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[Continued on next page]

(54) Title: NOVEL PROCESS FOR THE PREPARATION OF SACUBITRIL AND ITS INTERMEDIATES

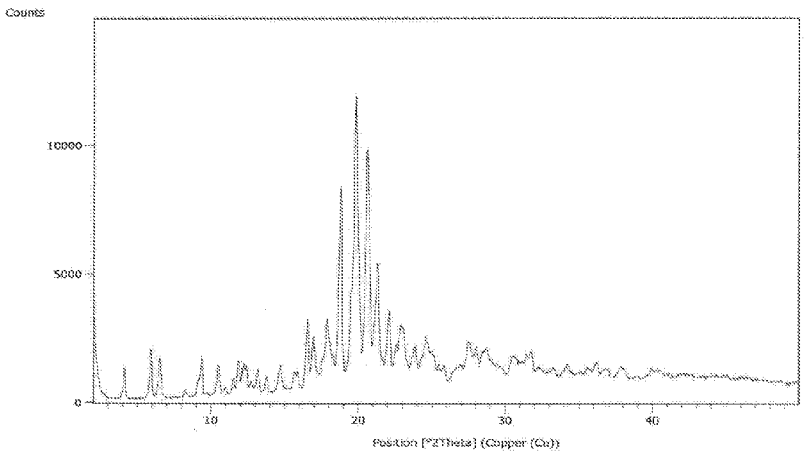

Figure 1- illustrates the powder X-ray diffraction pattern of crystalline Sacubitril.

(57) Abstract: A process for the preparation of sacubitril and its intermediates is disclosed. By practicing the methods disclosed herein, a solid form of sacubitril may be generated. A crystalline form of sacubitril is also disclosed.

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NOVEL PROCESS FOR THE PREPARATION OF SACUBITRIL AND ITS INTERMEDIATES

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of Indian provisional patent application no. 902/CHE/2015 filed on February 25, 2015, which is hereby incorporated by reference in its entirety.

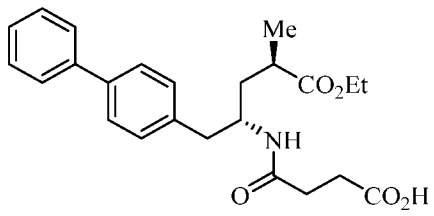
BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present disclosure relates generally to a process for the preparation of pharmaceutical active ingredients and more specifically tosacubitril. Intermediates formed during the process for preparing sacubitril are also disclosed. The present invention further relates to crystalline sacubitril.

BACKGROUND OF THE INVENTION

Sacubitril is chemically known as 3-[(1S,3R)-1-[(biphenyl-4-yl) methyl]-3-ethoxycarbonyl-1-butylcarbamoyl] propionic acid and has the structure shown in Formula-I. Sacubitril is an inhibitor of neprilysin and is often included and administered with valsartan. A combination of sacubitril and valsartanis marketed as ENTRESTO® by Novartis pharmaceuticals and is indicated for the treatment of heart failure.



Formula-I

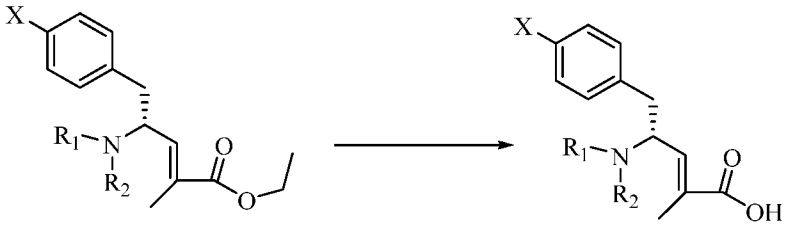
Sacubitril and processes for the preparation thereof aredisclosed in U.S. Patent No.5,217,996. International patent publications WO2008083967, WO2012025501, and WO2012025502 also disclose processes for the preparation of sacubitril.

The present invention provides a process for the preparation of sacubitril as well as intermediates formed during the preparation of sacubitril.

SUMMARY OF THE INVENTION

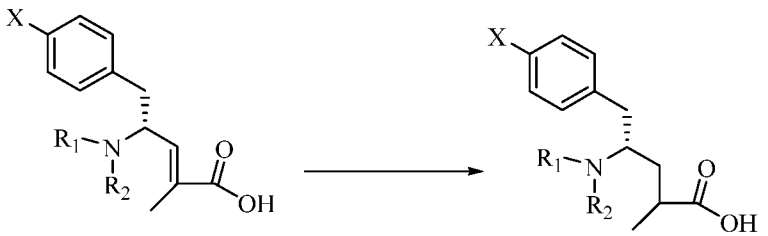
One aspect of the present invention provides a process for the preparation of sacubitril, which may be carried out by the following steps:

a) hydrolyzing Formula-VIII in the presence of a base and a solvent to prepareFormula-XI;



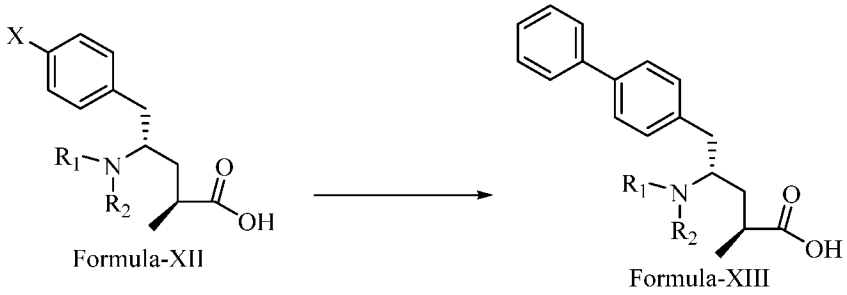
Formula-VIII Formula-XI

b) reducing Formula-XI to prepare Formula-XII;

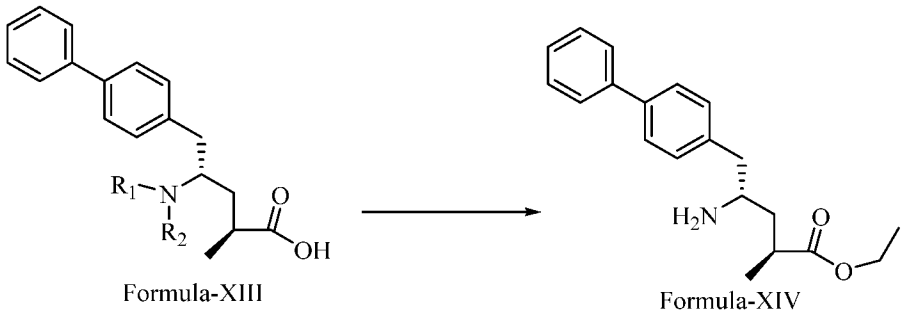


Formula-XI Formula-XII

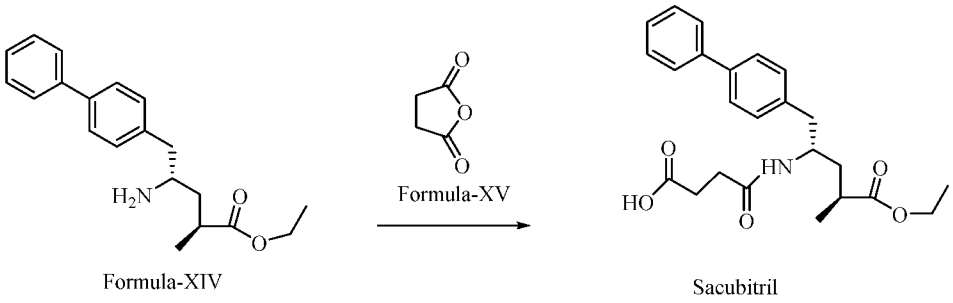
c) converting Formula-XII into Formula-XIII;



d) converting Formula-XIII into Formula-XIV; and



e) reacting Formula-XIV with Formula-XV to get sacubitril



Within the context of this embodiment, "R_1" and "R_2" are independently hydrogen or an amine protecting group and "X" is a halide selected from the group consisting of -F, -Cl, -Br, and -I.

Within the context of this embodiment, the base used in the hydrolyzing step may be an organic base or an inorganic base. Examples of suitable inorganic basesinclude alkaline metal hydroxides, alkaline metal bicarbonates, alkaline metal carbonates, and alkaline alkoxides. Examples of suitable alkaline metal hydroxide include lithium hydroxide, sodium hydroxide, and potassium hydroxide.

Within the context of this embodiment, the solvent used in the hydrolyzing step may an alcohol solvent, an ethereal solvent, or mixtures thereof.

Examples of suitable alcohol solventsinclude methanol, ethanol, n-propanol, isopropanol, and mixtures thereof.

Within the context of this embodiment, the conversion ofFormula-XII into Formula-XIII may be carried out in the presence of phenylboronic acid, a metal catalyst, and a solvent.

Examples of suitable metal catalysts include tetrakis(triphenylphosphine)palladium(0), bis(triphenylphosphine)palladium(II) dichloride, bis(dibenzylideneacetone) palladium(0)tris(dibenzylideneacetone)palladium(0), palladium(II) acetate, copper, cuprous bromide, cuprous iodide, and (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphtalene (rac-BINAP). The solvent may bean ethereal solvent, a hydrocarbon solvent, water, or mixtures thereof.

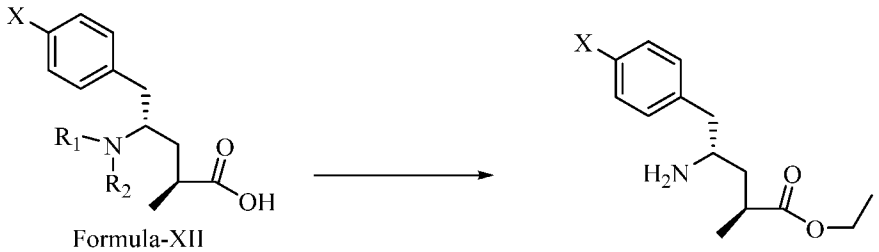
Within the context of this embodiment, Formula-XIII may be converted into Formula-XIV or its salt by esterification of the carboxylic acid group and deprotection of the amine. The esterification reaction may be carried out in the presence of a halogenation reagent and an alcohol solvent.

The halogenation reagent may be, for example, phosphorous oxychloride, phosphorous pentachloride, and thionyl chloride. In some useful embodiments, the alcohol solvent is ethanol.

Within the context of this embodiment, Formula-XIV may be optionally converted into a salt form of Formula-XIV.

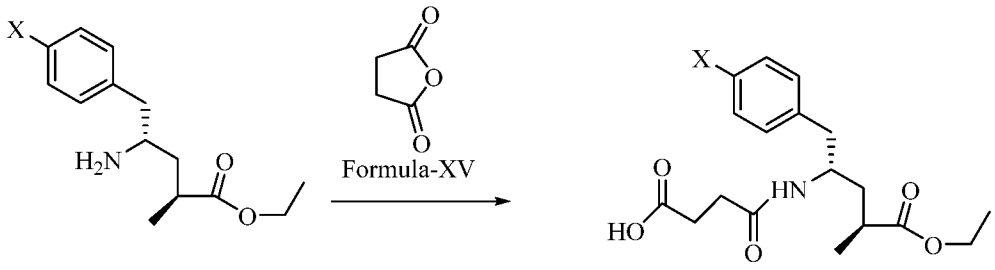
Another aspect of the present invention provides a process for the preparation of sacubitril,which may include the following steps:

a) converting Formula-XII into Formula-XVII;



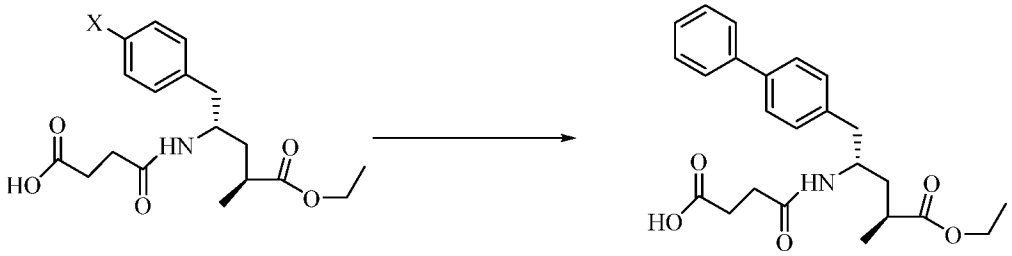
Formula-XII Formula-XVII

b) reacting Formula-XVII with Formula-XV to get Formula-XVI; and



Formula-XVII Formula-XVI

c) converting Formula-XVI into sacubitril



Formula-XVI Sacubitril

Within the context of this embodiment, "R_1" and "R_2" are independently hydrogen or an amine protecting group and "X" is a halide is -F, -Cl, -Br, and -I.

