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(54) Title: PROCESS FOR THE PREPARATION OF OMARIGLIPTIN

(57) Abstract: The present invention provides a process for preparing omarigliptin.



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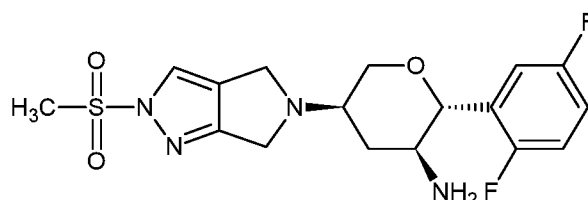
PROCESS FOR THE PREPARATION OF OMARIGLIPTIN

Field of the Invention

The present invention provides a process for preparing omarigliptin.

Background of the Invention

5 Omarigliptin, chemically (2*R*,3*S*,5*R*)-2-(2,5-difluorophenyl)-5-[2-(methylsulfonyl)-2,6-dihydropyrrolo[3,4-*c*]pyrazol-5(4*H*)-yl]tetrahydro-2*H*-pyran-3-amine, is represented by Formula I.



Formula I

10 Omarigliptin is a dipeptidyl peptidase-IV inhibitor being developed for the treatment of diabetes mellitus.

U.S. Patent No. 7,902,376 (“the ‘376 patent”) describes a process for the preparation of omarigliptin comprising the step of reacting ethyl *N*-(diphenylmethylene)glycinate of Formula A with 3-bromoprop-1-yne in the presence of
15 cesium carbonate to obtain a compound of Formula II.

The ‘376 patent also describes a process for the preparation of omarigliptin comprising the step of cycloisomerizing a compound of Formula VII using a transition metal catalyst in the presence of *N*-hydroxysuccinimide in DMF to obtain a compound of Formula VIII.

20 The ‘376 patent also describes a process for the preparation of omarigliptin comprising the step of condensing the compound of Formula IV with *N*,*O*-dimethylhydroxylamine hydrochloride using CDI (1,1’-carbonyldiimidazole) to obtain a compound of Formula V.

PCT Publication No. WO 2013/003250 describes a process for the preparation of
25 omarigliptin.

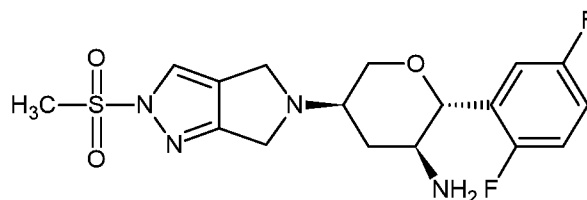
PCT Publication No. WO 2015/139859 describes a process for the preparation of tert-butyl-2-(2,5-difluorophenyl)-2-oxoethylcarbamate, an intermediate used for the preparation of omarigliptin.

The present invention provides an improved process for the preparation of omarigliptin and its intermediates.

Summary of the Invention

The present invention provides an easy, cost-effective, and industrially advantageous process for the preparation of omarigliptin and its intermediates.

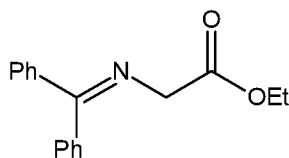
A first aspect of the present invention provides a process for the preparation of omarigliptin of Formula I,



Formula I

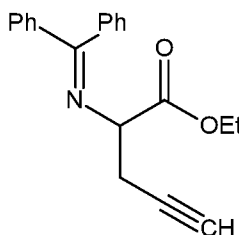
wherein the process comprises the steps of:

- a) reacting ethyl *N*-(diphenylmethylidene)glycinate of Formula A



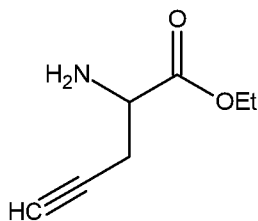
Formula A

with 3-bromoprop-1-yne using a pulverized metal hydroxide to obtain a compound of Formula II;



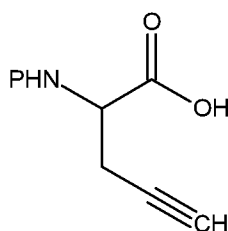
Formula II

- b) hydrolyzing the compound of Formula II to obtain a compound of Formula III;



