, 1,2-dichloroethane, or the like; aromatic hydrocarbon solvents, such as, for example, toluene, xylene, chlorobenzene, tetralin, or the like; nitrile solvents, such as, for example, acetonitrile, propionitrile, or the like;

Step (b) may be carried out in the presence of one or more suitable strong bases. Suitable bases that may be used in step (b) include, but are not limited to, lithium diisopropylamide, sodium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, sodium hydride, potassium hydride, sodium tert-butoxide, potassium tert-butoxide or any other strong base.

Step (b) may be carried out in one or more suitable solvents. Suitable solvents that may be used in step (b) include, but are not limited to, ether solvents, such as, for example, diethyl ether, diisopropyl ether, tert-butyl methyl ether, dibutyl ether, tetrahydrofuran, 1,2-dimethoxyethane, 2-methoxyethanol, 2-ethoxyethanol, anisole, 1,4-dioxane, or the like; polar aprotic solvents, such as, for example, N,N-dimethyl formamide, N,N-dimethyl acetamide, N-methyl pyrrolidone, pyridine, dimethyl sulphoxide, sulpholane, formamide, acetamide, propanamide, nitromethane, halogenated hydrocarbon solvents, such as, for example, dichloromethane, chloroform, 1,1,2-trichloroethane, 1,2-dichloroethene, or the like; aromatic hydrocarbon solvents, such as, for example, toluene, xylene, chlorobenzene, tetralin, or the like; nitrile solvents, such as, for example, acetonitrile, propionitrile, or the like;

Step (c) is the conversion of chloro compound of formula (19) to chloro amide of formula (20). This conversion involves insitu formation of hydroxylated intermediate or its derivative which may or may not be isolated, preferably these intermediate compounds are not isolated in the present invention.

The hydroxylation reaction of step (c) may be carried out in the presence of one or more suitable reagents. Suitable reagents that may be used include, but are not limited to hydrogen peroxide, benzoyl peroxide, cumene hydro peroxide, tert-butyl hydro peroxide or the like.

The hydroxylation reaction of step (c) may be carried out in the presence of one or more suitable strong acid or acid ion exchange resins. Suitable resin that may be used in step (c) include, but are not limited to amberlite IR120, amberlite 200C Na, amberlite SR 1L Na, Indion, Tulsion, Nafion or the like. Strong acids are sulfuric acid, hydrochloric acid or the like.

The resulted hydroxyl derivatives are converted to chloro amide of formula (20) in presence of suitable reagents and strong acid. Suitable reagents that may be used in

step (c) include, but are not limited to alkylsilanes such as trimethylsilane, triethylsilane or the like; phenylsilanes, halosilanes such as trichlorosilane or the like; tris(trialkylsilyl)silane such as tris(trimethylsilyl)silane or the like. The strong acids that may be used include, but are not limited to trifluoroacetic acid, indium tribromide, indium trichloride, tris(pentafluorophenyl)boron or the like.

Step (c) may be carried out in one or more suitable solvents. Suitable solvents that may be used in step (c) include, but are not limited to, ether solvents, such as, for example, diethyl ether, diisopropyl ether, tert-butyl methyl ether, dibutyl ether, tetrahydrofuran, 1,2-dimethoxyethane, 2-methoxyethanol, 2-ethoxyethanol, anisole, 1,4-dioxane, or the like; halogenated hydrocarbon solvents, such as, for example, dichloromethane, chloroform, 1,1,2-trichloroethane, 1,2-dichloroethene, or the like; aromatic hydrocarbon solvents, such as, for example, toluene, xylene, chlorobenzene, tetralin, or the like;

Step (d) may be carried out in the presence of one or more suitable reagents. Suitable reagents that may be used in step (d) include, but not limited to sodium acetate, potassium acetate, or the like.

Suitable phase transfer catalyst that may be used in step (d) include, but not limited to tetraalkyl ammonium halides such as tetrabutyl ammonium bromide, tertabutyl ammonium chloride, tetrabutyl ammonium iodide, tetraethyl ammonium bromide, tetraethyl ammonium chloride, or the like.

Step (d) may be carried out in one or more suitable solvents. Suitable solvents that may be used in step (d) include, but are not limited to, ether solvents, such as, for example, diethyl ether, diisopropyl ether, tert-butyl methyl ether, dibutyl ether, tetrahydrofuran, 1,2-dimethoxyethane, 2-methoxyethanol, 2-ethoxyethanol, anisole, 1,4-dioxane, or the like; halogenated hydrocarbon solvents, such as, for example, dichloromethane, chloroform, 1,1,2-trichloroethane, 1,2-dichloroethene, or the like; aromatic hydrocarbon solvents, such as, for example, toluene, xylene, chlorobenzene, tetralin, polar aprotic solvents, such as, for example, N,N-dimethyl formamide, N,N-dimethyl acetamide, N-methyl pyrrolidone, pyridine, dimethyl sulfoxide, sulfolane, formamide, acetamide, propanamide, nitromethane, or the like; or mixtures thereof.

Step (e) may be carried out in one or more organic or inorganic bases, such as, alkali metal hydroxides, such as, for example, lithium hydroxide, sodium hydroxide, potassium hydroxide, and cesium hydroxide; alkaline earth metal hydroxides, such as, for example, barium hydroxide, strontium hydroxide, magnesium hydroxide, calcium hydroxide, or the like; alkali metal carbonates, such as, for example, sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate, or the like; alkaline earth metal carbonates, such as, for example, magnesium carbonate, calcium carbonate, or the like; alkali metal bicarbonates, such as, for example, sodium bicarbonate, potassium bicarbonate, or the like. Alternatively, the reaction of step (e) may also be conducted in the presence of ion exchange resins including resins bound to ions, such as, for example, sodium, potassium, lithium, calcium, magnesium, substituted or unsubstituted ammonium, or the like; or mixtures thereof.

Step (e) may be carried out in one or more suitable solvents. Suitable solvents that may be used in step (e) include, but are not limited to; alcohol solvents, such as, for example, methanol, ethanol, propanol, 1-propanol, 2-propanol, butanol, pentanol, ethylene glycol, glycerol, or the like; ketone solvents, such as, for example, acetone, butanone, pentanone, methyl isobutyl ketone, or the like; ester solvents, such as, for example, ethyl formate, methyl acetate, ethyl acetate, propyl acetate, butyl acetate, methyl propanoate, ethyl propanoate, methyl butanoate, ethyl butanoate, or the like; ether solvents, such as, for example, diethyl ether, diisopropyl ether, t-butyl methyl ether, dibutyl ether, tetrahydrofuran, 1,2-dimethoxyethane, 2-methoxyethanol, 2-ethoxyethanol, anisole, or the like; aliphatic or alicyclic hydrocarbon solvents, such as, for example, hexane, heptane, pentane, cyclohexane, methylcyclohexane, or the like; halogenated hydrocarbon solvents, such as, for example, dichloromethane, chloroform, 1,1,2-trichloroethane, 1,2-dichloroethene, or the like; aromatic hydrocarbon solvents, such as, for example, toluene, xylene, chlorobenzene, tetralin, or the like; nitrile solvents, such as, for example, acetonitrile, propionitrile, or the like; or any mixtures thereof.

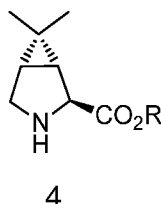
Step (f) may be carried out in the presence of one or more suitable lactam reducing reagents. Suitable reagents that may be used in step (f) include, but not

limited to lithium aluminium hydride, diisobutyl aluminium hydride, diborane, sodium borohydride or the like.

Step (f) may be carried out in one or more suitable solvents. Suitable solvents that may be used in step (f) include, but are not limited to, ether solvents, such as, for example, diethyl ether, diisopropyl ether, t-butyl methyl ether, dibutyl ether, tetrahydrofuran, 1,2-dimethoxyethane, 2-methoxyethanol, 2-ethoxyethanol, anisole, or the like; aliphatic or alicyclic hydrocarbon solvents, such as, for example, hexane, heptane, pentane, cyclohexane, methylcyclohexane, or the like; halogenated hydrocarbon solvents, such as, for example, dichloromethane, chloroform, 1,1,2-trichloroethane, 1,2-dichloroethene, or the like; aromatic hydrocarbon solvents, such as, for example, toluene, xylene, chlorobenzene, tetralin, or the like; or any mixtures thereof.

The temperature at which the above steps may be carried out in between about -15 °C and about 50 °C based on the solvent used in particular step. Preferably, the reaction steps are carried out under an inert atmosphere.

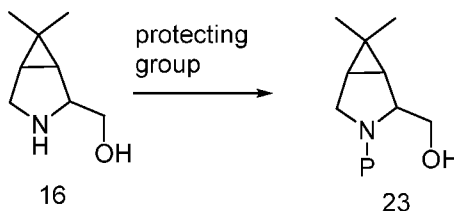
In fourth aspect, the present application provides process for preparing compound having the following structure of formula (4) or its stereoisomers and their pharmaceutically acceptable salts thereof:



wherein R= C₁-C₈ alkyl

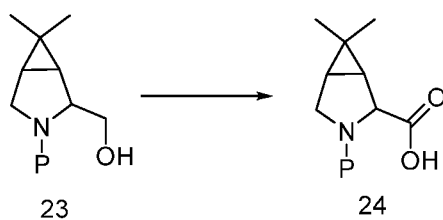
which comprises:

- (a) reacting amine alcohol of formula (16) with a nitrogen protecting reagent to provide nitrogen protected alcohol of formula (23),

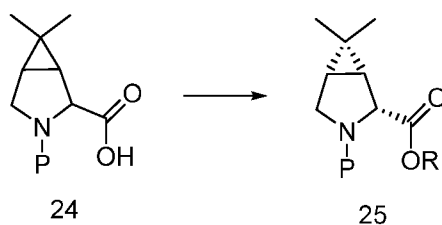


wherein P= amine protecting group

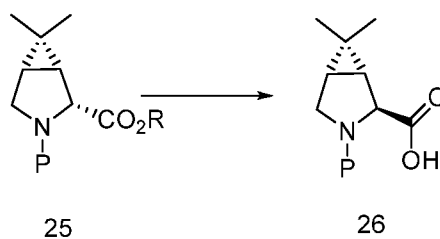
(b) oxidation of nitrogen protected alcohol of formula (23) to an acid of formula (24),



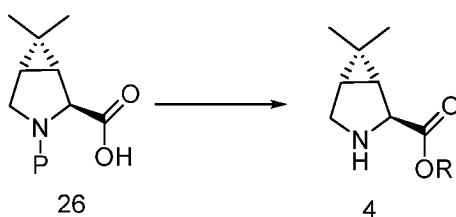
(c) esterification of acid of formula (24) to provide ester of formula (25)



(d) epimerization of ester of formula (25) to provide acid of formula (26),



(e) deprotection and esterification of acid of formula (26) to provide a compound of formula (4) or its stereoisomers and their pharmaceutically acceptable salts,



wherein R= C₁-C₈ alkyl

Step (a) may be carried out in the presence of one or more suitable amine protecting reagents. Suitable reagents that may be used in step (a) include, but not limited to benzyl, ditert-butyl dicarbonate, benzyl chloroformate,

fluorenylmethyloxycarbonyl chloride or the like. Any suitable amine protecting other than specified ones may also be used.

Step (a) may be carried out in one or more suitable solvents. Suitable solvents that may be used in step (a) include, but are not limited to alcohol solvents, such as, for example, methanol, ethanol, propanol, 1-propanol, 2-propanol, butanol, pentanol, ethylene glycol, glycerol, or the like; ketone solvents, such as, for example, acetone, butanone, pentanone, methyl isobutyl ketone, or the like; ester solvents, such as, for example, ethyl formate, methyl acetate, ethyl acetate, propyl acetate, butyl acetate, methyl propanoate, ethyl propanoate, methyl butanoate, ethyl butanoate, or the like; ether solvents, such as, for example, diethyl ether, diisopropyl ether, t-butyl methyl ether, dibutyl ether, tetrahydrofuran, 1,2-dimethoxyethane, 2-methoxyethanol, 2-ethoxyethanol, anisole, or the like; aliphatic or alicyclic hydrocarbon solvents, such as, for example, hexane, heptane, pentane, cyclohexane, methylcyclohexane, or the like; halogenated hydrocarbon solvents, such as, for example, dichloromethane, chloroform, 1,1,2-trichloroethane, 1,2-dichloroethene, or the like; aromatic hydrocarbon solvents, such as, for example, toluene, xylene, chlorobenzene, tetralin, or the like; nitrile solvents, such as, for example, acetonitrile, propionitrile, or the like; or any mixtures thereof.

Step (b) may be carried out in the presence of one or more suitable oxidizing reagents. Suitable reagents that may be used in step (b) include, but not limited to sodium dichromate or potassium dichromate in dilute acids such as sulfuric acid (Jones reagent), oxone, pyridinium chlorochromate, pyridinium dichromate, permanganate such as sodium or potassium or the like.

Step (b) may be carried out in one or more suitable solvents. Suitable solvents that may be used in step (b) include, but are not limited to ketone solvents, such as, for example, acetone, butanone, pentanone, methyl isobutyl ketone, or the like; ester solvents, such as, for example, ethyl formate, methyl acetate, ethyl acetate, propyl acetate, butyl acetate, methyl propanoate, ethyl propanoate, methyl butanoate, ethyl butanoate, or the like; ether solvents, such as, for example, diethyl ether, diisopropyl ether, t-butyl methyl ether, dibutyl ether, tetrahydrofuran, 1,2-dimethoxyethane, 2-methoxyethanol, 2-ethoxyethanol, anisole, or the like; aliphatic or alicyclic hydrocarbon

solvents, such as, for example, hexane, heptane, pentane, cyclohexane, methylcyclohexane, or the like; halogenated hydrocarbon solvents, such as, for example, dichloromethane, chloroform, 1,1,2-trichloroethane, 1,2-dichloroethene, or the like; aromatic hydrocarbon solvents, such as, for example, toluene, xylene, chlorobenzene, tetralin, or the like; or any mixtures thereof.

