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(54) Title: PROCESS FOR THE PREPARATION OF SACUBITRIL OR SALTS THEREOF

(57) Abstract: The present invention provides processes for the preparation of sacubitril or salts thereof. The present invention further provides intermediates of Formula IV, V and VI and their use for the preparation of sacubitril or salts thereof.



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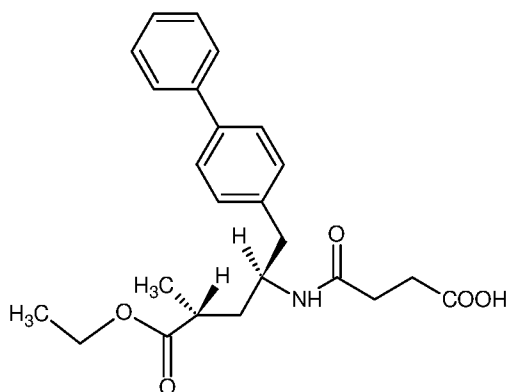
PROCESS FOR THE PREPARATION OF SACUBITRIL OR SALTS THEREOF

Field of the Invention

The present invention provides processes for the preparation of sacubitril or salts thereof. The present invention further provides intermediates of Formula IV, V and VI and their use for the preparation of sacubitril or salts thereof.

Background of the Invention

U.S. Patent No. 5,217,996, PCT Publication Nos. WO 2007/056546, WO 2008/031567, WO 2008/083967, WO 2009/090251, WO 2012/025502, WO 2012/025501, WO 2013/026773, and WO 2014/032627 provides processes for the preparation of sacubitril of Formula I or salts thereof. These applications are incorporated by reference into this application for their disclosure of processes for preparing sacubitril.



Formula I

15 Summary of the Invention

The present invention provides processes for the preparation of sacubitril or salts thereof. The present invention further provides intermediates of Formula IV, V and VI and their use for the preparation of sacubitril or salts thereof.

Detailed Description of the Invention

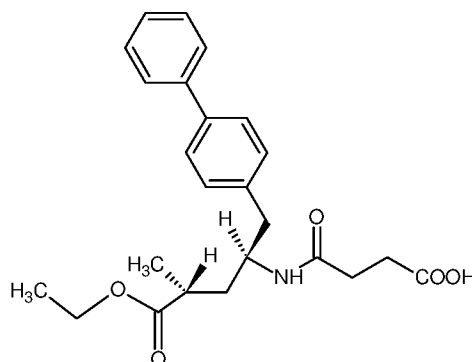
20 The term “about,” as used herein, refers to any value which lies within the range defined by a number up to $\pm 10\%$ of the value.

The term “ambient temperature,” as used herein, refers to the temperature in the range of 25°C to 35°C.

The term “treating,” “reacting,” or “converting,” includes combining, mixing, triturating, suspending, contacting, or a combination thereof.

The term “C₁₋₆ alkyl,” as used herein, refers to straight or branched aliphatic hydrocarbon, or cyclic aliphatic hydrocarbon, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, isopentyl, t-pentyl, cyclopropyl, cyclobutyl, cyclopentyl, or cyclohexyl.

A first aspect of the present invention provides a process for the preparation of sacubitril of Formula I or a salt thereof,

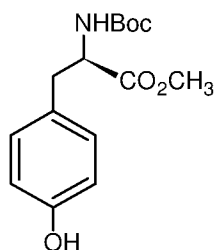


10

Formula I

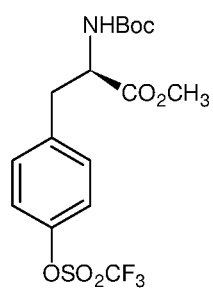
wherein the process comprises:

a) reacting a compound of Formula IX,

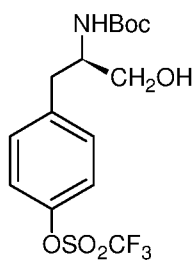
**Formula IX**

15

with trifluoromethyl sulfonyl containing reagent to obtain a compound of Formula VIII,

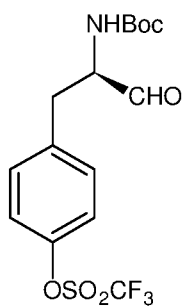
**Formula VIII**

b) reducing the compound of Formula VIII to obtain a compound of Formula VII,

**Formula VII**

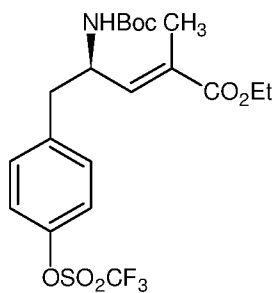
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c) oxidizing the compound of Formula VII to obtain a compound of Formula VI,

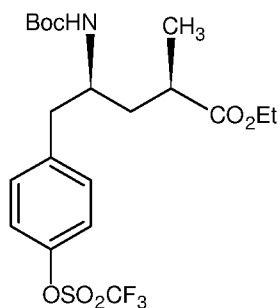
**Formula VI**

d) reacting the compound of Formula VI with ethyl 2-(triphenylphosphoranyl) propionate to obtain a compound of Formula V,

10

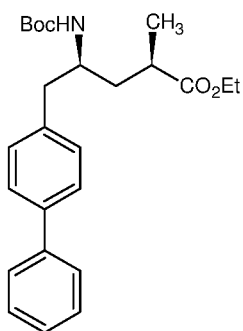
**Formula V**

- e) hydrogenating the compound of Formula V to obtain a compound of Formula IV,



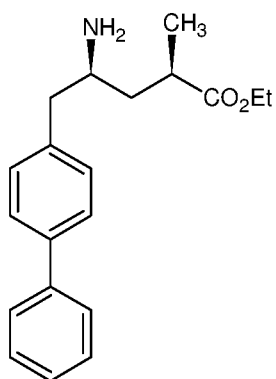
Formula IV

- 5 f) reacting the compound of Formula IV with phenylboronic acid to obtain a compound of Formula III,



Formula III

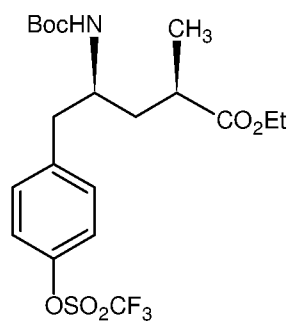
- g) deprotecting the compound of Formula III to obtain a compound of Formula II,
and



Formula II

- h) reacting the compound of Formula II with succinic anhydride to obtain sacubitril
of Formula I or a salt thereof.

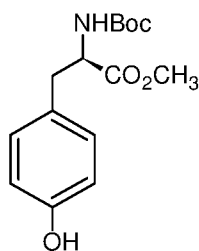
A second aspect of the present invention provides a process for the preparation of a compound of Formula IV,



Formula IV

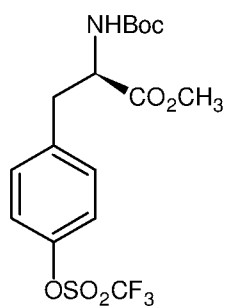
5 wherein the process comprises:

a) reacting a compound of Formula IX



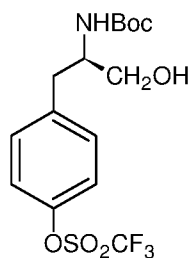
Formula IX

10 with trifluoromethyl sulfonyl containing reagent to obtain a compound of Formula VIII,

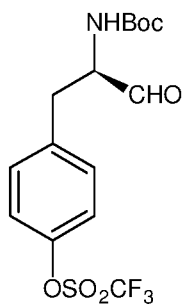


Formula VIII

b) reducing the compound of Formula VIII to obtain a compound of Formula VII,

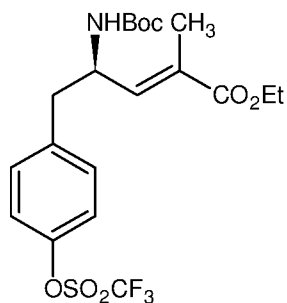
**Formula VII**

c) oxidizing the compound of Formula VII to obtain a compound of Formula VI,

**Formula VI**

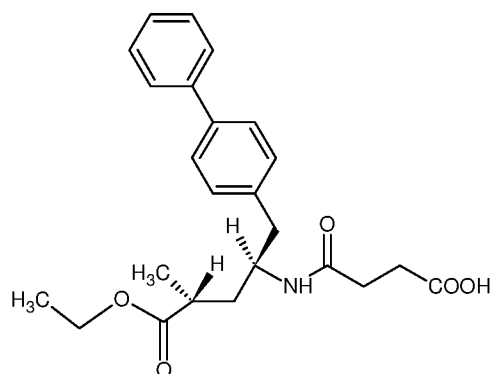
5

d) reacting the compound of Formula VI with ethyl 2-(triphenylphosphoranyl) propionate to obtain a compound of Formula V, and

**Formula V**

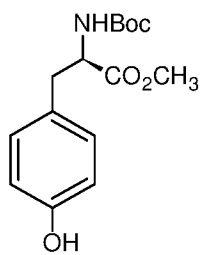
10 e) hydrogenating the compound of Formula V to obtain the compound of Formula IV.

A third aspect of the present invention provides a process for the preparation of sacubitril of Formula I or a salt thereof,

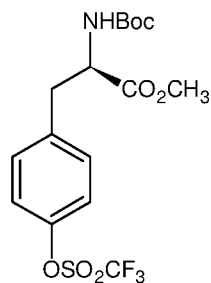
**Formula I**

wherein the process comprises:

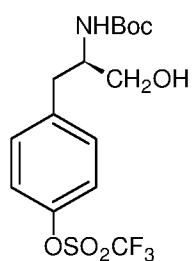
- a) reacting a compound of Formula IX

**Formula IX**

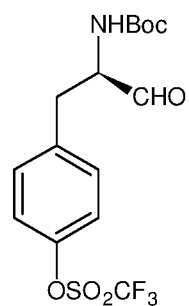
with trifluoromethyl sulfonyl containing reagent to obtain a compound of Formula VIII,

**Formula VIII**

- b) reducing the compound of Formula VIII to obtain a compound of Formula VII,

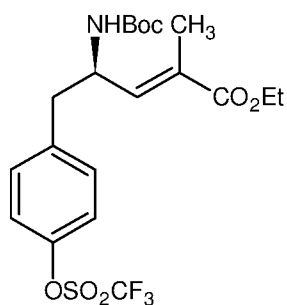
**Formula VII**

c) oxidizing the compound of Formula VII to obtain a compound of Formula VI,

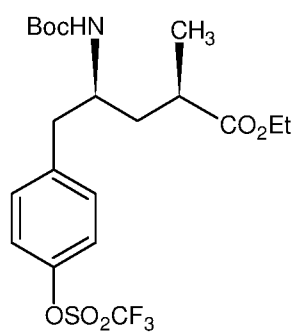
**Formula VI**

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d) reacting the compound of Formula VI with ethyl 2-(triphenylphosphoranyl) propionate to obtain a compound of Formula V,

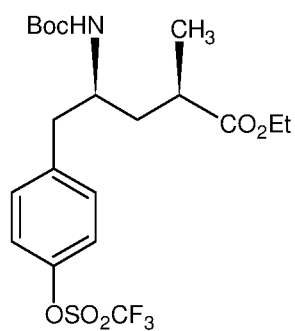
**Formula V**

10 e) hydrogenating the compound of Formula V to obtain a compound of Formula IV,
and

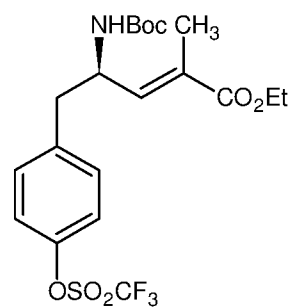
**Formula IV**

f) converting the compound of Formula IV to sacubitril of Formula I or a salt thereof.

A fourth aspect of the present invention provides a process for the preparation of a
 5 compound of Formula IV,

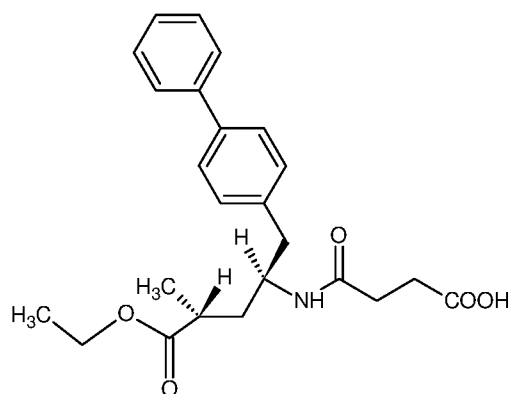
**Formula IV**

wherein the process comprises hydrogenating a compound of Formula V,

**Formula V**

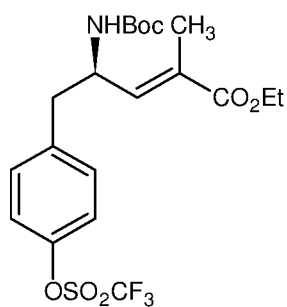
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A fifth aspect of the present invention provides a process for the preparation of
 sacubitril of Formula I or a salt thereof,

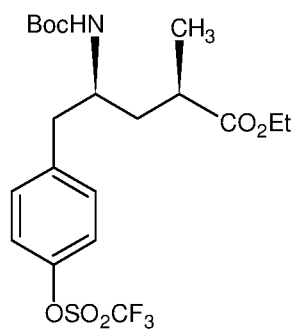
**Formula I**

wherein the process comprises:

- a) hydrogenating a compound of Formula V

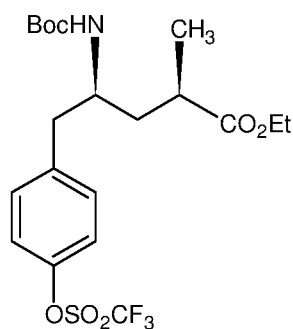
**Formula V**

to obtain a compound of Formula IV, and

**Formula IV**

- b) converting the compound of Formula IV to sacubitril of Formula I or a salt thereof.

