Title: PROCESS FOR THE PREPARATION OF 3,4-EPOXY-2-AMINO-1-SUBSTITUTED BUTANE DERIVATIVES AND INTERMEDIATE COMPOUNDS THEREOF

Formula I

R²-NH

\[ \begin{align*}
R^1 & \quad 1 \\
2 & \\
3 & \\
4 & \\
\end{align*} \]

Formula II

H₂N

\[ \begin{align*}
1 & \quad R^1 \\
2 & \\
3 & \\
4 & \\
\end{align*} \]

Formula III

R²-NH

\[ \begin{align*}
R^1 & \quad 1 \\
2 & \\
3 & \\
4 & \\
\end{align*} \]

Formula IV

R²-NH

\[ \begin{align*}
R^1 & \quad 1 \\
2 & \\
3 & \\
4 & \\
\end{align*} \]
before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))
PROCESS FOR THE PREPARATION OF 3,4-EPOXY-2-AMINO-1-SUBSTITUTED BUTANE DERIVATIVES AND INTERMEDIATE COMPOUNDS THEREOF

Field of the Invention

The present invention relates to production method of threo-3,4-epoxy-2-amino-1-substituted butane derivatives represented by general Formula I:

![Formula I](image)

wherein

- $R_1$ is phenyl,
- $R_2$ is hydrogen or amino protecting groups,
- $R_3$ is secondary or tertiary lower alkyl and configurations at 2 and 3 positions are either (2S,3R) or (2R,3S).

The carbon atom bonded to the radical $R_3$ in Formula I may be in (R)-, (S)- or (R,S)-configuration.

The compounds of Formula I are useful intermediates for the production of various HIV protease compounds. Particularly, (2S,3R)-3,4-epoxy-2-amino-1-substituted butane derivatives represented by general Formula Ia are useful pharmaceutical intermediates of atazanavir- an inhibitor of retroviral aspartate protease.

![Formula Ia](image)

The $R_1$, $R_2$ and $R_3$ in Formula Ia are same as described hereinabove for compound of Formula I.
Background of the Invention

Atazanavir and its bisulfate salt (1:1) are disclosed in U.S. Patent Nos. 5,849,911 and 6,087,383 respectively. Atazanavir bisulfate is chemically known as (35,85,95,125)-3,12-bis(l,l-dimethylethyl)-8-hydroxy-4,11-dioxo-9-(phenylmethyl)-6-[[4-(2-pyridinyl)phenyl][methyl]-2,5,6,10,13-pentaazatetradecanoidioic acid dimethyl ester, sulfate (1:1) and represented by following chemical structure-

![Chemical Structure of Atazanavir Bisulfate](image_url)

Atazanavir bisulfate is inhibitor of retroviral aspartate protease and also known to have high degree of inhibitory activity against the HIV virus.

Several methods for preparing various 3,4-epoxy-2-amino-l-substituted butane derivatives are published. U.S. Patent Nos. 5,849,911; 6,300,519 and 6,110,946 describe preparation of 3,4-epoxy-2-amino-l-substituted butane derivatives starting from 2-amino-3-substituted propanoic acid derivative. The acid is reduced to corresponding aldehyde which on further treatment with ylide compound (e.g. sulfur ylide compound) produces the desired 3,4-epoxy-2-amino-l-substituted butane derivative.

U.S. Patent No. 5,847,169 describes process for preparing 3,4-epoxy-2-amino-l-substituted butane derivatives comprising the steps of activating an aminodiol, acylating the aminodiol and reacting the acylated aminodiol with a base to form an epoxy compound. The methods disclosed in U.S. Patent No. 6,127,556 for the preparation of epoxy compounds or 3,4-epoxy-2-amino-l-substituted butane derivatives make use of halomethyl organometallic reagent and aminoaidehyde compound whereas U.S. Patent No. 6,278,002 describes the preparation of similar type of compounds by making use of quaternary ammonium salt or carboxylic acid metal salt. U.S. Patent No. 6,693,205 makes use of Mitsunobu reaction during preparation of 3,4-epoxy-2-amino-l-substituted butane derivatives.
Several other publications, for example, U.S. Patent Nos. 5,693,847; 6,344,572; 6,764,545; 6,765,100; 6,867,311; 6,605,732 and 7,122,696 mention preparation of various 3,4-epoxy-2-amino-1-substituted butane derivatives and are incorporated herein by reference.