Within the context of this embodiment, Formula-XII may be converted to Formula-XIII by esterification of the acid group and deprotection of the amine group. The esterification reaction may be carried out in the presence of a halogenation reagent and an alcoholsolvent.

Examples of suitable halogenation reagent includephosphorous oxychloride, phosphorous pentachloride, and thionyl chloride. In some embodiments, the alcohol solvent is ethanol.

Within the context of this embedment, the reacting ofFormula-XVII with Formula-XV may be carried out in the presence of a base and a halogenated solvent.

The base may be an inorganic base or an organic base.Examples of particularly useful organic basesinclude pyridine, triethylamine, and N,N-diisopropylethylamine.

The halogenated solvent may be, for example, dichloromethane, trichloroethylene, carbon tetrachloride, methyl chloroform, or mixtures thereof.

Within the context of this embodiment, the step of converting of Formula-XVI into sacubitrilmay be carried out in the presence of phenylboronic acid, a metal catalyst, and a solvent.

Examples of suitable metal catalysts include tetrakis(triphenylphosphine)palladium(0), bis(triphenylphosphine)palladium(II) dichloride, bis(dibenzylideneacetone) palladium(0)tris(dibenzylideneacetone)palladium(0), palladium(II) acetate, copper, cuprous bromide, cuprous iodide, and (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphtalene (rac-BINAP).

Examples of suitablesolventsinclude ethereal solvents, hydrocarbon solvents, water, and mixtures thereof.

Within the context of the present embodiment, Formula-XVII may be converted into a salt form of Formula-XVII.

Another aspect of the present invention provides solid sacubitril, which, may, in some embodiments be in crystalline form.

Within the context of the invention, solid crystalline sacubitril may be characterized bya powder X-ray diffraction pattern having significant peaks at 18.8, 19.4, 19.8, 20.6, and 21.3 (±) 0.2° 2-theta. Solid crystalline sacubitrilmay befurther characterized by the powder X-ray diffraction pattern in Figure 1.

BRIEF DESCRIPTION OF THE DRAWINGS

Further aspects of the present disclosure together with additional features contributing thereto and advantages accruing there from will be apparent from the following description of embodiments of the disclosure which are shown in the accompanying drawing figures wherein:

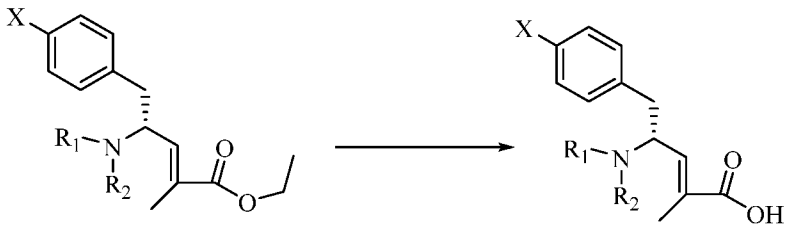
Figure 1isa powder X-ray diffraction pattern of crystalline sacubitril.

DETAILED DESCRIPTION OF THE INVENTION

One aspect of the present invention provides processes for the preparation of sacubitril.

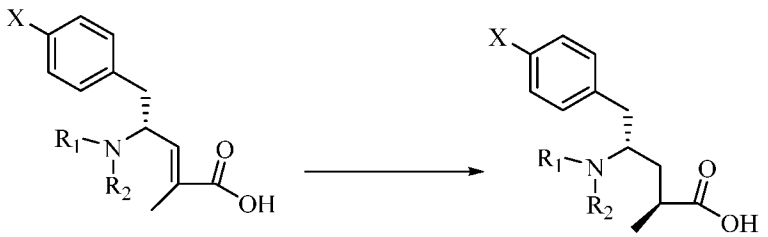
One embodiment provides a method for the preparation of Formula-XII, which may be carried out by the following steps:

a) hydrolyzing Formula-VIII into Formula-XI; and



Formula-VIII Formula-XI

b) reducing Formula-XI into Formula-XII



Formula-XI Formula-XII

Within the context of this embodiment, the "R_1" and "R_2" moieties are independently hydrogen or an amine protecting group.

Within the context of this embodiment, the "X" moiety is a halo group, for example, -F, -Cl, -Br, or -I.

Within the context of the present invention, the term"amine protecting group"is well known and familiar to one of skill in the art. Suitable protecting groups as well as conditions for use and removal can be found in standard works, for example, J. F. W. McOmie, "Protective Groups in Organic Chemistry", Plenum Press, London and New York 1973, in T. W. Greene and P. G. M. Wuts, "Protective Groups in Organic Synthesis", Third edition, Wiley, New York 1999, in "The Peptides"; Volume 3 (editors: E. Gross and J. Meienhofer), Academic Press, London and New York 1981 , in "Methoden der organischenChemie", Houben-Weyl, 4th edition, Vol. 15/1, Georg ThiemeVerlag, Stuttgart 1974, in H.-D. Jakubke and H. Jescheit, "Aminosauren, Peptide, Proteine", VerlagChemie, Weinheim, Deerfield Beach, and Basel 1982, and or in Jochen Lehmann, "Chemie der Kohlenhydrate: Monosaccharide und Derivate", Georg ThiemeVerlag, Stuttgart 1974.

Amine protecting groups include, for example, $-R^P$, $=R^Q$, $-C(O)R^0$, $-C(O)OR^0$,$-S(O)_2R^0$, and 2-nitrophenylsulfenyl, wherein

R^P is a $-C(R^{P1})_3$, wherein each R^{P1} is hydrogen or optionally substituted aryl, provided that at least one R^{P1} is not hydrogen;

R^Q is $=C(H)-R^0$; and

R^0 is hydrogen, C_{1-10} alkyl, C_{2-10} alkenyl, C_{1-10} haloalkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl, wherein each alkyl, aryl, and heteroaryl group is optionally substituted.

"Optionally substituted" as used herein means the reference group may be substituted by one or more groups (e.g., 1 to 5, or 1 to 3, or 1 to 2 groups or 1 group) that are each independently halo, alkyl, alkoxy, nitro, cyano, tri(C_{1-3}alkyl)silyl (e.g., trimethylsilyl).

Particular examples of amine protecting groups include, carbonyls (e.g., methyl carbamate, 9-fluorenylmethyoxycarbonyl (Fmoc), trichloroethoxycarbonyl (Troc), tert-butyloxycarbonyl (BOC), 2-trimethylsilylethyloxycarbonyl (Teoc), allyloxycarbonyl (Alloc), p-

methoxybenzylcarbonyl (Moz), and carboxybenzyl (Cbz)), sulfonyls (e.g., p-toluenesufonyl (Ts), trimethylsilylethanesulfoyl (Ses), tert-butylsulfonyl (Bus), 4-methoxyphenylsulfonyl, 4-nitrobenzenesulfonyl (nosyl)), trityl (trt), benzyl (Bn), 3,4-dimethyoxybenzyl (Dmpm), p-methoxybenzyl (PMB), p-methoxyphenyl (PMP), acetyl (Ac), formyl, trifluoroacetyl (Tfa), benzoyl (Bz), and2-nitrophenylsulfenyl (Nps).

The term “alkenyl” as used herein, means a straight or branched chain hydrocarbon containing from 2 to 10 carbons, unless otherwise specified, and containing at least one carbon-carbon double bond. Representative examples of alkenyl include, but are not limited to, ethenyl, 2-propenyl, 2-methyl-2-propenyl, 3-butenyl, 4-pentenyl, 5-hexenyl, 2-heptenyl, 2-methyl-l-heptenyl, 3-decenyl, and 3,7-dimethylocta-2,6-dienyl.

The term "alkoxy" as used herein, means an alkyl group, as defined herein, appended to the parent molecular moiety through an oxygen atom. Representative examples of alkoxy include, but are not limited to, methoxy, ethoxy, propoxy, 2-propoxy, butoxy, tert-butoxy, pentyloxy, and hexyloxy.

The term “alkyl” as used herein, means a straight or branched chain hydrocarbon containing from 1 to 10 carbon atoms, unless otherwise specified. Representative examples of alkyl include, but are not limited to, methyl, ethyl, n-propyl, iso-propyl, n-butyl, sec-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, neopentyl, n-hexyl, 3-methylhexyl, 2,2-dimethylpentyl, 2,3-dimethylpentyl, n-heptyl, n-octyl, n-nonyl, and n-decyl.

The term “aryl” as used herein, means a monocyclic (i.e., phenyl), bicyclic, or tricyclic ring fused or bridged system containing at least one phenyl ring. Non-phenyl rings that are part of a bicyclic or tricyclic ring system may be fully or partially saturated, may contain one or more heteroatoms, each selected from N, S, and O, and may be optionally substituted with one or two oxo and/or thia groups. Examples of aryl groups include phenyl, napthyl, anthracenyl, and fluorenyl.

The term “arylalkyl” as used herein, means an aryl group, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of

arylalkyl include, but are not limited to, benzyl, 2-phenylethyl, 3-phenylpropyl, fluorenylmethyl and 2-naphth-2-ylethyl.

The term "halo" or "halogen" as used herein means -F, -Cl, -Br, or -I.

The term "haloalkyl" as used herein, means at least one halogen, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of haloalkyl include, but are not limited to, chloromethyl, 2-fluoroethyl, trifluoromethyl, pentafluoroethyl, perfluorononyl, and 2-chloro-3-fluoropentyl.

The term "heteroaryl" as used herein, means a monocyclic, bicyclic, or tricyclic ring system containing at least one heteroaromatic ring. Any additional rings that are part of a bicyclic or tricyclic ring system may be fully or partially saturated or may be aromatic rings, and each may optionally contain one or more heteroatoms, each selected from N, S, and O. Representative examples of monocyclic and bicyclicheteroaryl include, but are not limited to, furyl, imidazolyl, isoxazolyl, isothiazolyl, oxadiazolyl, oxazolyl, pyridinyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyrazolyl, pyrrolyl, tetrazolyl, thiadiazolyl, thiazolyl, thienyl, triazolyl,triazinyl. benzimidazolyl, benzofuranyl, benzothienyl, benzoxadiazolyl, benzoxathiadiazolyl, benzothiazolyl, cinnolinyl, dihydroquinolinyl, furopyridinyl, indazolyl, indolyl, isoquinolinyl, naphthyridinyl, quinolinyl, purinyl, and tetrahydroquinolin-yl.

The term "heteroarylalkyl" as used herein, means a heteroaryl, as defined herein, appended to the parent molecular moiety through an alkyl group, as defined herein. Representative examples of heteroarylalkyl include, but are not limited to, furylmethyl, imidazolylmethyl, pyridinylethyl, pyridinylmethyl, pyrimidinylmethyl, and thienylmethyl.

The term "oxo" as used herein means a =O group. The term "thia" as used herein means a =S group.

Within the context of this embodiment, examples of particularly suitable amine protecting groups includecarboxybenzyl (Cbz), tert-butyloxycarbonyl (BOC), benzyl, and trityl groups.