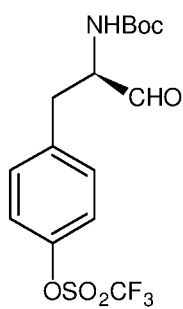
A sixth aspect of the present invention provides a process for the preparation of a compound of Formula IV,



Formula IV

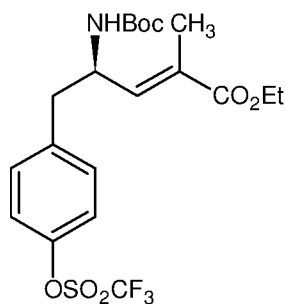
5 wherein the process comprises:

a) reacting a compound of Formula VI



Formula VI

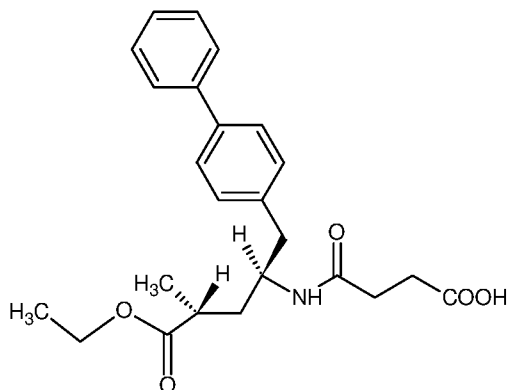
with ethyl 2-(triphenylphosphoranyl) propionate to obtain a compound of Formula V, and



Formula V

b) hydrogenating the compound of Formula V to obtain the compound of Formula IV.

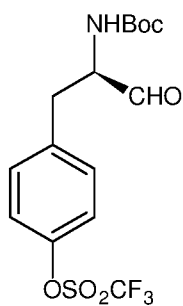
A seventh aspect of the present invention provides a process for the preparation of sacubitril of Formula I or a salt thereof,



Formula I

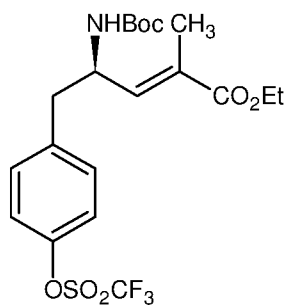
5 wherein the process comprises:

a) reacting a compound of Formula VI



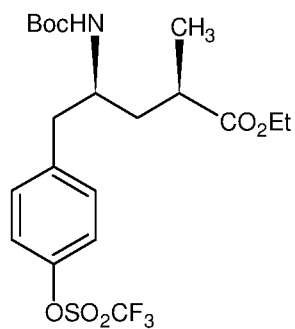
Formula VI

with ethyl 2-(triphenylphosphoranyl) propionate to obtain a compound of Formula V,



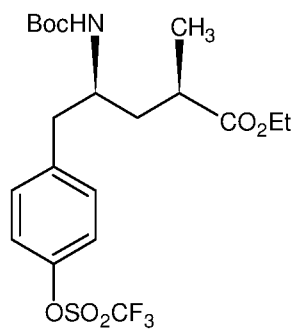
Formula V

b) hydrogenating the compound of Formula V to obtain a compound of Formula IV,
and

**Formula IV**

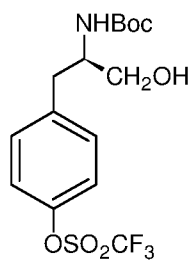
c) converting the compound of Formula IV to sacubitril of Formula I or a salt thereof.

An eighth aspect of the present invention provides a process for the preparation of
 5 a compound of Formula IV,

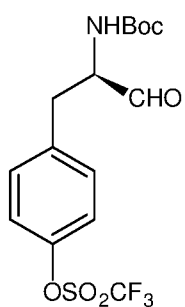
**Formula IV**

wherein the process comprises:

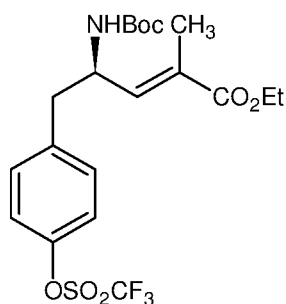
a) oxidizing a compound of Formula VII

**Formula VII**

to obtain a compound of Formula VI,

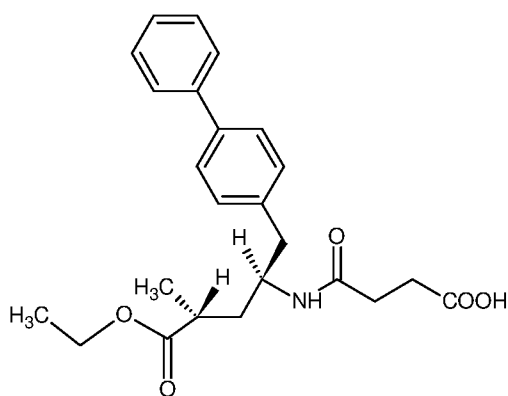
**Formula VI**

- b) reacting the compound of Formula VI with ethyl 2-(triphenylphosphoranyl) propionate to obtain a compound of Formula V, and

**Formula V**

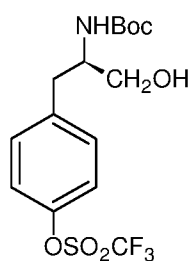
- c) hydrogenating the compound of Formula V to obtain the compound of Formula IV.

A ninth aspect of the present invention provides a process for the preparation of sacubitril of Formula I or a salt thereof,

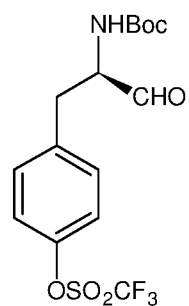
**Formula I**

wherein the process comprises:

- a) oxidizing a compound of Formula VII

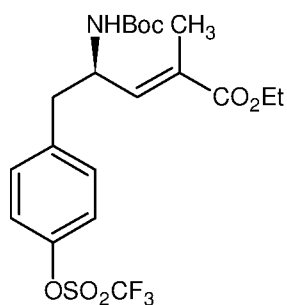
**Formula VII**

to obtain a compound of Formula VI,

**Formula VI**

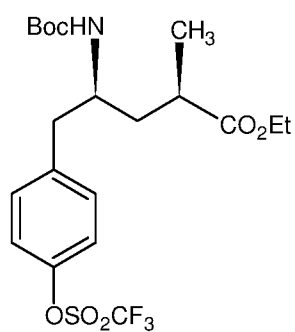
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- b) reacting the compound of Formula VI with ethyl 2-(triphenylphosphoranyl) propionate to obtain a compound of Formula V,

**Formula V**

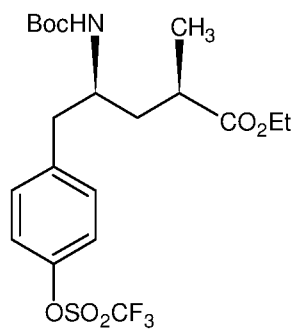
10

- c) hydrogenating the compound of Formula V to obtain a compound of Formula IV,
and

**Formula IV**

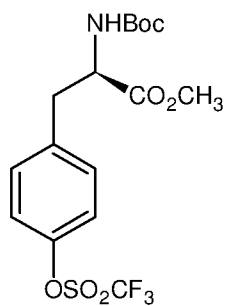
d) converting the compound of Formula IV to sacubitril of Formula I or a salt thereof.

A tenth aspect of the present invention provides a process for the preparation of a
 5 compound of Formula IV,

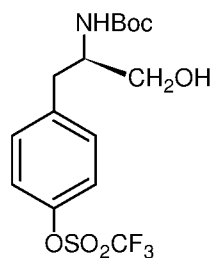
**Formula IV**

wherein the process comprises:

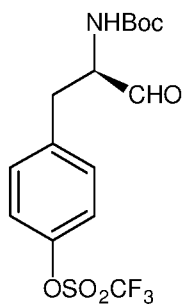
a) reducing a compound of Formula VIII

**Formula VIII**

to obtain a compound of Formula VII,

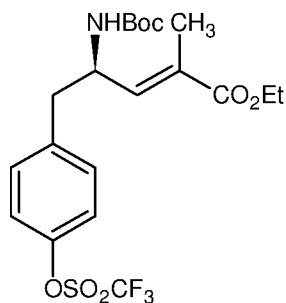
**Formula VII**

b) oxidizing the compound of Formula VII to obtain a compound of Formula VI,

**Formula VI**

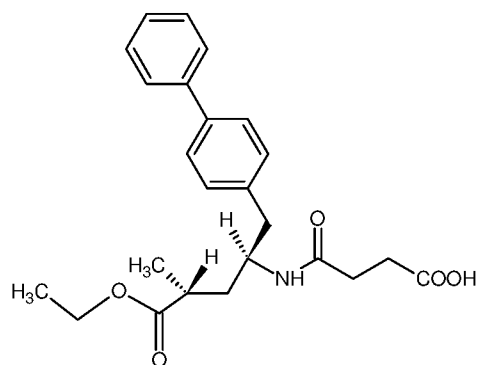
5

c) reacting the compound of Formula VI with ethyl 2-(triphenylphosphoranyl) propionate to obtain a compound of Formula V, and

**Formula V**

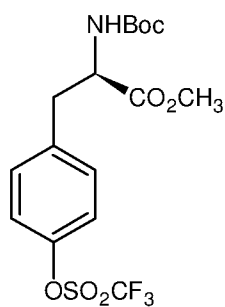
10 d) hydrogenating the compound of Formula V to obtain the compound of Formula IV.

An eleventh aspect of the present invention provides a process for the preparation of a sacubitril of Formula I or a salt thereof,

**Formula I**

wherein the process comprises:

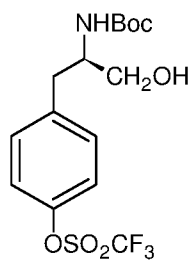
- a) reducing a compound of Formula VIII



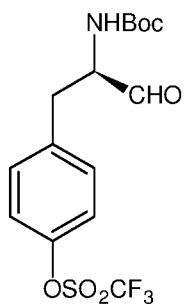
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Formula VIII

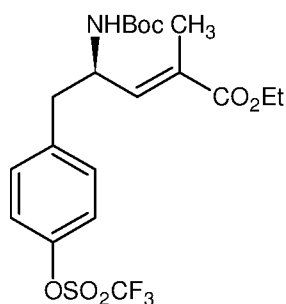
to obtain a compound of Formula VII,

**Formula VII**

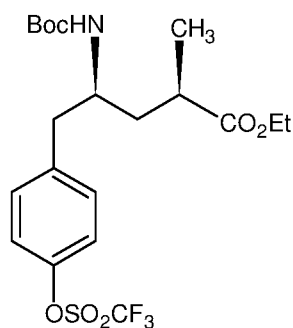
- 10 b) oxidizing the compound of Formula VII to obtain a compound of Formula VI,

**Formula VI**

- c) reacting the compound of Formula VI with ethyl 2-(triphenylphosphoranyl) propionate to obtain a compound of Formula V,

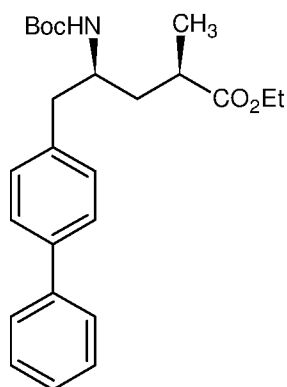
**Formula V**

- d) hydrogenating the compound of Formula V to obtain a compound of Formula IV,
and

**Formula IV**

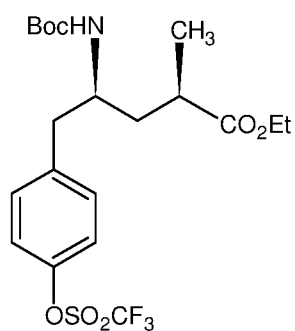
- e) converting the compound of Formula IV to sacubitril of Formula I or a salt thereof.

A twelfth aspect of the present invention provides a process for the preparation of a compound of Formula III,



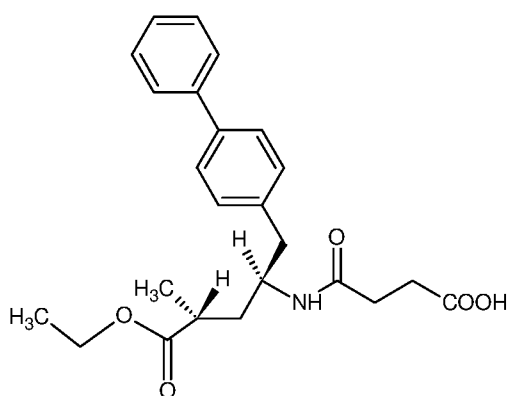
Formula III

wherein the process comprises reacting a compound of Formula IV with phenylboronic acid.



Formula IV

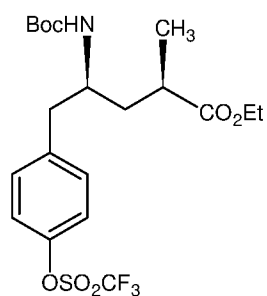
A thirteenth aspect of the present invention provides a process for the preparation of sacubitril of Formula I or a salt thereof,



Formula I

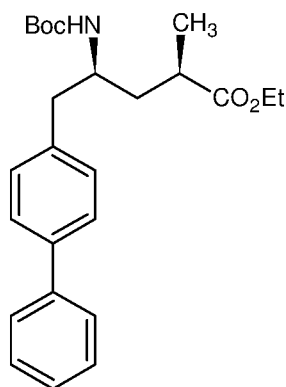
wherein the process comprises:

a) reacting a compound of Formula IV



Formula IV

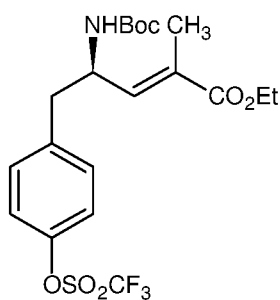
with phenylboronic acid to obtain a compound of Formula III, and



Formula III

b) converting the compound of Formula III to sacubitril of Formula I or a salt thereof.

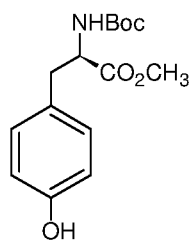
A fourteenth aspect of the present invention provides a process for the preparation of a compound of Formula V,



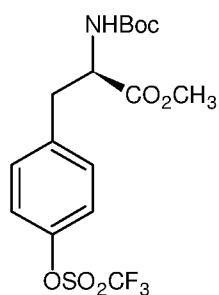
Formula V

wherein the process comprises:

a) reacting a compound of Formula IX

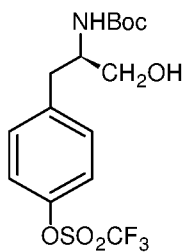
**Formula IX**

with trifluoromethyl sulfonyl containing reagent to obtain a compound of Formula VIII,

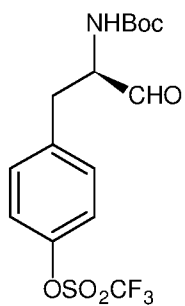
**Formula VIII**

5

b) reducing the compound of Formula VIII to obtain a compound of Formula VII,

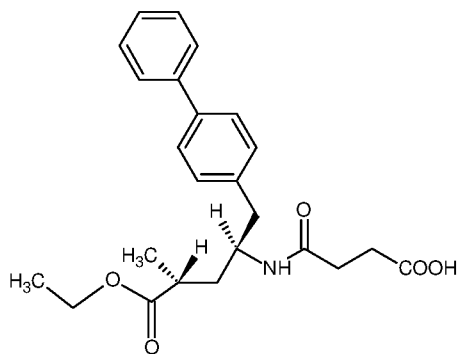
**Formula VII**

10 c) oxidizing the compound of Formula VII to obtain a compound of Formula VI, and

**Formula VI**

- d) reacting the compound of Formula VI with ethyl 2-(triphenylphosphoranyl) propionate to obtain the compound of Formula V.