Most of the prior-art processes for the preparation of 3,4-epoxy-2-amino-1-substituted butane derivatives suffer from one or more disadvantages such as use of expensive and inaccessible raw materials, commercially impractical and hazardous reaction conditions, time consuming multi-step reaction sequences employing unstable and/or dangerous intermediates and production of isomeric mixtures resulting in low yields of pure substance due to lengthy separation procedures that are impractical for larger scale production.

Summary of the Invention

The present invention overcomes the disadvantages associated with the prior art by providing a process for the preparation of compounds of the Formula I using reagents and conditions which are convenient to operate on commercial scale and operationally safe.

The threeo-4-halo-3-hydroxy-2-amino-1-substituted butane derivative represented by general Formula II serves as substrate in the preparation method of 3,4-epoxy-2-amino-1-substituted butane derivatives (Formula-I) of present invention.

![Formula II](image)

The R^1, R^2, R^3 in Formula-II are same as mentioned hereinabove for the compounds of Formula I and X represents halogen atom, such as a chlorine, bromine, fluorine or iodine.

The carbon atom bonded to the radical R^3 in Formula II, may be in the (R)-, (S)- or (R,S)-configuration.

The configurations at positions 2 and 3 in the above Formula II are either (2S,3R) or (2R,3S). The preferred configuration is (2S,3R) as represented by Formula Ha.
To prepare threo-3,4-epoxy-2-amino-l-substituted butane derivatives having (2S,3R) configuration (Formula-Ia), the above threo-4-halo-3-hydroxy-2-amino-l-substituted butane derivative should have the (2S,3R) configuration (Formula-IIa).

Similarly, for obtaining the (2R,3S) product, the substrate should be of (2R,3S) configuration.

Thus, the present invention provides efficient process for the preparation of compounds of the Formulae I and II.

**Detailed Description of the Invention**

The term "about" as used herein (unless specified), when used along values assigned to certain measurements and parameters means a variation of 10% from such values, or in case of a range of values, means a 10% variation from both the lower and upper limits of such ranges.

The term 'Tower alkyl' is meant for 'C_{1-4} alkyl'. Preferably, the Tower alkyl' is selected from the group comprising of tert-butyl, sec-butyl, isobutyl, n-butyl, isopropyl, n-propyl, ethyl and methyl.

The term 'amino protecting groups' can be any protecting group known to a person skilled in the art. Some non-limiting examples are lower alkoxy carbonyl (such as tert-butoxycarbonyl, methoxycarbonyl etc.), aryl-lower alkoxy carbonyl (such as benzyl oxycarbonyl) or acyl protecting group (such as CH3CO, trifluoroacetyl).

The term 'Atazanavir bisulfate' as employed herein refers to Atazanavir bisulfate as well as Atazanavir sulfate.

A first aspect of the present invention provides process for the preparation of 4-halo-3-hydroxy-2-amino-l-substituted butane derivative represented by Formula II
which comprises reacting compound of Formula III or salt thereof

with an active ester of acid of Formula IV

wherein

- $R^1$ is phenyl,
- $R^2$ is hydrogen or amino protecting groups,
- $R^3$ is secondary or tertiary lower alkyl and
- $X$ is chlorine, bromine, fluorine or iodine.

In an embodiment of this aspect, the compounds of Formula II and III are either in (2S.3R) or (2R.3S) configuration.

In another embodiment of this aspect, the carbon atom bonded to the radical $R^3$ in Formula II and IV can be in (R)-, (S)- or (R,S)-configuration.

In another embodiment of this aspect, the reaction can be performed in presence of base and organic solvent.

The 'base' as used herein can be selected from the group comprising of alkali metal hydroxide, alkaline earth metal hydroxide, alkali metal carbonate, alkaline earth
metal carbonate, alkali metal phosphate and alkaline earth metal phosphate. The base can be an organic base. Some non-limiting examples of base are NaOH, KOH, Mg(OH)\(_2\), K\(_2\)HPO\(_4\), MgC\(_2\)O\(_4\), Na\(_2\)CO\(_3\), K\(_2\)CO\(_3\), triethylamine, diisopropylethylamine and/or N-methyl morpholine.

The Organic solvent' as used herein can be selected from the group comprising methylene chloride, ethyl acetate, butyl acetate, dichloroethane, tetrahydrofuran, acetonitrile and N,N-dimethylformamide or mixture(s) thereof.

The acid of Formula IV can be converted into its active ester by reaction of the acid with coupling agent selected from the group comprising O-(1,2-dihydro-2-oxo-1-pyridyl)-N,N,N\(_1\),N\(_1\)-tetramethyluronium-tetrafluoro-borate (TPTU), 1-hydroxybenzotriazole (HOBT) and N-ethyl-N'-dimethylaminopropyl carbodiimide (EDC).