According to this embodiment, Formula-VIII may be hydrolyzed into Formula-XI. This reaction may be carried out in the presence of an inorganic base and a solvent. Examples of inorganic basesinclude alkaline metal hydroxides, alkaline metal bicarbonates, alkaline metal carbonates, and alkaline alkoxides. Examples of alkaline metal hydroxides include lithium hydroxide, sodium hydroxide, and potassium hydroxide. Examples of alkaline metal bicarbonates include sodium bicarbonate and potassium bicarbonate. Examples of alkaline metal carbonates include sodium carbonate, potassium carbonate, and cesium carbonate. Examples of alkaline alkoxides include sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, and potassium propoxide.

Within the context of this embodiment, the solvent may be, for example, an alcohol solvent, an ethereal solvent, or mixtures thereof. Examples of suitable alcohol solvents include methanol, ethanol, n-propanol,isopropanol, and mixtures thereof. Examples of suitable ethereal solvent include tetrahydrofuran, diethyl ether, 1,4-dioxane, methyl tert-butyl ether, and mixtures thereof.

Next, Formula-XImay bereduced to Formula-XII. Within the context of this embodiment, this may be carried out in the presence of a reducing agent, a chiral ligand, and a solvent. Examples of suitable reducing agents includeborane, sodium borohydride, lithiumborohydride, sodiumcyanoborohydride, sodiumtriacetoxyborohydride, bis(dibenzylideneacetone) palladium(0),tris(dibenzylideneacetone)palladium(0),palladium(II) acetate, copper, cuprous bromide, cuprous iodide, and (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphtalene (rac-BINAP), and diiodo(p-cymene)ruthenium(II) dimer. In some embodiments, diiodo(p-cymene)ruthenium(II) dimer is used as a reducing agent.

Examples of suitable chiral ligandsincludeMandyphos ligands, Walphos ligands, Josiphosligands, and Solphos ligands. In some embodiments, Mandyphos ligands are used as chiral ligands.

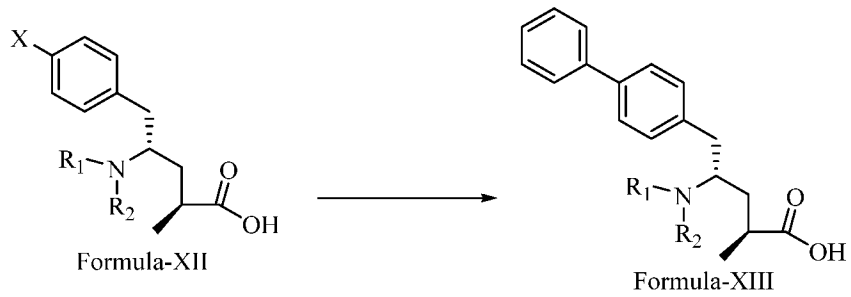
Examples of suitable solventsincludealcoholsolvents, ethereal solvents, and mixtures thereof. Examples of alcohol solventsinclude methanol, ethanol, n-propanol, isopropanol, and mixtures thereof. Examples of ethereal solventsincludetetrahydrofuran, diethyl ether, 1,4-dioxane, methyl tert-butyl ether, and mixtures thereof. In some embodiments, methanol is used as a solvent.

Within the context of the present invention, Formula-XII may be formed as an intermediate in the preparation of sacubitril.

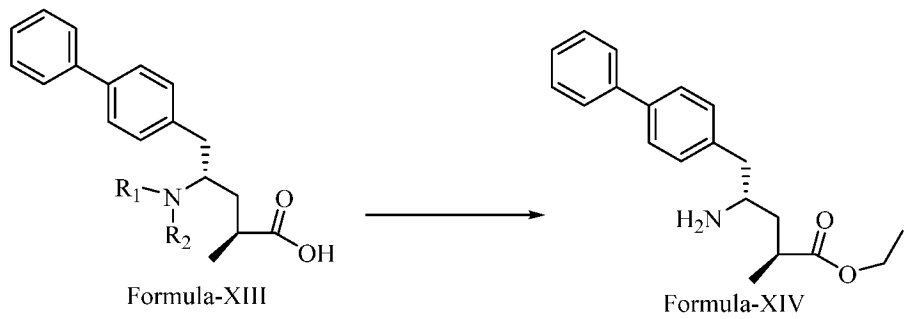
Another aspect of the present invention provides methods for converting Formula-XII to sacubitril.

In one embodiment, Formula-XII can be converted to sacubitril by the following steps:

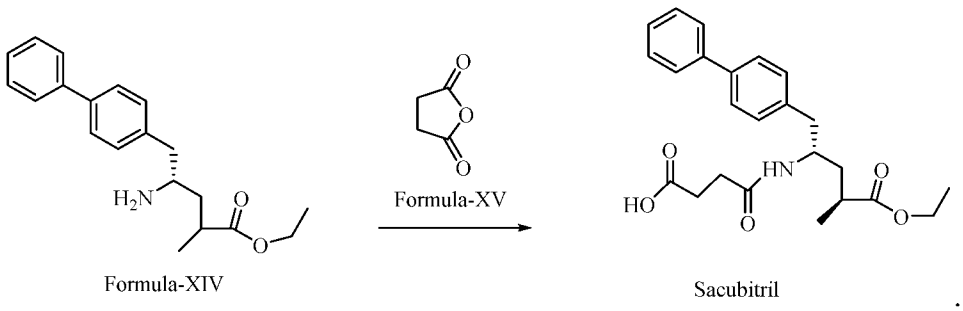
a) converting Formula-XII into Formula-XIII;



b) converting Formula-XIII into Formula-XIV or asalt thereof; and



c) reacting Formula-XIV with Formula-XV to get sacubitril



Within the context of this embodiment, the "R_1" and "R_2" moieties are independently hydrogen or an amine protecting group.

As noted above, "amine protecting groups" are well known in the art and one of skill in the art will be familiar with a variety of amine protecting groups that will be suitable in this embodiment. For example, in some embodiments, a carboxybenzyl (Cbz), atert-butyloxycarbonyl (BOC), a benzyl group, or a trityl group is used as a protecting group.

Within the context of this embodiment, the "X" moiety is a halo group, for example, -F, -Cl, -Br, or -I.

According to this embodiment, Formula-XIImay be converted into Formula-XIII. This may be carried out by reacting Formula-XII with phenylboronic acid in the presence of a metal catalyst, a buffer, anda solvent. Examples of suitable metal catalystsincludetetrakis(triphenylphosphine)palladium(0),bis(triphenylphosphine)palladium(II) dichloride, bis(dibenzylideneacetone)palladium(0)tris(dibenzylideneacetone)palladium(0), palladium(II) acetate, copper, cuprous bromide, cuprous iodide, and (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphtalene (rac-BINAP). In some embodiments, palladium acetate was used as a metal catalyst.

Examples of suitable buffersinclude phosphate bufferssuch as sodiumphosphate buffers and potassium phosphate buffers. One of skill in the art will be familiar with the use and preparation of these and other well-known suitable buffer solutions that would be useful in the context of this step of this embodiment.

The solvent may be, for example, an ethereal solvent, a hydrocarbon solvent, water, or mixtures thereof. Examples of suitable ethereal solvents include1,4-dioxane, diethyl ether, ethyl tert-butyl ether, methyl tert-butyl ether, tetrahydrofuran, and mixtures thereof. Examples of suitable hydrocarbon solvents includetoluene, xylene,and mixtures thereof. In some embodiments, water was used as a solvent.

Within the context of this embodiment, Formula-XIIImay then be converted into Formula-XIV byesterification of the carboxylic acid moietyand deprotection of the amine group. The

esterification of the carboxylic acid moiety may be carried out by procedures well known in art. For example, the carboxylic acid group may first be converted to an acidhalide through a halogenation reaction and the acid halide may then be reacted with ethanol. Halogenation may be carried out using well-known reagents such as phosphorous oxychloride, phosphorous pentachloride,or thionyl chloride.

Deprotection of the amine group may also be carried out by methods well known to one of skill in the art, who will be familiar with and knowledgeable regarding suitable deprotection conditions for the variety of protecting groups that may be used within the context of the present embodiment. For example, many protecting groups may be removed by hydrogenolysis or through the use of an acid or a base. In some embodiments, deprotection may occur during esterification, for example, while halogenating using reagents such as phosphorous oxychloride, phosphorous pentachloride,or thionyl chloride.

Next, Formula-XIV may be optionally converted into a salt of Formula-XIV.Conversion of Formula-XIV into its salt may increase the purity of the product formed which, in turn, may increase yields and purity of subsequent products of subsequent reactions, including the final sacubitril product. Methods for converting compounds into their salt forms are well known in the art, and may be carried out, for example, by reacting a free base moiety on a molecule with a suitable acid reagent.

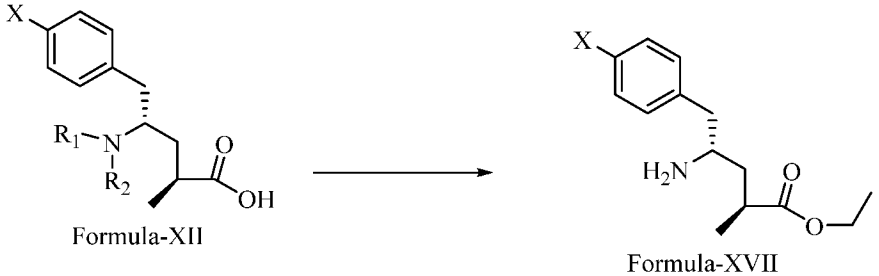
For example, Formula-XIV can be reacted to obtain a salt of Formula-XIV. In some embodiments, the hydrochloride salt of Formula-XIV is formed.

According to this embodiment, Formula-XIV, or a salt thereof,may then bereacted with Formula-XV to get sacubitril. Methods for obtaining sacubitril from Formula-XIV are well-known in the art, for example,by following procedures disclosed in US 5,217,996, which is hereby incorporated by reference. Within the context of this embodiment, this reaction may becarried out in the presence of a base and a halogenated solvent. The base may be an organic base or an inorganic base. Examples of suitable inorganic basesinclude alkaline metal hydroxides, alkaline metal bicarbonates, alkaline metal carbonates, and alkaline alkoxides. Examples of alkaline metal hydroxides include sodium hydroxide and potassium hydroxide. Examples of alkaline

metal bicarbonates include sodium bicarbonate and potassium bicarbonate. Examples of alkaline metal carbonates include sodium carbonate, potassium carbonate, and cesium carbonate. Examples of alkaline alkoxides include sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium propoxide, sodium tert-butoxide, and potassium tert-butoxide. Examples of suitable organic basesinclude pyridine, triethylamine, and N,N-diisopropylethylamine.Examplesof suitable halogenated solvent includedichloromethane, trichloroethylene, carbon tetrachloride, methyl chloroform, and mixtures thereof.