Step (c) may be carried out in the presence of one or more suitable bases. Suitable bases that may be used in step (c) include, but are not limited to, organic bases, such as, for example, triethylamine, tributylamine, N-methylmorpholine, N,N-diisopropylethylamine, N-methylpyrrolidine, pyridine, 4-(N,N-dimethyl amino)pyridine, morpholine, imidazole, 2-methylimidazole, 4-methylimidazole, 1,4-diazabicyclo[2.2.2]octane ("DABCO"), 1,8-diazabicyclo[5.4.0]undec-7-ene ("DBU"), or the like; Step (c) may be carried out in one or more inorganic bases, such as, for example, alkali metal hydroxides, such as, for example, lithium hydroxide, sodium hydroxide, potassium hydroxide, and cesium hydroxide; alkaline earth metal hydroxides, such as, for example, barium hydroxide, strontium hydroxide, magnesium hydroxide, calcium hydroxide, or the like; alkali metal carbonates, such as, for example, sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate, or the like; alkaline earth metal carbonates, such as, for example, magnesium carbonate, calcium carbonate, or the like; alkali metal bicarbonates, such as, for example, sodium bicarbonate, potassium bicarbonate, or the like; or mixtures thereof.

Step (c) may be carried out in the presence of one or more suitable alkylating reagents. Suitable reagents that may be used in step (c) include, but not limited to alkyl halides such as methyl iodide, methyl bromide, ethyl iodide or the like; dialkyl carbonate such as dimethyl carbonate, diethyl carbonate or the like; dialkyl sulfate such as dimethyl sulfate, diethyl sulfate, ethyl methyl sulfate or the like; diazomethane or the like; or mixtures thereof

The compound of formula (25) may contain other enantiomer and this mixture may be optionally purified to get single required enantiomer by the methods known in the art.

Step (c) may be carried out in one or more suitable solvents. Suitable solvents that may be used in step (c) include, but are not limited to alcohol solvents, such as, for

example, methanol, ethanol, propanol, 1-propanol, 2-propanol, butanol, pentanol, ethylene glycol, glycerol, or the like; ketone solvents, such as, for example, acetone, butanone, pentanone, methyl isobutyl ketone, or the like; ester solvents, such as, for example, ethyl formate, methyl acetate, ethyl acetate, propyl acetate, butyl acetate, methyl propanoate, ethyl propanoate, methyl butanoate, ethyl butanoate, or the like; ether solvents, such as, for example, diethyl ether, diisopropyl ether, t-butyl methyl ether, dibutyl ether, tetrahydrofuran, 1,2-dimethoxyethane, 2-methoxyethanol, 2-ethoxyethanol, anisole, or the like; aliphatic or alicyclic hydrocarbon solvents, such as, for example, hexane, heptane, pentane, cyclohexane, methylcyclohexane, or the like; halogenated hydrocarbon solvents, such as, for example, dichloromethane, chloroform, 1,1,2-trichloroethane, 1,2-dichloroethene, or the like; aromatic hydrocarbon solvents, such as, for example, toluene, xylene, chlorobenzene, tetralin, or the like; nitrile solvents, such as, for example, acetonitrile, propionitrile, or the like; or any mixtures thereof.

The epimerization reaction of step (d) may be carried out in presence of one or more bases, such as, for example, metal alkoxides such as sodium methoxide, potassium methoxide or the like; alkali metal hydroxides, such as, for example, lithium hydroxide, sodium hydroxide, potassium hydroxide, and cesium hydroxide; alkaline earth metal hydroxides, such as, for example, barium hydroxide, strontium hydroxide, magnesium hydroxide, calcium hydroxide, or the like; alkali metal carbonates, such as, for example, sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate, or the like; alkaline earth metal carbonates, such as, for example, magnesium carbonate, calcium carbonate, or the like; alkali metal bicarbonates, such as, for example, sodium bicarbonate, potassium bicarbonate, or the like; or mixtures thereof.

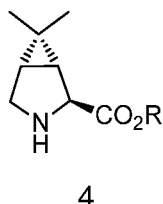
Step (d) may be carried out in one or more suitable solvents. Suitable solvents that may be used in step (d) include, but are not limited to; alcohol solvents, such as, for example, methanol, ethanol, propanol, 1-propanol, 2-propanol, butanol, pentanol, ethylene glycol, glycerol, or the like; ketone solvents, such as, for example, acetone, butanone, pentanone, methyl isobutyl ketone, or the like; ester solvents, such as, for example, ethyl formate, methyl acetate, ethyl acetate, propyl acetate, butyl acetate,

methyl propanoate, ethyl propanoate, methyl butanoate, ethyl butanoate, or the like; ether solvents, such as, for example, diethyl ether, diisopropyl ether, t-butyl methyl ether, dibutyl ether, tetrahydrofuran, 1,2-dimethoxyethane, 2-methoxyethanol, 2-ethoxyethanol, anisole, or the like; aliphatic or alicyclic hydrocarbon solvents, such as, for example, hexane, heptane, pentane, cyclohexane, methylcyclohexane, or the like; halogenated hydrocarbon solvents, such as, for example, dichloromethane, chloroform, 1,1,2-trichloroethane, 1,2-dichloroethene, or the like; aromatic hydrocarbon solvents, such as, for example, toluene, xylene, chlorobenzene, tetralin, or the like; nitrile solvents, such as, for example, acetonitrile, propionitrile, or the like; or any mixtures thereof.

The deprotection reaction of step (e) may be carried out as per the process disclosed in the art. For example, according to the process disclosed in US 7,012,066.

The temperature at which the above steps may be carried out is in between about -15 °C and about 150 °C, based on the solvent used in particular step. Preferably, the reaction steps are carried out under an inert atmosphere.

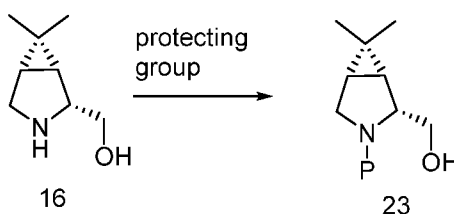
In fifth aspect, the present application provides process for preparing compound having the following structure of formula (4) or its stereoisomers and their pharmaceutically acceptable salts thereof:



wherein R= C₁-C₈ alkyl

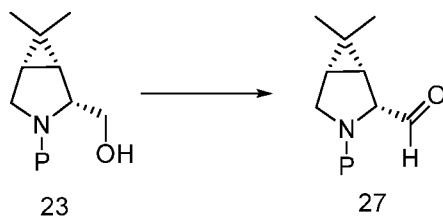
which comprises:

(a) reacting amine alcohol of formula (16) with a nitrogen protecting reagent to provide nitrogen protected alcohol of formula (23),

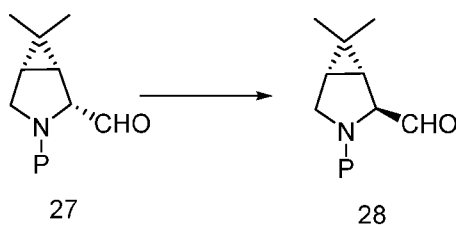


wherein P= amine protecting group

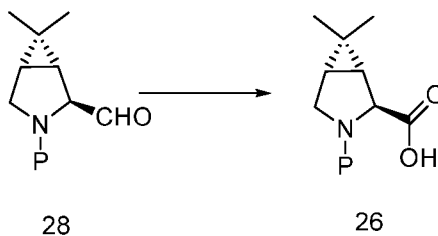
(b) oxidation of nitrogen protected alcohol of formula (23) to an aldehyde of formula (27),



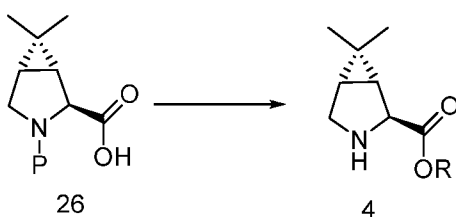
(c) epimerization of aldehyde of formula (27) to provide compound of formula (28)



(d) oxidation of aldehyde of formula (28) to provide acid of formula (26),



(e) deprotection and esterification of acid of formula (26) to provide a compound of formula (4) or its stereoisomers and their pharmaceutically acceptable salts thereof



wherein R= C₁-C₈ alkyl

The reagents and solvents for steps (a), (c) and (e) may be selected from one or more suitable reagents and solvents as described in steps (a), (d) and (e) of fourth embodiment.

Step (b) of fifth aspect of invention involves the conversion of alcohol to aldehyde and can be carried out in one or more suitable reagents. Suitable reagents that may be used in step (b) include, but are not limited to TEMPO, TEMPO with alkali hypohalides like calcium hypochlorite, sodium hypochlorites, Pyridinium sulfur trioxide complex, Dess-martin reagent, pyridinium dichromate, pyridinium chlorochromate, Jones reagent. Suitable oxidation that may be used in step (b) include, but are not limited to Jones, Moffatt, Swern oxidation. Suitable reagent for Swern oxidation is dimethylsulfoxide in presence of dehydration agent. Suitable dehydration agent includes, but is not limited to oxalyl chloride, cyanuric chloride, trifluoroacetic anhydride or the like. Suitable base for Swern oxidation include, but are not limited to triethylamine, diisopropylamine, diisopropylethylamine or the like.

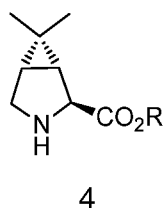
Step (b) may be carried out in one or more suitable solvents. Suitable solvents that may be used in step (b) include, but are not limited to, ether solvents, such as, for example, diethyl ether, diisopropyl ether, t-butyl methyl ether, dibutyl ether, tetrahydrofuran, 1,2-dimethoxyethane, 2-methoxyethanol, 2-ethoxyethanol, anisole, or the like; halogenated hydrocarbon solvents, such as, for example, dichloromethane, chloroform, 1,1,2-trichloroethane, 1,2-dichloroethene, or the like or any mixtures thereof.

Step (d) may be carried out in the presence of one or more suitable oxidizing reagents. Suitable reagents that may be used in step (d) include, but not limited to sodium dichromate or potassium dichromate in dilute acids such as sulfuric acid (Jones reagent), oxone, pyridinium chlorochromate, pyridinium dichromate, sodium permanganate, potassium permanganate or the like.

Step (d) for oxidation of aldehyde to acid may be carried out in one or more suitable solvents and reagents as described for step (b) of fourth embodiment.

The temperature at which the above steps may be carried out in between about -20 °C and about 50 °C based on the solvent used in particular step. Preferably, the reaction steps may be carried out under an inert atmosphere.

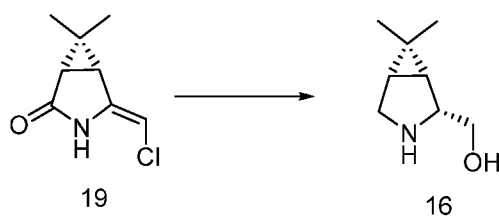
In sixth aspect, the present application provides process for preparing compound having the following structure of formula (4) or its stereoisomers and their pharmaceutically acceptable salts thereof:



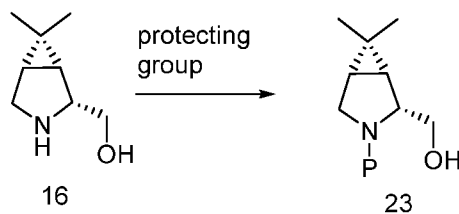
wherein R= C₁-C₈ alkyl

which comprises:

- (a) conversion of chloro compound of formula (19) to amine alcohol of formula (16),

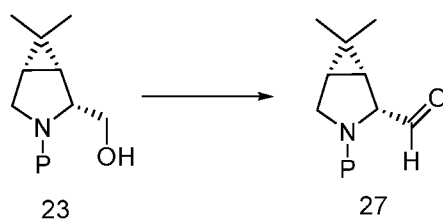


- (b) reacting amine alcohol of formula (16) with a nitrogen protecting reagent to provide nitrogen protected alcohol of formula (23),

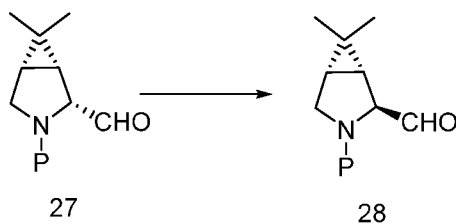


wherein P= amine protecting group

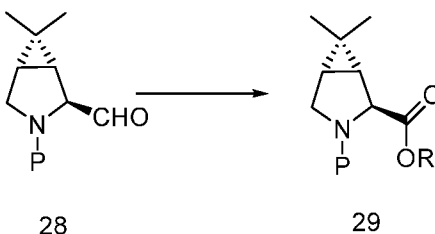
- (c) oxidation of nitrogen protected alcohol of formula (23) to an aldehyde of formula (27),



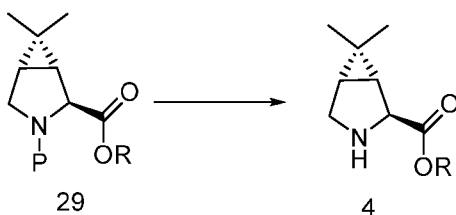
- (d) epimerization of aldehyde of formula (27) to provide compound of formula (28)



(e) oxidation of aldehyde of formula (28) to provide ester of formula (29),



(f) deprotection of ester of formula (29) to provide a compound of formula (4) or its stereoisomers and their pharmaceutically acceptable salts,



wherein R^8 =alkyl or aryl

wherein $R^8=R=C_1$ - C_8 alkyl

Step (a) may be carried out in the presence of one or more suitable reducing reagents. Suitable reducing reagents that may be used in step (a) include, but not limited to lithium aluminium hydride, sodium borohydride, diborane, diborane generated in situ like $NaBH_4$ with BF_3 etherate, sodium borohydride BF_3 THF complex, sodium borohydride and iodine, sodium borohydride in presence of acids like sulfuric acid, phosphoric acid, methanesulfonic acid and the like.