Formula III

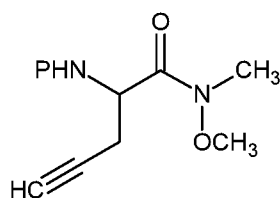
- c) protecting the compound of Formula III to obtain a compound of Formula IV,



Formula IV

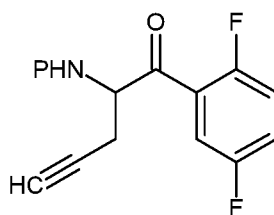
wherein P is an amine protecting group;

- d) condensing the compound of Formula IV with N,O-bisdimethylhydroxylamine hydrochloride using an acid activating agent in the presence of a base to obtain a compound of Formula V;



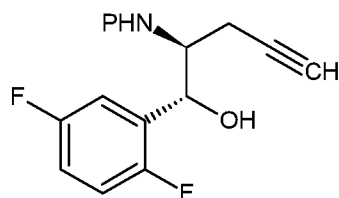
Formula V

- e) reacting the compound of Formula V with 2-bromo-1,4-difluorobenzene in the presence of a Grignard reagent to obtain a compound of Formula VI;



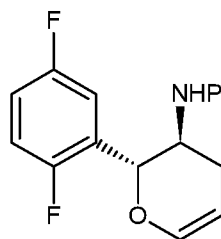
Formula VI

- f) reducing the compound of Formula VI to obtain a compound of Formula VII;



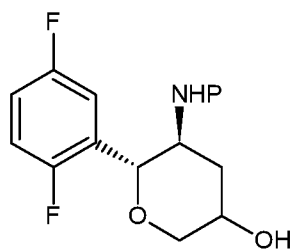
Formula VII

- 5 g) cycloisomerizing the compound of Formula VII in the presence of a sodium salt of a cycloisomerizing agent in a solvent to obtain a compound of Formula VIII;



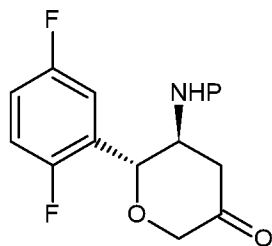
Formula VIII

- h) converting the compound of Formula VIII to a compound of Formula IX;



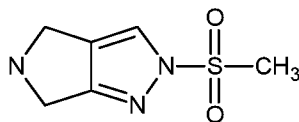
Formula IX

- i) oxidizing the compound of Formula IX to a compound of Formula X;



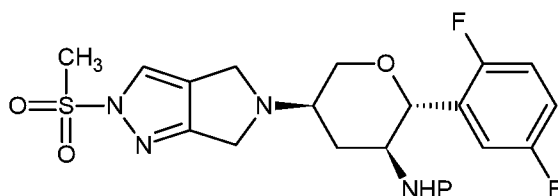
Formula X

- j) reductive amination of the compound of Formula X with a compound of Formula XIV or its salts



Formula XIV

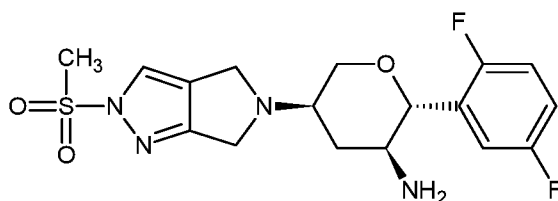
- 5 to obtain a compound of Formula XV; and



Formula XV

- k) deprotecting the compound of Formula XV to obtain omarigliptin of Formula I.