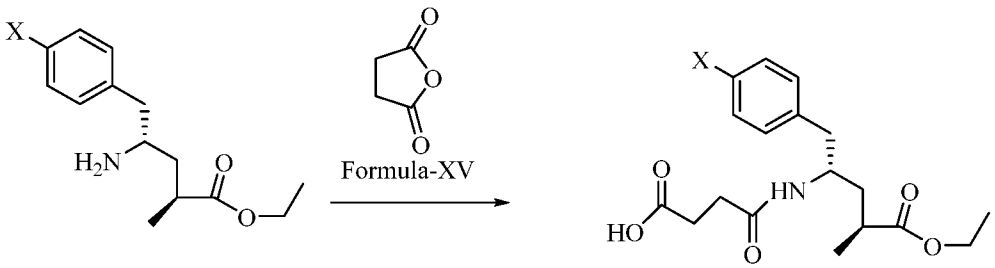
In another embodiment, Formula-XII may be converted to sacubitrilby the following steps:

a) converting Formula-XII into Formula-XVII or its salt;



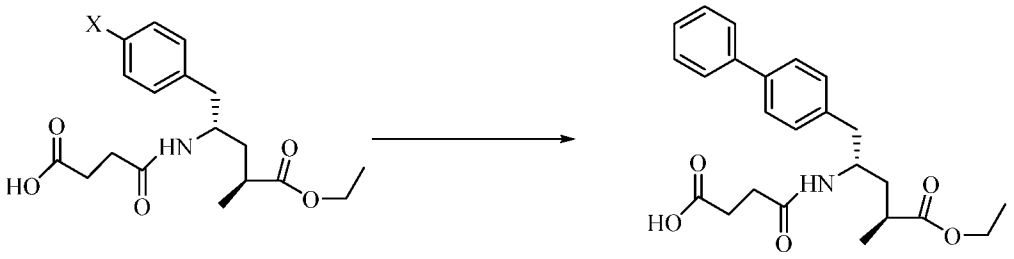
Formula-XII Formula-XVII

b) reacting Formula-XVII with Formula-XV to get Formula-XVI; and



Formula-XVII Formula-XVI

c) converting Formula-XVI into sacubitril



Formula-XVI

Sacubitril

Within the context of this embodiment, the "R_1" and "R_2" moieties are independently hydrogen or an amine protecting group and the "X" moiety is a halo group, for example, -F, -Cl, -Br, or -I. As noted above, "amine protecting groups" are well known in the art and one of skill in the art will be familiar with a variety of amine protecting groups that will be suitable in this embodiment. For example, in some embodiments, a carboxybenzyl (Cbz), atert-butyloxycarbonyl (BOC), a benzyl group, or a trityl group is used as a protecting group.

According to this embodiment, Formula-XII may be converted into Formula-XVIIby esterification of the carboxylic acid moiety and deprotection of the amine group. The esterification of the carboxylic acid moiety may be carried out by procedures well known in art. For example, the carboxylic acid group may first be converted to an acid halide through a halogenation reaction and the acid halide may then be reacted with ethanol. Halogenation may be carried out using well-known reagents such as phosphorous oxychloride, phosphorous pentachloride, or thionyl chloride.

Deprotection of the amine group may also be carried out by methods well known to one of skill in the art, who will be familiar with and knowledgeable regarding suitable deprotection conditions for the variety of protecting groups that may be used within the context of the present embodiment. For example, many protecting groups may be removed by hydrogenolysis or through the use of an acid or a base. In some embodiments, deprotection may occur during esterification, for example, while halogenating using reagents such as phosphorous oxychloride, phosphorous pentachloride, or thionyl chloride.

Within the context of this embodiment, Formula-XVII may be optionally converted into a salt of Formula-XVII.Conversion of Formula-XVII into a salt may increase the purity of the product

formed which, in turn, may increase yields and purity of subsequent products of subsequent reactions, including the final sacubitril product. Methods for converting compounds into their salt forms are well known in the art, and may be carried out, for example, by reacting a free base moiety on a molecule with a suitable acid reagent.

Next, Formula-XVII, or a salt thereof,may be reacted with Formula-XV to get Formula-XVI. Within the context of this embodiment, this reaction may be carried outin the presence of a base and a halogenated solvent.

The base may be an organic base or an inorganic base. Examples of suitable inorganic basesinclude alkaline metal hydroxides, alkaline metal bicarbonates, alkaline metal carbonates, and alkaline alkoxides.Examples of alkaline metal hydroxides include sodium hydroxide and potassium hydroxide. Examples of alkaline metal bicarbonates include sodium bicarbonate and potassium bicarbonate. Examples of alkaline metal carbonates include sodium carbonate, potassium carbonate, and cesium carbonate. Examples of alkaline alkoxides include sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium propoxide, sodium tert-butoxide, and potassium tert-butoxide. Examples of suitable organic basesinclude pyridine, triethylamine, and N,N-diisopropylethylamine.In some embodiments, triethylamine is used as a base. Examples of suitable halogenated solvent includedichloromethane, trichloroethylene, carbon tetrachloride, methyl chloroform, and mixtures thereof.

Within the context of this embodiment, this reaction may be further carried out in the presence of a catalytic amount of 4-dimethylaminopyridine.

According to this embodiment, Formula-XVI may then be converted into sacubitril. This reaction may be carried out by reacting Formula-XVI with phenylboronic acid in the presence of a metal catalyst, a buffer, and a solvent. Examples of suitable metal catalyst include tetrakis(triphenylphosphine)palladium(0), bis(triphenylphosphine)palladium(II) dichloride, bis(dibenzylideneacetone)palladium(0)tris(dibenzylideneacetone)palladium(0), palladium(II) acetate, copper, cuprous bromide, cuprous iodide, and (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphtalene (rac-BINAP). In some embodiments, bis(triphenylphosphine)palladium(II) dichloride is used as a metal catalyst.

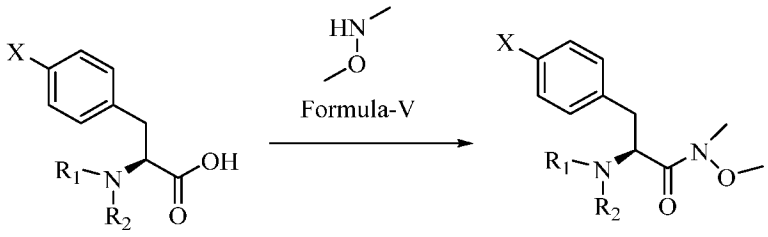
Examples of suitable buffersinclude phosphate buffers, for example, such as sodium phosphate buffers and potassium phosphate buffers. One of skill in the art will be familiar with the use and preparation of these and other well-known suitable buffer solutions that would be useful in the context of this step of this embodiment.

The solvent may be, for example, an ethereal solvent, a hydrocarbon solvent, water, or mixtures thereof. Examples of suitable ethereal solvents include1,4-dioxane, diethyl ether, ethyl tert-butyl ether, methyl tert-butyl ether, tetrahydrofuran, 1,2-dimethoxyethane, and mixtures thereof.Examples of suitable hydrocarbon solvents includetoluene, xylene, and mixtures thereof.

In some embodiments, a mixture of 1,2-dimethyoxyethane and water is used as a solvent.

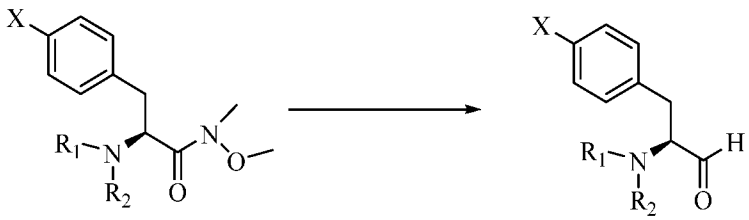
Another aspect of the present invention provides another method for the preparation of sacubitril, which may be carried out by the following steps:

a) reacting Formula-IV with Formula-V to get Formula-VI;



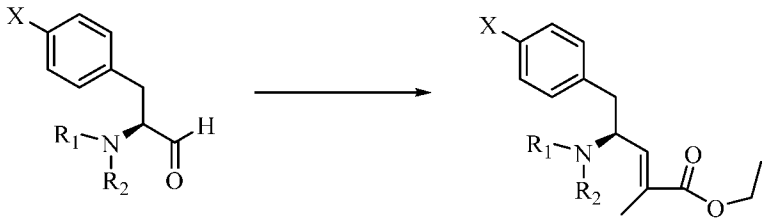
Formula-IV Formula-VI

b) converting Formula-VI to Formula-VIin the presence of a reducing agent;



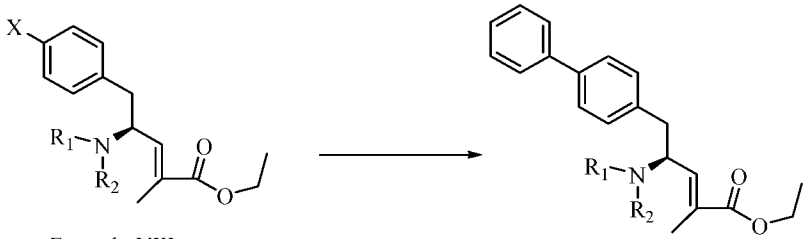
Formula-VI Formula-VII

c) converting Formula-VII into Formula-VIII;



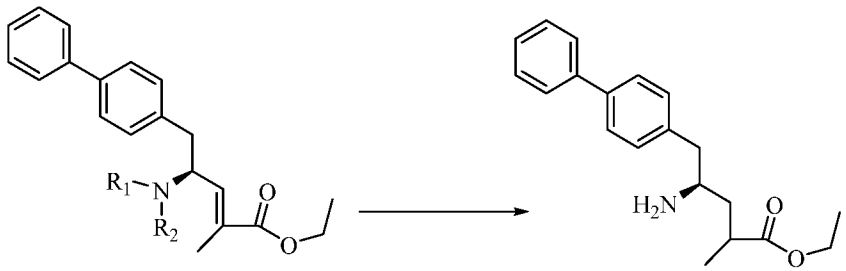
Formula- VII Formula-VIII

d) converting Formula-VIII into Formula-IX;



Formula-VIII Formula-IX

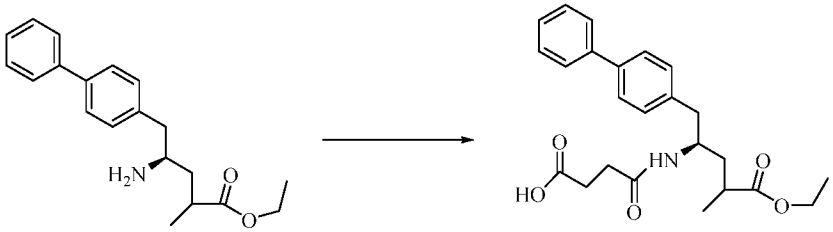
e) converting Formula-IX into Formula-X;



Formula-IX Formula-X

f) optionally increasing the chiral purity of Formula-X; and

g) convertingFormula-X into sacubitril.



Formula-X Sacubitril

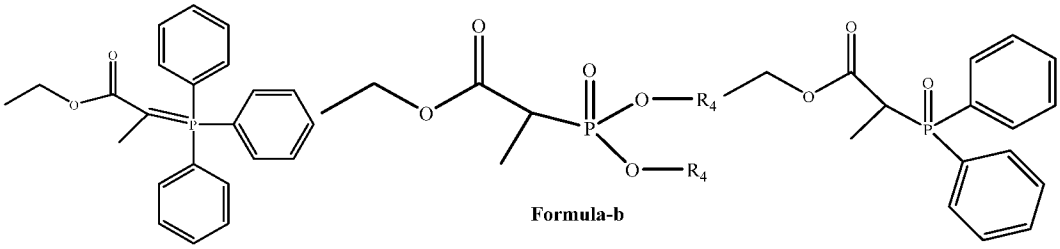
Within the context of this embodiment, the "R_1" and "R_2" moieties are independently hydrogen or an amine protecting group, as previously described above. Within the context of this embodiment, examples of suitable amine protecting groups include carboxybenzyl (Cbz), tert-butyloxycarbonyl (BOC), benzyl groups, and trityl groups.

Within the context of this embodiment, the "X" moiety is a halo group, for example, -F, -Cl, -Br, or -I.

According to this embodiment, Formula-IV may be reacted with Formula-V in the presence of a suitable reagent and a solventto get Formula-VI. Examples of suitable reagents include coupling agents such as 1,1'-carbonyldiimidazole, dicyclohexylcarbodiimide, and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimideHCl. The solvent may be, for example, dichloromethane, acetone, dimethylacetamide, dimethyl formamide, acetonitrile, tetrahydrofuran, toluene, ethyl acetate, or mixtures thereof. In some embodiments, 1,1'-carbonyldiimidazole is used to carry out this reaction and dimethyl formamide is used as a solvent.