In another embodiment of this aspect, the active ester of an acid of Formula IV can be represented by following compound of Formula V

![Formula V](image)

**Formula V**

In another embodiment of this aspect, the reaction of compound of Formula III with active ester of acid of Formula IV can be performed at temperature selected from about 5°C to about 40°C.

In another embodiment of this aspect, the compound of Formula III in its hydrochloride salt form can be reacted with active ester of compound of Formula IV.

Accordingly, the compound of Formula III in its salt form is reacted with active ester of acid of Formula IV in presence of base and organic solvent at temperature selected from about 5°C to about 40°C. The reaction is performed at pH range of 5 to 7. The so produced compound of Formula II is then isolated from the reaction mixture.
In another embodiment of this aspect, the obtained 4-halo-3-hydroxy-2-amino-1-substituted butane derivative of Formula II has (2S,3R) configuration and can be represented by Formula-IIa.

The compounds of Formula II and Ha can be further used as intermediates in the preparation of Atazanavir or salt thereof.

A second aspect of the present invention provides process for preparation of threo-3,4-epoxy-2-amino-1-substituted butane derivative represented by Formula I:

![Formula I]

which comprises

a) reacting compound of Formula III or salt thereof

![Formula III]

with active ester of acid of Formula IV

![Formula IV]

to produce 4-halo-3-hydroxy-2-amino-1-substituted butane derivative of Formula II
b) treating compound of Formula II produced in step a) with base

c) isolating threo-3,4-epoxy-2-amino-1-substituted butane derivative

(I) from the reaction mixture of step b)

wherein

R\(^1\) is phenyl,
R\(^2\) is hydrogen or amino protecting groups,
R\(^3\) is secondary or tertiary lower alkyl and
X is chlorine, bromine, fluorine or iodine.

In an embodiment of this aspect, the compounds of Formula I, II and III can be in (2S,3R) or (2R,3S) configuration.

In another embodiment of this aspect, the carbon atom bonded to the radical R\(^3\) in Formula I, II and IV can be in (R)-, (S)- or (R,S)-configuration.

In another embodiment of this aspect, the step a) can be performed in presence of base and organic solvent.

The 'base' as used herein in steps a) and b) can be selected from the group comprising alkali metal hydroxide, alkaline earth metal hydroxide, alkali metal carbonate, alkaline earth metal carbonate, alkali metal phosphate and alkaline earth metal phosphate.

The base can be an organic base. Some non-limiting examples of base are NaOH, KOH, Mg(OH)\(_2\), K\(_2\)HPO\(_4\), MgCO\(_3\), Na\(_2\)CO\(_3\), K\(_2\)CO\(_3\), triethylamine, diisopropylethylamine and/or N-methyl morpholine.

The Organic solvent' as used herein in step a) can be selected from the group comprising methylene chloride, ethyl acetate, butyl acetate, dichloroethane, tetrahydrofuran, acetonitrile and/or N,N-dimethylformamide.

The acid of Formula IV can be converted into its active ester by the reaction of the acid with coupling agent selected from the group comprising of O-(1,2-dihydro-2-oxo-1-pyridyl)-N,N,N\(^1\),N\(^1\)-tetramethyluronium-tetrafluoro-borate (TPTU), 1-
hydroxybenzotriazole (HOBT) and N-ethyl-N’-dimethylaminopropyl carbodiimide (EDC).

In another embodiment of this aspect, the active ester of an acid of Formula IV can be represented by following compound of Formula V

Formula V

In another embodiment of this aspect, the step a) reaction can be performed at temperature selected from about 5°C to about 40°C.

In another embodiment of this aspect, the compound of Formula III can be reacted with compound of Formula IV in the form of its hydrochloride salt.

In another embodiment of this aspect, 4-halo-3-hydroxy-2-amino-1-substituted butane derivative compound of Formula II obtained in step a) has (2S,3R) configuration.

In another embodiment of this aspect, the step b) can be performed in presence of polar organic solvent. The polar organic solvent with or without water can be used.