A fifteenth aspect of the present invention provides a process for the preparation of sacubitril of Formula I or a salt thereof,

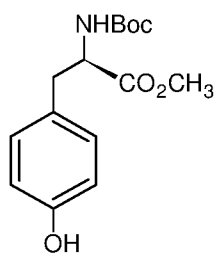


5

Formula I

wherein the process comprises:

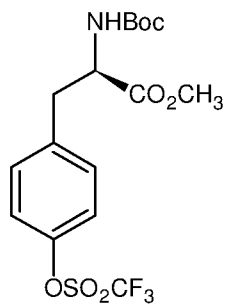
- a) reacting a compound of Formula IX



10

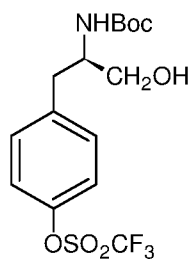
Formula IX

with trifluoromethyl sulfonyl containing reagent to obtain a compound of Formula VIII,



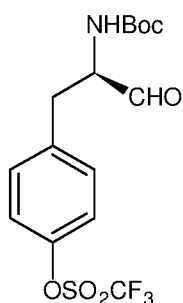
Formula VIII

- b) reducing the compound of Formula VIII to obtain a compound of Formula VII,



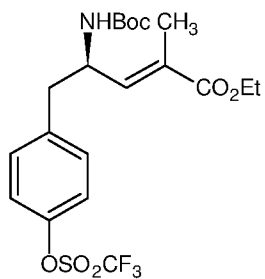
Formula VII

- c) oxidizing the compound of Formula VII to obtain a compound of Formula VI,



Formula VI

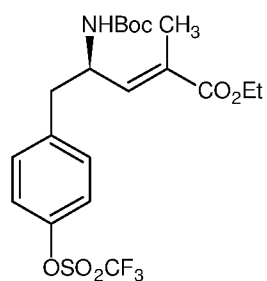
- d) reacting the compound of Formula VI with ethyl 2-(triphenylphosphoranyl) propionate to obtain a compound of Formula V, and



Formula V

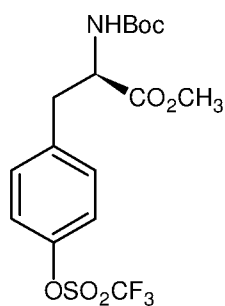
- e) converting the compound of Formula V to sacubitril of Formula I or a salt thereof.

A sixteenth aspect of the present invention provides a process for the preparation of a compound of Formula V,

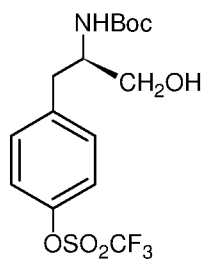
**Formula V**

wherein the process comprises:

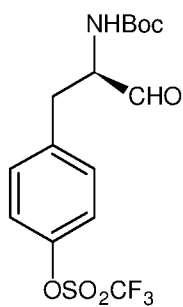
- a) reducing a compound of Formula VIII

**Formula VIII**

to obtain a compound of Formula VII,

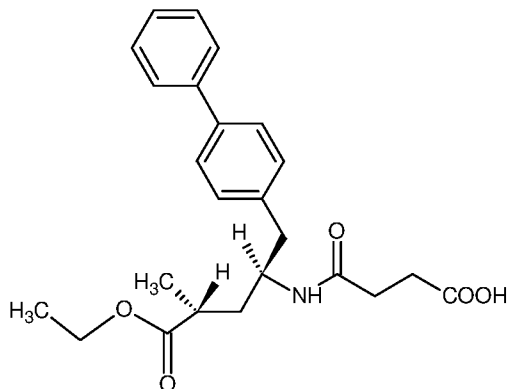
**Formula VII**

- b) oxidizing the compound of Formula VII to obtain a compound of Formula VI, and

**Formula VI**

- c) reacting the compound of Formula VI with ethyl 2-(triphenylphosphoranyl) propionate to obtain the compound of Formula V.

A seventeenth aspect of the present invention provides a process for the preparation of sacubitril of Formula I or a salt thereof,

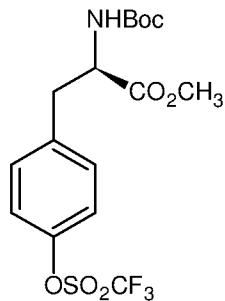


5

Formula I

wherein the process comprises:

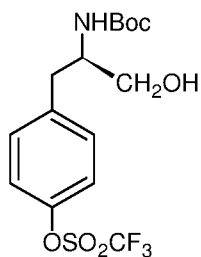
- a) reducing a compound of Formula VIII



10

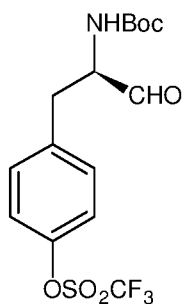
Formula VIII

to obtain a compound of Formula VII,



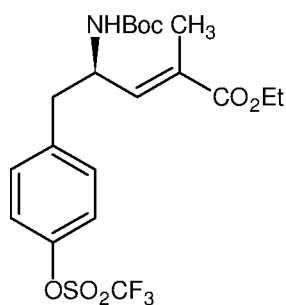
Formula VII

- b) oxidizing the compound of Formula VII to obtain a compound of Formula VI,



Formula VI

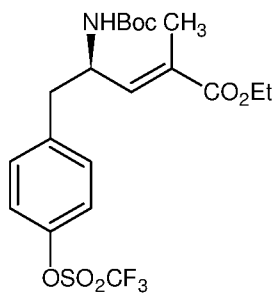
- 5 c) reacting the compound of Formula VI with ethyl 2-(triphenylphosphoranyl) propionate to obtain a compound of Formula V, and



Formula V

- d) converting the compound of Formula V to sacubitril of Formula I or a salt thereof.

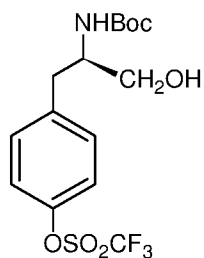
10 An eighteenth aspect of the present invention provides a process for the preparation of a compound of Formula V,



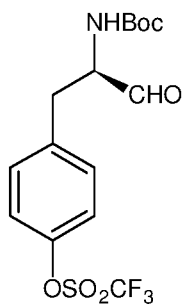
Formula V

wherein the process comprises:

- a) oxidizing a compound of Formula VII

**Formula VII**

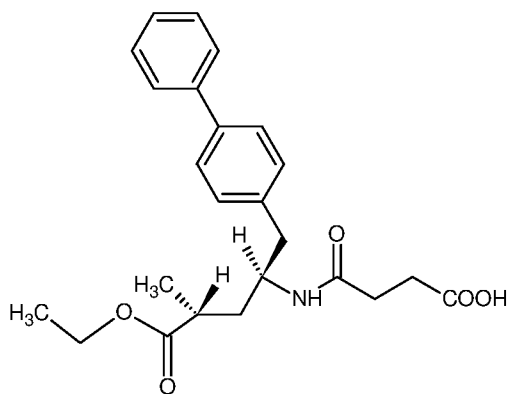
to obtain a compound of Formula VI, and

**Formula VI**

5

- b) reacting the compound of Formula VI with ethyl 2-(triphenylphosphoranyl) propionate to obtain the compound of Formula V.

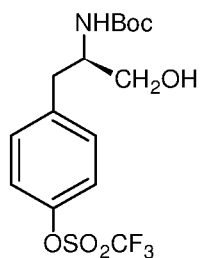
A nineteenth aspect of the present invention provides a process for the preparation of sacubitril of Formula I or a salt thereof,

**Formula I**

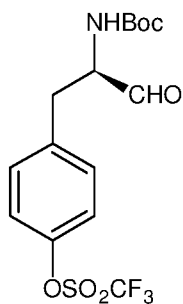
10

wherein the process comprises:

- a) oxidizing a compound of Formula VII

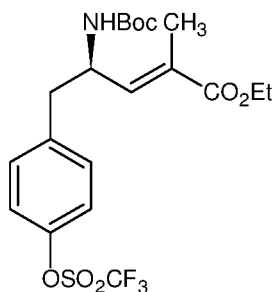
**Formula VII**

to obtain a compound of Formula VI,

**Formula VI**

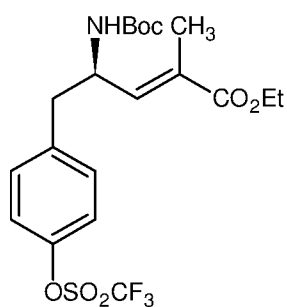
5

- b) reacting the compound of Formula VI with ethyl 2-(triphenylphosphoranyl) propionate to obtain a compound of Formula V, and

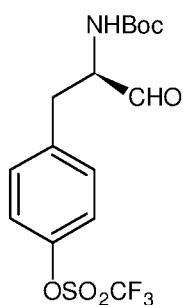
**Formula V**

- 10 c) converting the compound of Formula V to sacubitril of Formula I or a salt thereof.

A twentieth aspect of the present invention provides a process for the preparation of a compound of Formula V,

**Formula V**

wherein the process comprises reacting a compound of Formula VI

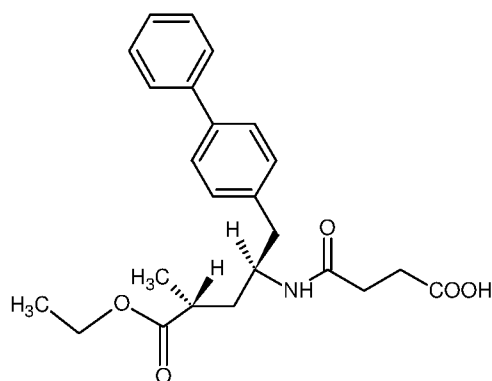


5

Formula VI

with ethyl 2-(triphenylphosphoranyl) propionate.

A twenty first aspect of the present invention provides a process for the preparation of sacubitril of Formula I or a salt thereof,

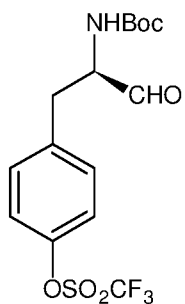


10

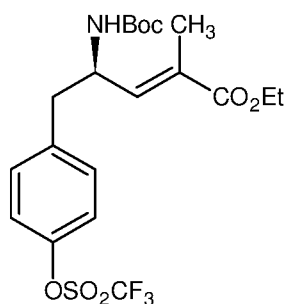
Formula I

wherein the process comprises:

- a) reacting a compound of Formula VI

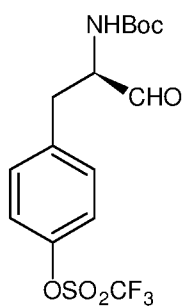
**Formula VI**

with ethyl 2-(triphenylphosphoranyl) propionate to obtain a compound of Formula V, and

**Formula V**

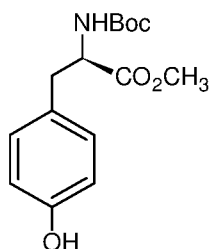
b) converting the compound of Formula V to sacubitril of Formula I or a salt thereof.

A twenty second aspect of the present invention provides a process for the preparation of a compound of Formula VI,

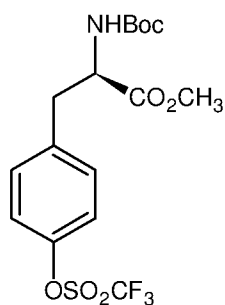
**Formula VI**

wherein the process comprises:

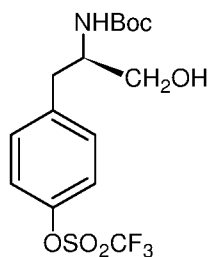
a) reacting a compound of Formula IX

**Formula IX**

with trifluoromethyl sulfonyl containing reagent to obtain a compound of Formula VIII,

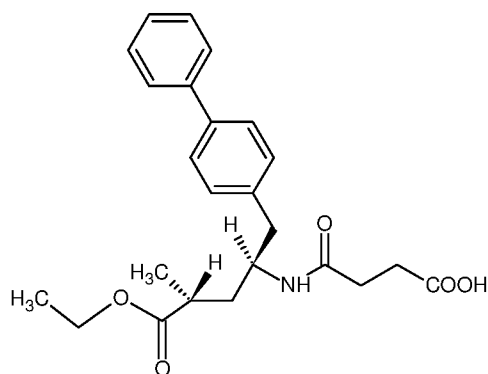
**Formula VIII**

b) reducing the compound of Formula VIII to obtain a compound of Formula VII, and

**Formula VII**

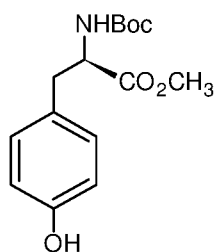
c) oxidizing the compound of Formula VII to obtain the compound of Formula VI.

A twenty third aspect of the present invention provides a process for the preparation of sacubitril of Formula I or a salt thereof,

**Formula I**

wherein the process comprises:

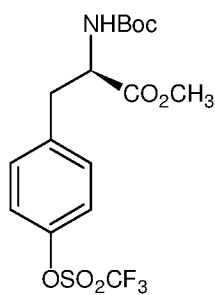
- a) reacting a compound of Formula IX



5

Formula IX

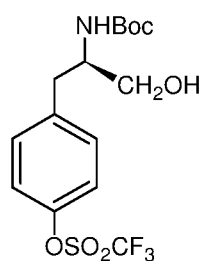
with trifluoromethyl sulfonyl containing reagent to obtain a compound of Formula VIII,



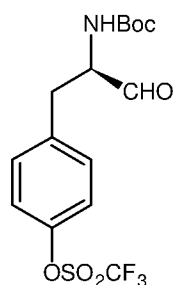
10

Formula VIII

- b) reducing the compound of Formula VIII to obtain a compound of Formula VII,

**Formula VII**

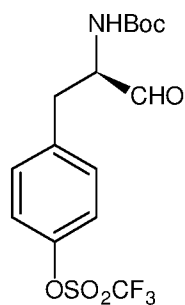
c) oxidizing the compound of Formula VII to obtain a compound of Formula VI, and

**Formula VI**

5

d) converting the compound of Formula VI to sacubitril of Formula I or a salt thereof.