Step (a) may be carried out in the presence of one or more additional suitable reagents. Suitable reagents that may be used in step (a) include, but not limited to hydrogen peroxide, Per acids, Oxone, Sodium perborate, persulphates or the like. These suitable reagents may be optionally be used along with the reducing agents described in previous paragraph

Step (a) may be carried out in one or more suitable solvents. Suitable solvents that may be used in step (b) include, but are not limited to, ether solvents, such as, for example, diethyl ether, diisopropyl ether, t-butyl methyl ether, dibutyl ether, tetrahydrofuran, 1,2-dimethoxyethane, 2-methoxyethanol, 2-ethoxyethanol, anisole, or the like; halogenated hydrocarbon solvents, such as, for example, dichloromethane, chloroform, 1,1,2-trichloroethane, 1,2-dichloroethene, aliphatic or alicyclic hydrocarbon solvents, such as, for example, hexane, heptane, pentane, cyclohexane, methylcyclohexane, or the like; halogenated hydrocarbon solvents, such as, for example, dichloromethane, chloroform, 1,1,2-trichloroethane, 1,2-dichloroethene, or the like; aromatic hydrocarbon solvents, such as, for example, toluene, xylene, chlorobenzene, tetralin, or the like or aprotic solvents like dimethylformamide, dimethylacetamide or the like or any mixtures thereof.

The reagents and solvents for steps (b), (c) and (d) may be selected from one or more suitable reagents and solvents as described in steps (a), (b), (c) of fifth embodiment.

Step (e) may be carried out in the presence of one or more suitable reagents. Suitable reagents that may be used in step (d) include, but not limited to N-Bromosuccinimide (NBS), N-Iodosucciminide (NIS) or the like, hypochlorites such as calcium hypochlorite, sodium hypochlorite or the like.

Step (e) may be carried out in the presence of one or more suitable bases. Suitable bases that may be used in step (c) include, but are not limited to, organic bases, such as, for example, triethylamine, tributylamine, N-methylmorpholine, N,N-diisopropylethylamine, N-methylpyrrolidine, pyridine, 4-(N,N-dimethyl amino)pyridine, morpholine, imidazole, 2-methylimidazole, 4-methylimidazole or the like; Step (d) may be carried out in one or more inorganic bases, such as, for example, alkali metal hydroxides, such as, for example, lithium hydroxide, sodium hydroxide, potassium hydroxide, and cesium hydroxide; alkaline earth metal hydroxides, such as, for example, barium hydroxide, strontium hydroxide, magnesium hydroxide, calcium hydroxide, or the like; alkali metal carbonates, such as, for example, sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate, or the like; alkaline earth metal carbonates, such as, for example, magnesium carbonate, calcium carbonate, or

the like; alkali metal bicarbonates, such as, for example, sodium bicarbonate, potassium bicarbonate, or the like; or mixtures thereof.

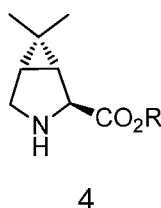
Suitable solvents that may be used in step (e) include, but are not limited to, alcohol solvents, such as, for example, methanol, ethanol, propanol, 2-propanol, butanol, pentanol or ethylene glycol or glycerol, or the like.

The deprotection reaction of step (f) may be carried out in one or more acids such as, inorganic or organic acids, for example, ammonium sulfate, ammonium nitrate, ammonium chloride, citric acid, alkyl sulfonic acid, hydrofluoric acid, hydrochloric acid, hydrobromic acid, hydroiodic acid, periodic acid, sulphuric acid, phosphoric acid, polyphosphoric acid, phosphorous acid, nitric acid, nitrous acid, or the like.

Suitable solvents that may be used in step (f) include, but are not limited to, ester solvents, such as, for example, ethyl formate, methyl acetate, ethyl acetate, propyl acetate, butyl acetate, methyl propanoate, ethyl propanoate, methyl butanoate, ethyl butanoate, or the like; ether solvents, such as, for example, diethyl ether, diisopropyl ether, t-butyl methyl ether, dibutyl ether, tetrahydrofuran, 1,2-dimethoxyethane, 2-methoxyethanol, 2-ethoxyethanol, anisole, or the like.

The temperature at which the above steps may be carried out in between about -20 °C and about 100 °C based on the solvent used in particular step. Preferably, the reaction steps may be carried out under an inert atmosphere.

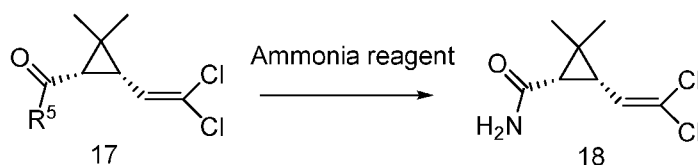
In seventh aspect, the present application provides process for preparing compound having the following structure of formula (4) or its stereoisomers and their pharmaceutically acceptable salts thereof:



wherein R= C₁-C₈ alkyl

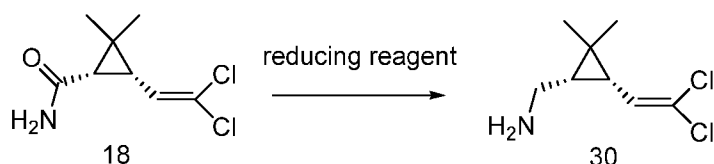
which comprises:

(a) reacting a compound of formula (17) with a reagent of ammonia in a suitable solvent to provide a compound of formula (18)

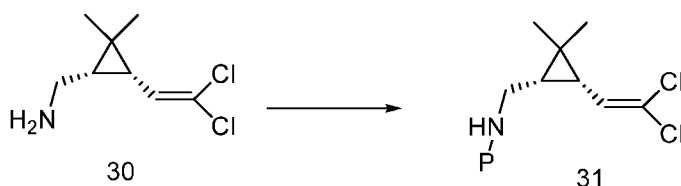


wherein wherein R^5 = hydroxyl; halogen selected from a group of chloro, bromo and iodo; OR^6 ; and R^6 is C_1 - C_8 alkyl

(b) reacting a compound of formula (18) with a reducing agent in a suitable solvent to provide a compound of formula (30)

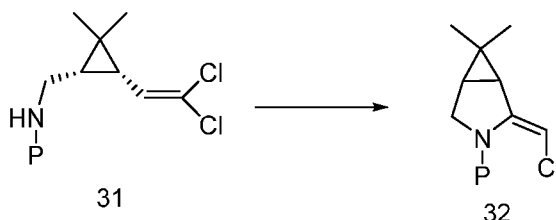


(c) converting a compound of formula (30) to an amino protected compound of formula (31)

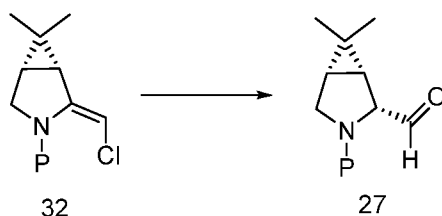


wherein P = amine protecting group

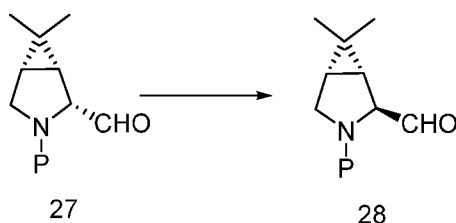
(d) converting amino protected compound of formula (31) to a chloro compound of formula (32)



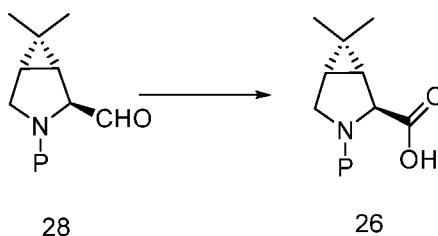
(e) oxidation of chloro compound of formula (32) to an aldehyde of formula (27),



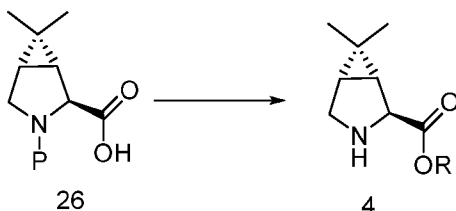
(f) epimerization of aldehyde of formula (27) to provide compound of formula (28)



(g) oxidation of aldehyde of formula (28) to provide acid of formula (26),



(h) deprotection and esterification of acid of formula (26) to provide a compound of formula (4) or its stereoisomers and their pharmaceutically acceptable salts thereof



wherein R= C₁-C₈ alkyl, P=amino protecting group

The reagents and solvents for step (a), (b) and (d) may be selected from one or more suitable reagents and solvents as described in step (a), (f) and (b) of third embodiment.

The reagents and solvents for step (c) and (e) may be selected from one or more suitable reagents and solvents as described in step (b) and (a) of sixth embodiment.

The reagents and solvents for steps (f), (g) and (h) may be selected from one or more suitable reagents and solvents as described in steps (c), (d), (e) of fifth embodiment.

The temperature at which the above steps may be carried out is between about -20 °C and about 50 °C based on the solvent used in particular step. Preferably, the reaction steps may be carried out under an inert atmosphere.

The processes of the present invention may also include isolation of individual intermediate or processed for further steps without isolation wherever applicable.

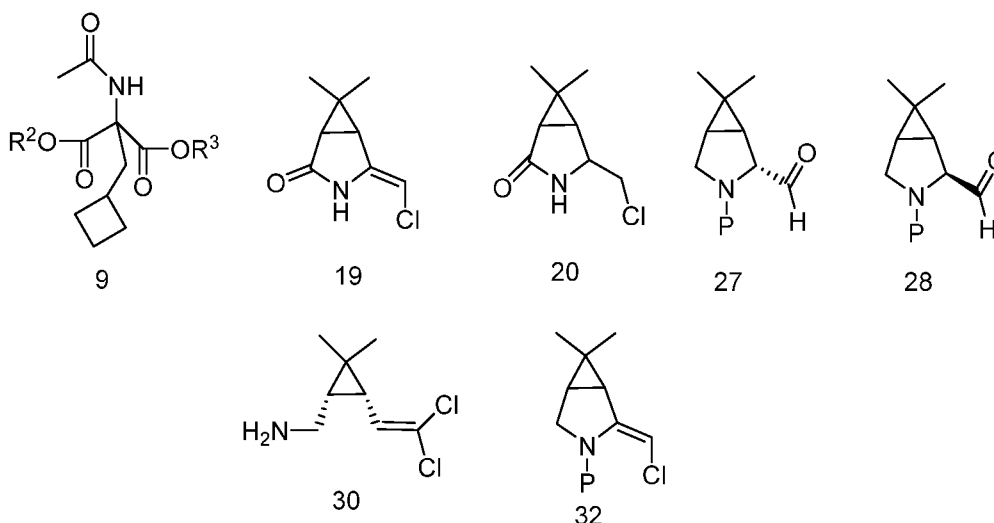
The processes of the present invention may also include conversion of any free base obtained in the present application to suitable pharmaceutically acceptable salts by the methods known in art.

Isolation and purification of the intermediates prepared according to present invention can be effected, if desired, by any suitable separation or purification procedure such as, for example, filtration, centrifugation, extraction, acid-base treatment, crystallization, conventional isolation and refining means such as concentration, concentration under reduced pressure, solvent-extraction, crystallization, phase-transfer chromatography, column chromatography, or by a combination of these procedures.

The intermediates of boceprevir prepared according to the present application are having a purity of about 85.0% to about 99.9% by HPLC conditions.

The processes of the present application are not only environment friendly but also offer shorter reaction time and provide better purity and yield. The processes may be practiced on an industrial scale.

Eighth aspect of the present application provides novel intermediate compounds which are suitable for the preparation of boceprevir, its intermediates or their pharmaceutically acceptable salts.



wherein P= amine protecting group

Ninth aspect of the present application provides a process for the preparation of boceprevir of formula (1) or its pharmaceutically acceptable salts using the compound of formula (2), (3) and (4) or their stereoisomers and their pharmaceutically acceptable salts prepared according to process of the present application.

Compounds of formulas (2), (3) and (4) or their stereoisomers and their pharmaceutically acceptable salts prepared according to processes of the present application may be converted in to boceprevir of formula (1) by any process including the processes described in the art. For example, the processes described in US 7,012,066, US 7,326,795 and US7,528,263.

Tenth aspect of the present application provides pharmaceutical compositions comprising boceprevir of formula (1) or its pharmaceutically acceptable salts by using compounds of formula (2), (3) and (4) or their stereoisomers and their pharmaceutically acceptable salts prepared according to process of the present application together with one or more pharmaceutically acceptable excipient, carrier and diluents.

Certain specific aspects and embodiments of the present invention will be explained in more detail with reference to the following examples, which are provided for purposes of illustration only and should not be construed as limiting the scope of the present invention in any manner.

EXAMPLES

Example 1: Preparation of (S)-methyl 2-amino-3,3-dimethylbutanoate (tert-leucine methyl ester) (5):

Tert-leucine (10 g) and methanol (100 mL) are charged in to a round bottom flask at 25-35°C and stirred for 5-10 minutes. The mixture is cooled to 0°C and thionyl chloride (13.7 g) is added slowly to the above mixture. The reaction mixture is heated to reflux temperature and maintained for 43-44 hours till the completion of reaction as monitored by TLC. The reaction mixture is cooled to 40-45°C and subjected to distillation under reduced pressure. Chloroform (100 mL) is added to the reaction mass and stirred from 5-10 minutes. The resultant mixture is washed with a solution of NaHCO₃ (10%v/v, 100 mL) and separated the organic layer. The organic layer is dried over sodium sulphate (2 g) and the solvent from the organic layer is evaporated at 40-45°C under reduced pressure to afford 8.2 g of the title compound.