The 'polar organic solvent' is not particularly restricted but includes, among others, aprotic polar organic solvents such as acetone, methyl ethyl ketone, tetrahydrofuran, 1,4-dioxane, 1,3-dioxolane, 1,2-dimethoxyethane, diethylene glycol dimethyl ether, trimethylene glycol dimethyl ether, tetraethylene glycol dimethyl ether, polyethylene glycol dimethyl ether, 1,2-diethoxyethane, diethylene glycol diethyl ether, Methylene glycol diethyl ether, tetraethylene glycol diethyl ether, polyethylene glycol diethyl ether, acetonitrile, dimethyl formamide and dimethyl sulfoxide or mixture(s) thereof; protic polar organic solvents such as alcohols, for example methanol, ethanol, n-propanol, isopropanol, n-butanol, sec-butanol, isobutanol and tert-butanol or mixture(s) thereof.

In another embodiment of this aspect, the step b) can be performed at temperature selected from 0°C to 10°C.

In another embodiment of this aspect, compound of Formula I can be isolated from the reaction mixture by extracting it with ether solvent (e.g. diethyl ether).
Accordingly, the compound of Formula III in its salt form is reacted with an active ester of acid of Formula IV in presence of base and organic solvent at a temperature from about 5°C to about 40°C. The reaction is performed at pH range of 5 to 7. The so produced compound of Formula II is then isolated from the reaction mixture.

The compound of Formula II is treated with base in polar organic solvent and water to produce the desired threo-3,4-epoxy-2-amino-1-substituted butane derivative of Formula I.

The so produced compound of Formula I is then isolated from the reaction mixture after neutralizing the reaction mixture by adding sodium dihydrogen orthophosphate solution into it. Ether (e.g. diethyl ether) can be added to the reaction mixture to extract the compound of Formula I from the organic layer. The extracted compound of Formula I can be purified using hydrocarbon solvent (e.g. hexane).

The compound of Formula I can be further used as intermediates for the preparation of Atazanavir or salt thereof.

A third aspect of the present invention provides process for the preparation of methyl [(2S)-1-[[2S,3R)-4-chloro-3-hydroxy-1-phenylbutan-2-yl]amino]-3,3-dimethyl-1-oxobutan-2-yl] carbamate represented by Formula VI

![Formula VI](image)

which comprises reacting (2S,3R)-2-amino-4-chloro-1-phenylbutan-3-ol represented by Formula VII or salt thereof

![Formula VII](image)
with an active ester of (2S)-2-[(methoxycarbonyl)amino]-3,3-dimethylbutanoic acid represented by Formula VIII.

![Formula VIII](image)

**Formula VIII**

In an embodiment of this aspect, the reaction of compound of Formula VII or salt thereof with an active ester of acid of Formula VIII can be performed in presence of base and organic solvent.

The base and organic solvent used herein in this aspect are the same as mentioned in first aspect of the present invention. The base and organic solvent used in first aspect for the preparation of compound of Formula II comprising reaction of compound of Formula III or salt thereof with active ester of acid of Formula IV can also be employed herein in this aspect of the invention but for the preparation of compound of Formula VI comprising reaction of compound of Formula VII or salt thereof with active ester of acid of Formula VIII.

The acid of Formula VIII can be converted into its active ester by the reaction of the acid with coupling agent selected from the group comprising of O-[(1,2-dihydro-2-oxo-1-pyridyl)N,N,N₁,N₁-tetramethyluronium-tetrafluoro-borate (TPTU), 1-hydroxybenzotriazole (HOBT) and N-ethyl-N’-dimethylaminopropyl carbodiimide (EDC).

In another embodiment of this aspect, the active ester of an acid of Formula VIII can be represented by following Formula IX

![Formula IX](image)
In another embodiment of this aspect, the reaction of compound of Formula VII or salt thereof with active ester of acid of Formula VIII can be performed at temperature selected from about 5°C to about 40°C.

In another embodiment of this aspect, the compound of Formula VII in its hydrochloride salt form can be reacted with active ester of compound of Formula VIII.

Accordingly, the compound of Formula VII in its salt form is reacted with an active ester of acid of Formula VIII in presence of base and organic solvent at temperature selected from about 5°C to about 40°C. The reaction is performed at pH range of 5 to 7. The so produced compound of Formula VI is then isolated from the reaction mixture.

The compound of Formula VI can be used as an intermediate in the preparation of Atazanavir or salt thereof.