Next,Formula-VI may be converted into Formula-VII in the presence of a reducing agent. Examples of suitable reducing agents include lithium aluminum hydride, sodium hydride, DIBAL-H, and sodium bis(2-methyoxyethoxy)aluminumhydride (vitride). The reaction may be carried out in the presence of a suitable solvent, for example, a hydrocarbon solvent. Examples of suitable hydrocarbon solvents includetoluene,ethers such as tetrahydrofuran and 1,4-dioxane, and mixtures thereof. In some embodiments, sodium bis(2-methyoxyethoxy)aluminumhydride is used as a reducing agent and toluene is used as a solvent.

According to this embodiment,Formula-VII may then beconverted toFormula-VIII. This may be carried out in the presence of a Wittig reagent and a suitable solvent. Examples of suitable Wittig reagentsinclude those shown below asFormula-a, Formula-b and Formula-c.



Formula-a

Formula-b

wherin R_4 is selected from alkyl and aryl

Formula-c

Examples of suitable solvents include dichloromethane, dimethylacetamide, dimethyl formamide, acetonitrile, tetrahydrofuran, and mixtures thereof.

Next, Formula-VIII may be converted into Formula-IX. This may be carried out by reacting Formula-VIII with phenylboronic acid in the presence of a metal catalyst, a base, and a suitable solvent. Examples of suitable metal catalystsuseful with the context of this embodiment include tetrakis(triphenylphosphine) palladium and bis(triphenylphosphine) palladium(II) dichloride. Examples of suitable solvents include ethereal solvents, hydrocarbon solvents, and mixtures thereof. Examples of suitable ethereal solvents include 1,4-dioxane, diethyl ether, ethyl tert-butyl ether, methyl tert-butyl ether, tetrahydrofuran, and mixtures thereof. Examples of suitable hydrocarbon solvents include toluene, xylene, and mixtures thereof. In some embodiments, bis(triphenylphosphine) palladium(II) dichloride is used as a metal catalyst and toluene is used as a solvent.

Examples of suitable basesinclude alkaline metal hydroxides, alkaline metal bicarbonates, alkaline metal carbonates, and alkaline alkoxides. Examples of alkaline metal hydroxides include sodium hydroxide and potassium hydroxide. Examples of alkaline metal bicarbonates include sodium bicarbonate and potassium bicarbonate. Examples of alkaline metal carbonates include sodium carbonate, potassium carbonate, and cesium carbonate. Examples of alkaline alkoxides include sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium propoxide, sodium tert-butoxide, and potassium tert-butoxide.

According to this embodiment, if R_1 and/or R_2 are amineprotecting groups, Formula-IX may then be converted to Formula-X by deprotecting of Formula-X, if necessary, and by reducing Formula-IX. If both R_1 and $R_2$are hydrogen, no deprotection is necessary. As noted before, the conditions required for deprotection of the amine group depend on the protecting group and one

of skill in the art will be familiar and recognize suitable conditions for carrying out this reaction. For example, Formula-IX (wherein R_1 and R_2 are benzyl) may be reduced and deprotectedusing a metal catalyst, such as Pd/C, in the presence of a hydrogen source and asolvent. Examples of suitable solventsinclude methanol, ethanol, isopropanol, ethyl acetate, isopropyl acetate, tetrahydrofuran, and mixtures thereof.

Next,the chiral purity of Formula-X may optionally be increased. This may be carried out byforming an acid addition salt of Formula-X. Within the context of this invention, this step may increase the purity of the "2S, 4R" enantiomer of Formula-X (where Formula-X is chemically named (2S, 4R)-ethyl 5-(biphenyl-4-yl)-4-(amino)-2-methylpentanoate). The conversion of Formula-X to an acid addition salt may be carried out by reacting Formula-X with an inorganic or an organic acid.Examples of suitable inorganic acids include hydrochloric acid andhydrobromic acid. Examples of suitable organic acids include acetic acid, fumaric acid, succinic acid, citric acid, mandelic acid, and tartaric acid.

According to this embodiment Formula-X may be further converted into sacubitril. This may be carried out by methods well-known in the art, for example, by those disclosed in US 5,217,996. For example,Formula-X may be reacted with succinic anhydride in the presence of a base and a halogenated solvent. The base may be an inorganic base oraninorganic base. Examples of suitable inorganic basesinclude alkaline metal hydroxides, alkaline metal bicarbonates, alkaline metal carbonates, and alkaline alkoxides. Examples of alkaline metal hydroxides include sodium hydroxide and potassium hydroxide. Examples of alkaline metal bicarbonates include sodium bicarbonate and potassium bicarbonate. Examples of alkaline metal carbonates include sodium carbonate, potassium carbonate, and cesium carbonate. Examples of alkaline alkoxides include sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium propoxide, sodium tert-butoxide, and potassium tert-butoxide. Examples of suitable organic basesinclude pyridine, triethylamine, and N,N-diisopropylethylamine. Examples of suitable halogenated solvent includedichloromethane, trichloroethylene, carbon tetrachloride, and methyl chloroform.

Prior art processes for the preparation of sacubitril result, such as those in US 5,217,996, provide a final sacubitril product as an oil. In contrast, by practicing the methods disclosed herein below,

sacubitril may be obtained as a solid. Thus, another aspect of the present invention provides a novel crystalline form of sacubitril.

The solid crystalline sacubitril prepared by methods disclosed herein be characterized by their powder X-ray diffraction (PXRD) pattern. Thus, the PXRD pattern of the crystalline sacubitrilobtained by methods disclosed herein was measured on a PANalyticalX'pert pro powder diffractometer equipped with goniometer of θ/2θ configuration and X'celerator detector. The Cu-anode X-ray tube was operated at 40kV and 30mA. The experiments were conducted over the 2θ range of 2.0°-50.0°, 0.030° step size and 50 seconds step time.

In one embodiment, crystalline sacubitril may be characterized by a PXRD pattern having characteristic peaks at 18.8, 19.4, 19.8, 20.6, and 21.3 (±) 0.2° 2-theta.

Crystalline sacubitril may be further characterized by powder X-ray diffraction having characteristic peaks at 16.5, 17.8, 18.8, 19.4, 19.8, 20.6, 21.3, 22.0, and 22.8 and 21.3 (±) 0.2° 2-theta.

The crystalline sacubitrilmaybe further characterized by the PXRD pattern as depicted in Figure 1.

Another aspect of the present invention provides processes for the preparation of crystallinesacubitril.

In one embodiment, crystalline sacubitril may be prepared by the following steps:

a) dissolving sacubitril in a solvent;
b) removing the solvent;
c) adding anon-polar solvent; and
d) isolatingcrystallinesacubitril.

According to this embodiment, sacubitril may be first dissolved in a solvent. Within the context of this embodiment, the sacubitril may be in any form, for example, an oil such as disclosed above.The solvent may be, for example, an alcohol solvent, a ketone solvent, anester solvent, a

nitrile solvent, or mixtures thereof. Examples of suitable alcohol solvents include methanol, ethanol, n-propanol, isopropanol, and mixtures thereof. Examples of suitable ketone solvents include acetone, methylethyl ketone, methylisobutyl ketone, and mixtures thereof. Examples of suitableester solvents include methyl acetate, ethyl acetate, isopropyl acetate,tert-butyl acetate, and mixtures thereof. A suitable nitrile solvent may be, for example, acetonitrile.

Next, the solvent may be removed. This may be carried out by methods well-known in the art, for example, by distillation or evaporation.

According to this embodiment, a non-polar solvent may then be added. The non-polar solvent may be, for example, an ether solvent, a hydrocarbon solvent, or mixtures thereof. Within the context of this embodiment, adding a non-polar solvent may cause a precipitate to form.

Examples of suitable ether solvent include tetrahydrofuran, diethyl ether, diisopropyl ether, 1,4-dioxane, methyl tert-butyl ether, and mixtures thereof. Examples of suitablehydrocarbon solvents include pentane, hexane,cyclohexane, and mixtures thereof.

Next, crystalline sacubitril may be isolated. This may be carried out by methods well-known in the art, for example, by filtering the solution and drying the obtained solid to result in crystalline sacubitril.

In another embodiment, crystalline sacubitril may be prepared by the following steps:

a) dissolving sacubitril in a polar solvent;
b) adding a non-polar solvent; and
c) isolating crystalline sacubitril.

According to this embodiment, sacubitril may be first dissolved in a polar solvent. Examples of suitable polar solvent include alcohol solvents, ketone solvents,ester solvents, and mixtures thereof.

Examples of suitable alcohol solvents include methanol, ethanol, n-propanol, isopropanol, and mixtures thereof. Examples of suitable ketone solvents include acetone, methylethyl ketone,

methylisobutyl ketone, and mixtures thereof. Examples of suitable ester solvents include methyl acetate, ethyl acetate, isopropyl acetate, tert-butyl acetate, and mixtures thereof.

According to this embodiment, a non-polar solvent may then be added. The non-polar solvent may be, for example, an ether solvent, a hydrocarbon solvent, or mixtures thereof.

Examples of suitable ether solvents include tetrahydrofuran, diethyl ether, diisopropyl ether, 1,4-dioxane, methyl tert-butyl ether, and mixtures thereof. Examples of suitable hydrocarbon solvents include pentane, hexane, cyclohexane, and mixtures thereof.

In some embodiments of the present invention, the non-polar solvent may optionally be added at an elevated temperature, for example, from about 35 °C to about 60 °C. In certain embodiments, the non-polar solvent is added at a temperature of about 40°C to about 50 °C.

In some embodiments where the reaction was carried out at an elevated temperature, the solution may then be cooled, for example, to a temperature of about 5 °C to about 30 °C. In certain embodiments, the solution is cooled to about 20 °C to about 30 °C.

Within the context of the present embodiment, a solid may be formed upon addition of the non-polar solvent. Solid may also be formed during the optional steps of heating then cooling the solution. In some embodiments, the optional heating and cooling of the solution as described above may facilitate formation of a solid.

Crystalline sacubitril may then be isolated. Isolation of solid crystalline sacubitril may be carried out by methods well known in the art, for example, by filtering the solution and drying the obtained solid.

The sacubitril disclosed herein may be used in preparation of trisodiumsacubitril valsartanand may be incorporated into oral pharmaceutical dosage forms, for example, a capsule or tablet. Dosage forms that include thesacubitril may be useful for reducing the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure and reduced ejection fraction. Dosage forms may, in some embodiments, contain additional active pharmaceutical ingredients, such as valsartan.

The oral dosage forms containing sacubitril may further comprise one or more additional pharmaceutically acceptable excipients such as, for example, microcrystalline cellulose, hydroxypropyl cellulose, crospovidone, magnesium stearate, talc, colloidal silicon dioxide, and mixtures thereof.

Capsules or tablets containing sacubitril disclosed herein may include a coating that contains one or more excipients, artificial flavorings, artificial colorings, or mixtures thereof. For example, the coatings may contain hypromellose, titanium dioxide, polyethylene glycol, talc, iron oxide red, iron oxide black, iron oxide yellow, or mixtures thereof. One of skill in the art will recognize a variety of excipients that would be useful for creating suitable coatings for a final dosage form of that contains sacubitril.

Within the context of the present invention, dosage forms containing sacubitril disclosed herein may have between about 24 mg to about 97 mg of sacubitril per dose. Particularly useful embodiments of the present invention contain 24 mg sacubitril, 49 mg sacubitril, or 97 mg sacubitril.

All patents and patent applications cited herein by reference should be considered in their entirety. The following examples are provided to illustrate the process of the present invention. They, are however, not intended to limiting the scope of the present invention in any way and several variants of these examples would be evident to person ordinarily skilled in the art.

EXAMPLES

Example 1:Process for the preparation of tert-butyl [(2R)-1-(4-bromophenyl)-3-hydroxypropan-2-yl] carbamate

4-bromo-D-phenylalanine (50 g) was taken in methanol (300 mL) and thionyl chloride (36.2g) was added and maintained at 60-65 °C for 4 hours. The reaction mass was concentrated and dissolved in dichloromethane (500 mL) at 25-35 °C. The mass was further cooled to 5-15 °C after which triethyl amine (41.4 g) and boc-anhydride (bi-tert-butyl dicarbonate) were added. The reaction mixture was maintained at 25-30 °C for 6 hours. Water (200 mL) was added and the reaction mass pH was adjusted to 3-4 using dilute HCl solution. The aqueous and organic layers were separated and the organic layer was washed with 10% brine solution (200 mL). The organic layer was concentrated and hexane (200 mL) was added to isolate methyl 4-bromo-N-(tert-butoxycarbonyl)-D-phenylalanine (60 g).