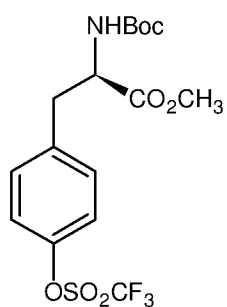
A twenty fourth aspect of the present invention provides a process for the preparation of a compound of Formula VI,

**Formula VI**

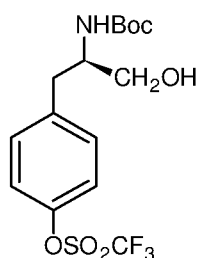
10

wherein the process comprises:

a) reducing a compound of Formula VIII

**Formula VIII**

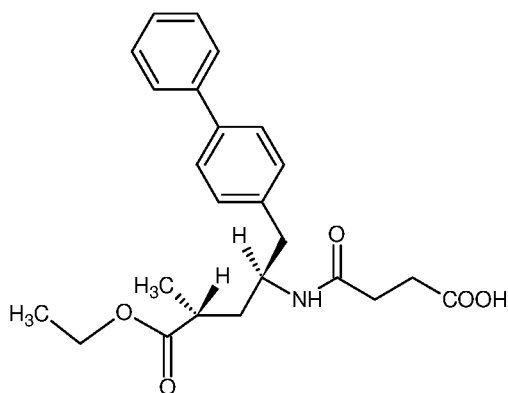
to obtain a compound of Formula VII, and

**Formula VII**

5

b) oxidizing the compound of Formula VII to obtain the compound of Formula VI.

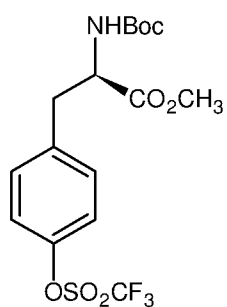
A twenty fifth aspect of the present invention provides a process for the preparation of sacubitril of Formula I or a salt thereof,

**Formula I**

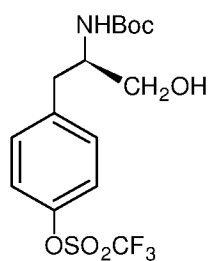
10

wherein the process comprises:

a) reducing a compound of Formula VIII,

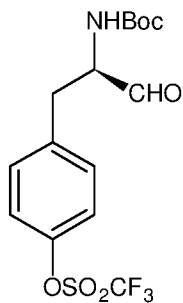
**Formula VIII**

to obtain a compound of Formula VII

**Formula VII**

5

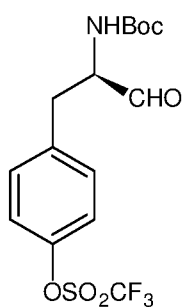
b) oxidizing the compound of Formula VII to obtain a compound of Formula VI, and

**Formula VI**

c) converting the compound of Formula VI to sacubitril of Formula I or a salt thereof.

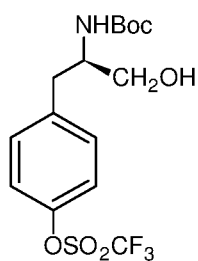
10

A twenty sixth aspect of the present invention provides a process for the preparation of a compound of Formula VI,



Formula VI

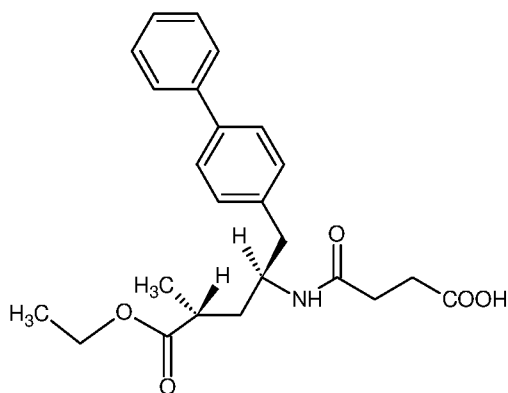
wherein the process comprises oxidizing a compound of Formula VII.



Formula VII

5

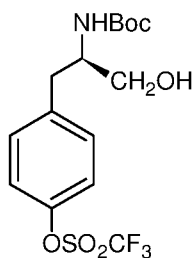
A twenty seventh aspect of the present invention provides a process for the preparation of sacubitril of Formula I or a salt thereof,



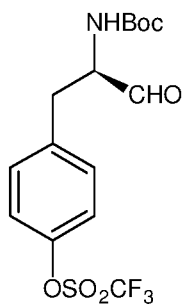
Formula I

10 wherein the process comprises:

- a) oxidizing a compound of Formula VII

**Formula VII**

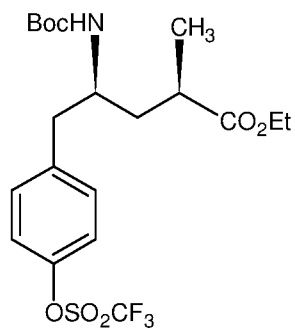
to obtain a compound of Formula VI, and

**Formula VI**

5

b) converting the compound of Formula VI to sacubitril of Formula I or a salt thereof.

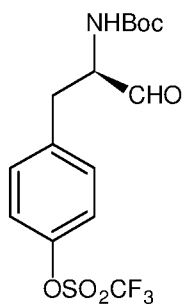
A twenty eighth aspect of the present invention provides a process for the preparation of a compound of Formula IV,

**Formula IV**

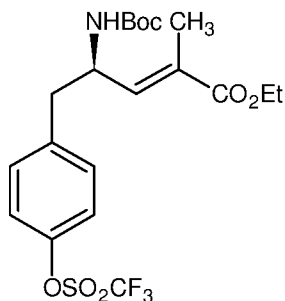
10

wherein the process comprises:

a) reacting a compound of Formula VI

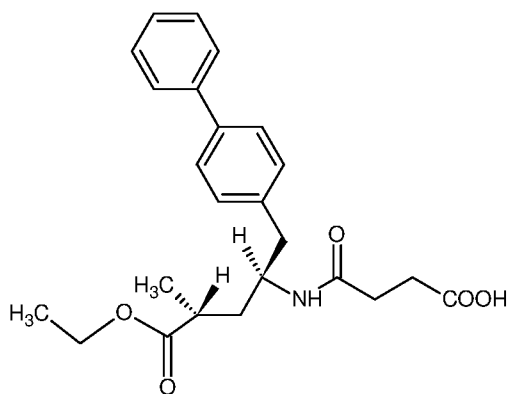
**Formula VI**

with ethyl 2-(triphenylphosphoranyl) propionate to obtain a compound of Formula V, and

**Formula V**

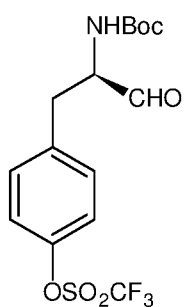
b) hydrogenating the compound of Formula V to obtain the compound of Formula IV.

A twenty ninth aspect of the present invention provides a process for the preparation of sacubitril of Formula I or a salt thereof,

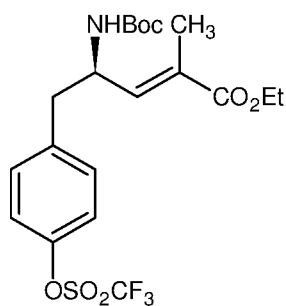
**Formula I**

wherein the process comprises:

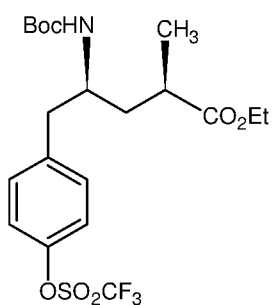
a) reacting a compound of Formula VI

**Formula VI**

with ethyl 2-(triphenylphosphoranyl) propionate to obtain a compound of Formula V,

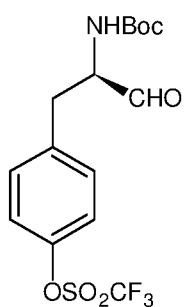
**Formula V**

- b) hydrogenating the compound of Formula V to obtain a compound of Formula IV,
and

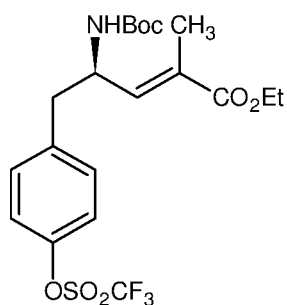
**Formula IV**

- c) converting the compound of Formula IV to sacubitril of Formula I or a salt thereof.

A thirtieth aspect of the present invention provides a compound of Formula VI.

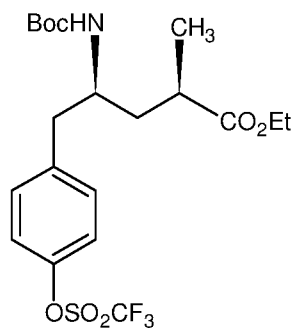
**Formula VI**

A thirty first aspect of the present invention provides a compound of Formula V.

**Formula V**

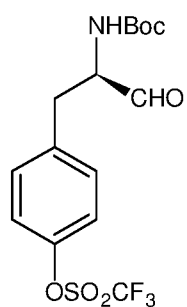
5

A thirty second aspect of the present invention provides a compound of Formula IV.

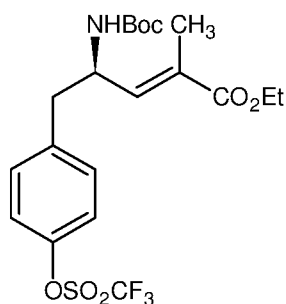
**Formula IV**

10

A thirty third aspect of the present invention provides use of a compound of Formula VI for the preparation of Sacubitril or a salt thereof.

**Formula VI**

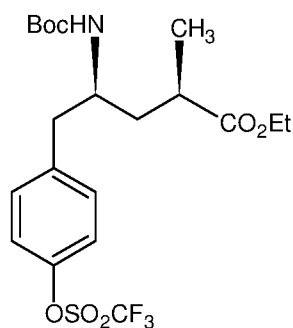
A thirty fourth aspect of the present invention provides use of a compound of Formula V for the preparation of Sacubitril or a salt thereof.



5

Formula V

A thirty fifth aspect of the present invention provides use of a compound of Formula IV for the preparation of sacubitril or a salt thereof.



10

Formula IV

The compound of Formula IX is prepared by any method known in the art, for example, European Patent No. 0,462,531 B, and U.S. Patent No. 7,375,231, both of which are incorporated by reference in this application for the methods for preparing the compound of Formula IX.

The compound of Formula IX is reacted with trifluoromethyl sulfonyl containing reagent to obtain a compound of Formula VIII in the presence of a base in a solvent.

The trifluoromethyl sulfonyl containing reagent is selected from the group consisting of trifluoromethyl sulfonic acid, trifluoromethyl sulfonyl chloride, and trifluoromethyl sulfonyl anhydride.

The base is selected from the group consisting of an organic and an inorganic base. Examples of an organic base include ethylamine, propyl amine, isopropyl amine, and triethyl amine. Examples of an inorganic base include hydroxides, carbonates and bicarbonates of alkali and alkaline metals, for example, sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, calcium carbonate, barium carbonate, magnesium carbonate, sodium bicarbonate, potassium bicarbonate, and magnesium bicarbonate.

The solvent is selected from the group consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated hydrocarbons, polar aprotic solvents, and mixtures thereof. Examples of aromatic hydrocarbons include toluene or benzene. Examples of ketones include acetone or methyl ethyl ketone. Examples of esters include ethyl acetate, n-propyl acetate, isopropyl acetate, or n-butyl acetate. Examples of ethers include methyl *t*-butyl ether or tetrahydrofuran. Examples of alkanols include primary, secondary and tertiary alcohols having from one to six carbon atoms. Suitable alkanols include methanol, ethanol, 1-propanol, 2-propanol, or butanol. Examples of halogenated hydrocarbons include dichloromethane, chloroform, or 1,2-dichloroethane. Examples of polar aprotic solvents include N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile, or N-methylpyrrolidone.

The compound of Formula IX is reacted with trifluoromethyl sulfonyl containing reagent at a temperature of about -10°C to about 55°C, for example, at about 0°C to about 45°C.

The compound of Formula IX is reacted with trifluoromethyl sulfonyl containing reagent for about 1 hour to about 5 hours, for example, for about 1 hour to about 2 hours.

The compound of Formula VIII may be isolated by methods including concentration, distillation, decantation, filtration, evaporation, centrifugation, or a combination thereof, and may further be dried.

The compound of Formula VIII is reduced to the compound of Formula VII in the presence of a buffer and a reducing agent in a solvent.

The buffer is selected from the group consisting of potassium hydrogen phosphate, di-potassium hydrogen phosphate, sodium hydrogen phosphate, and di-sodium hydrogen phosphate.

The reducing agent is selected from the group consisting of sodium borohydride, lithium aluminum hydride, diisobutylaluminum hydride, and borane.

The solvent is selected from the group consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated hydrocarbons, polar aprotic solvents, and mixtures thereof. Examples of aromatic hydrocarbons include toluene or benzene. Examples of ketones include acetone or methyl ethyl ketone. Examples of esters include ethyl acetate, n-propyl acetate, isopropyl acetate, or n-butyl acetate. Examples of ethers include methyl *t*-butyl ether or tetrahydrofuran. Examples of alkanols include primary, secondary and tertiary alcohols having from one to six carbon atoms. Suitable alkanols include methanol, ethanol, 1-propanol, 2-propanol, or butanol. Examples of halogenated hydrocarbons include dichloromethane, chloroform, or 1,2-dichloroethane. Examples of polar aprotic solvents include N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile, or N-methylpyrrolidone.

The compound of Formula VIII is reduced to the compound of Formula VII at a temperature of about 10°C to about 55°C, for example, at about 20°C to about 45°C.

The compound of Formula VIII is reduced to the compound of Formula VII for about 1 hour to about 5 hours, for example for about 2 hours to about 4 hours.

The compound of Formula VII may be isolated by methods including concentration, distillation, decantation, filtration, evaporation, centrifugation, or a combination thereof, and may further be dried.

The compound of Formula VII is oxidized to the compound of Formula VI in the presence of an oxidizing agent and a base in a solvent.

The oxidizing agent is selected from the group consisting of sodium hypochlorite/2,2,6,6-tetramethylpiperidinoxy (TEMPO), potassium permanganate, potassium dichromate, pyridinium chlorochromate (PCC), Dess-Martin periodinane (DMP), oxalyl chloride/dimethyl sulfoxide (DMSO), and chromium oxide/pyridine.