A fourth aspect of the present invention provides process for the preparation of methyl [(2S)-3,3-dimethyl-1-((1S)-1-[(2R)-oxiran-2-yl]-2-phenylethyl]amino)-1-oxobut-2-yl]carbamate represented by Formula X:

\[
\text{Formula X}
\]

which comprises

a) reacting (2S,3R)-2-amino-4-chloro-l-phenylbutan-3-ol represented by Formula VII or salt thereof with an active ester of (2S)-2-[(methoxycarbonyl)amino]-3,3-dimethylbutanoic acid represented by Formula VIII
to produce methyl [(2S)-l-[(2S,3R)-4-chloro-3-hydroxy-1-phenylbutan-2-yl]amino]-3,3-dimethyl-l-oxobutan-2-yl]carbamate represented by Formula VI

Formula VI

b) treating compound of Formula VI produced in step a) with base

c) isolating methyl [(2S)-3,3-dimethyl-l-[(lS)-l-[(2R)-oxiran-2-yl]-2-phenylethyl]amino]-l-oxobutan-2-yl]carbamate represented by Formula X from the reaction mixture of step b).

In another embodiment of this aspect, the step a) can be performed in presence of base and organic solvent.

The 'base' as used herein in steps a) and b) can be selected from the group comprising alkali metal hydroxide, alkaline earth metal hydroxide, alkali metal carbonate, alkaline earth metal carbonate, alkali metal phosphate and alkaline earth metal phosphate. The base can be an organic base. Some non-limiting examples of base are NaOH, KOH, Mg(OH)₂, K₂HPO₄, MgCO₃, Na₂CO₃, K₂CO₃, triethylamine, diisopropylethylamine and/or N-methyl morpholine.

The Organic solvent' as used herein in step a) can be selected from the group comprising methylene chloride, ethyl acetate, butyl acetate, dichloroethane, tetrahydrofuran, acetonitrile and/or N,N-dimethylformamide.

The acid of Formula VIII can be converted into its active ester by the reaction of the acid with coupling agent selected from the group comprising of O-(1,2-dihydro-2-oxo-1-pyridyl)-N,N,N¹,N¹-tetramethyluronium-tetrafluoro-borate (TPTU), 1-
hydroxybenzotriazole (HOBT) and N-ethyl-N'-dimethylaminopropyl carbodiimide (EDC).

In another embodiment of this aspect, the active ester of an acid of Formula VIII can be represented by following Formula IX

\[ \text{Formula IX} \]

In another embodiment of this aspect, the step a) reaction can be performed at temperature selected from about 5°C to about 40°C.

In another embodiment of this aspect, the compound of Formula VII in its hydrochloride salt form can be reacted with active ester of compound of Formula VIII.

In another embodiment of this aspect, the step b) can be performed in presence of polar organic solvent. The polar organic solvent with or without water can be used.

The 'polar organic solvent' is not particularly restricted but includes, among others, aprotic polar organic solvents such as acetone, methyl ethyl ketone, tetrahydrofuran, 1,4-dioxane, 1,3-dioxolane, 1,2-dimethoxyethane, diethylene glycol dimethyl ether, trimethylene glycol dimethyl ether, tetraethylene glycol dimethyl ether, polyethylene glycol dimethyl ether, 1,2-diethoxyethane, diethylene glycol diethyl ether, Methylene glycol diethyl ether, tetraethylene glycol diethyl ether, polyethylene glycol diethyl ether, acetonitrile, dimethyl formamide and dimethyl sulfoxide or mixture(s) thereof; protic polar organic solvents such as alcohols, for example methanol, ethanol, n-propanol, isopropanol, n-butanol, sec-butanol, isobutanol and tert-butanol or mixture(s) thereof.

In another embodiment of this aspect, the step b) can be performed at temperature selected from 0°C to 100°C.

In another embodiment of this aspect, compound of Formula X can be isolated from the reaction mixture by extracting it with ether solvent (e.g. diethyl ether).
Accordingly, the compound of Formula VII in its salt form is reacted with an active ester of acid of Formula VIII in presence of base and organic solvent at temperature selected from about 5°C to about 40°C. The reaction is performed at pH range of 5 to 7. The so produced compound of Formula VI is then isolated from the reaction mixture.

The compound of Formula VI is treated with base in polar organic solvent and water to produce the desired methyl [(2S)-3,3-dimethyl-l-[(1S)-1-[(2R)-oxiran-2-yl]-2-phenylethyl] amino]-l-oxobutan-2-yl] carbamate represented by Formula X.

The so produced compound of Formula X is then isolated from the reaction mixture after neutralizing the reaction mixture by adding sodium dihydrogen orthophosphate solution into it. Ether (e.g. diethyl ether) can be added to the reaction mixture to extract the compound of Formula X from the organic layer. The extracted compound of Formula X can be purified using hydrocarbon solvent (e.g. hexane).

The compound of Formula X can be further used as an intermediate in the preparation of Atazanavir or salt thereof.