Example 2: Preparation of (S)-2-(3-tert-butyl-ureido)-3,3-dimethyl-butyric acid methyl ester (6):

Tert-leucine methyl ester hydrochloride (10 g) and tetrahydrofuran (150 mL) are charged in to a round bottom flask and stirred for 5-10 minutes. The mixture is cooled to 0-5°C, triethylamine (8.4 mL) is added to the mixture and maintained for 10-15 minutes. 1,1'-carbonyldiimidazole (8.9 g) is added to the reaction mixture at 0-5°C and maintained at the same temperature for 3 hours. Tert-butylamine (11.6 mL) is added to the above reaction mixture at 5-10°C. Reaction mixture is maintained at 25-35°C for 2-3 hours, filtered the mixture and subjected the resultant filtrate to distillation at 40-45°C under reduced pressure. The reaction mass is washed with water (100 mL) and chloroform (100 mL). The aqueous and organic layers are separated, aqueous layer extracted with chloroform (100 mL) and combined organic layers washed with water (100 mL). Organic layer dried over sodium sulfate (2 g) and solvent is evaporated completely at 45°C under reduced pressure. The obtained reaction mass is subjected to column chromatography by using 3% v/v methanol/chloroform. The collected fractions are evaporated completely under reduced pressure at 45-50°C to afford 11.5 g of the title compound.

Example 3: Preparation of (S)-2-(3-tert-butyl-ureido)-3,3-dimethyl-butyric acid (2):

(S)-2-(3-tert-butyl-ureido)-3,3-dimethyl-butyric acid methyl ester (2.0 g) and tetrahydrofuran (10 mL) are charged in to a round bottom flask and stirred for 5-10 minutes at 25-35°C. A solution of LiOH.H₂O (2.5 N; 20 mL) is added to the mixture at 25-35°C and maintained for 24-25 hours. Unreacted starting material is extracted with ethyl acetate (50 mL). The aqueous layer pH is adjusted to 2.0 with HCl (1.5 mL) and extracted with ethyl acetate. The organic layer solvent is evaporated completely at below 45°C under reduced pressure. The obtained reaction mass is subjected to column chromatography by using ethyl acetate/hexane (2:8). The collected fractions are evaporated completely under reduced pressure at 45-50°C to afford 300 mg of the title compound.

Example 4: Preparation of diethyl-2-acetamido-2-(cyclobutyl methyl) malonate (9):

Diethyl-2-acetamido malonate (10 g) and dimethylsulfoxide (100 mL) are charged in to a round bottom flask under nitrogen atmosphere at 25-35 °C. Cesium carbonate (22.5 g) is added to the reaction mixture under nitrogen atmosphere at 25-35 °C. Bromomethyl cyclobutane (5.8 mL) is added to the reaction mixture under nitrogen atmosphere at 25-35 °C. The reaction mixture is heated to 60 °C and maintained for 12 hours till the completion of reaction as monitored by TLC. The reaction mixture is cooled to 25-35 °C, poured in to ice-cold water (200 mL) and extracted with ethyl acetate (3X100 mL). The combined organic layer is washed with cold water (3X100 mL), followed by with brine solution (200 mL) and dried over anhydrous sodium sulphate. The solvent from the organic layer is evaporated under reduced pressure at 50 °C to afford 11 g of the title compound. Purity by HPLC: 86.6%

Example 5: Preparation of 2-amino-3-cyclobutyl-1-propanoic acid hydrochloride (10):

Diethyl-2-acetamido-2-(cyclobutyl methyl) malonate (11.3 g) is charged in to a round bottom flask at 25-35 °C. 35% HCl (56.5 mL) is added to the above contents at 0 °C. The reaction mixture is heated to 100 °C and maintained for 12 hours till the completion of reaction as monitored by TLC. The reaction mixture is concentrated under reduced pressure at 55 °C. The obtained reaction mass is triturated with hexane (2X100 mL). The obtained solid is filtered and dried under reduced pressure at 25-35 °C to afford 6.5 g of the title compound. Purity by HPLC: 98%

Example 6: Preparation of methyl 2-amino-3-cyclobutyl-1-propanoate hydrochloride (11):

2-amino-3-cyclobutyl propanoic acid hydrochloride (6.5 g) and methanol (65 mL) are charged in to a round bottom flask at 25-35 °C under reduced pressure. Thionyl chloride (6.75 mL) is added slowly to the reaction mixture at 0 °C and stirred for 10 minutes. The reaction mixture is heated to 70 °C and maintained for 16 hours till the completion of the reaction as monitored by TLC. The reaction mixture is concentrated under reduced pressure at 50 °C. The obtained reaction mass is triturated with hexane. The obtained

solid is filtered and dried under reduced pressure at 25-35°C to afford 6.9 g of the title compound. Purity by ELSD: 95.85%

Example 7: Preparation of methyl 2-tert-butoxycarbonylamino-3-cyclobutyl-1-propanoate (12):

Methyl 2-amino-3-cyclobutyl propanoate hydrochloride (6.9 g), triethylamine (10 mL) and tetrahydrofuran (70 mL) are charged in to a round bottom flask at 25-35°C under nitrogen atmosphere. The reaction mixture is cooled to 0°C and boc-anhydride (9.47 mL) is added slowly to the reaction mixture. The reaction mixture is heated to 25-35°C and stirred for 3 hours till the completion of the reaction as monitored by TLC. The reaction mixture is poured in to water (250 mL) and extracted with ethyl acetate (3X100 mL). The combined organic layer is washed with brine (2X75 mL) and dried over anhydrous sodium sulphate (50 g). The solvent from the organic layer is concentrated under reduced pressure at 50°C. The resultant reaction mass is subjected to column chromatography by using ethyl acetate/hexane (2:8) to afford 7.1 g of the title compound. Purity by ELSD: 97.7%

Example 8: Preparation of 2-tert-butoxycarbonylamino-3-cyclobutyl-1-propanal (13):

Methyl 2-tert-butoxycarbonylamino-3-cyclobutyl-1-propanoate (7.5 g) and ether (150 mL) are charged in to a round bottom flask under nitrogen atmosphere. The reaction mixture is cooled to -78°C, diisobutylaluminium hydride (30.4 mL) is added slowly to the mixture and maintained at the same temperature for 20 minutes till the completion of the reaction as monitored by TLC. The reaction mixture is quenched with a solution of aqueous ammonium chloride (50 mL) at -78°C. The reaction mixture temperature is warmed slowly to 25-35°C and extracted with ether (2X100 mL). The combined organic layer is washed with water (2X50 mL) and dried over sodium sulphate (200 mg). The solvent from the organic layer is evaporated under reduced pressure at below 40°C to afford 6.9 g of the title compound.

Example 9: Preparation of 3-tert-butoxycarbonylamino-3-cyclobutylmethyl-2-hydroxy-propionitrile (14):

2-tert-butoxycarbonylamino-3-cyclobutyl-1-propanal (6.4 g) and dichloromethane (64 mL) are charged in to a round bottom flask at 25-35°C. The mixture is cooled to 0°C, triethylamine (5.8 mL) is added to the reaction mixture and stirred for 10 minutes. Acetone cyanohydrin (5.1 mL) is added to the reaction mixture at 0°C. The reaction mixture is warmed to 25-35°C and maintained for 6 hours till the completion of the reaction as monitored by TLC. The reaction mixture is poured into ice cold water (200 mL). The organic layer is separated, washed with 5% citric acid solution (50 mL), brine (50 mL) and dried over anhydrous sodium sulphate (50 g). The solvent from the organic layer is evaporated under reduced pressure to afford 5 g of the title compound. Purity by HPLC: 99.9%

Example 10: Preparation of 3-tert-butoxycarbonylamino-3-cyclobutylmethyl-2-hydroxy-propionamide (15):

3-tert-butoxycarbonylamino-3-cyclobutylmethyl-2-hydroxy-propionitrile (5 g), dimethylsulfoxide (12.5 mL) and acetone (37.5 mL) are charged in to a round bottom flask at 25-35°C under nitrogen atmosphere. Potassium carbonate (2.98 g) is added to the reaction mixture under nitrogen atmosphere. The reaction mixture is heated to 65°C and hydrogen peroxide (11.1 mL) is added slowly to the reaction mixture and maintained for 3 hours till the completion of the reaction as monitored by TLC. The reaction mixture is cooled to 25-35°C and the solvent from the mixture is concentrated under reduced pressure at 50°C. The resultant reaction mass is added to cold water (100 mL) and stirred for 10 minutes at 25-35°C. The obtained solid is filtered and dried under reduced pressure. The filtrate is extracted with dichloromethane (2X100 mL) and the organic layer is washed with water (2X50 mL), brine (100 mL) and dried over sodium sulphate (2 g). The solvent from the organic layer is evaporated under reduced pressure at below 50°C. The resultant reaction mass is triturated with hexane (20 mL), filtered the solid and dried under reduced pressure at 25-35°C to afford 4.8 g of the title compound. Purity by HPLC: 99.8%

Example 11: Preparation of 3-amino-3-cyclobutylmethyl-2-hydroxy-propionamide hydrochloride (3):

3-tert-butoxycarbonylamino-3-cyclobutylmethyl-2-hydroxy-propionamide (8.3 g) and dioxane (80 mL) are charged in to a round bottom flask at 25-35°C. The reaction mixture is cooled to 0°C and a solution of hydrochloric acid in dioxane (40 mL) is added to the mixture. The reaction mixture is stirred at the same temperature for 10 minutes. The temperature of the reaction mixture is raised to 25-35°C and maintained for 6 hours till the completion of the reaction as monitored by TLC. The solvent from the reaction mixture is evaporated under reduced pressure. The resultant reaction mass is triturated with methyltertiarybutylether (300 mL), filtered the solid and dried under reduced pressure to afford 6.3 g of the title compound. Purity by HPLC: 99.9%

Example 12: Preparation of (S)-2-(3-tert-butyl-ureido)-3,3-dimethyl-butyric acid (2):

1,1'-carbonyldiimidazole (11 g) and tetrahydrofuran (40 mL) are charged in to a round bottom flask at 25-35°C and stirred for 5-10 minutes. The mixture is cooled to 0-5°C and a mixture of tertiary butyl amine (5 g) in tetrahydrofuran (10 mL) is added to the mixture. The reaction mixture is maintained at 0-5°C for 2 hours. Tertiary leucine (8.9 g) and water (30 mL) are added in to another round bottom flask, the mixture is cooled to below 15°C and pH of the mixture is adjusted to 11-12 with 15% solution of sodium hydroxide (50 mL). Above prepared solution of tertiary butyl amine-CDI complex is added to the reaction mixture containing tertiary leucine at 10-15°C. The reaction mixture is maintained at 20-25°C for 3 hours till the completion of the reaction as monitored by TLC. Ethyl acetate (100 mL) is added to the reaction mixture and separated the organic layer. The pH of the aqueous layer is adjusted to 2-3 with 2N HCl solution (30 mL). Ethyl acetate (100 mL) is added to the above aqueous layer, separated the organic layer, washed with water (100 mL) and dried over sodium sulphate. The solvent from the organic layer is evaporated under reduced pressure at 40-45°C to afford 8 g of the title compound.

Example 13: Resolution of Cis-Cypermethric acid (17):

cis-cypermethric acid (100 g; 0.478 moles) and Isopropyl alcohol (2.5 L) was charged in to the reaction flask and maintained at 25-35°C. (R)-phenylethyl amine (63.75 g; 0.526 moles) was added slowly at 25-35°C and the reaction mixture stirred till formation of solid at 25-35°C. The reaction mixture was stirred at 80-90°C till formation of clear solution. The reaction mixture was cooled slowly to 25-35°C and stirred further for 2-3 h at 25-35°C. The solid material was filtered under vacuum at 25-35°C and added water (1 L) at 25-35°C. 2N HCl solution was slowly added to the reaction mass at 25-35°C (pH of the soln is ~2). The reaction mass was stirred for 2-3 h at 25-35°C. The solid material was filtered under vacuum at 25-35 °C.

Purity: 95-98%

Example 14: Preparation of 3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane carboxamide (18):

Cis-Cypermethric acid chloride (300g, 1.318 moles) was added to dichloromethane (3000ml) and cooled to -10°C. Ammonia gas was passed into the reaction mixture till the completion of reaction. After the completion of reaction, the reaction mixture was warmed to RT and water (2000ml) was added. Organic layer was separated and aqueous layer was extracted with dichloromethane (900ml). the combined organic layer was washed with brine (1500ml), dried over anhydrous sodium sulfate and concentrated under reduced pressure at below 45°C. The crude material after concentration was diluted wit hexane (600ml) and stirred for 10minutes at RT. The solid material was filtered and dried at RT to give the title compound as white solid.

Yield: 226g (82.4%)

HPLC: 98.5%

Example 15: Preparation of ((1S,3S)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropyl)methanamine (30):

To a solution of 3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane carboxamide (0.1g, 0.0004 mol) in THF (1.5 mL) was added Borane-DMS solution (0.14g, 0.0018 mol) at 0-10 °C under nitrogen atmosphere. Reaction mixture was stirred for 24-30 h at 25-35 °C. After completion of reaction, the reaction mass was quenched with methanol (0.2 mL)

followed by 2M HCl solution (1 mL) at 0-10 °C, after stirring for 10 to 15 minutes, added 10 % NaOH solution (2.0 mL) and extracted with ethyl acetate (2 mLX2). Combined organic layer dried over anhydrous Na₂SO₄. Organic solvent was evaporated completely under vacuum and crude product was purified by column chromatography using 4% ammonia in dichloromethane to afford brown color liquid product. (Yield: 66%).

Example 16: Preparation of benzyl (((1S,3S)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropyl)methyl)carbamate (31):

To a solution of ((1S,3S)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropyl) methanamine (2.5 g, 0.013 mol) in THF (25 mL) was added sodium bicarbonate (3.25 g, 0.0387 mol), water (25 mL) at 25-35 °C then added 80% Cbz-Cl (3.29 g, 0.019 mol) slowly to the reaction mixture and stirred for 3-4 h at 25-35 °C. After reaction completion, the reaction mass was extracted with ethyl acetate (25 mL X 2). Combined organic layer was washed with water (12.5 mL) and followed by 10 % brine solution (12.5 mL). Organic solvent was evaporated completely under vacuum and crude product was purified by column chromatography using 5% ethyl acetate in hexane to afford pale yellow color liquid (1.80 g, Yield: 43%).