The base is selected from the group consisting of an organic and an inorganic base. Examples of an organic base include ethylamine, propyl amine, isopropyl amine, and triethyl amine. Examples of an inorganic base include hydroxides, carbonates and bicarbonates of alkali and alkaline metals, for example, sodium hydroxide, potassium
5 hydroxide, barium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, calcium carbonate, barium carbonate, magnesium carbonate, sodium bicarbonate, potassium bicarbonate, and magnesium bicarbonate.

The solvent is selected from the group consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated hydrocarbons, polar aprotic solvents, and
10 mixtures thereof. Examples of aromatic hydrocarbons include toluene or benzene. Examples of ketones include acetone or methyl ethyl ketone. Examples of esters include ethyl acetate, n-propyl acetate, isopropyl acetate, or n-butyl acetate. Examples of ethers include methyl *t*-butyl ether or tetrahydrofuran. Examples of alkanols include primary, secondary and tertiary alcohols having from one to six carbon atoms. Suitable alkanols
15 include methanol, ethanol, 1-propanol, 2-propanol, or butanol. Examples of halogenated hydrocarbons include dichloromethane, chloroform, or 1,2-dichloroethane. Examples of polar aprotic solvents include N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile, or N-methylpyrrolidone.

The compound of Formula VII is oxidized to the compound of Formula VI at a
20 temperature of about -10°C to about 45°C, for example, at about -10°C to about 25°C.

The compound of Formula VII is oxidized to the compound of Formula VI for about 0.5 hour to about 5 hours, for example, for about 1 hour to about 3 hours.

The compound of Formula VI may be used as such in the next step or may be isolated from the mixture by methods including concentration, distillation, decantation,
25 filtration, evaporation, centrifugation, or a combination thereof, and may further be dried.

The compound of Formula VI is reacted with ethyl 2-(triphenylphosphoranyl) propionate to obtain the compound of Formula V in a solvent.

The solvent is selected from the group consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated hydrocarbons, polar aprotic solvents, and
30 mixtures thereof. Examples of aromatic hydrocarbons include toluene or benzene. Examples of ketones include acetone or methyl ethyl ketone. Examples of esters include ethyl acetate, n-propyl acetate, isopropyl acetate, or n-butyl acetate. Examples of ethers

include methyl *t*-butyl ether or tetrahydrofuran. Examples of alkanols include primary, secondary and tertiary alcohols having from one to six carbon atoms. Suitable alkanols include methanol, ethanol, 1-propanol, 2-propanol, or butanol. Examples of halogenated hydrocarbons include dichloromethane, chloroform, or 1,2-dichloroethane. Examples of
5 polar aprotic solvents include N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile, or N-methylpyrrolidone.

The compound of Formula VI is reacted with ethyl 2-(triphenylphosphoranyl) propionate at a temperature of about 20°C to about 45°C, for example, at about 20°C to about 25°C.

10 The compound of Formula VI is reacted with ethyl 2-(triphenylphosphoranyl) propionate for about 10 hours to about 20 hours, for example, for about 15 hours to 18 hours.

The compound of Formula V may be isolated by methods including concentration, distillation, decantation, filtration, evaporation, centrifugation, or a combination thereof,
15 and may further be dried.

The compound of Formula V is hydrogenated to the compound of Formula IV in the presence of a hydrogenating agent in a solvent.

The hydrogenating agent is selected from the group consisting of transition metal/carbon, and an organometallic complex optionally in the presence of a chiral ligand.

20 The transition metal is selected from the group consisting of palladium, manganese, rhenium, iron, ruthenium, osmium, cobalt, rhodium, and iridium.

The chiral ligand is selected from the group consisting of carbon monoxide, halides, phosphines, naphthols, 1,1'-bi-2-naphthol (BINOL), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), $\alpha,\alpha,\alpha,\alpha$ -tetraaryl-1,3-dioxolane-4,5-dimethanols (TADDOL),
25 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane (DIOP), bis(oxazoline) ligands (BOX) and DuPhos (a phosphine ligand), cymene and mixtures thereof.

The solvent is selected from the group consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated hydrocarbons, polar aprotic solvents, and
30 mixtures thereof. Examples of aromatic hydrocarbons include toluene or benzene. Examples of ketones include acetone or methyl ethyl ketone. Examples of esters include

ethyl acetate, n-propyl acetate, isopropyl acetate, or n-butyl acetate. Examples of ethers include methyl *t*-butyl ether or tetrahydrofuran. Examples of alkanols include primary, secondary and tertiary alcohols having from one to six carbon atoms. Suitable alkanols include methanol, ethanol, 1-propanol, 2-propanol, or butanol. Examples of halogenated
5 hydrocarbons include dichloromethane, chloroform, or 1,2-dichloroethane. Examples of polar aprotic solvents include N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile, or N-methylpyrrolidone.

The compound of Formula V is hydrogenated to the compound of Formula IV at a temperature of about 20°C to about 45°C, for example, at about 20°C to about 25°C.

10 The compound of Formula V is hydrogenating to the compound of Formula IV for about 1 hour to about 10 hours, for example, for about 2 hours to about 5 hours.

The compound of Formula IV may be isolated by methods including concentration, distillation, decantation, filtration, evaporation, centrifugation, or a combination thereof, and may further be dried.

15 The compound of Formula IV is reacted with phenylboronic acid to obtain the compound of Formula III in the presence of a coupling agent and a base in a solvent.

The coupling agent is selected from the group consisting of tetrakis(triphenylphosphine) palladium(0), tris(dibenzylideneacetone)dipalladium and bis(dibenzylideneacetone)palladium (0).

20 The base is selected from the group consisting of an organic and an inorganic base. Examples of an organic base include ethylamine, propyl amine, isopropyl amine, and triethylamine. Examples of an inorganic base include hydroxides, carbonates and bicarbonates of alkali and alkaline metals, for example, sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate,
25 calcium carbonate, barium carbonate, magnesium carbonate, sodium bicarbonate, potassium bicarbonate, and magnesium bicarbonate.

The solvent is selected from the group consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated hydrocarbons, polar aprotic solvents, and mixtures thereof. Examples of aromatic hydrocarbons include toluene or benzene.

30 Examples of ketones include acetone or methyl ethyl ketone. Examples of esters include ethyl acetate, n-propyl acetate, isopropyl acetate, or n-butyl acetate. Examples of ethers include methyl *t*-butyl ether or tetrahydrofuran. Examples of alkanols include primary,

secondary and tertiary alcohols having from one to six carbon atoms. Suitable alkanols include methanol, ethanol, 1-propanol, 2-propanol, or butanol. Examples of halogenated hydrocarbons include dichloromethane, chloroform, or 1,2-dichloroethane. Examples of polar aprotic solvents include N,N-dimethylformamide, N,N-dimethylacetamide, 5 dimethylsulphoxide, acetonitrile, or N-methylpyrrolidone.

The compound of Formula IV is reacted with phenylboronic acid at a temperature of about 20°C to about 100°C, for example, at about 20°C to about 85°C.

The compound of Formula IV is reacted with phenylboronic acid for about 1 hour to about 10 hours, for example, for about 2 hours to about 5 hours.

10 The compound of Formula III may be isolated by methods including concentration, distillation, decantation, filtration, evaporation, centrifugation, or a combination thereof, and may further be dried.

The compound of Formula III is deprotected to obtain the compound of Formula II in the presence of a deprotecting agent in a solvent.

15 The deprotecting agent is selected from the group consisting of hydrochloric acid, trifluoroacetic acid, sulfuric acid, p-toluene sulfonic acid, and methane sulfonic acid

The solvent is selected from the group consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated hydrocarbons, polar aprotic solvents, and mixtures thereof. Examples of aromatic hydrocarbons include toluene or benzene.

20 Examples of ketones include acetone or methyl ethyl ketone. Examples of esters include ethyl acetate, n-propyl acetate, isopropyl acetate, or n-butyl acetate. Examples of ethers include methyl *t*-butyl ether or tetrahydrofuran. Examples of alkanols include primary, secondary and tertiary alcohols having from one to six carbon atoms. Suitable alkanols include methanol, ethanol, 1-propanol, 2-propanol, or butanol. Examples of halogenated 25 hydrocarbons include dichloromethane, chloroform, or 1,2-dichloroethane. Examples of polar aprotic solvents include N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile, or N-methylpyrrolidone.

The compound of Formula III is deprotected to the compound of Formula II at a temperature of about 20°C to about 75°C, for example, at about 30°C to about 70°C.

30 The compound of Formula III is deprotected to the compound of Formula II for about 0.5 hours to about 4 hours, for example, for about 1 hour to about 2 hours.

The compound of Formula II may be isolated by methods including concentration, distillation, decantation, filtration, evaporation, centrifugation, or a combination thereof, and may further be dried.

5 The compound of Formula II is reacted with succinic anhydride to obtain sacubitril of Formula I in the presence of a base in a solvent.

The base is selected from the group consisting of an organic and an inorganic base. Examples of an organic base include ethylamine, propyl amine, isopropyl amine, and triethylamine. Examples of an inorganic base include hydroxides, carbonates and bicarbonates of alkali and alkaline metals, for example, sodium hydroxide, potassium
10 hydroxide, barium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, calcium carbonate, barium carbonate, magnesium carbonate, sodium bicarbonate, potassium bicarbonate, and magnesium bicarbonate.

The solvent is selected from the group consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated hydrocarbons, polar aprotic solvents, and
15 mixtures thereof. Examples of aromatic hydrocarbon include toluene or benzene. Examples of ketones include acetone or methyl ethyl ketone. Examples of esters include ethyl acetate, n-propyl acetate, isopropyl acetate, or n-butyl acetate. Examples of ethers include methyl *t*-butyl ether or tetrahydrofuran. Examples of alkanols include primary, secondary and tertiary alcohols having from one to six carbon atoms. Suitable alkanols
20 include methanol, ethanol, 1-propanol, 2-propanol, or butanol. Examples of halogenated hydrocarbons include dichloromethane, chloroform, or 1,2-dichloroethane. Examples of polar aprotic solvents include N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile, or N-methylpyrrolidone.

25 The compound of Formula II is reacted with succinic anhydride at a temperature of about 5°C to about 30°C, for example, at about 5°C to about 20°C.

The compound of Formula II is reacted with succinic anhydride for about 1 hour to about 10 hours, for example, for about 1 hour to about 5 hours.

Sacubitril of compound of Formula I may be isolated by methods including concentration, distillation, decantation, filtration, evaporation, centrifugation, or a
30 combination thereof, and may further be dried.

Sacubitril of Formula I may be further converted to its salt or to a solid form of sacubitril and an angiotensin receptor antagonist, for example, valsartan, irbesartan,

telmisartan, in their salt form or their hydrates, by the analogous methods provided in PCT Publication No. WO 2007/056546 and U.S. Patent No. 7,468,390, which are incorporated herein by reference, or process as described herein.

5 Examples of salts include monovalent salt or bivalent salt. The monovalent salt includes lithium, sodium, potassium, rubidium, cesium, or NR_4^+ (wherein R is hydrogen or C_{1-6} alkyl). The bivalent salt includes barium, magnesium, calcium, zinc, and strontium salt. The salt of sacubitril of compound of Formula I also includes benzathine, choline, diethanolamine, ethylenediamine, meglumine, diethylamine, piperazine, or benzylamine salt.

10 While the present invention has been described in terms of its specific aspects and embodiments, 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.

The following examples are for illustrative purposes only and should not be construed as limiting the scope of the invention in any way.

15 EXAMPLES

Example 1: Preparation of methyl N-(tert-butoxycarbonyl)-O-[(trifluoromethyl) sulfonyl]-D-tyrosinate (Formula VIII)

Toluene (400 mL) was added to methyl N-(tert-butoxycarbonyl)-D-tyrosinate (a compound of Formula IX) (100.0 g) at 20°C to 25°C. The mixture was cooled to 0°C to 5°C and triethyl amine (71.3 mL) was added. Trifluoromethyl sulfonyl anhydride (68.6 mL) was drop wise added to the reaction mixture at 0°C to 5°C and then the reaction mixture was stirred at 5°C to 15°C for 1.5 hours. Water (200 mL) was added to the reaction mixture at 20°C to 25°C and the reaction mixture was stirred at 20°C to 25°C for 15 minutes. The layers obtained were separated and toluene (400 mL) was recovered from the organic layer under 150 mm to 9 mm of Hg pressure at 40°C to 45°C for 1.0 hour to obtain the title compound.

20
25

Yield: 140.0 g

Example 2: Preparation of 4-[(2R)-2-[(tert-butoxycarbonyl)amino]-3-hydroxypropyl] phenyl trifluoromethanesulfonate (Formula VII)

30 2-Propanol (600 mL) was added to a compound of Formula VIII (120.0 g; example 1) at 20°C to 25°C. A solution of potassium hydrogen phosphate ((144.0 g) in water (150

mL)) was added to the mixture and the reaction mixture was cooled to 5°C to 10°C. A solution of sodium borohydride ((24.9 g) in water (90 mL)) was added to the reaction mixture at 10°C to 15°C and the reaction mixture was stirred at 20°C to 25°C for 2 hours. The layers obtained were separated and 2-propanol (600 mL) was recovered from the reaction mixture under 150 mm to 9 mm of Hg pressure at 40°C to 45°C. Ethyl acetate (360 mL) was added to the reaction mixture followed by the addition of water (240 mL). The reaction mixture was cooled to 10°C to 15°C and the pH was adjusted to 5.0 to 5.5 by adding 1N hydrochloric acid (15 mL) at 10°C to 15°C. The reaction mixture was stirred for 15 minutes and the layers obtained were separated. The ethyl acetate (360 mL) obtained was recovered from the reaction mixture under 190 mm to 9 mm of Hg pressure at 40°C to 45°C for 40 minutes to obtain the title compound.

Yield: 110.0 g

Example 3: Preparation of 4-{{(2*R*)-2-[(*tert*-butoxycarbonyl)amino]-3-oxopropyl}phenyl trifluoromethanesulfonate (Formula VI)

Dichloromethane (840 mL) was added to a compound of Formula VII (105.0 g; example 2) at 20°C to 25°C. De-ionized water (262.5 mL) was added and the reaction mixture was cooled to -10°C to -5°C. Sodium bromide (13.5 g), sodium bicarbonate (44.1 g) and TEMPO (2.99 g) were added to the reaction mixture at -10°C to -5°C. A solution of 7% sodium hypochlorite (475 mL) was added to the reaction mixture at -10°C to -5°C and stirred for 1 hour. A solution of 20% sodium thiosulfate (100 mL) was added to the reaction mixture at -10°C to 0°C and stirred for 40 minutes at 0°C to 10°C. The layers obtained were separated and dichloromethane layer was washed with sodium chloride solution (20%, 500 mL). Dichloromethane layer (900 mL) was collected and was used as such in the next step.