Example2:Process for the preparation of tert-butyl [(2R)-1-(4-bromophenyl)-3-hydroxypropan-2-yl] carbamate (Formula-XII)

4-bromo-N-(tert-butoxycarbonyl)-D-phenylalanine (40 g) was taken in ethanol (300 mL) and sodium borohydride (8.4 g) was added lot wise at 25-35 °C. The reaction mass was stirred for 4 hours at 25-35 °C.The reaction mass was quenched with ammonium chloride solution (15 g in 200 mL) and the product was extractedinto ethyl acetate (150 mL). The organic layer was concentrated at reduced pressure and hexane (120 mL) was added to isolatetert-butyl [(2R)-1-(4-bromophenyl)-3-hydroxypropan-2-yl] carbamate (38 g).

Example 3:Process for the preparation of (2E, 4R)-5-(4-bromophenyl)-4-[(tert-butoxycarbonyl) amino-2-methylpent-2-enoic acid (Formula-XI)

Tert-butyl [(2R)-1-(4-bromophenyl)-3-hydroxypropan-2-yl] carbamate (25 g) was dissolved in ethyl acetate (500 mL). TEMPO(0.59 g) was addedat room temperature, followed by a sodium bicarbonate solution (9.5 g in 75 mL water) and a sodium bromide solution (14.5 g in 75 mL water). The reaction mass was cooled to 0-5 °C and aqueous sodium hypochlorite solution (~15 %, 93.9 mL)was added. The reaction mass was stirred for 2 hours and the organic and aqueous

layers were separated. Sodium thiosulfate (8 g in 125 mL water) was added to the reaction mass and the layers were separated. The organic layer containedthe tert-butyl [(2R)-1-(4-bromophenyl)-3-oxypropan-2-yl] carbamate product. This same organic layer was taken for further reaction without any purification. A Wittig reagent (i.e.,ethyl 2-(triphenyl-5-phosphanylidene)propanoate (31.5 g)) was added to the organic layer and the reaction mass was stirred for 2 hours at 25-35 °C. The reaction mass was concentrated completely under vacuum after which diisopropyl ether (125 mL) was added to the residue. The reaction mass was stirred for 2 hours at ambient temperature and the reaction mass wasfiltered. Thefiltrate was concentrated completely under vacuum to get a residue of ethyl (2E, 4R)-5-(4-bromophenyl)-4-[(tert-butoxycarbonyl) amino]-2-methylpent-enoate (Formula-VIII).Theresidue (Formula-VIII) was dissolved in ethanol (300 mL) and lithium hydroxide solution (9.5 g in 125 mL water) was added to the solution at 50-55 °C. The reaction mass was stirred at 75-85 °C for 2 hours.The pH of the reaction mass was adjusted to 4.5-5.0 with an aqueous acetic acid solution and the reaction mass was stirred at 75-85 °C for 1 hour before cooling the mass to 0-5 °C. The solution was filtered to obtained a solid, which was washed with ethanol to get (2E, 4R)-5-(4-bromophenyl)-4-[(tert-butoxycarbonyl) amino-2-methylpent-2-enoic acid solid (Formula-XI, 15.5 g).

Example4:Process for the preparation of (2R, 4S)-5-(4-bromophenyl)-4-[(tert-butoxycarbonyl) amino]-2-methylpentanoic acid (Formula-XII)

(2E, 4R)-5-(4-bromophenyl)-4-[(tert-butoxycarbonyl) amino-2-methylpent-2-enoic acid (Formula-XI, 10 g) was dissolved in methanol (200 mL), which was autoclaved. Diiodo(p-cymene)ruthenium(II) dimer (0.125 g) and Mandyphos-SL-M004-1(0.25 g) were then added. The solution was degassed with nitrogen after which hydrogen pressure (15-20 kg)was applied. The reaction mass was stirred at 55-65 °C for 7 hours, after which the reaction completion mass was cooled to ambient temperature.The solution was then treated with CECAactivated carbon and the aqueous and organic layers were separated. The organic layer was concentrated completely under vacuum to get a solid, which were dissolved in ethyl acetate (30 mL) at 45-55 °C. Hexane (100 mL) was added at 45-55 °C and the mass was stirred for 30 minutes at 45-55 °C after which the reaction mass was cooled to ambient temperature. The solution was filtered to get (2R, 4S)-5-(4-bromophenyl)-4-[(tert-butoxycarbonyl) amino]-2-methylpentanoic acid as a solid (Formula-XII, 8 g).

Example5:Process for the preparation of ethyl (2R, 4S)-4-amino-5-(4-bromophenyl)-2-methylpentanoate hydrochloride(hydrochloride salt of Formula-XVII)

(2R, 4S)-5-(4-bromophenyl)-4-[(tert-butoxycarbonyl) amino]-2-methylpentanoic acid (Formula-XII, 1 g) was dissolved in ethanol (10 mL) at 70-75 °C. Thionyl chloride (0.5 g) was added and the reaction mass was stirred for 3hours at 70-75 °C after which the reaction mass was completely concentrated under vacuum to get asolid. Heptane (10 mL) was added to the solidat 60-65 °C, the solution was cooled to ambient temperature, then filtered to get ethyl(2R,4S)-4-amino-5-(4-bromophenyl)-2-methylpentanoate hydrochlorideas a solid (hydrochloride salt of Formula-XVII, 1.0 g).

Example 6:Process for the preparation of 4-{[(2S, 4R)-1-(4-bromophenyl)-5-ethoxy-4-methyl-5-oxopentan-2-yl] amino}-4-oxobutanoic acid (Formula-XVI)

Ethyl (2R,4S)-4-amino-5-(4-bromophenyl)-2-methylpentanoate hydrochloride (hydrochloride salt of Formula-XVII,0.6 g) was dissolved in dichloromethane (12 mL) and the mass wascooled to 0-5 °C. A catalytic amount of 4-dimethylaminopyridine and succinic anhydride (Formula-XV, 0.2 g) were then added. Triethylamine (0.26 g) was added and the reaction mass was stirred at 25-35 °C for 3 hours, after which the organic layer was washed with a 1N HCl solution and 10%brine solution. The organic layer was concentrated completely under vacuum to get 4-{[(2S, 4R)-1-(4-bromophenyl)-5-ethoxy-4-methyl-5-oxopentan-2-yl] amino}-4-oxobutanoic acid (Formula-XVI, 0.7g).

Example7:Process for the preparation of 4-{[(2S, 4R)-1-(biphenyl-4-yl)-5-ethoxy-4-methyl-5-oxopentan-2-yl] amino}-4-oxobutanoic acid (sacubitril)

4-{[(2S, 4R)-1-(4-bromophenyl)-5-ethoxy-4-methyl-5-oxopentan-2-yl] amino}-4-oxobutanoic acid (1 g) was taken in water (30 mL) to which 1,2-dimethoxyethane (20 mL) and phenylboronic acid (0.44 g) was added under nitrogen atmosphere. Dipotassium hydrogen phosphate (2.0 g) and formic acid (5.5 mg) was added at 20-30 °C. The solution was purged with nitrogen gas for 30 min. Bis(triphenylphosphine)Pd(II) chloride (0.17g) was added under nitrogen atmosphere and the temperature was raised to 80-90 °C.The reaction progresswas monitored by HPLC. After completion of the reaction,the reaction mixture was concentrated under vacuum, methyl

tert-butyl ether (10 mL) was added, and the pH was adjusted to 10-11 using 1N sodium hydroxide. The aqueous layer was separated and extracted with methyl tert-butyl ether (10 mL). Ethyl acetate (30 mL) was added to aqueous layer and the pH was adjusted to 3-4 using 1N HCl. The organic layer was separated and concentrated to obtain a residue. Diisopropylether (5 mL) was added to the residue and solid crystalline sacubitril 4-{[(2S, 4R)-1-(biphenyl-4-yl)-5-ethoxy-4-methyl-5-oxopentan-2-yl] amino}-4-oxobutanoic acid was isolated (0.75 g).

Example8:Process for the preparation of product (2R, 4S)-5-(biphenyl-4-yl)-4-[(tert-butoxycarbonyl) amino]-2-methylpentanoic acid (Formula-XIII)

(2R, 4S)-5-(4-bromophenyl)-4-[(tert-butoxycarbonyl) amino]-2-methylpentanoic acid (Formula-XII, 10 g) was dissolved in water (100 mL). Phenylboronic acid (4.7 g), dipotassium hydrogen phosphate (0.5 g), and formic acid (0.059 g) were then added at 25-35 °C. The solution was purged with nitrogen for 30 mins after whichpalladium acetate (0.29 g) was added. The reaction mass was stirred at 35-45 °C for 6 hours. The pH of the reaction mass was adjusted to 10-11 with sodium hydroxide solution, after which ethyl acetate was added. The aqueous and organic layers were separated and the pH of the aqueous layer was adjusted to 3-4 with HCl. The aqueous layer was extracted with ethyl acetate and concentrated completely under vacuum and the residue was dissolved in ethyl acetate (40 mL) at 50-55 °C. Hexane (80 mL) was added at 50-55 °C and the solution was cooled to ambient temperature. The solution was then filtered to obtain a solid product of (2R, 4S)-5-(biphenyl-4-yl)-4-[(tert-butoxycarbonyl) amino]-2-methylpentanoic acid (Formula-XIII, 8 g).

Example9:Process for the preparation of ethyl (2R, 4S)-4-amino-5-(biphenyl)-2-methylpentanoate hydrochloride (hydrochloride salt of Formula-XIV)

(2R, 4S)-5-(biphenyl-4-yl)-4-[(tert-butoxycarbonyl) amino]-2-methylpentanoic acid (Formula-XIII, 100 g) was dissolved in ethanol (600 mL) at 70-75 °C. Thionylchloride (35.7 g) was added at 70-75 °C and the reaction mass was stirred for 3 hours, followed by concentration under vacuum to get asolid. Ethyl acetate (500 mL) was added to the solid and the reaction mass was cooled to ambient temperature, stirred for 2 hours, then filtered to get (2R,4S)-4-amino-5-(biphenyl)-2-methylpentanoate hydrochloride (hydrochloride salt of Formula-XIV, 80 g).

Example10:Process for the preparation of 4-{[(2S, 4R)-1-(biphenyl-4-yl)-5-ethoxy-4-methyl-5-oxopentan-2-yl] amino}-4-oxobutanoic acid (sacubitril)

(2R,4S)-4-amino-5-(biphenyl)-2-methylpentanoate hydrochloride (hydrochloride salt of Formula-XIV, 170 g) was dissolved in dichloromethane (1360 mL) and the solution was cooled to 5-10 °C. 4-dimethylaminopyridine(1.0 g) and succinic anhydride (61.1 g) were added. A solution of triethylamine (74 g) was added. The reaction mass was stirred at ambient temperature for 3 hours. After reaction completion, reaction mass was washed with 1N HCl solution (850 mL) followed by brine solution (850 mL). The organic layer was then concentrated under vacuum to obtain a residue and cooled to ambient temperature. Diisopropylether (850 mL) was added to the residue and stirred for2 hours. The solution was filtered to obtain a solid which was dried to get the crystalline material of sacubitril (165 g).