A fifth aspect of the present invention provides threeo-4-halo-3-hydroxy-2-amino-l-substituted butane derivative represented by general Formula II

\[
\begin{align*}
\text{Formula II} & \\
R^2 & \text{is phenyl,} \\
R^3 & \text{is hydrogen or amino protecting groups,} \\
X & \text{is chlorine, bromine, fluorine or iodine.}
\end{align*}
\]

In an embodiment of this aspect, the compound of Formula II can be in (2S, 3R) or (2R, 3S) configuration.

In another embodiment of this aspect, the carbon atom bonded to the radical R^3 in Formula II can be in (R)-, (S)- or (R,S)-configuration.
Another embodiment of this aspect provides methyl [(2S)-l-{ [(2S,3R)-4-chloro-3-hydroxy- 1-phenylbutan-2-yl] amino }-3,3-dimethyl- 1-oxobutan-2-yl] carbamate represented by Formula VI

![Chemical Structure](https://example.com/structure.png)

**Formula VI**

In another embodiment of this aspect, the compounds of Formula II and VI can be used as intermediates for Atazanavir or its salt preparation.

The preparation method of compounds of Formula II and VI are described hereinabove in first and third aspect, respectively, of the present invention.

While the present invention has been described in terms of its specific aspects, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

In the following section aspects are described by way of examples to illustrate the processes of the invention. However, these are not intended in any way to limit the scope of the present invention. Several variants of these examples would be evident to persons ordinarily skilled in the art.

**Preparation of starting materials**

(2S)-2-(methoxycarbonyl)aminol-3,3-dimethylbutanoic acid

![Chemical Structure](https://example.com/structure.png)

**Formula VIII**
23.5 ml of methyl chloroformate was added over a period of 20 minutes to a solution of 20 g of 2(S)-amino-3,3-dimethyl-butyric acid in a mixture of 252 ml of 2N aqueous sodium hydroxide solution and 80 ml of dioxane and the reaction solution was heated at 60°C for 14 hours. It was cooled to room temperature and then washed 2 times with methylene chloride. The aqueous phase was acidified to pH 2 with 4N aqueous hydrochloric acid and extracted three times with ethyl acetate. The organic extracts were combined, dried (Na₂SO₄) and concentrated by evaporation, the product started to solidify. The solidified solid was digested with hexane yielded (2S)-2-[(methoxycarbonyl)amino]-3,3-dimethylbutanoic acid in the form of a white powder.

M.p. 106°-108°C

Active Ester of (2S)-2-(methoxycarbonyl)amino1-3,3-dimethyrbutanoic acid

To a 3000 mL, 3-neck round bottom flask fitted with mechanical stirrer, addition funnel, nitrogen inlet, and temperature probe was added (2S)-2-[(methoxycarbonyl)amino]-3,3-dimethylbutanoic acid (VIII; 77.2g), 1-hydroxybenzotriazole (HOBT) (60.8g), and N-ethyl-N'-dimethylaminopropyl carbodiimide (EDC; 82.0 g) followed by CH₂Cl₂ (880 ml) and the mixture was stirred at ambient temperature (18-25°C) until formation of the active ester was completed, as judged by HPLC.

Example 1: Preparation of methyl [(2S)-1-? r(2S,3R)-4-chloro-3-hydroxy-1-phenylbutan-2-vHamino]-3,3-dimethyl-1-oxobutan-2-vHcarbamate (Formula VI)
To (2S)-2-[(methoxycarbonyl)amino]-3,3-dimethylbutanoic acid (VIII; 92.19 g), HOBT (72.13 g), EDC hydrochloride (98.289 g) and dichloromethane (800 ml) were added at 20-25°C and the solution was stirred for 3 hours at 20-25°C. A solution of K₂HPO₄ (120 g) in de-ionized water (800 ml) was added to the solution at 20-25°C and then it was cooled to 10-15°C.

Another prepared solution of (2S,3R)-2-amino-4-chloro-l-phenylbutan-3-ol (Formula-VII) (100 g) in de-ionized water (400 ml) was drop-wise added to the cooled (10-15°C) solution over a period of 1-2 hours. The reaction mixture so prepared was stirred at ambient temperature for 13-14 hours maintaining pH of the mixture in the range of 5 to 7. Completion of the reaction was monitored by TLC (Thin layer chromatography). After completion of the reaction, organic layer was separated and aqueous sodium hydroxide solution (40 g of NaOH dissolved in 800 ml of de-ionized water) was added to it at 10-15°C. The solution was then stirred for 30 minutes and again organic layer was separated. The organic layer was washed with 5% diluted hydrochloride solution (750 ml) at 10-15°C and then with de-ionized water (800 ml). The solvent was completely removed from the organic layer under vacuum at not more then 45°C to obtain the titled compound of Formula VI.