Mass: 397.4 [M + H]⁺; **MS/MS:** 398.2, 358.2, 356.3, 344.3, 326.3, 300.1, 156.2, 142.2.

Example 4: Preparation of ethyl (2*E*,4*R*)-4-[(*tert*-butoxycarbonyl)amino]-2-methyl-5-(4-{{(trifluoromethyl)sulfonyl}oxy}phenyl)pent-2-enoate (Formula V)

Ethyl 2-(triphenylphosphoranyl) propionate (120.6 g) was added to dichloromethane solution (900 mL) of a compound of Formula VI (example 3) at 20°C to 25°C and stirred for 16 hours. Dichloromethane (900 mL) was recovered under 400 mm to 10 mm of Hg pressure at 40°C to 45°C. The solid obtained was purified using silica gel

column using ethyl acetate: hexane solvent system as 5:95 (10 L) to obtain the title compound.

Yield: 72.0 g

¹H NMR (400 MHz, CDCl₃), δ (in ppm): 7.20 (d, 2H), 7.13 (d, 2H), 6.43 (d, 1H), 4.58 (bs, 1NH), 4.19 (m, 3H), 2.88 (s, 1H), 2.74 (s, 1H), 1.97 (s, 1H), 1.87 (s, 1H), 1.60 (s, 2H), 1.20 (s, 3H), 1.28 (s 9H).

Mass: 481.4 [M + H]⁺; **MS/MS:** 482.4, 426.3, 382.2, 365.2, 336.2, 155.1, 127.0.

Example 5: Preparation of ethyl (2*R*,4*S*)-4-[(tert-butoxycarbonyl)amino]-2-methyl-5-(4-[[trifluoromethyl)sulfonyl]oxy}phenyl)pentanoate (Formula IV)

10 Methanol (210 mL) was added to the compound of Formula V (30.0 g; example 4) at 20°C to 25°C. Palladium/carbon (10% wet, 1.5 g) was added to the reaction mixture. The reaction mixture obtained was kept in Parr apparatus under hydrogen pressure (3.5-4.0 Kg) at 20°C to 25°C and stirred for 4 hours. The reaction mixture obtained was filtered through celite. The methanol (210 mL) was recovered from the reaction mixture
15 under 190 mm to 9 mm of Hg pressure at 40°C to 45°C to obtain the solid material (29.0 g). The solid material (29.0 g) was purified using silicagel column using ethyl acetate: hexane solvent system as 5: 95 (4 L) to obtain the title compound.

Yield: 24.5 g

¹H NMR (400 MHz, CDCl₃), δ (in ppm): 7.19 (d, J = 7.1 Hz, 2H), 7.11 (d, J = 7.1 Hz, 2H), 4.29 (m, 1H), 4.06 (m, 1H), 3.79 (m, 1H), 2.71 (m, 2H), 2.66 (m, 1H), 1.96 (m, 1H), 1.38 (s, 9H), 1.28 (t, 3H), 1.13 (d, 3H).

Mass: 483.4 [M + H]⁺; **MS/MS:** 484.4, 428.4, 385.2, 367.2, 336.3, 293.2, 236.2.

Example 6: Preparation of ethyl (2*R*,4*S*)-5-(biphenyl-4-yl)-4-[(tert-butoxycarbonyl)amino]-2-methylpentanoate (Formula III)

25 Toluene (240 mL) was added to the compound of Formula IV (24.0 g; example 5) at 20°C to 25°C. Phenylboronic acid (12.1 g), potassium carbonate (13.7 g) and tetrakis(triphenylphosphine) palladium(0) (1.72 g) were added sequentially to the mixture at 20°C to 25°C. The reaction mixture was degassed by purging with nitrogen gas for 10 minutes. The reaction mixture was heated to 80°C to 85°C and stirred for 2 hours. The
30 reaction mixture was cooled to 20°C to 25°C and filtered through celite. Toluene layer was washed with aqueous sodium hydroxide solution (5%, 100 mL), 1N hydrochloric acid

(100 mL) and de-ionized water (100 mL) sequentially. Toluene (290 mL) was recovered from the reaction mixture under 150 mm to 9 mm of Hg pressure at 40°C to 45°C to obtain the solid material (27.0 g). The solid material (27.0 g) was purified using silica gel column using ethyl acetate: hexane solvent system as 5: 95 (3 L) to obtain the title compound.

Yield: 18.0 g

Example 7: Preparation of ethyl (2*R*,4*S*)-4-amino-5-(biphenyl-4-yl)-2-methylpentanoate (Formula II)

A solution of hydrochloric acid in ethanol (10%, 32 mL) was added to the compound of Formula III (16.0 g; example 6) at 20°C to 25°C. The reaction mixture was heated to 65°C to 70°C and stirred for 1 hour. The reaction mixture was further cooled to 20°C to 25°C. Ethanol (80 mL) was recovered from the reaction mixture under 150 mm to 9 mm of Hg at 40°C to 45°C. The solid material (20 g) obtained was dissolved in toluene (64 mL) and water (48 mL) and the reaction mixture was cooled to 5°C to 10°C. The pH was adjusted to 9 by adding aqueous sodium hydroxide solution (10%, 15 mL) at 5°C to 10°C and the reaction mixture was stirred for 15 minutes. The layers obtained were separated at 20°C to 25°C. The toluene layer (48 mL) was collected and used as such in the next step.

Example 8: Preparation of sacubitril (Formula I)

Succinic anhydride (5.0 g) and diisopropyl ethyl amine (4.0 mL) were added to toluene (32 mL) at 5°C to 10°C. A solution of the compound of Formula II in toluene (64.0 mL; example 7) was added to the reaction mixture at 5°C to 10°C. The reaction mixture was stirred at 5°C to 10°C for 1 hour. Water (30 mL) was added to the reaction mixture and the pH of the solution was adjusted to 2.0 by adding 1N hydrochloric acid (15 mL) at 5°C to 10°C. The reaction mixture was stirred at 5°C to 10°C for 10 minutes. The layers obtained were separated and the toluene (90 mL) was recovered from the organic layer under 400 mm to 9 mm of Hg pressure for 40 minutes to obtain the title compound.

Yield: 20.0 g

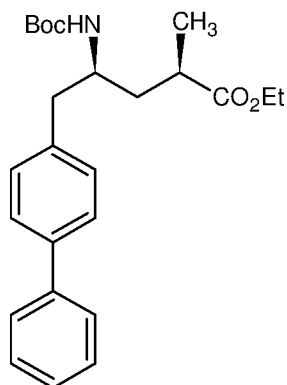
Example 9: Preparation of sodium salt of sacubitril (Formula I)

Sacubitril (130.0 g) was added to methanol (520 mL) and the reaction mixture was cooled to 5°C to 10°C. A solution of sodium hydroxide (12.26 g in 30 mL of water) was

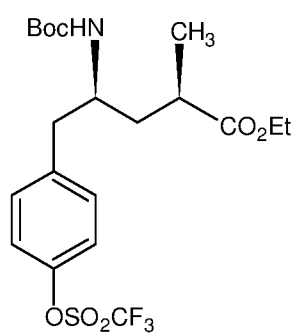
- added to the reaction mixture at 5°C to 10°C and the reaction mixture was stirred for 2 hours. Methanol and water (530 mL) were recovered from the reaction mixture under reduced 200 mm to 10 mm of Hg pressure at 40°C to 45°C. Acetone (390 mL) was added to the reaction mixture at 40°C to 45°C and the mixture was stirred for 15 minutes.
- 5 Acetone (390 mL) was recovered from the reaction mixture under reduced 300 mm to 10 mm of Hg pressure at 40°C to 45°C. Cyclohexane (390 mL) was added to the reaction mixture and stirred for 30 minutes at 20°C to 25°C. The reaction mixture was filtered and washed with cyclohexane (130 mL) to obtain the solid material (135 g) and dried under vacuum at 650 mm to 680 mm of Hg at 40°C to 45°C for 20 hours to obtain the title
- 10 compound.
- Yield: 116.0 g

We Claim:

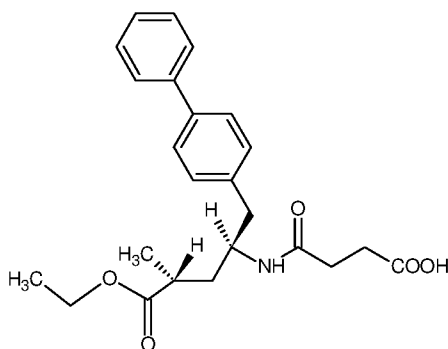
1. A process for the preparation of a compound of Formula III,

**Formula III**

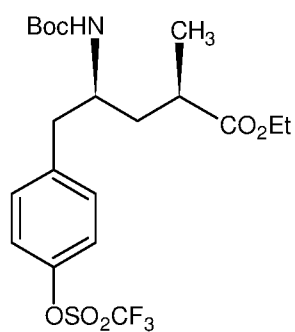
- wherein the process comprises reacting a compound of Formula IV with phenylboronic acid.

**Formula IV**

2. The process according to claim 1, wherein the compound of Formula III is further converted into sacubitril of Formula I or a salt thereof.

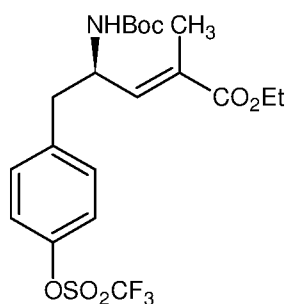
**Formula I**

- 1 3. A process for the preparation of a compound of Formula IV,



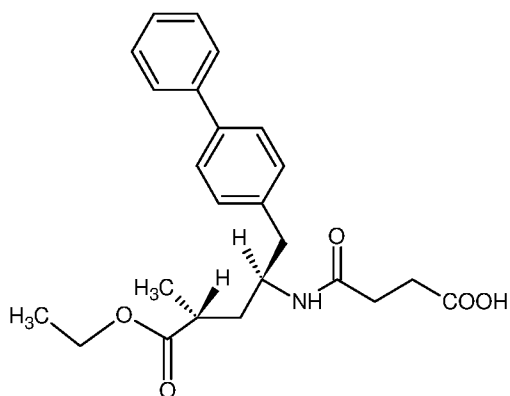
2
3 **Formula IV**

- 4 wherein the process comprises hydrogenating a compound of Formula V.



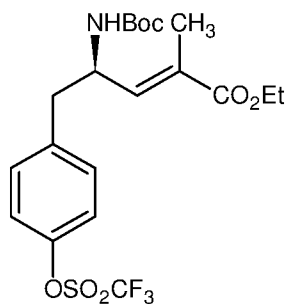
5
6 **Formula V**

- 1 4. The process according to claim 3, wherein the compound of Formula IV is further
2 converted into sacubitril of Formula I or a salt thereof.



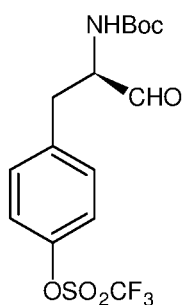
3
4 **Formula I**

- 1 5. A process for the preparation of a compound of Formula V,



Formula V

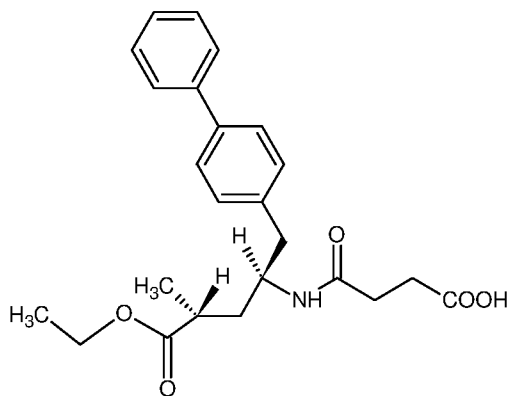
wherein the process comprises reacting a compound of Formula VI



Formula VI

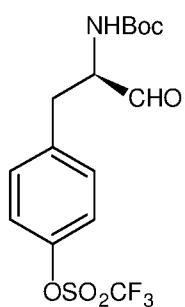
with ethyl 2-(triphenylphosphoranyl) propionate.

6. The process according to claim 5, wherein the compound of Formula V is further converted into sacubitril of Formula I or a salt thereof.



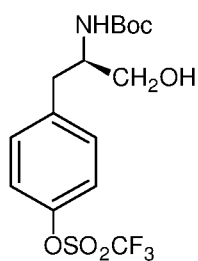
Formula I

7. A process for the preparation of a compound of Formula VI,



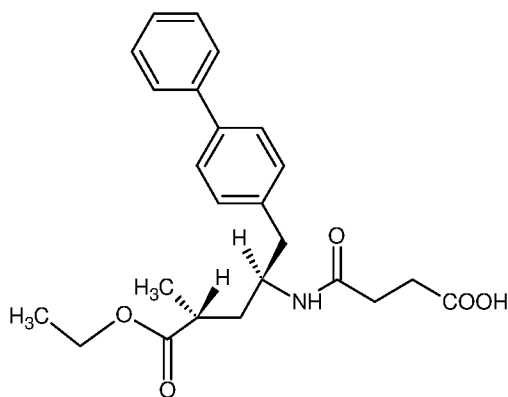
Formula VI

wherein the process comprises oxidizing a compound of Formula VII.



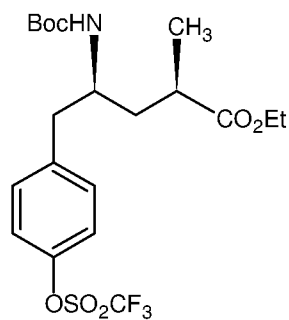
Formula VII

8. The process according to claim 7, wherein the compound of Formula VI is further converted into sacubitril of Formula I or a salt thereof.