Example11: Process for the preparation of (R)-5-(4-bromophenyl)-4-(dibenzylamino)-2-methylpent-2-enoic acid

5-(4-bromo-phenyl)-4-dibenzylamino-2-methyl-pent-2-enoic acid ethyl ester (5 g) was dissolved in methanol (10 mL) and tetrahydrofuran (25 mL). Sodium hydroxide (0.6 g) dissolved in water (15 mL) was added to the reaction mass which was then heated to 45-50 °Cand maintained until reaction completion. After reaction completion, water (25 mL) was added and the layers were separated. The pH of the aqueous layer was adjusted to 3-4 with 1N HCl and then extracted with ethyl acetate (50 mL). The ethyl acetate layer was concentrated to get (R)-5-(4-bromophenyl)-4-(dibenzylamino)-2-methylpent-2-enoic acid (4.3 g).

Example12: Process for the preparation of (2R,4S)-5-(4-bromophenyl)-4-(dibenzylamino)-2-methylpentanoate

5-(4-bromo-phenyl)-4-dibenzylamino-2-methyl-pent-2-enoic acid ethyl ester (1 g) was dissolved in methanol (30 mL). Separately, Ru-dimer (15mg) &MandyphosSL-M004-1(30mg) or (S)-Ru-diacetate-BINAP (45 mg) were dissolved in methanol (10 mL) and the solution were added to the above reaction mass. The reaction mass was hydrogenated at 20kg pressure at 60-65 °C. After reactioncompletion, the reaction mass was filtered, concentrated, and purified by column

chromatography to get (2R, 4S)-ethyl 5-(4-bromophenyl)-4-(dibenzylamino)-2-methylpentanoate (0.8 g).

Example13: Process for the preparation of (S)-3-(4-bromophenyl)-2-(dibenzylamino) propanoic acid

Sodium hydroxide (8.2 g) was dissolved in water (125 mL). Potassium carbonate (28.3 g) and 4-bromo-L-phenyl alanine (25 g) were added. The reaction temperature was raised to 85-90 °C andbenzyl bromide (59.5 g) was added slowly while maintaining thetemperature at95-100 °C for 24 hours. After completion of reaction, the reaction mass was cooled to 30 ± 5 °C and a mixture of water (125 mL) and heptane(125 mL) were added. The organic layer was separated and concentrated to get a residue. A mixture of sodium hydroxide (10.6 g dissolved in 115 mL of water) and tetrabutylammonium bromide (0.3 g) were added and the temperature was raised to 90-100 °C for 15 hours. The reaction mass was cooled to 30 ± 5 °C. The layers were separated and a mixture of ethanol (75 mL) and water (175 mL)were added to aqueous layer. The reaction mass pH was adjusted to 3-4 with anHCl solution and the temperature of the reaction mass was raised to 70-75 °C. The reaction mass was cooled to 25-30 °C and filtered to get (S)-3-(4-bromophenyl)-2-(dibenzylamino)propanoic acid.

Example14: Process for the preparation of (S)-3-(4-bromophenyl)-2-(dibenzylamino) propanal (Formula-VII)

N, N-dibenzyl-L-bromo tyrosine (Formula-IV, 20 g) was dissolved in dimethylformamide (100 mL). Carbonyldiimidazole (9.2 g) was added and the reaction mass was stirred for 2 hours. N,O-dimethylhydroxylamine HCl(Formula-V, 6 g) and pyridine(4.4 g) were then added. The reaction mass was stirred for 12-15 hours and quenched into a mixture of water (100 mL) and methyl tert-butyl ether (MTBE, 100 mL). The layers were separated and the organic layer was washed with dilute HCl solution followed by concentration. The obtained residue was dissolved intoluene (100 mL) under nitrogen and thereaction mass was cooled to -25 °C. Vitride (19.5 g) was added slowly, maintaining the reaction massat -25 to -30 °C. The pH of the reaction mass was adjusted to 3-4 using dilute HCl solution. The layers were separated and the organic layer was washed with 1% disodium EDTA solution followed by 10% brine solution. The organic

layer was then concentrated to get(S)-3-(4-bromophenyl)-2-(dibenzylamino)propanal (Formula-VII).

Example15: Process for the preparation of (S, Z)-ethyl 5-(4-bromophenyl)-4-(dibenzylamino)-2-methylpent-2-enoate (Formula-VIII)

(S)-3-(4-bromophenyl)-2-(dibenzylamino) propanal(Formula-VII, 8.5 g) was dissolved in dichloromethane (90 mL) and the reaction mass was cooled to 0-5 °C. AWittig reagent(9.5 g) was added and the temperature of the reaction mass was raisedto 25 ± 3 °C. The reaction mass was stirred for 12 hoursand concentrated to get aresidue. The obtained residue was passed through a column using a 0-20% solution of ethyl acetate in hexanes as an eluent to get (S,Z)-ethyl-5-(4-bromophenyl)-4-(dibenzylamino)-2-methylpent-2-enoate (Formula-VIII).

Example16: Process for the preparation of (S, Z)-ethyl 5-(biphenyl-4-yl)-4-(dibenzylamino)-2-methylpent-2-enoate (Formula-IX)

(S,Z)-ethyl-5-(4-bromophenyl)-4-(dibenzylamino)-2-methylpent-2-enoate(Formula-VIII, 3 g) was dissolved in toluene (60 mL). Phenylboronic acid (1.5 g) and potassium carbonate (1.4 g) wereadded at 25-30 °C. Bis(triphenylphosphinum) Pd (II) chloride (0.2 g) was then added and the temperature was raised to 90-95 °C. The reaction mass was cooled to room temperature andsaturated sodium bicarbonate solution (30 mL) was added. The layers were separated and the organic layer was washed with 10% citric acid solution (30 mL) and brine solution (20%) followed by concentration to get (S, Z)-ethyl 5-(biphenyl-4-yl)-4-(dibenzylamino)-2-methylpent-2-enoate (Formula-IX).

Example17: Process for the preparation of (2S, 4R)-ethyl 5-(biphenyl-4-yl)-4-(amino)-2-methylpentanoate (Formula-X)

(S, Z)-5-biphenyl-4-yl-4-dibenzylamino-2-methyl-pent-2-enoic acid ethyl ester (Formula-IX, 2 g) was dissolved in methanol (100 mL). Hydrochloric acid(0.2 mL) and 10% Pd-C (0.2 g) wereadded and the solution was hydrogenated at 30-35 °C for 20 hours. The obtainedreaction mass was filtered and concentrated. The product was isolated using methyltert-butyl ether (25

mL)to get the hydrochloride salt of ethyl 5-(biphenyl-4-yl)-4-(amino)-2-methylpentanoate (80:20 (2S,4R):(2R,4R); Formula-X).

Example18:Preparationof pure compound (2S, 4R)-ethyl 5-(biphenyl-4-yl)-4-(amino)-2-methylpentanoate L-tartrate (Formula-X)

(2S, 4R)-ethyl-5-(biphenyl-4-yl)-4-(amino)-2-methylpentanoate(80:20(2S,4R):(2R,4R); Formula-IX, 3 g) was dissolved in ethanol (31 mL) and stirred. L-tartaric acid (1.44 g) was added. The reaction mass temperature was raised to 60-65 °C for 30 min then cooled to 25-30 °C. The reaction mass was stirred for 12 hours at same temperature. The obtainedsolution was filtered to obtain a solid which wasdried under vacuum at 50-55 °C to get substantially pure (2S, 4R)-ethyl 5-(biphenyl-4-yl)-4-(amino)-2-methylpentanoate L-tartrate salt (Formula-X).

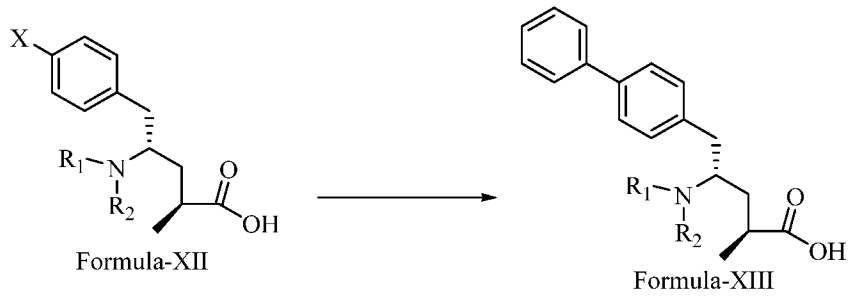
Example 19: Process for the preparation of 4-{[(2S, 4R)-1-(biphenyl-4-yl)-5-ethoxy-4-methyl-5-oxopentan-2-yl] amino}-4-oxobutanoic acid (sacubitril)

(2R,4S)-4-amino-5-(biphenyl)-2-methylpentanoate hydrochloride (Formula-X, 10 g) was dissolved in dichloromethane(60 mL). The solution was cooled to 5-10 °Cafter which4-dimethylaminopyridine(0.1 g) and succinic anhydride (3.6 g) were added. Triethylamine (4.3 g) was then added. The reaction mass was stirred at ambient temperature for 3hours. After reaction completion, the reaction mass was washed with 1N HCl solution (2x30 mL) followed by brine solution (30 mL). The organic layer was then concentrated under vacuum at 50-55 °C and extracted with ethyl acetate (2x10 mL) to get a residue which was then dissolved in ethyl acetate (5 mL). Hexane (100 mL) was slowly added at 40-50 °C. The reaction mass was then cooled to 20-30 °C temperature, stirred for 2 hours, and filtered. The solid crystalline material of sacubitril was then dried to get sacubitril (8.0 g).

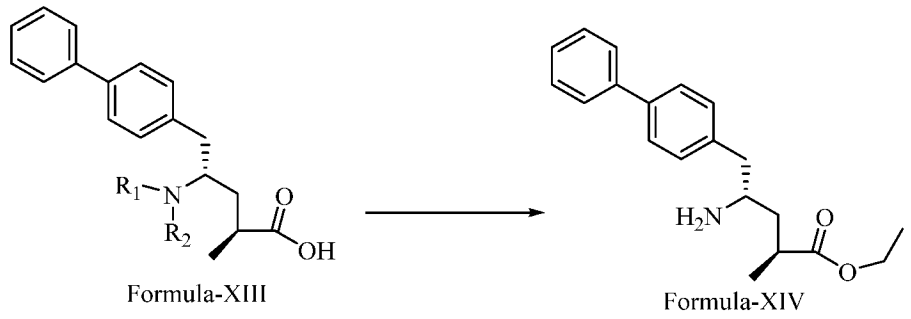
We claim:

1. A process for the preparation of sacubitril process comprising the steps of:

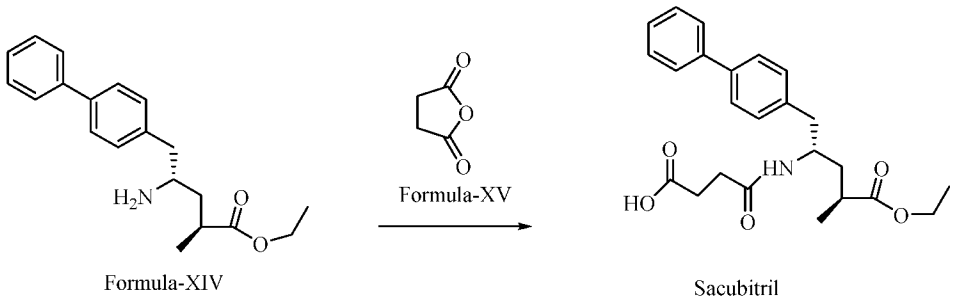
a) converting Formula-XII into Formula-XIII;



b) converting Formula-XIII into Formula-XIV; and



c) reacting Formula-XIV with Formula-XV to get sacubitril



wherein "R_1" and "R_2" are independently hydrogen or an amine protecting group and "X" is a halide selected from the group consisting of -F, -Cl, -Br, and -I.

2. The process according to claim 1, wherein the conversion ofFormula-XII into Formula-XIII is carried out in the presence of phenylboronic acid, a metal catalyst, and a solvent.

3. The process according to claim 2, wherein the metal catalyst selected from the group consisting of tetrakis(triphenylphosphine)palladium(0), bis(triphenylphosphine)palladium(II) dichloride, bis(dibenzylideneacetone) palladium(0)tris(dibenzylideneacetone)palladium(0), palladium(II) acetate, copper, cuprous bromide, cuprous iodide, and (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphtalene (rac-BINAP).