Yield (w/w) = 1.45
Example 2: Preparation of methyl r(2S)-3,3-dimethyl-l-((lS)-l-r(2R)-oxiran-2-yl-2-
phenylethyl I amino)-l-oxobutan-2-ylH carbamate (Formula X)

Formula X

To methyl [(2S)-l-[(2S,3R)-4-chloro-3-hydroxy-l-phenylbutan-2-yl]amino]-3,3-
dimethyl-l-oxobutan-2-yl] carbamate (VI; 100 g), tetrahydrofuran (450 ml), ethanol (260
ml) and de-ionized water (87 ml) were added at ambient temperature. The solution was
cooled to 0-5°C and then aqueous KOH solution (39 g of KOH dissolved in 39 ml de-
ionized water) was added to it at 0-5°C. The resultant reaction mixture was stirred at 0-
5°C for 2-3 hours. Completion of the reaction was monitored by TLC (Thin layer
chromatography). After completion of the reaction, 6% sodium dihydrogen
orthophosphate solution (725 ml) and diethyl ether (750 ml) were added to the reaction
mixture at 0-5°C and the solution was stirred for 10-15 minutes. The organic layer so
formed was separated and de-ionized water (500 ml) was added to it at ambient
temperature and stirred for 2 minutes. The organic layer was again separated and solvent
was completely recovered under vacuum. To the residue, hexanes (300 ml) were added
and it was stirred for 30 minutes at 5-10°C. The solid, so obtained, was washed with
hexanes (100 ml) and dried at 35-40°C under vacuum to obtain the titled compound of
Formula X.

Yield (w/w) = 0.803
We Claim:

1. A process for the preparation of 4-halo-3-hydroxy-2-amino-1-substituted butane derivative represented by Formula II

   \[
   \begin{array}{c}
   \text{Formula II} \\
   \end{array}
   \]

   which comprises reacting compound of Formula III or salt thereof

   \[
   \begin{array}{c}
   \text{Formula III} \\
   \end{array}
   \]

   with an active ester of acid of Formula IV

   \[
   \begin{array}{c}
   \text{Formula IV} \\
   \end{array}
   \]

   wherein
   
   1. \( R^1 \) is phenyl,
   2. \( R^2 \) is hydrogen or amino protecting groups,
   3. \( R^3 \) is secondary or tertiary lower alkyl and
   4. \( X \) is chlorine, bromine, fluorine or iodine.

2. The process according to claim 1 wherein the reaction is performed in presence of base and organic solvent.
A process for preparation of threo-3,4-epoxy-2-amino-1-substituted butane derivative represented by Formula I:

Formula I

which comprises

a) reacting compound of Formula III or salt thereof

Formula III

with active ester of acid of Formula IV

Formula IV

to produce 4-halo-3-hydroxy-2-amino-1-substituted butane derivative of

Formula II

b) treating compound of Formula II produced in step a) with base
c) isolating threo-3,4-epoxy-2-amino-1-substituted butane derivative (I) from the reaction mixture of step b)

wherein
R\(^1\) is phenyl,
R\(^2\) is hydrogen or amino protecting groups,
R\(^3\) is secondary or tertiary lower alkyl and
X is chlorine, bromine, fluorine or iodine.

4. The process according to claim 3 wherein the step a) reaction is performed in
presence of base and organic solvent.

5. The process according to claim 1 or 3 wherein active ester of acid of Formula IV is
prepared by reacting the acid with coupling agent selected from the group
comprising of O-(1,2-dihydro-2-oxo-1-pyridyl)-N,N,N\(^1\),N\(^1\)-tetramethyluronium-tetrafluoro-borate (TPTU), 1-hydroxybenzotriazole (HOBT) and N-ethyl-N'
dimethylaminopropyl carbodiimide (EDC).

6. The process according to claim 1 or 3 wherein the active ester is represented by
general Formula V

\[
R^2\text{NH} \quad \text{O} \quad N\quad N
\]
\[
\text{R}^3 \quad \text{O} \quad \text{N} \quad \text{N} \quad \text{N} \quad \text{R}^2 \quad \text{O} \quad \text{N} \quad \text{N} \quad \text{N}
\]

Formula V

7. The process according to claim 3 wherein the step b) reaction is performed in
presence of polar organic solvent optionally with water.