Example 17: Preparation of benzyl (1R,5S,E)-2-(chloromethylene)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (32):

The solution of benzyl (((1S,3S)-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropyl)methyl) carbamate (1.4 g, 0.0046 mol) in DMAc (7.5 mL) was slowly added to the suspension of NaH (60 %) (0.33 g, 0.0138 mol) in DMAc (7.5 mL) at 0 - 5°C under nitrogen atmosphere. The temperature of reaction mass was slowly raised to 20-25 °C and stirred for 2-3 h at same temperature. After completion of reaction, the reaction mixture was cooled to 0-5 °C, added acetic acid (0.25 mL) slowly followed by water. Product extracted with MTBE (2 X 15 mL), combined organic layer was washed with water and brine solution. The organic layer was concentrated at below 50°C under vacuum to afford the title product as yellow color liquid.

Example 18: Preparation of benzyl (1R,5S)-2-formyl-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (27):

Borane-THF complex (1.53 g, 0.0175 mol) was added to the mixture of benzyl (1R,5S,E)-2-(chloromethylene)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (1.7 g, 0.0058 mol) in THF (17 mL) at -20 to -30 °C under nitrogen atmosphere. The temperature of reaction mass temperature was slowly raised to ambient temperature and continued stirring for 10 h. After completion of reaction, the reaction mass was cooled to 0 °C, quenched with water (5.1 mL) at below 5 °C then added 20% aq. NaOH solution (6.8 mL) followed by 30% aq. H₂O₂ solution (5.1 mL) at below 5 °C. Stirred mixture for 2-3 h at below 5 °C and extracted with MTBE (2X 17 mL). Combined organic layer was washed with water, 20% aq. sodium bisulphate solution, water followed by 10% brine solution. The organic layer was dried over sodium sulphate, concentrated under reduced pressure. The obtained residue was purified by column chromatography using ethyl acetate: hexane to afford the title product (yield: 0.51 g, yield%: 32.08 %).

Example 19: Preparation of 3-benzyl 2-methyl (1R,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2,3-dicarboxylate (26):

To a solution of benzyl (1R,5S)-2-formyl-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (**28**) (0.2 g, 0.00073 mol) in Acetone (1.4 mL) was added Jones reagent (0.6 mL) and Acetone (1.4 mL) at -10 °C and stirred for 2-3 h at -10 °C. After completion of reaction, the reaction mass was cooled to 0 °C, quenched with IPA (0.6 mL) and stirred for 10-15 min at 0-5 °C. The reaction mass was filtered through Celite bed, the filtrate was evaporated under vacuum and to the residue was added saturated sodium bicarbonate (5.0 mL) and washed with ethyl acetate (5.0 mL). The aqueous layer was acidified with saturated citric acid (2.0 mL) and extracted with ethyl acetate (5.0 mL). The solvent was evaporated under vacuum to afford corresponding carboxylic acid which was confirmed by Proton NMR. To the obtained acid was added acetone (6.0 mL), Potassium carbonate (0.23 g, 0.0036 mol), and methyl iodide (0.11 mL, 0.0036 mol) at 25-35 °C and stirred for 24-36 h at ambient temperature. After completion of reaction, the organic solvent was removed under vacuum and to the residue was added saturated sodium bicarbonate and product was extracted with ethyl

acetate (6.0 mL). The solvent was evaporated under vacuum to afford crude ester (0.05 g, Yield: 23 %).

Example 20: Preparation of 4-(chloromethylene) -6,6- dimethyl-3-azabicyclo [3.1.0] hexan-2-one (19):

Sodium hydride (115.2g, 2.88 moles) was taken in hexane (400ml), stirred for 10 minutes and the supernatant hexane layer was decanted. Dimethyl acetamide (1000ml) was added slowly to the sodium hydride at 0°C. 3-(2,2-dichlorovinyl)-2,2-dimethyl cyclopropane carboxamide (**18**) (200 g, 0.961 moles) was dissolved in dimethyl acetamide and added drop wise to the mass containing sodium hydride at 0°C and stirred for 15 minutes. The reaction mixture was warmed to RT and stirred for 6 hours. After the completion of reaction, the reaction mixture was poured into ice cold water (3500ml). The pH was adjusted to 2-2.5 using 2N HCl. The obtained solid was filtered, washed with ice water (2x800ml) and dried under vacuum at 45°C to give title compound as yellow solid.

Yield: 102g (61.8%)

HPLC: 99.5%

Example 21: Preparation of 4-(chloromethyl)-6,6-dimethyl- 3-azabicyclo [3.1.0] hexan-2-one (20):

Hydrogen peroxide solution (2.2 L) was charged to 4-(chloromethylene) -6,6- dimethyl-3-azabicyclo [3.1.0] hexan-2-one (110g, 0.641 moles) at RT and stirred for 5 minutes. Amberlite IR120 (110 g) was added to the reaction mixture at RT and stirred for 5 hours. After the completion of reaction, the reaction mixture was poured into water (1L) and extracted with ethyl acetate (3x1000ml). The combined organic layers were washed with brine (1000ml), dried over anhydrous sodium sulfate and concentrated under reduced pressure at 50-55°C to give pale yellow solid. The solid (100g, 0.523 moles) was charged to dichloromethane (1500 ml) and cooled to 5-10°C. Triethylsilane (101.75g, 0.877 moles) was added to the reaction mixture at 5-10°C and stirred for 10 minutes. Trifluoroacetic acid (633.3g, 1.130 moles) was added slowly to the reaction mixture at 5-10°C and stirred for 10 minutes. Reaction mixture was warmed to RT and

stirred for 16 hours. After completion of reaction, the reaction mixture was quenched with saturated sodium bicarbonate solution (3000ml). Organic layer was separated and aqueous layer was extracted with dichlormethane (2x500ml). Combined organic layers were dried over sodium sulfate and concentrated under reduced pressure at 40-45°C. The crude material was purified by column chromatography using 50% ethyl acetate-hexane solvent system to give the title compound as a colorless liquid.

Yield: 60g (59.3%)

HPLC: 97.91%

Example 22: Preparation of (6,6-dimethyl-4-oxo-3-azabicyclo [3.1.0] hexan-2-yl) methyl acetate (21):

4-(chloromethyl)-6,6-dimethyl- 3-azabicyclo [3.1.0] hexan-2-one (80g, 0.462 moles) was charged into toluene (800ml) at RT. Sodium acetate (151.6g, 1.849 moles) and tetrabutyl ammonium bromide (149 g, 0.462 moles) was added to reaction mixture at RT. The reaction mixture was heated to 110-115°C and stirred for 18 hours. After completion of reaction, ice cold water (1500 ml) was added and extracted with ethyl acetate (3x750ml). The combined organic layer was washed with brine (500 ml), dried over sodium sulfate and concentrated under reduced pressure at 50-55°C. The crude material was diluted with hexane (100ml) and stirred for 10 minutes at RT. The solid obtained was filtered and dried at RT to give title compound as pale yellow solid.

Yield: 59g (64%)

HPLC: 89.67%

Example 23: Preparation of 4-(hydroxymethyl) -6,6-dimethyl-3-azabicyclo [3.1.0] hexan-2-one (22):

(6,6-dimethyl-4-oxo-3-azabicyclo [3.1.0] hexan-2-yl) methyl acetate (59.0g, 0.2994 moles) was charged into methanol (600ml) at RT and stirred for 10 minutes. Potassium carbonate (49.5g, 0.3593 moles) was added to the reaction mixture at RT and stirred for 2 hours. After the completion of reaction, the reaction mixture was filtered through celite and washed with methanol (2x75ml) and filtrate was concentrated under reduced pressure at 50-55°C. The crude residue was dissolved in water (40ml) and extracted with ethyl acetate (3x300ml). The combined organic extracts were washed with brine

(75ml), dried over sodium sulfate and concentrated under reduced pressure at 50-55 °C to give title compound as pale yellow solid.

Yield: 40g (80%)

HPLC: 96.75%

Example 24: Preparation of (6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2-yl)methanol (16):

4-(hydroxymethyl) -6,6-dimethyl-3-azabicyclo [3.1.0] hexan-2-one (47g, 0.303 moles) was charged into tetrahydrofuran (940ml) under nitrogen atmosphere at RT and stirred for 10 minutes. Lithium aluminium hydride (69.13g, 1.819 moles) was added portion wise to the reaction mixture at RT for 30 minutes. The reaction mixture was heated at 65 °C and stirred for 16 hours. After the completion of reaction, the reaction mixture was cooled to 0 °C and quenched with saturated sodium sulfate solution (200ml). Ethyl acetate (1000ml) was added to the reaction mixture and stirred for 15 minutes and filtered through celite bed and washed with ethyl acetate (2x500ml). Combined filtrate concentrated under reduced pressure at 50-55 °C to give title compound as colorless liquid.

Yield: 40g

Example 25: Preparation of tert-butyl 2-(hydroxymethyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (23):

(6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2-yl)methanol (16) (40g, 0.2836 moles) was charged into dichloromethane (400ml) under nitrogen atmosphere. Boc anhydride (68.1g, 0.312 moles) was added dropwise to the reaction mixture at RT and stirred for 2 hours at RT. After the completion of reaction, the reaction mixture was concentrated under reduced pressure at 35-40 °C. Crude residue was dissolved in methanol (300ml) and potassium carbonate (30g) was added and stirred for 1 hour at RT. The undissolved was filtered and washed with methanol (50ml). The combined filtrate was concentrated under vacuum at 35-40 °C. The crude compound was dissolved in dichloromethane (400ml) and washed with water (2x300ml), dried over sodium sulfate and concentrated under reduced pressure to get crude compound. The crude

compound was purified by column chromatography with solvent system 10-15% ethyl acetate-hexane to give title compound as a pale yellow solid.

Yield: 40g (54.7%)

HPLC: 98.34%

Example 26: Preparation of 3-(tert-butoxycarbonyl)-6,6-dimethyl-3-azabicyclo [3.1.0]hexane-2-carboxylic acid (24):

Jones reagent (60ml) was charged into acetone (70ml) under nitrogen at RT and cooled to -5 to -10°C. Tert-butyl 2-(hydroxymethyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (10g, 0.0415 moles) dissolved in acetone (70ml) was added slowly to the reaction mixture at -5°C. The reaction mixture was warmed to RT and stirred for 16 hours. After the completion of reaction, isopropyl alcohol (20ml) was added to the reaction mixture and stirred for 1 hour at RT. The reaction mixture was filtered through the celite, washed with acetone (20ml) and filtrate was concentrated to get the residue. The obtained residue was dissolved in saturated sodium bicarbonate solution (50ml) and washed with ethyl acetate (2x50ml). The aqueous layer was acidified with saturated citric acid and extracted with ethyl acetate (2x75ml). The combined organic layers were washed with brine (20 ml) and concentrated under reduced pressure at below 55°C to give title compound as a colorless liquid.

Yield: 5g (47.3%)

HPLC: 97.27%

Example 27: Preparation of 3-tert-butyl 2-methyl 6,6-dimethyl-3-azabicyclo [3.1.0]hexane-2,3-dicarboxylate (25):

3-(tert-butoxycarbonyl)-6,6-dimethyl-3-azabicyclo [3.1.0]hexane-2-carboxylic acid (1g, 0.0039 moles) and cesium carbonate (1.78g, 0.0054 moles) were charged into dimethylformamide (10ml) under nitrogen atmosphere at RT. Methyl iodide (1g, 0.0070 moles) was added slowly at RT and stirred for 4 hours at RT. After the completion of reaction, the reaction mixture was quenched with ice cold water (30ml) and extracted with MTBE (3x20ml). The combined organic layers were washed with brine (20ml) and concentrated under reduced pressure at below 55°C to give crude compound. The

crude compound was purified by column chromatography using solvent system 10% ethyl acetate-hexane to give title compound as a pale yellow liquid.

Yield: 350mg (33%)

HPLC: 89.19%

Example 28: Preparation of 3-(tert-butoxycarbonyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (26):

(1S,2R,5R)-3-tert-butyl 2-methyl 6,6-dimethyl-3-azabicyclo [3.1.0]hexane-2,3-dicarboxylate (0.14g, 0.0005 moles) was charged into methanol (5ml) under nitrogen atmosphere at RT. Sodium methoxide (0.113g, 0.0070 moles) was added slowly at RT and stirred for 10 min at RT. The reaction mixture was heated at reflux and stirred for 16 hours. After the completion of reaction, the reaction mixture was concentrated under reduced pressure at below 50°C. Crude residue was quenched with ice cold water (30ml) and washed with ethyl acetate (10ml). Resulting aqueous layer was cooled to 10°C, acidified with citric acid (pH 3-3.5) and extracted with ethyl acetate (2x15ml). The combined organic layers were washed with brine (20ml) and concentrated under reduced pressure at temperature less than 55°C to give crude title compound as a white solid

Yield: 110mg (83%)

HPLC: 96.63%

Example 29: Preparation of tert-butyl 2-formyl-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (27):

Oxalyl chloride (10.27g, 0.0809 moles) was charged into dichloromethane (50ml) under nitrogen atmosphere at RT and cooled to -75-78°C. Dimethylsulfoxide (6.8g, 0.0871 moles) was taken in dichloromethane (50ml) and added to the reaction mixture at -78°C. (6,6-dimethyl-3-azabicyclo[3.1.0]hexan-2-yl)methanol (**23**) (15g, 0.2836 moles) dissolved in dichloromethane (200ml) was added to reaction mixture dropwise under nitrogen atmosphere at -78°C. The reaction mixture was warmed to 20-25°C and stirred for 45 minutes. After the completion of reaction the reaction mixture was quenched with ice cold water (200ml), stirred for 10 minutes and the layers were separated. The

aqueous layer was extracted with dichloromethane (100ml). Combined organic layers were washed with 1N HCl (200ml), saturated bicarbonate solution (200ml) and concentrated under reduced pressure at below 40°C to give the title compound as a brown color liquid.