4. The process according to claim 2, wherein the solvent is selected from the group consisting of ethereal solvents, hydrocarbon solvents, water, and mixtures thereof.

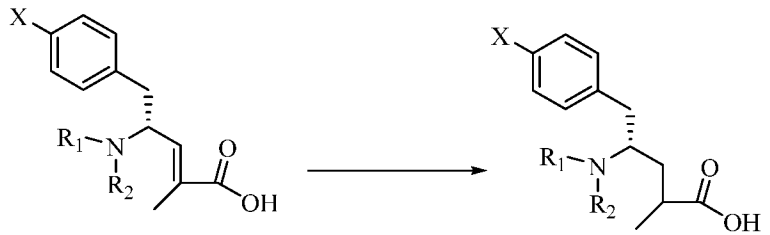
5. The process according to claim 1, wherein Formula-XIII is converted into Formula-XIV or its salt by esterification of the carboxylic acid group and deprotection of the amine.

6. The process according to claim 5, wherein the esterification reaction is carried out in the presence of a halogenation reagent and an alcohol solvent.

7. The process according to claim 6, wherein the halogenation reagent is selected from the group consisting of phosphorous oxychloride, phosphorous pentachloride, and thionyl chloride.

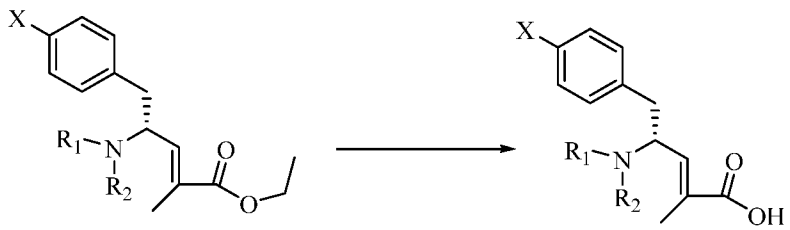
8. The process according to claim 6, wherein the alcohol solvent is ethanol.

9. The process according to claim 1, wherein compound of formula-XII is prepared by reducing the compound of formula-XI.



Formula-XI Formula-XII

10. The process according to claim 9, wherein compound of formula-XI is prepared by hydrolyzing the compound of formula-VIII in presence of base and solvent.



Formula-VIII Formula-XI

11. The process according to claim 10, wherein the base is an organic base or an inorganic base.

12. The process according to claim 11, wherein the inorganic base is selected from the group consisting of alkaline metal hydroxides, alkaline metal bicarbonates, alkaline metal carbonates, and alkaline alkoxides.

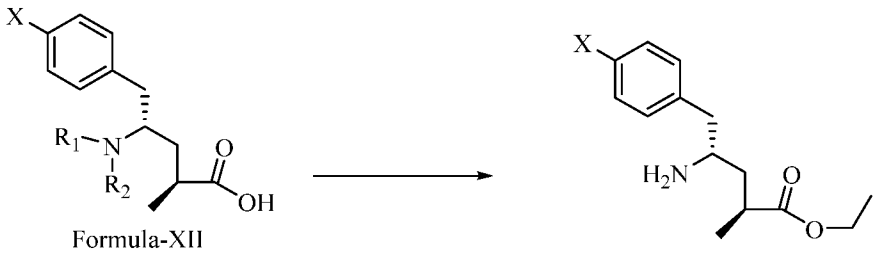
13. The process according to claim 12, wherein the alkaline metal hydroxide is selected from the group consisting of lithium hydroxide, sodium hydroxide, and potassium hydroxide.

14. The process according to claim10, wherein the solvent is selected from the group consisting of alcohol solvents, ethereal solvents, and mixtures thereof.

15. The process according to claim 14, wherein the alcohol solvent is selected from the group consisting of methanol, ethanol, n-propanol, isopropanol, and mixtures thereof.

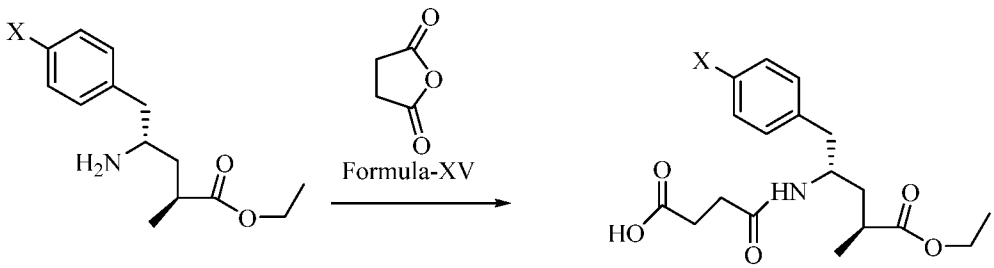
16. A process for the preparation of sacubitril process, comprising the steps of:

a) converting Formula-XII into Formula-XVII;



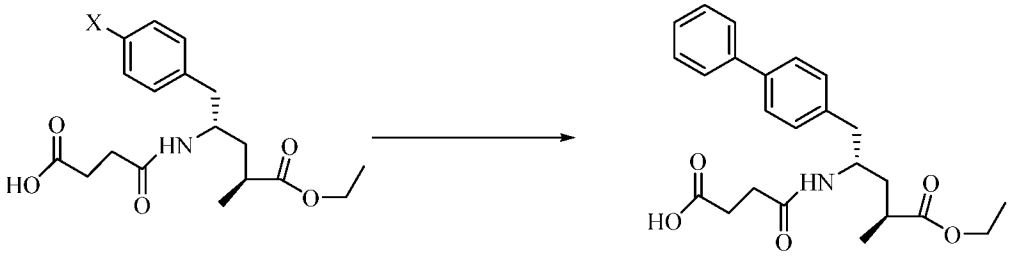
Formula-XII Formula-XVII

b) reacting Formula-XVII with Formula-XV to get Formula-XVI; and



Formula-XVII Formula-XVI

c) converting Formula-XVI into sacubitril



Formula-XVI

Sacubitril

wherein "R_1" and "R_2" are independently hydrogen or an amine protecting group and "X" is a halide selected from the group consisting of -F, -Cl, -Br, and -I.

17. The process according to claim 16, wherein Formula-XII is converted Formula-XVII by esterification of the acid group and deprotection of the amine group.

18. The process according to claim 17, wherein esterification reaction is carried out in the presence of a halogenation reagent and an alcoholsolvent.

19. The process according to claim 18, wherein the halogenation reagent is selected from the group consisting of phosphorous oxychloride, phosphorous pentachloride, and thionyl chloride.

20. The process according to claim 18, wherein the alcohol solvent is ethanol.

21. The process according to claim 16, wherein the reacting ofFormula-XVII with Formula-XV is carried out in the presence of a base and a halogenated solvent.

22. The process according to claim 21, wherein the base is an inorganic base or an organic base.

23. The process according to claim 22, wherein the organic base is selected from the group consisting of pyridine, triethylamine, and N,N-diisopropylethylamine.

24. The process according to claim 21, wherein the halogenated solvent is selected from the group consisting of dichloromethane, trichloroethylene, carbon tetrachloride, methyl chloroform, and mixtures thereof.

25. The process according to claim 16, wherein the step of converting of Formula-XVI into sacubitrilis carried out in the presence of phenylboronic acid, a metal catalyst, and a solvent.

26. The process according to claim 25, wherein the metal catalyst is selected from the group consisting of tetrakis(triphenylphosphine)palladium(0), bis(triphenylphosphine)palladium(II) dichloride, bis(dibenzylideneacetone) palladium(0)tris(dibenzylideneacetone)palladium(0), palladium(II) acetate, copper, cuprous bromide, cuprous iodide, and (±)-2,2'-bis(diphenylphosphino)-1,1'-binaphtalene (rac-BINAP).

27. The process according to claim 25, wherein the solvent is selected from the group consisting of ethereal solvents, hydrocarbon solvents,water, and mixtures thereof.

28. Solid sacubitril.

29. The solid sacubitril of claim 28, wherein the solid sacubitril is in crystalline form.

30. The crystalline solid sacubitril of claim 29, wherein the solid crystalline sacubitril is characterized bya powder X-ray diffraction pattern having significantpeaks at 18.8, 19.4, 19.8, 20.6, and 21.3 (±) 0.2° 2-theta.

31. The solid crystalline sacubitril of claim 30, further characterized by the powder X-ray diffraction pattern in Figure 1.

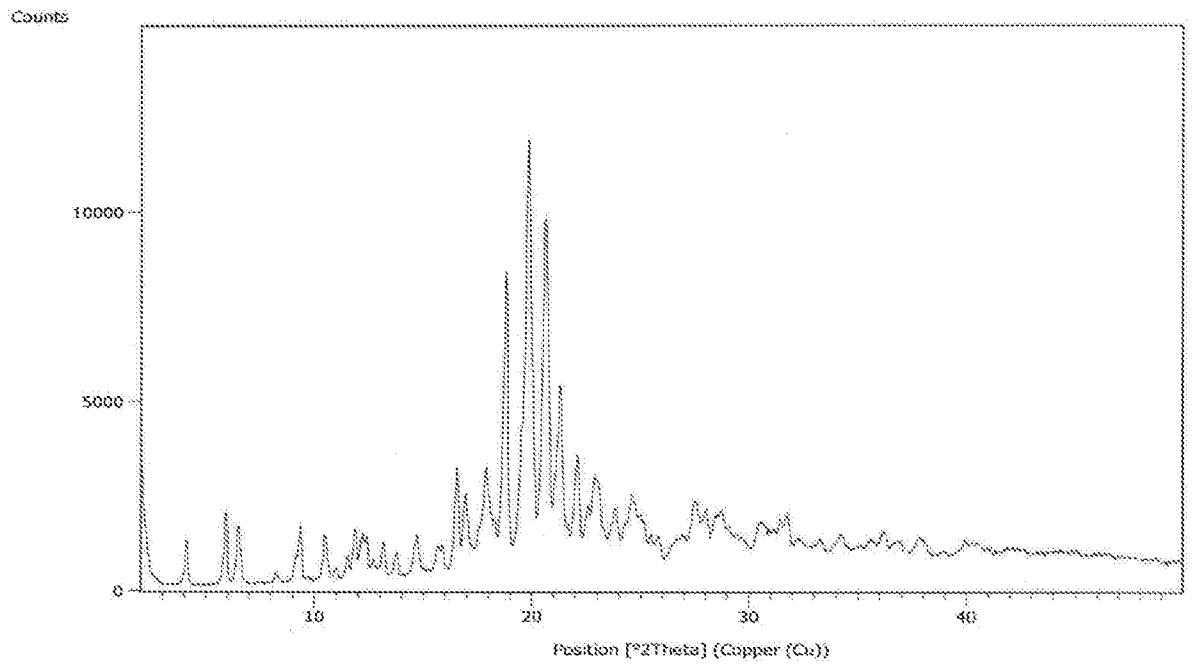


Figure 1- illustrates the powder X-ray diffraction pattern of crystalline Sacubitril.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2016/050065

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C231/02 C07C235/74
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07C C07B

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GARY M KSANDER ET AL: "Dicarboxylic Acid Dipeptide Neutral Endopeptidase Inhibitors", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, [Online] vol. 38, no. 10, 1 May 1995 (1995-05-01), pages 1689-1700, XP008154341, ISSN: 0022-2623, DOI: 10.1021/JM00010A014 Retrieved from the Internet: URL:http://pubs.acs.org/journals/jmcmar/index.html> [retrieved on 1995-05-01] the whole document -----	1-27
E	WO 2016/029828 A1 (SHANGHAI HANSOH BIOMEDICAL CO LTD [CN]; JIANGSU HANSOH PHARMACEUTICAL) 3 March 2016 (2016-03-03) the whole document -----	1,2
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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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Date of the actual completion of the international search	Date of mailing of the international search report
10 June 2016	20/06/2016

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INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2016/050065

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