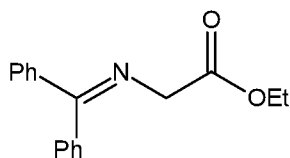
- A second aspect of the present invention provides a process for the preparation of
10 omarigliptin of Formula I,



Formula I

comprising the steps of:

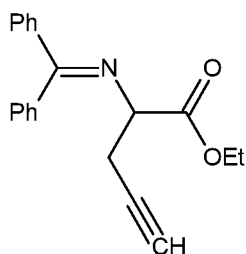
- a) reacting ethyl *N*-(diphenylmethylidene)glycinate of Formula A



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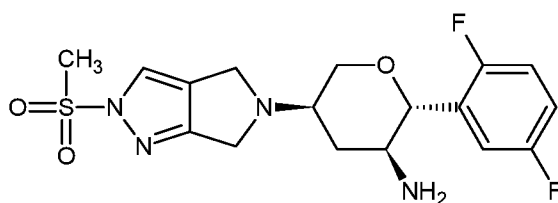
Formula A

with 3-bromoprop-1-yne in the presence of a pulverized metal hydroxide to obtain a compound of Formula II; and

**Formula II**

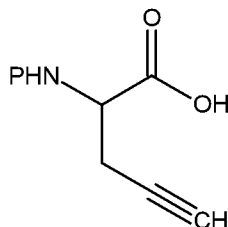
b) converting the compound of Formula II to omarigliptin of Formula I.

A third aspect of the present invention provides a process for the preparation of
 5 omarigliptin of Formula I,

**Formula I**

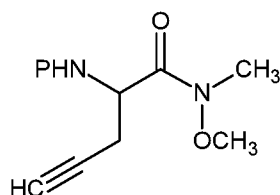
wherein the process comprises the steps of:

a) condensing a compound of Formula IV,

**Formula IV**

wherein P is an amine protecting group,

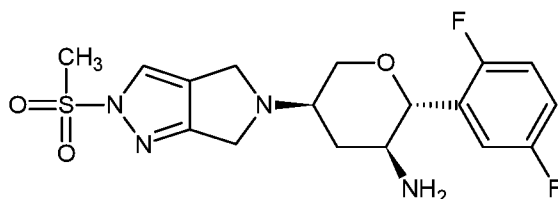
with N,O-bisdimethylhydroxylamine hydrochloride using an acid activating
 agent in the presence of a base to obtain a compound of Formula V; and



Formula V

- b) converting the compound of Formula V to omarigliptin of Formula I.

A fourth aspect of the present invention provides a process for the preparation of omarigliptin of Formula I,

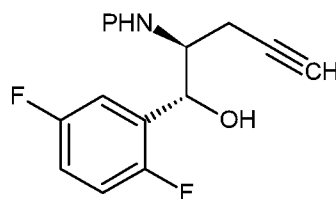


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Formula I

wherein the process comprises the steps of:

- a) cycloisomerizing the compound of Formula VII,

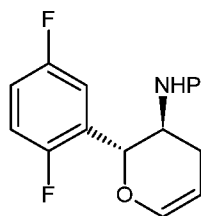


10

Formula VII

wherein P is an amine protecting group,

in the presence of a sodium salt of a cycloisomerizing agent in a solvent to obtain a compound of Formula VIII; and

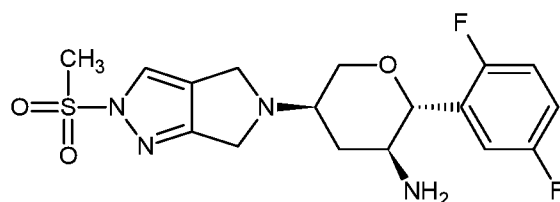


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Formula VIII

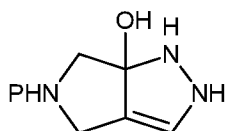
- b) converting the compound of Formula VIII to omarigliptin of Formula I.

A fifth aspect of the present invention provides a process for the preparation of omarigliptin of Formula I,

**Formula I**

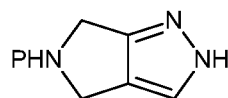
wherein the process comprises the steps of:

- a) treating a compound of Formula XI,

**Formula XI**

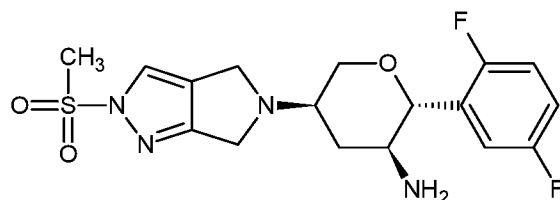
wherein P is an amine protecting group,

with an organic acid to obtain a compound of Formula XII; and

**Formula XII**

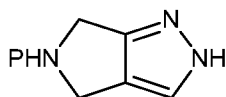
- b) converting the compound of Formula XII to omarigliptin of Formula I.