Yield: 14g (94%)

HPLC: 83.53%

Example 30: Preparation of tert-butyl 2-formyl-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (28):

Tert-butyl 2-formyl-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (14g, 0.0585 moles) was charged into dichloromethane (140ml) under nitrogen atmosphere at RT. DBU (4.45, 0.0292 moles) was added dropwise to the reaction mixture at RT and stirred for 3 hours. After the completion of reaction, the reaction mixture was quenched with ice cold water (200ml), stirred for 10 minutes and the layers were separated. The aqueous layer was extracted with dichloromethane (100ml). Combined organic layers were washed with brine solution (100ml) and concentrated under reduced pressure at below 40°C to give the title compound as a pale yellow liquid.

Yield: 14g

Example 31: Preparation of 3-(tert-butoxycarbonyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylic acid (26):

Tert-butyl 2-formyl-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (14g, 0.0585 moles) was charged into acetone (280ml) under nitrogen atmosphere at RT and cooled to -30°C. Jones reagent (42ml) dissolved in acetone (30ml) was added slowly to the reaction mixture at -30°C. The reaction mixture was warmed to 5°C and stirred for 1 hour. After the completion of reaction, isopropyl alcohol (30ml) was added to reaction and stirred for 1 hour at RT. The reaction mixture was filtered through celite and washed with acetone (20ml) and concentrated under vacuum. The residue was dissolved in saturated sodium bicarbonate solution (100ml) and washed with ethyl acetate (2x50ml). The aqueous layer was acidified with saturated citric acid solution

(pH3-3.5) and extracted with ethyl acetate (2x100ml). The combined organic layers were concentrated under reduced pressure at below 55 °C to give the title compound as a white color solid.

Yield: 8.6g (58%)

HPLC: 94.50%

Example 32: Preparation of 3-(tert-butyl) 2-methyl (1R,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2,3-dicarboxylate (29):

To a solution of tert-butyl 2-formyl-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-3-carboxylate (**28**) (0.5 g, 0.0021 mol) in MeOH (5 mL) was added potassium carbonate (0.576g, 0.0042 mol) under nitrogen atmosphere at 25-35 °C and stirred for 30 min at 25-35 °C. The reaction mixture was cooled to 5-10 °C and then added *N*-bromo succinimide (0.93 g, 0.0052 mol) under nitrogen atmosphere and stirred for overnight at 25-30 °C under dark conditions.) Reaction mass was washed with 10% sodium thiosulphate solution (5 mL, 10 vol), concentrated to remove methanol under vacuum below 50 °C. Charged ethyl acetate (20 mL) into residue and separated the layers. Aqueous layer was extracted with ethyl acetate (10 mL). Combined organic layers were washed with saturated sodium chloride and dried over anhydrous sodium sulphate. Solvent was evaporated under vacuum at below 50 °C to afford pale yellow oil. (Wt: 0.55 g (crude), Yield= 98 %).

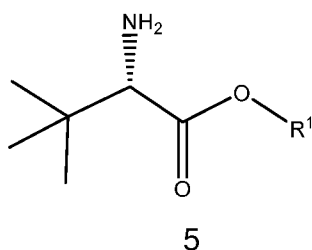
Example 33: Preparation of methyl (1R,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxylate (4):

Ethyl acetate hydrochloride solution (62 mL) was added to the solution of 3-(tert-butyl) 2-methyl (1R,5S)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2,3-dicarboxylate (3.2 g, 0.0118 mol) in 1,4 dioxane (15.5 mL) at 10 °C, reaction mass temperature raised to 25 °C and stirred for 15min. After completion of reaction, concentrated the reaction mass and co distilled with toluene to remove trace level of dioxane. MTBE (15.5 mL) was added to the residue and stirred for 30 min at room temperature. Obtained solid was filtered and washed with MTBE (9.3 mL). The solid was dried under vacuum at below 50 °C to afford title compound. (Yield-72.2 %, Purity – 86.2 %)

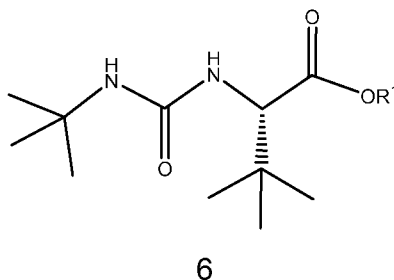
We Claim:

1. A method for preparation of a compound of formula (2) or a salt thereof, which comprises:

(a) reacting a compound of formula (5) or a pharmaceutically acceptable salt thereof,



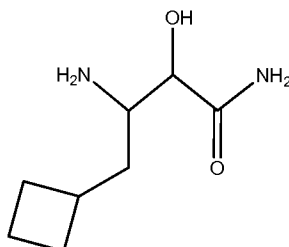
wherein R¹ represents hydrogen, an alkyl group, substituted alkyl group or an aryl group; with a reagent and tertiary butyl amine, or a compound derived there from to provide a compound of formula (6),



(b) optionally, converting a compound of formula (6) to a compound of formula (2) or a salt thereof.

2. The reagent of step (a) according to claim 1 is selected from N, N'-carbonyldiimidazole (CDI), alkyl chloroformates and dialkyl carbonates.

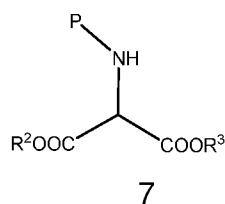
3. A method for preparation of 3-amino-3-cyclobutylmethyl-2-hydroxy-propionamide of formula (3) or a salt thereof:



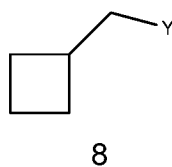
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which comprises:

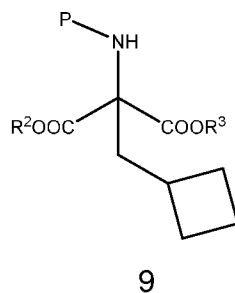
(a) reacting a compound of formula (7),



wherein R² or R³ represents an alkyl group; P represents a protecting group; with a compound of formula (8),

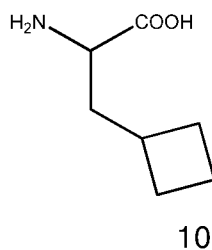


wherein Y represents halo group; to provide a compound of formula (9),

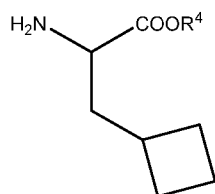


wherein R², R³ and P are as described previously;

(b) reacting a compound of formula (9) with a reagent to provide a compound of formula (10) or a salt thereof,



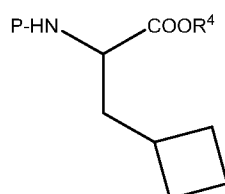
(c) converting a compound of formula (10) or a salt thereof to a compound of formula (11),



11

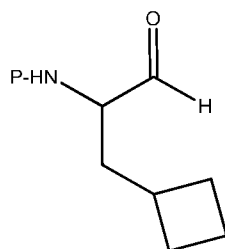
wherein R^4 is same as either R^2 or R^3 and are described previously;

(d) protecting the compound of formula (11) to provide a compound of formula (12),



12

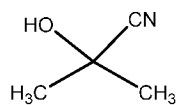
(e) reducing the compound of formula (12) to provide a compound of formula (13),



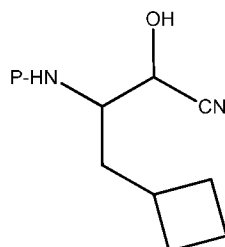
13

wherein P is a protecting group.

(f) reacting the compound of formula (13) with

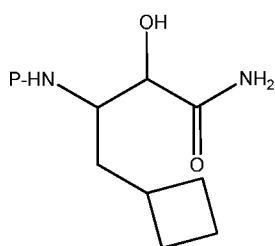


to provide a compound of formula (14),



14

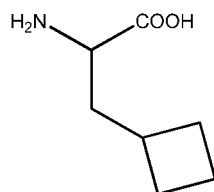
(g) converting the compound of formula (14) to provide a compound of formula (15),



15

(h) deprotecting the compound of formula (15) to provide a compound of formula (3) or a salt thereof.

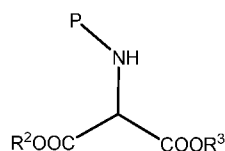
4. A method for preparation of compound of formula (10) or a salt thereof:



10

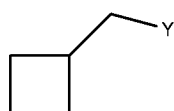
which comprises:

(a) reacting a compound of formula (7),



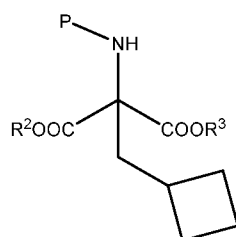
7

wherein R^2 or R^3 represents an alkyl group; P represents a protecting group; with a compound of formula (8),



8

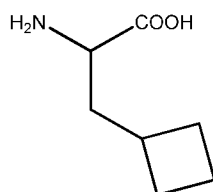
wherein Y represents halo group; to provide a compound of formula (9),



9

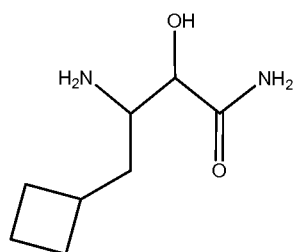
wherein R^2 , R^3 and P are as described previously;

(b) reacting a compound of formula (9) with a reagent to provide a compound of formula (10) or a salt thereof,



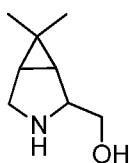
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5. Use of compound of formula (9) in the preparation of compound of formula (3) or a salt thereof



3

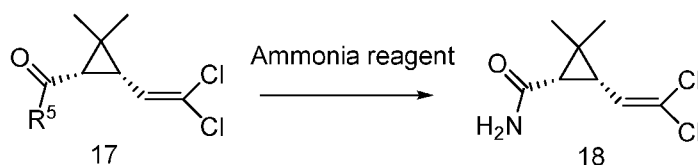
6. A method for preparation of amine alcohol of formula (16) or its stereo isomers and its pharmaceutically acceptable salts thereof



16

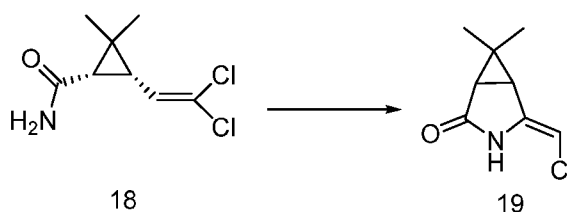
which comprises:

(a) reacting a compound of formula (17) with a reagent of ammonia in a suitable solvent to provide a compound of formula (18)

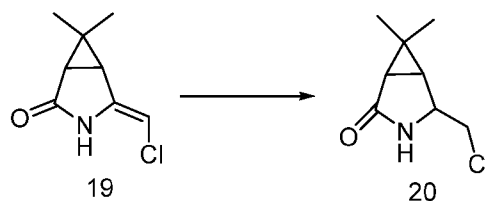


wherein R^5 = hydroxyl; halogen selected from a group of chloro, bromo and iodo; OR^6 ; and R^6 is C_1 - C_8 alkyl

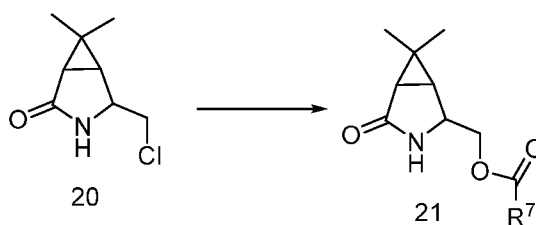
(b) converting a compound of formula (18) to a chloro compound of formula (19)



(c) converting chloro compound of formula (19) to chloro amide of formula (20).

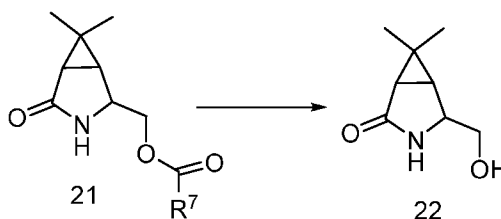


(d) converting chloro amide of formula (20) to ester of formula (21)



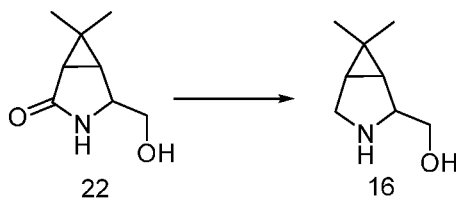
wherein R^7 = alkyl or aryl

(e) converting ester of formula (21) to amide alcohol of formula (22).

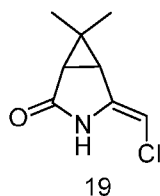


wherein R^7 = alkyl or aryl

(f) reduction of amide alcohol of formula (22) to amine alcohol of formula (16).

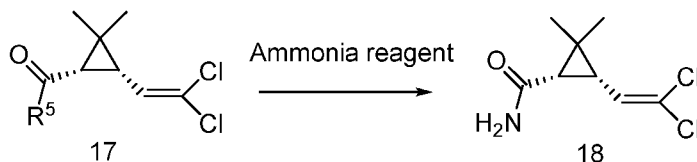


7. A method for preparation of chloro compound of formula (19) or its stereo isomers and its pharmaceutically acceptable salts thereof



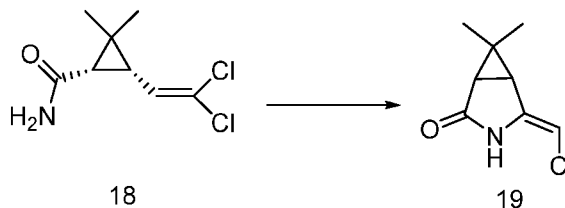
which comprises:

(a) reacting a compound of formula (17) with a reagent of ammonia in a suitable solvent to provide a compound of formula (18)

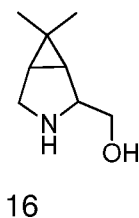


wherein R^5 = hydroxyl; halogen selected from a group of chloro, bromo and iodo; OR^6 ; and R^6 is C_1 - C_8 alkyl

(b) converting a compound of formula (18) to a chloro compound of formula (19)

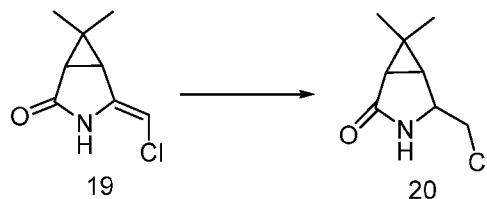


8. A method for preparation of amine alcohol of formula (16) or its stereo isomers and its pharmaceutically acceptable salts thereof

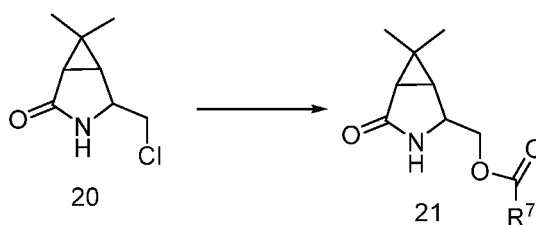


which comprises:

(a) converting chloro compound of formula (19) to chloro amide of formula (20).