8. A process for the preparation of methyl [(2S)-1-{[(2S,3R)-4-chloro-3-hydroxy-1-
phenylbutan-2-yl]amino}-3,3-dimethyl-1-oxobutan-2-yl]carbamate represented by
Formula VI

\[
\text{H}_2\text{C} \quad \text{O} \quad \text{C} \quad \text{NH} \quad \text{OH} \quad \text{Cl}
\]
\[
\text{H}_2\text{C} \quad \text{O} \quad \text{NH} \quad \text{O} \quad \text{H} \quad \text{Cl}
\]

Formula VI
which comprises reacting (2S,3R)-2-amino-4-chloro-l-phenylbutan-3-ol represented by Formula VII or salt thereof

\[
\begin{align*}
\text{Formula VII} \\
\end{align*}
\]

with an active ester of (2S)-2-[(methoxycarbonyl)amino]-3,3-dimethylbutanoic acid represented by Formula VIII.

\[
\begin{align*}
\text{Formula VIII} \\
\end{align*}
\]

The process according to claim 8 wherein the reaction is performed in presence of base and organic solvent.

A process for the preparation of methyl [(2S)-3,3-dimethyl-l-[(1S)-l-[(2R)-oxiran-2-yl]-2-phenylethyl]amino]-l-oxobutan-2-yl]carbamate represented by Formula X:

\[
\begin{align*}
\text{Formula X} \\
\end{align*}
\]

which comprises

a) reacting (2S,3R)-2-amino-4-chloro-l-phenylbutan-3-ol represented by Formula VII or salt thereof
with an active ester of (2S)-2-[(methoxycarbonyl)amino]-3,3-
dimethylbutanoic acid represented by Formula VIII

to produce methyl [(2S)-1-[(2S,3R)-4-chloro-3-hydroxy-1-phenylbutan-2-
yl]amino]-3,3-dimethyl-1-oxobutan-2-yl]carbamate represented by

Formulas a) b) c)

11. The process according to claim 10 wherein the step a) reaction is performed in
presence of base and organic solvent.
12. The process according to claim 8 or 10 wherein active ester of acid of Formula
VIII is prepared by reacting the acid with coupling agent selected from the group
comprising of O-(1,2-dihydro-2-oxo-1-pyridyl)-N,N,N\textsuperscript{1},N\textsuperscript{-}tetramethyluronium-tetrafluoro-borate (TPTU), 1-hydroxybenzotriazole (HOBT) and N-ethyl-N\textsuperscript{-}dimethylaminopropyl carbodiimide (EDC).

13. The process according to claim 8 or 10 wherein the active ester is represented by Formula IX

![Formula IX](image)

14. The process according to claim 10 wherein the step b) reaction is performed in presence of polar organic solvent optionally with water.

15. A threo-4-halo-3-hydroxy-2-amino-1-substituted butane compound represented by general Formula II

![Formula II](image)

wherein

R\textsuperscript{1} is phenyl,

R\textsuperscript{2} is hydrogen or amino protecting groups,

R\textsuperscript{3} is secondary or tertiary lower alkyl and

X is chlorine, bromine, fluorine or iodine.

16. The compound according to claim 15 wherein the compound is methyl \{(2S)-I-\{(2S,3R)-4-chloro-3-hydroxy-1-phenylbutan-2-yl\}amino\}-3,3-dimethyl-1-oxobutan-2-yl\}carbamate represented by Formula VI
17. Use of compound of Formula II or VI for the preparation of atazanavir or salt thereof.

18. Use of compound of Formula I or X for the preparation of atazanavir or salt thereof.
**INTERNATIONAL SEARCH REPORT**

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C269/06 C07D213/42 C07D303/36 C07C271/22

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

B. RELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C C07D

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

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>Y</td>
<td>page 3821; compounds 3A-G</td>
<td>3-18</td>
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<tr>
<td>Y</td>
<td>page 136</td>
<td>3-18</td>
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Further documents are listed in the continuation of Box C.

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| X        | See patent family annex. | |

Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
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- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search: 6 August 2009

Date of mailing of the international search report: 11/09/2009

Name and mailing address of the ISA/ European Patent Office, P.B. 5816 Patentlaan 2 NL - 2280 HV Rijswijk, Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

Authorized officer: Steendijk, Martin

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<td>US 6 300 519 B (FASSLER ALEXANDER [GB] ET AL) 9 October 2001 (2001-10-09) cited in the application example 46</td>
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