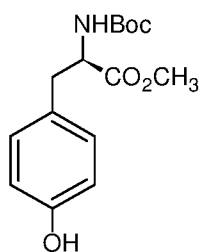
Formula I

9. A process for the preparation of a compound of Formula IV,

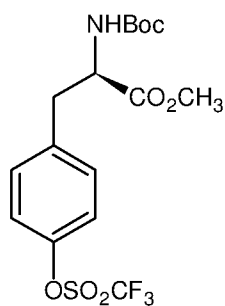
**Formula IV**

wherein the process comprises:

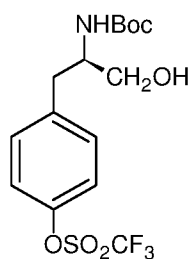
a) reacting a compound of Formula IX

**Formula IX**

with trifluoromethyl sulfonyl containing reagent to obtain a compound of Formula VIII,

**Formula VIII**

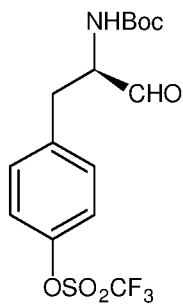
b) reducing the compound of Formula VIII to obtain a compound of Formula VII,



13

Formula VII

14 c) oxidizing the compound of Formula VII to obtain a compound of Formula VI,



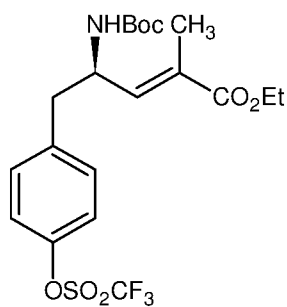
15

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Formula VI

17 d) reacting the compound of Formula VI with ethyl 2-(triphenylphosphoranyl)

18 propionate to obtain a compound of Formula V, and



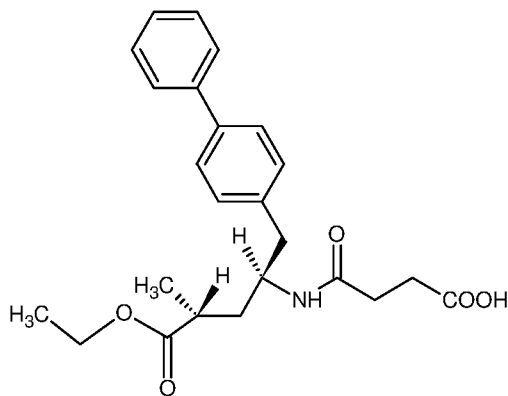
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Formula V

21 e) hydrogenating the compound of Formula V to obtain the compound of Formula IV.

1 10. The process according to claim 9, wherein the compound of Formula IV is further
 2 converted into sacubitril of Formula I or a salt thereof.

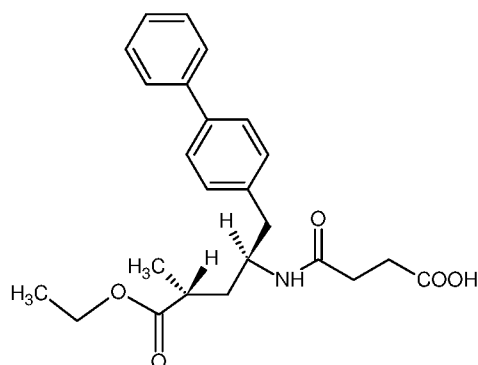


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Formula I

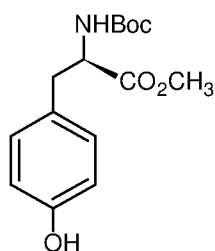
- 1 11. A process for the preparation of sacubitril of Formula I or a salt thereof,



2
3 **Formula I**

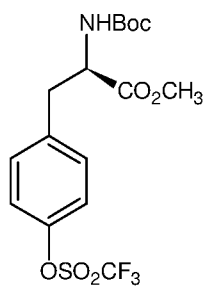
4 wherein the process comprises:

- 5 a) reacting a compound of Formula IX,



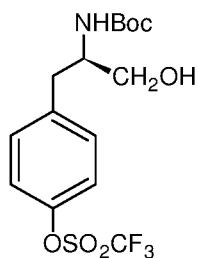
6
7 **Formula IX**

8 with trifluoromethyl sulfonyl containing reagent to obtain a compound of Formula VIII,



9
10 **Formula VIII**

- 11 b) reducing the compound of Formula VIII to obtain a compound of Formula VII,

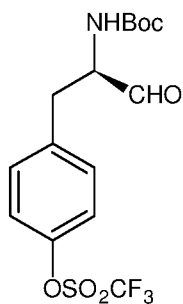


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Formula VII

14 c) oxidizing the compound of Formula VII to obtain a compound of Formula VI,

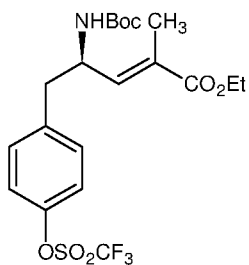


15

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Formula VI

17 d) reacting the compound of Formula VI with ethyl 2-(triphenylphosphoranyl)
18 propionate to obtain a compound of Formula V,

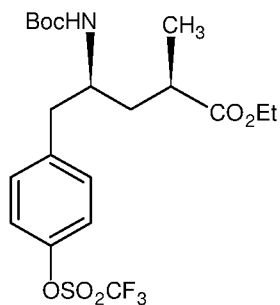


19

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Formula V

21 e) hydrogenating the compound of Formula V to obtain a compound of Formula IV,

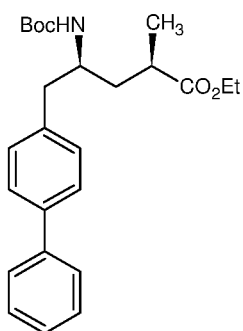


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Formula IV

- 24 f) reacting the compound of Formula IV with phenylboronic acid to obtain a
 25 compound of Formula III,

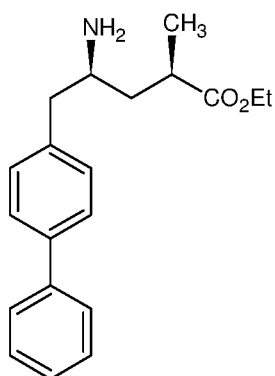


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Formula III

- 28 g) deprotecting the compound of Formula III to obtain a compound of Formula II,
 29 and



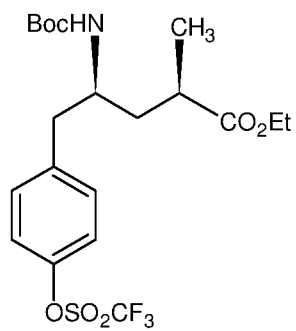
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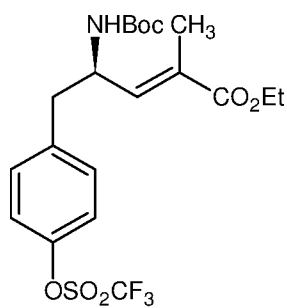
Formula II

- 32 h) reacting the compound of Formula II with succinic anhydride to obtain sacubitril
 33 of Formula I or a salt thereof.

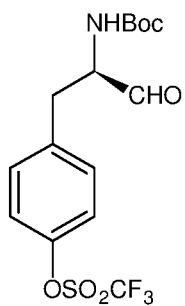
1 12. A compound of Formula IV,

**Formula IV**

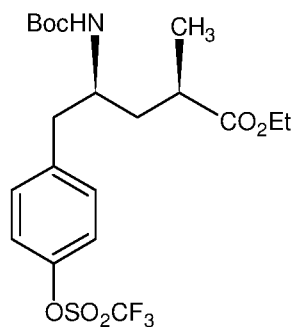
13. A compound of Formula V,

**Formula V**

14. A compound of Formula VI,

**Formula VI**

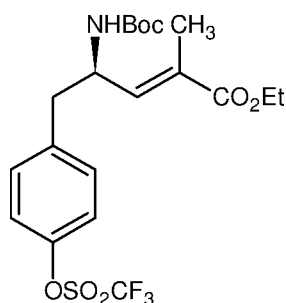
- 1 15. Use of a compound of Formula IV for the preparation of sacubitril or a salt thereof.



2

3 **Formula IV**

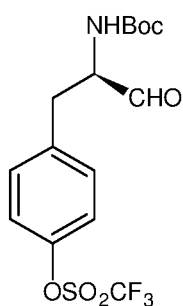
- 1 16. Use of a compound of Formula V for the preparation of Sacubitril or a salt thereof.



2

3 **Formula V**

- 1 17. Use of a compound of Formula VI for the preparation of Sacubitril or a salt
2 thereof.



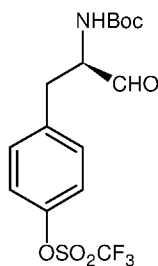
3

4 **Formula VI**

- 1 18. The process according to claim 1, wherein the compound of Formula IV is reacted
2 with phenylboronic acid in the presence of a coupling agent and a base in a solvent.

- 1 19. The process according to claim 18, wherein the coupling agent is selected from the
2 group consisting of tetrakis(triphenylphosphine) palladium(0),
3 tris(dibenzylideneacetone)dipalladium and bis(dibenzylideneacetone)palladium (0).

- 1 20. The process according to claim 18, wherein the base is selected from the group
2 consisting of an organic and an inorganic base.
- 1 21. The process according to claim 18, wherein the solvent is selected from the group
2 consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated
3 hydrocarbons, polar aprotic solvents, and mixtures thereof.
- 1 22. The process according to claim 3, wherein the compound of Formula V is
2 hydrogenated in the presence of a hydrogenating agent in a solvent.
- 1 23. The process according to claim 22, wherein the hydrogenating agent is selected
2 from the group consisting of metal/ carbon and an organometallic complex optionally in
3 the presence of a chiral ligand.
- 1 24. The process according to claim 22, wherein the solvent is selected from the group
2 consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated
3 hydrocarbons, polar aprotic solvents, and mixtures thereof.
- 1 25. The process according to claim 23, wherein the transition metal is selected from
2 the group consisting of palladium, manganese, rhenium, iron, ruthenium, osmium, cobalt,
3 rhodium, and iridium.
- 1 26. The process according to claim 23, wherein the chiral ligand is selected from the
2 group consisting of carbon monoxide, halides, phosphines, naphthols, 1,1'-bi-2-naphthol
3 (BINOL), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), $\alpha,\alpha,\alpha,\alpha$ -tetraaryl-1,3-
4 dioxolane-4,5-dimethanols (TADDOL), 2,3-O-isopropylidene-2,3-dihydroxy-1,4-
5 bis(diphenylphosphino)butane (DIOP), bis(oxazoline) ligands (BOX) and DuPhos (a
6 phosphine ligand), cymene and mixtures thereof.
- 1 27. The process according to claim 3, wherein the compound of Formula V is prepared
2 by reacting a compound of Formula VI



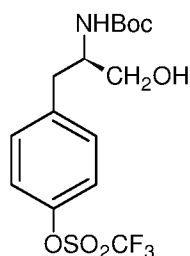
3
4 **Formula VI**

- 5 with ethyl 2-(triphenylphosphoranyl) propionate.

1 28. The process according to claim 27, wherein the reaction of the compound of the
2 Formula VI with ethyl 2-(triphenylphosphoranyl) propionate is carried out in a solvent.

1 29. The process according to claim 28, wherein the solvent is selected from the group
2 consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated
3 hydrocarbons, polar aprotic solvents, and mixtures thereof.

1 30. The process according to claim 27, wherein the compound of Formula VI is
2 prepared by oxidizing a compound of Formula VII.



3
4 **Formula VII**

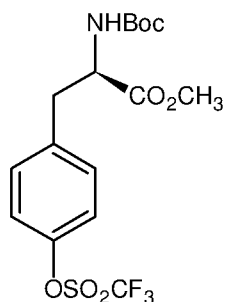
1 31. The process according to claim 30, wherein the oxidation is carried out in the
2 presence of an oxidizing agent and a base in a solvent.

1 32. The process according to claim 31, wherein the oxidizing agent is selected from the
2 group consisting of sodium hypochlorite/2,2,6,6-tetramethylpiperidinoxy (TEMPO),
3 potassium permanganate, potassium dichromate, pyridinium chlorochromate (PCC), dess-
4 martin periodinane (DMP), oxalyl chloride/dimethyl sulfoxide (DMSO) , and chromium
5 oxide/pyridine.

1 33. The process according to claim 31, wherein the base is selected from the group
2 consisting of an organic and an inorganic base.

1 34. The process according to claim 31, wherein the solvent is selected from the group
2 consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated
3 hydrocarbons, polar aprotic solvents, and mixtures thereof.

1 35. The process according to claim 30, wherein the compound of Formula VII is
2 prepared by reducing a compound of Formula VIII.



Formula VIII

36. The process according to claim 35, wherein the reduction is carried out in the presence of a buffer and a reducing agent in a solvent.

37. The process according to claim 36, wherein the buffer is selected from the group consisting of potassium hydrogen phosphate, di-potassium hydrogen phosphate, sodium hydrogen phosphate, and di-sodium hydrogen phosphate.

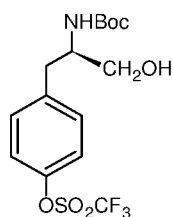
38. The process according to claim 36, wherein the reducing agent is selected from the group consisting of sodium borohydride, lithium aluminum hydride, diisobutylaluminum hydride, and borane.

39. The process according to claim 36, wherein the solvent is selected from the group consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated hydrocarbons, polar aprotic solvents, and mixtures thereof.

40. The process according to claim 5, wherein the reaction of the compound of Formula VI with ethyl 2-(triphenyl)phosphoranyl)propionate is carried out in a solvent.

41. The process according to claim 40, wherein the solvent is selected from the group consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated hydrocarbons, polar aprotic solvents, and mixtures thereof.

42. The process according to claim 5, wherein the compound of Formula VI is prepared by oxidizing a compound of Formula VII.



Formula VII

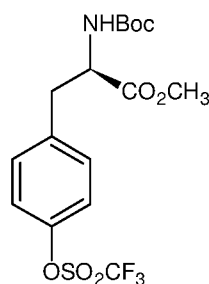
1 43. The process according to claim 42, wherein the oxidation of the compound of
2 Formula VII is carried out in the presence of an oxidizing agent and a base in a solvent.

1 44. The process according to claim 43, wherein the oxidizing agent is selected from the
2 group consisting of sodium hypochlorite/2,2,6,6-tetramethylpiperidinoxy (TEMPO),
3 potassium permanganate, potassium dichromate, pyridinium chlorochromate (PCC), dess-
4 martin periodinane (DMP), oxalyl chloride/dimethyl sulfoxide (DMSO), and chromium
5 oxide/pyridine.

1 45. The process according to claim 43, wherein the base is selected from the group
2 consisting of an organic and an inorganic base.

1 46. The process according to claim 43, wherein the solvent is selected from the group
2 consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated
3 hydrocarbons, polar aprotic solvents, and mixtures thereof.

1 47. The process according to claim 42, wherein the compound of Formula VII is
2 prepared by reducing a compound of Formula VIII.



3
4 **Formula VIII**

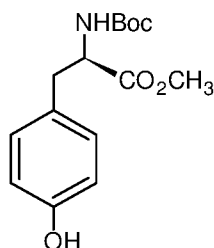
1 48. The process according to claim 47, wherein the reduction of the compound of
2 Formula VIII is carried out in the presence of a buffer and a reducing agent in a solvent.