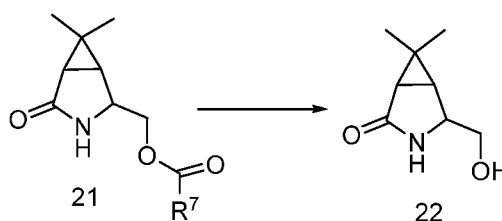


(b) converting chloro amide of formula (20) to ester of formula (21)



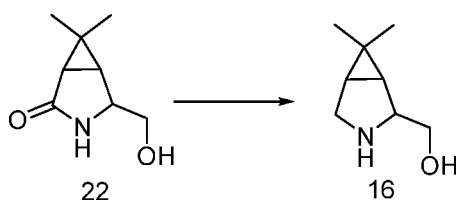
wherein R^7 =alkyl or aryl

(c) converting ester of formula (21) to amide alcohol of formula (22).

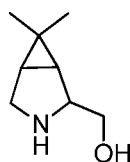


wherein R^7 =alkyl or aryl

(d) reduction of amide alcohol of formula (22) to amine alcohol of formula (16).

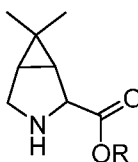


9. Use of compounds of formulae (19), (20) or (21) in the preparation of compound of formula (16) or its stereoisomers and their pharmaceutically acceptable salts thereof:



16

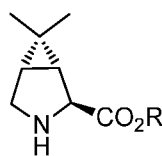
10. A method for preparation of compound of formula (4) or its stereo isomers and its pharmaceutically acceptable salts using amine alcohol of formula (16) prepared according to any of preceding claims



4

wherein R= C₁-C₈ alkyl

11. A method for preparation of compound of formula (4) or its stereoisomers and their pharmaceutically acceptable salts thereof:

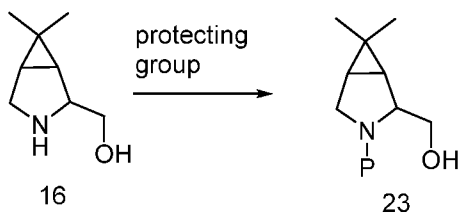


4

wherein R= C₁-C₈ alkyl

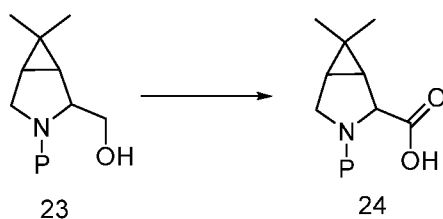
which comprises:

- (a) reacting amine alcohol of formula (16) with a nitrogen protecting reagent to provide nitrogen protected alcohol of formula (23),

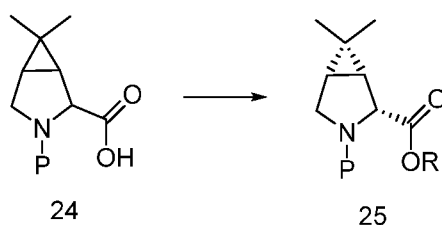


wherein P= Protecting group

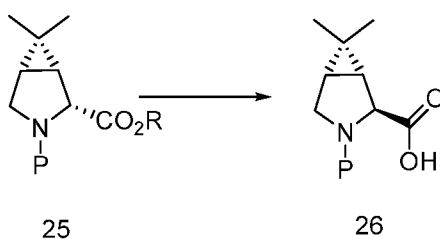
- (b) oxidation of nitrogen protected alcohol of formula (23) to an acid of formula (24),



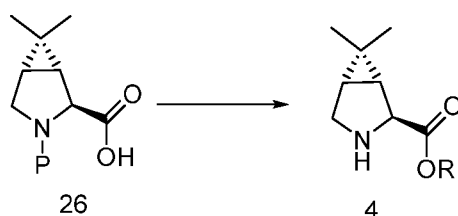
(c) esterification of acid of formula (24) to provide ester of formula (25)



(d) epimerization of ester of formula (25) to provide acid of formula (26),

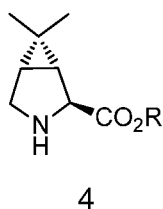


(e) deprotection and esterification of acid of formula (26) to provide a compound of formula (4) or its stereoisomers and their pharmaceutically acceptable salts,



wherein R= C₁-C₈ alkyl

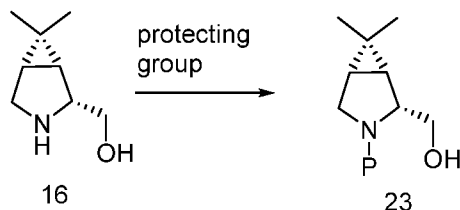
12. A method for preparation of compound of formula (4) or its stereoisomers and their pharmaceutically acceptable salts thereof:



wherein R= C₁-C₈ alkyl

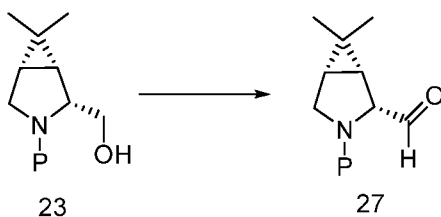
which comprises:

- (a) reacting amine alcohol of formula (16) with a nitrogen protecting reagent to provide nitrogen protected alcohol of formula (23),

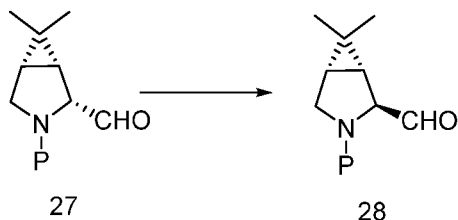


wherein P= Protecting group

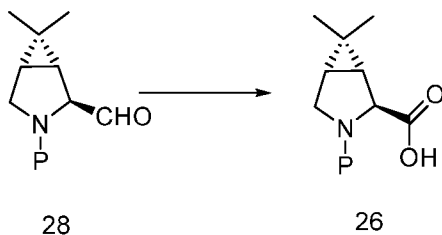
- (b) oxidation of nitrogen protected alcohol of formula (23) to an aldehyde of formula (27),



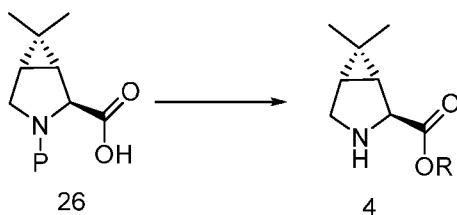
- (c) epimerization of aldehyde of formula (27) to provide compound of formula (28)



- (d) oxidation of aldehyde of formula (28) to provide acid of formula (26),

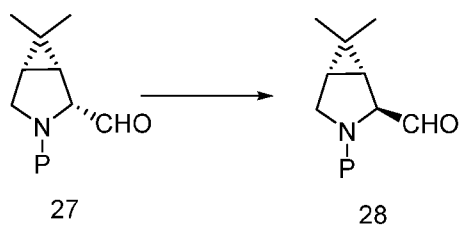


- (e) deprotection and esterification of acid of formula (26) to provide a compound of formula (4) or its stereoisomers and their pharmaceutically acceptable salts,

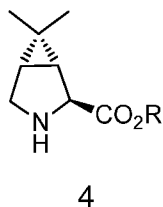


wherein R= C₁-C₈ alkyl

13. A method for epimerization of aldehyde of formula (27) to provide compound of formula (28)



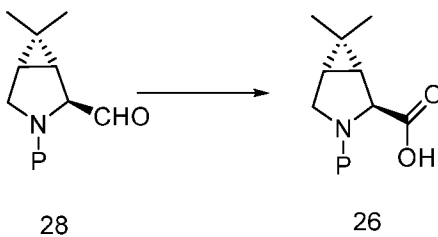
14. A method for preparation of compound of formula (4) or its stereoisomers and their pharmaceutically acceptable salts thereof:



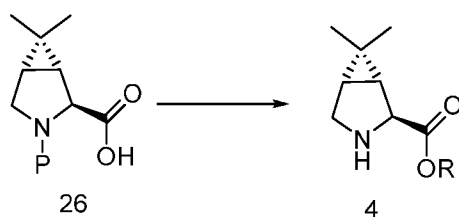
wherein R= C₁-C₈ alkyl

which comprises:

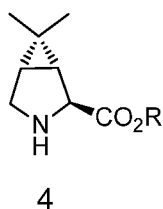
(a) oxidation of aldehyde of formula (28) to provide acid of formula (26),



(b) deprotection and esterification of acid of formula (26) to provide a compound of formula (4) or its stereoisomers and their pharmaceutically acceptable salts,

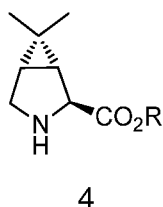


15. Use of aldehyde of formulae (27) or (28) in preparation of compound of formula (4) or its stereoisomers and their pharmaceutically acceptable salts thereof:



wherein R= C₁-C₈ alkyl

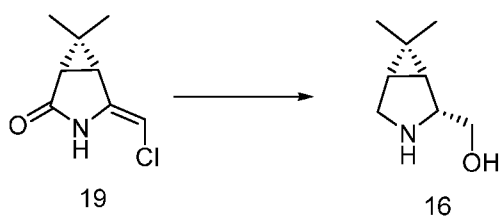
16. A method for preparation of compound of formula (4) or its stereoisomers and their pharmaceutically acceptable salts thereof:



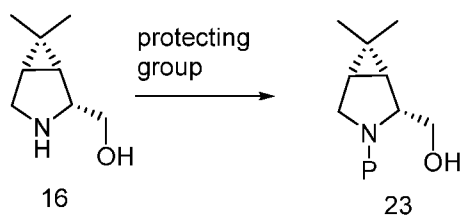
wherein R= C₁-C₈ alkyl

which comprises:

(a) conversion of chloro compound of formula (19) to amine alcohol of formula (16),

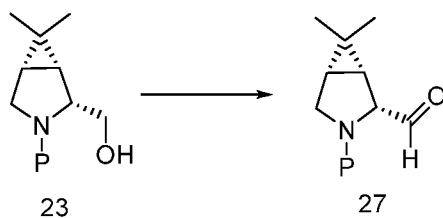


(b) reacting amine alcohol of formula (16) with a nitrogen protecting reagent to provide nitrogen protected alcohol of formula (23),

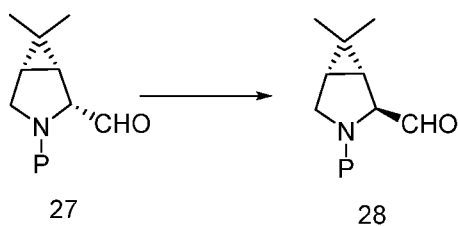


wherein P= protecting group

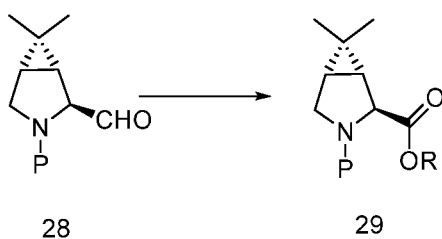
(c) oxidation of nitrogen protected alcohol of formula (23) to an aldehyde of formula (27),



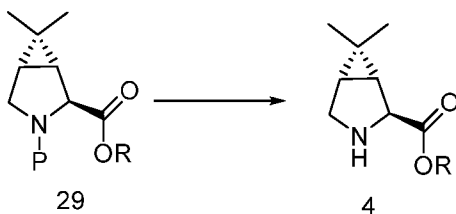
(d) epimerization of aldehyde of formula (27) to provide compound of formula (28)



(e) oxidation of aldehyde of formula (28) to provide ester of formula (29),

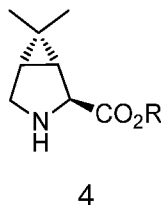


(f) deprotection of ester of formula (29) to provide a compound of formula (4) or its stereoisomers and their pharmaceutically acceptable salts,



wherein R= C₁-C₈ alkyl

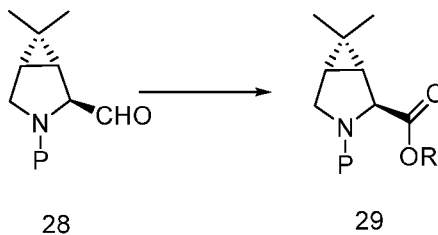
17. A method for preparation of compound having the formula (4) or its stereoisomers and their pharmaceutically acceptable salts thereof:



wherein R= C₁-C₈ alkyl

which comprises:

(a) oxidation of aldehyde of formula (28) to provide ester of formula (29),

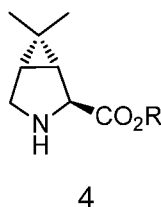


wherein P= protecting group

(b) deprotection of ester of formula (29) to provide a compound of formula (4) or its stereoisomers and their pharmaceutically acceptable salts,

18. The method of oxidation of step (a) according to claim 17 is carried out in presence of N-Bromosuccinimide, N-iodosuccinimide, calcium hypochlorite, sodium hypochlorite or the like.

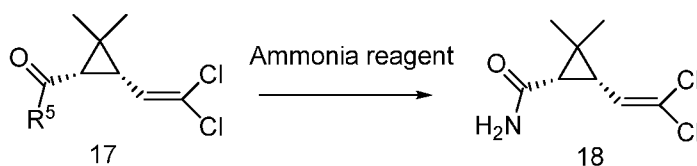
19. A method for preparation of compound having the formula (4) or its stereoisomers and their pharmaceutically acceptable salts thereof:



wherein R= C₁-C₈ alkyl

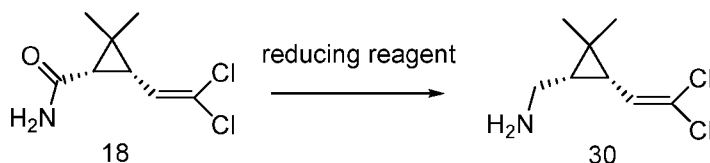
which comprises:

(a) reacting a compound of formula (17) with a reagent of ammonia in a suitable solvent to provide a compound of formula (18)

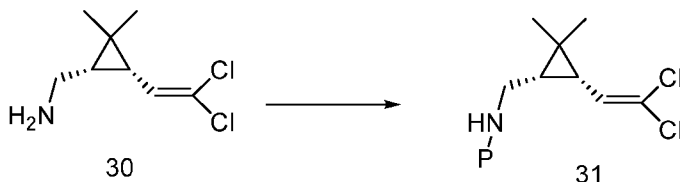


wherein R^5 = hydroxyl; halogen selected from a group of chloro, bromo and iodo; OR^6 ; and R^6 is C_1 - C_8 alkyl

(b) reacting a compound of formula (18) with a reducing agent in a suitable solvent to provide a compound of formula (30)

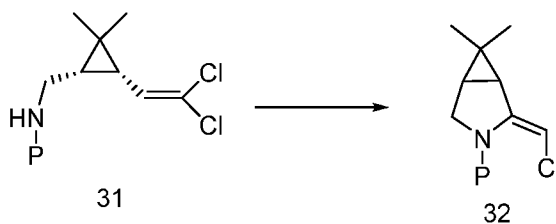


(c) converting a compound of formula (30) to a amino protected compound of formula (31)

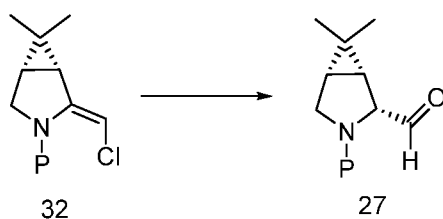


P=amino protecting group

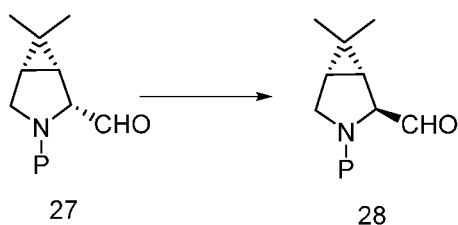
(d) converting amino protected compound of formula (31) to a chloro compound of formula (32)



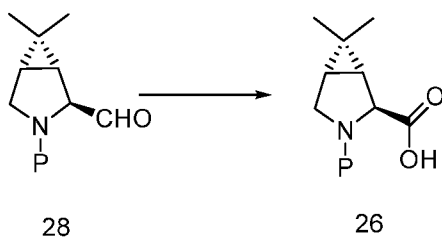
(e) oxidation of chloro compound of formula (32) to an aldehyde of formula (27),



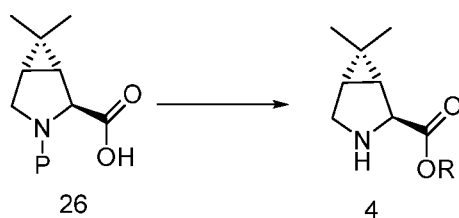
(f) epimerization of aldehyde of formula (27) to provide compound of formula (28)



(g) oxidation of aldehyde of formula (28) to provide acid of formula (26),

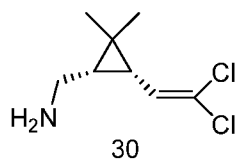


(h) deprotection and esterification of acid of formula (26) to provide a compound of formula (4) or its stereoisomers and their pharmaceutically acceptable salts thereof



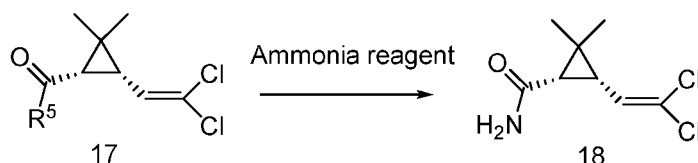
wherein R= C₁-C₈ alkyl, P=amino protecting group

20. A method for preparation of compound having the formula (30) or its stereoisomers and their pharmaceutically acceptable salts thereof:



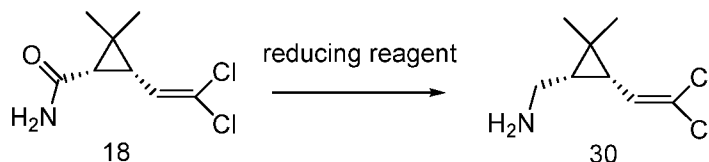
which comprises:

(a) reacting a compound of formula (17) with a reagent of ammonia in a suitable solvent to provide a compound of formula (18)

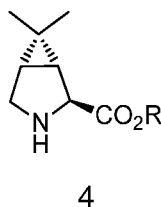


wherein R^5 = hydroxyl; halogen selected from a group of chloro, bromo and iodo; OR^6 ; and R^6 is C_1 - C_8 alkyl

(b) reacting a compound of formula (18) with a reducing agent in a suitable solvent to provide a compound of formula (30)



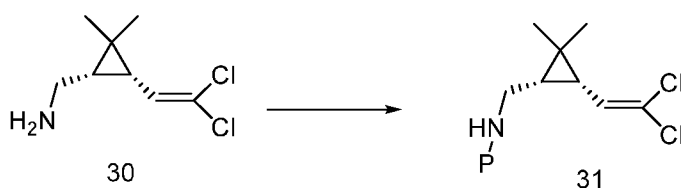
21. A method for preparation of compound having the formula (4) or its stereoisomers and their pharmaceutically acceptable salts thereof:



wherein R = C_1 - C_8 alkyl

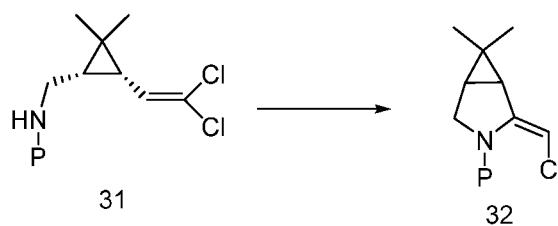
which comprises:

(a) converting a compound of formula (30) to a amino protected compound of formula (31)

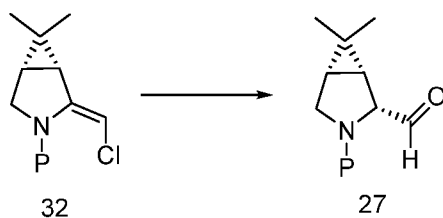


wherein P = Protecting group

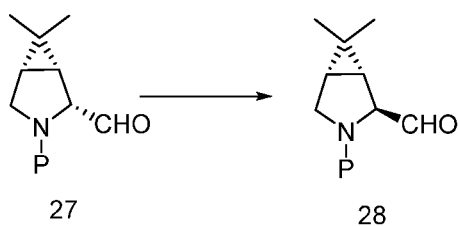
(b) converting amino protected compound of formula (31) to a chloro compound of formula (32)



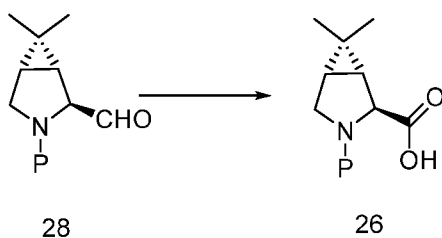
(c) oxidation of chloro compound of formula (32) to an aldehyde of formula (27),



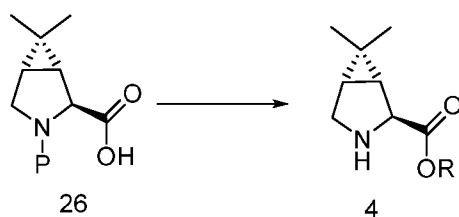
(d) epimerization of aldehyde of formula (27) to provide compound of formula (28)



(h) oxidation of aldehyde of formula (28) to provide acid of formula (26),

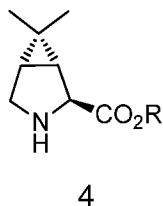


(f) deprotection and esterification of acid of formula (26) to provide a compound of formula (4) or its stereoisomers and their pharmaceutically acceptable salts,



wherein R= C₁-C₈ alkyl

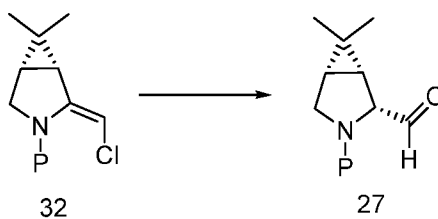
22. A method for preparation of compound having the formula (4) or its stereoisomers and their pharmaceutically acceptable salts thereof:



wherein R= C₁-C₈ alkyl

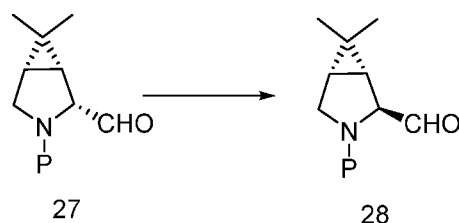
which comprises:

- (a) oxidation of chloro compound of formula (32) to an aldehyde of formula (27),

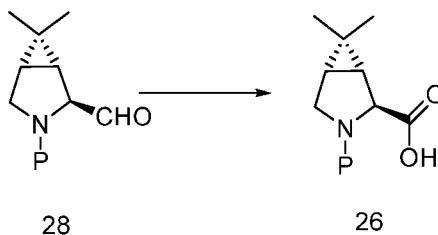


wherein P= Protecting group

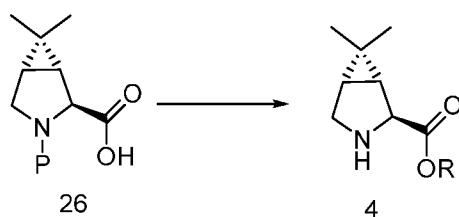
- (b) epimerization of aldehyde of formula (27) to provide compound of formula (28)



- (c) oxidation of aldehyde of formula (28) to provide acid of formula (26),

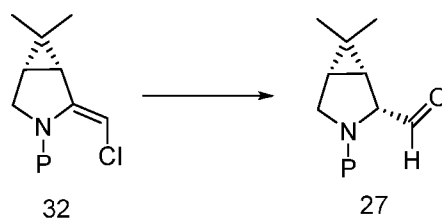


- (d) deprotection and esterification of acid of formula (26) to provide a compound of formula (4) or its stereoisomers and their pharmaceutically acceptable salts



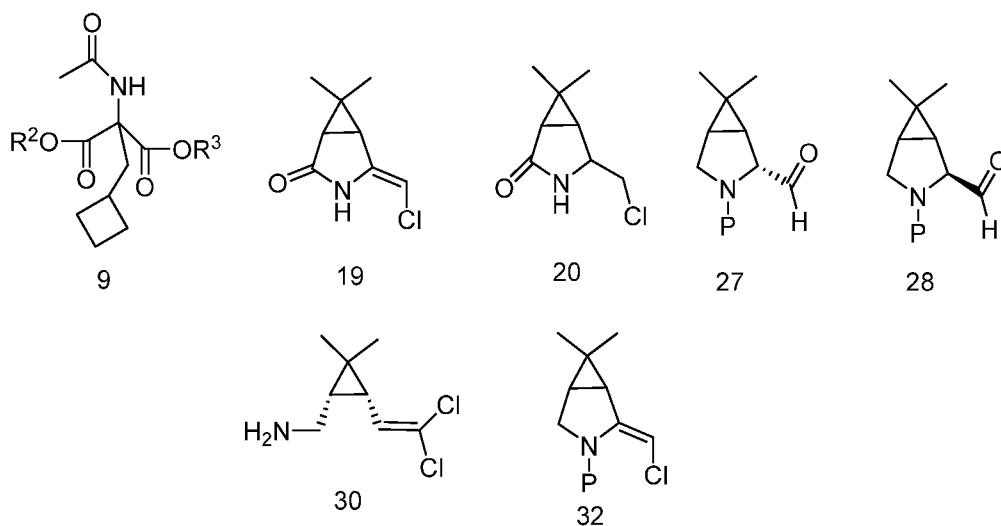
wherein R= C₁-C₈ alkyl

23. A method for oxidation of chloro compound of formula (32) to an aldehyde of formula (27)



wherein P= Protecting group

24. Compounds of formulae (9), (19), (20), (27), (28), (30), (32) or their stereoisomers and their pharmaceutically acceptable salts thereof.



wherein P= amine protecting group, R² or R³ represents an alkyl group

25. Use of compounds of claim 24 in the preparation of boceprevir or its pharmaceutically acceptable salts thereof.

26. A method for preparation of boceprevir of formula (1) or its pharmaceutically acceptable salts using the compound of formula (2) or its stereoisomers and their pharmaceutically acceptable salts prepared according to any of the preceding claims.

27. A method for preparation of boceprevir of formula (1) or its pharmaceutically acceptable salts using the compound of formula (3) or its stereoisomers and their pharmaceutically acceptable salts prepared according to any of the preceding claims.

28. A method for preparation of boceprevir of formula (1) or its pharmaceutically acceptable salts using the compound of formula (4) or its stereoisomers and their pharmaceutically acceptable salts prepared according any of the preceding claims

29. Pharmaceutical compositions comprising boceprevir of formula (1) or its pharmaceutically acceptable salts prepared from compounds of formula (2), (3) and (4) or their stereoisomers and their pharmaceutically acceptable salts prepared according to preceding claims together with one or more pharmaceutically acceptable excipient, carrier and diluents.