1 49. The process according to claim 48, wherein the buffer is selected from the group
2 consisting of potassium hydrogen phosphate, di- potassium hydrogen phosphate, sodium
3 hydrogen phosphate, and di-sodium hydrogen phosphate.

1 50. The process according to claim 48, wherein the reducing agent is selected from the
2 group consisting of sodium borohydride, lithium aluminum hydride, diisobutylaluminum
3 hydride, and borane.

1 51. The process according to claim 48, wherein the solvent is selected from the group
2 consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated
3 hydrocarbons, polar aprotic solvents, and mixtures thereof.

- 1 52. The process according to claim 47, wherein the compound of Formula VIII is
 2 prepared by reacting a compound of Formula IX



3

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Formula IX

- 5 with a trifluoromethyl sulfonyl containing reagent in the presence of a base in a solvent.

- 1 53. The process according to claim 52, wherein the trifluoromethyl sulfonyl containing
 2 reagent is selected from the group consisting of trifluoromethyl sulfonic acid,
 3 trifluoromethyl sulfonyl chloride, and trifluoromethyl sulfonyl anhydride.

- 1 54. The process according to claim 52, wherein the base is selected from the group
 2 consisting of an organic and an inorganic base.

- 1 55. The process according to claim 52, wherein the solvent is selected from the group
 2 consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated
 3 hydrocarbons, polar aprotic solvents, and mixtures thereof.

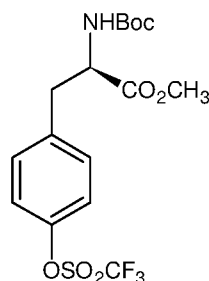
- 1 56. The process according to claim 7, wherein the compound of Formula VII is
 2 oxidized in the presence of an oxidizing agent and a base in a solvent.

- 1 57. The process according to claim 56, wherein the oxidizing agent is selected from
 2 the group consisting of sodium hypochlorite/2,2,6,6-tetramethylpiperidinoxy (TEMPO),
 3 potassium permanganate, potassium dichromate, pyridinium chlorochromate (PCC), Dess-
 4 martin periodinane (DMP), oxalyl chloride/dimethyl sulfoxide (DMSO), and chromium
 5 oxide/pyridine.

- 1 58. The process according to claim 56, wherein the base is selected from the group
 2 consisting of an organic and an inorganic base.

- 1 59. The process according to claim 56, wherein the solvent is selected from the group
 2 consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated
 3 hydrocarbons, polar aprotic solvents, and mixtures thereof.

- 1 60. The process according to claim 7, wherein the compound of Formula VII is
 2 prepared by reducing a compound of Formula VIII.



Formula VIII

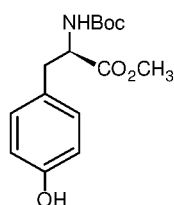
61. The process according to claim 60, wherein the reduction of the compound of Formula VIII is carried out in the presence of a buffer and a reducing agent in a solvent.

62. The process according to claim 61, wherein the buffer is selected from the group consisting of potassium hydrogen phosphate, di-potassium hydrogen phosphate, sodium hydrogen phosphate, and di-sodium hydrogen phosphate.

63. The process according to claim 61, wherein the reducing agent is selected from the group consisting of sodium borohydride, lithium aluminum hydride, diisobutylaluminum hydride, and borane.

64. The process according to claim 61, wherein the solvent is selected from the group consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated hydrocarbons, polar aprotic solvents, and mixtures thereof.

65. The process according to claim 60, wherein the compound of Formula VIII is prepared by reacting a compound of Formula IX



Formula IX

with a trifluoromethyl sulfonyl containing reagent in the presence of a base in a solvent.

66. The process according to claim 65, wherein the trifluoromethyl sulfonyl containing reagent is selected from the group consisting of trifluoromethyl sulfonic acid, trifluoromethyl sulfonyl chloride, and trifluoromethyl sulfonyl anhydride.

67. The process according to claim 65, wherein the base is selected from the group consisting of an organic and an inorganic base.

- 1 68. The process according to claim 65, wherein the solvent is selected from the group
2 consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated
3 hydrocarbons, polar aprotic solvents, and mixtures thereof.
- 1 69. The process according to claim 9, wherein the reaction of the compound of
2 Formula IX with a trifluoromethyl sulfonyl containing reagent is carried out in the
3 presence of a base in a solvent.
- 1 70. The process according to claim 69, wherein the trifluoromethyl sulfonyl containing
2 reagent is selected from the group consisting of trifluoromethyl sulfonic acid,
3 trifluoromethyl sulfonyl chloride, and trifluoromethyl sulfonyl anhydride.
- 1 71. The process according to claim 69, wherein the base is selected from the group
2 consisting of an organic and an inorganic base.
- 1 72. The process according to claim 69, wherein the solvent is selected from the group
2 consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated
3 hydrocarbons, polar aprotic solvents, and mixtures thereof.
- 1 73. The process according to claim 9, wherein the reduction of the compound of
2 Formula VIII is carried out in the presence of a buffer and a reducing agent in a solvent.
- 1 74. The process according to claim 73, wherein the buffer is selected from the group
2 consisting of potassium hydrogen phosphate, di- potassium hydrogen phosphate, sodium
3 hydrogen phosphate, and di-sodium hydrogen phosphate.
- 1 75. The process according to claim 73, wherein the reducing agent is selected from the
2 group consisting of sodium borohydride, lithium aluminum hydride, diisobutylaluminum
3 hydride, and borane.
- 1 76. The process according to claim 73, wherein the solvent is selected from the group
2 consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated
3 hydrocarbons, polar aprotic solvents, and mixtures thereof.
- 1 77. The process according to claim 9, wherein the oxidation of the compound of
2 Formula VII is carried out in the presence of an oxidizing agent and a base in a solvent.
- 1 78. The process according to claim 77, wherein the oxidizing agent is selected from
2 the group consisting of sodium hypochlorite/2,2,6,6-tetramethylpiperidinoxy (TEMPO),
3 potassium permanganate, potassium dichromate, pyridinium chlorochromate (PCC), dess-
4 martin periodinane (DMP), oxalyl chloride/dimethyl sulfoxide (DMSO), and chromium
5 oxide/pyridine.
- 1 79. The process according to claim 77, wherein the base is selected from the group
2 consisting of an organic and an inorganic base.

- 1 80. The process according to claim 77, wherein the solvent is selected from the group
2 consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated
3 hydrocarbons, polar aprotic solvents, and mixtures thereof.
- 1 81. The process according to claim 9, wherein the reaction of the compound of
2 Formula VI with ethyl 2-(triphenylphosphoranyl) propionate is carried out in a solvent.
- 1 82. The process according to claim 81, wherein the solvent is selected from the group
2 consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated
3 hydrocarbons, polar aprotic solvents, and mixtures thereof.
- 1 83. The process according to claim 9, wherein the hydrogenation of the compound of
2 Formula V is carried out in the presence of a hydrogenating agent in a solvent.
- 1 84. The process according to claim 83, wherein the hydrogenating agent is selected
2 from the group consisting of transition metal/ carbon, and an organometallic complex
3 optionally in the presence of a chiral ligand.
- 1 85. The process according to claim 84, wherein the transition metal is selected from
2 the group consisting of palladium, manganese, rhenium, iron, ruthenium, osmium, cobalt,
3 rhodium, and iridium.
- 1 86. The process according to claim 84, wherein the chiral ligand is selected from the
2 group consisting of carbon monoxide, halides, phosphines, naphthols, 1,1'-bi-2-naphthol
3 (BINOL), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), $\alpha,\alpha,\alpha,\alpha$ -tetraaryl-1,3-
4 dioxolane-4,5-dimethanols (TADDOL), 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-
5 bis(diphenylphosphino)butane (DIOP), bis(oxazoline) ligands (BOX) and DuPhos (a
6 phosphine ligand), cymene and mixtures thereof.
- 1 87. The process according to claim 83, wherein the solvent is selected from the group
2 consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated
3 hydrocarbons, polar aprotic solvents, and mixtures thereof.
- 1 88. The process according to claim 11, wherein the reaction of the compound of
2 Formula IX with a trifluoromethyl sulfonyl containing reagent is carried out in the
3 presence of a base in a solvent.
- 1 89. The process according to claim 88, wherein the trifluoromethyl sulfonyl containing
2 reagent is selected from the group consisting of trifluoromethyl sulfonic acid,
3 trifluoromethyl sulfonyl chloride, and trifluoromethyl sulfonyl anhydride.
- 1 90. The process according to claim 88, wherein the base is selected from the group
2 consisting of an organic and an inorganic base.

- 1 91. The process according to claim 88, wherein the solvent is selected from the group
2 consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated
3 hydrocarbons, polar aprotic solvents, and mixtures thereof.
- 1 92. The process according to claim 11, wherein the reduction of the compound of
2 Formula VIII is carried out in the presence of a buffer and a reducing agent in a solvent.
- 1 93. The process according to claim 92, wherein the buffer is selected from the group
2 consisting of potassium hydrogen phosphate, di-potassium hydrogen phosphate, sodium
3 hydrogen phosphate, and di-sodium hydrogen phosphate.
- 1 94. The process according to claim 92, wherein the reducing agent is selected from the
2 group consisting of sodium borohydride, lithium aluminum hydride, diisobutylaluminum
3 hydride, and borane.
- 1 95. The process according to claim 92, wherein the solvent is selected from the group
2 consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated
3 hydrocarbons, polar aprotic solvents, and mixtures thereof.
- 1 96. The process according to claim 11, wherein the oxidation of the compound of
2 Formula VII is carried out in the presence of an oxidizing agent and a base in a solvent.
- 1 97. The process according to claim 96, wherein the oxidizing agent is selected from
2 the group consisting of sodium hypochlorite/2,2,6,6-tetramethylpiperidinoxy (TEMPO),
3 potassium permanganate, potassium dichromate, pyridinium chlorochromate (PCC), Dess-
4 martin periodinane (DMP), oxalyl chloride/dimethyl sulfoxide (DMSO), and chromium
5 oxide/pyridine.
- 1 98. The process according to claim 96, wherein the base is selected from the group
2 consisting of an organic and an inorganic base.
- 1 99. The process according to claim 96, wherein the solvent is selected from the group
2 consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated
3 hydrocarbons, polar aprotic solvents, and mixtures thereof.
- 1 100. The process according to claim 11, wherein the reaction of the compound of
2 Formula VI with ethyl 2-(triphenylphosphoranyl) propionate is carried out in a solvent.
- 1 101. The process according to claim 100, wherein the solvent is selected from the group
2 consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated
3 hydrocarbons, polar aprotic solvents, and mixtures thereof.
- 1 102. The process according to claim 11, wherein the hydrogenation of the compound of
2 Formula V is carried out in the presence of a hydrogenating agent in a solvent.

- 1 103. The process according to claim 102, wherein the hydrogenating agent is selected
2 from the group consisting of transition metal/ carbon, and an organometallic complex
3 optionally in the presence of a chiral ligand.
- 1 104. The process according to claim 103, wherein the transition metal is selected from
2 the group consisting of palladium, manganese, rhenium, iron, ruthenium, osmium, cobalt,
3 rhodium, and iridium.
- 1 105. The process according to claim 103, wherein the chiral ligand is selected from the
2 group consisting of carbon monoxide, halides, phosphines, naphthols, 1,1'-bi-2-naphthol
3 (BINOL), 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP), $\alpha,\alpha,\alpha,\alpha$ -tetraaryl-1,3-
4 dioxolane-4,5-dimethanols (TADDOL), 2,3-O-isopropylidene-2,3-dihydroxy-1,4-
5 bis(diphenylphosphino)butane (DIOP), bis(oxazoline) ligands (BOX) and DuPhos (a
6 phosphine ligand), cymene and mixtures thereof.
- 1 106. The process according to claim 102, wherein the solvent is selected from the group
2 consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated
3 hydrocarbons, polar aprotic solvents, and mixtures thereof.
- 1 107. The process according to claim 11, wherein the reaction of the compound of
2 Formula IV with phenylboronic acid is carried out in the presence of a coupling agent and
3 a base in a solvent.
- 1 108. The process according to claim 107, wherein the coupling agent is selected from
2 the group consisting of tetrakis(triphenylphosphine) palladium(0),
3 tris(dibenzylideneacetone)dipalladium and bis(dibenzylideneacetone)palladium (0).
- 1 109. The process according to claim 107, wherein the base is selected from the group
2 consisting of an organic and an inorganic base.
- 1 110. The process according to claim 107, wherein the solvent is selected from the group
2 consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated
3 hydrocarbons, polar aprotic solvents, and mixtures thereof.
- 1 111. The process according to claim 11, wherein the deprotection of the compound of
2 Formula III is carried out in the presence of a deprotecting agent in a solvent.
- 1 112. The process according to claim 111, wherein the deprotecting agent is selected
2 from the group consisting of hydrochloric acid, trifluoroacetic acid, sulfuric acid, p-
3 toluene sulfonic acid, and methane sulfonic acid.
- 1 113. The process according to claim 111, wherein the solvent is selected from the group
2 consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated
3 hydrocarbons, polar aprotic solvents, and mixtures thereof.

- 1 114. The process according to claim 11, wherein the reaction of the compound of
2 Formula II with succinic anhydride is carried out in the presence of a base in a solvent.
- 1 115. The process according to claim 114, wherein the base is selected from the group
2 consisting of an organic and an inorganic base.
- 1 116. The process according to claim 114, wherein the solvent is selected from the group
2 consisting of water, aromatic hydrocarbons, ketones, esters, ethers, alkanols, halogenated
3 hydrocarbons, polar aprotic solvents, and mixtures thereof.

INTERNATIONAL SEARCH REPORT

International application No.

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A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/21; A61K 31/41; A61K 31/216; C07C 231/02; C07C 231/24; C07C 233/47 (2017.01)

CPC - A61K 31/21; A61K 31/41; A61K 31/216; C07C 231/02; C07C 231/24; C07C 233/47 (2017.01)

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)

See Search History document

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)

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2014/0296559 A1 (DSM FINE CHEMICALS AUSTRIA NFG GMBH & CO KG) 02 October 2014 (02.10.2014) entire document	1-116
A	US 2009/0156585 A1 (FENG et al) 18 June 2009 (18.06.2009) entire document	1-116
A	WO 2008/031567 A1 (NOVARTIS AG) 20 March 2008 (20.03.2008) entire document	1-116

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

* Special categories of cited documents:

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"E" earlier application or patent but published on or after the international filing date

"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

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

01 May 2017

Date of mailing of the international search report

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