A sixth aspect of the present invention provides a process for the preparation of omarigliptin of Formula I,

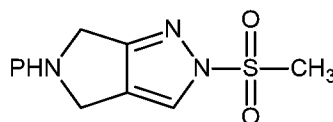
**Formula I**

wherein the process comprises the steps of:

- a) reacting a compound of Formula XII

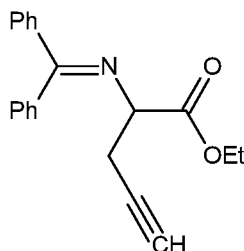
**Formula XII**

with methylsulfonyl chloride in the presence of a non-nucleophilic base in THF or DMF or mixtures thereof with non polar solvents and other polar aprotic solvents to obtain a compound of Formula XIII; and

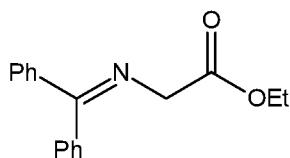
**Formula XIII**

b) converting the compound of Formula XIII to omarigliptin of Formula I.

A seventh aspect of the present invention provides a process for the preparation of a compound of Formula II,

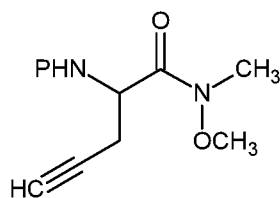
**Formula II**

wherein the process comprises reacting ethyl *N*-(diphenylmethylidene)glycinate of Formula A

**Formula A**

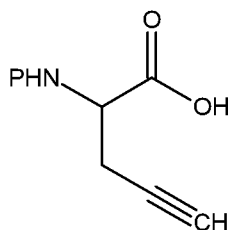
with 3-bromoprop-1-yne in the presence of a pulverized metal hydroxide to obtain the compound of Formula II.

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

**Formula V**

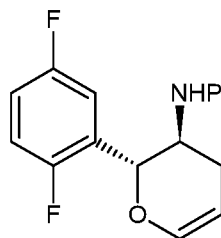
wherein P is an amine protecting group,

comprising condensing a compound of Formula IV

**Formula IV**

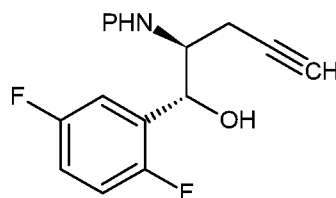
with N,O-bisdimethylhydroxylamine hydrochloride using an acid activating agent in the presence of a base to obtain the compound of Formula V.

A ninth aspect of the present invention provides a process for the preparation of a compound of Formula VIII,

**Formula VIII**

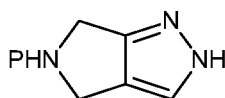
wherein P is an amine protecting group,

comprising cycloisomerizing a compound of Formula VII

**Formula VII**

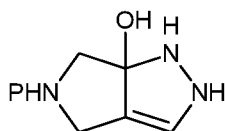
in the presence of a sodium salt of a cycloisomerizing agent in a solvent to obtain the compound of Formula VIII.

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

**Formula XII**

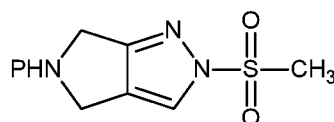
wherein P is an amine protecting group,

- 10 comprising treating a compound of Formula XI

**Formula XI**

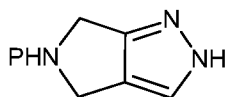
with an organic acid to obtain the compound of Formula XII.

- 15 An eleventh aspect of the present invention provides a process for the preparation of a compound of Formula XIII,

**Formula XIII**

wherein P is an amine protecting group,

comprising reacting a compound of Formula XII

**Formula XII**

with methylsulfonyl chloride in the presence of a non-nucleophilic base in THF or DMF or mixtures thereof with non polar solvents and other polar aprotic solvents.

5

Detailed Description of the Invention:

List of Abbreviations:

Ar	aryl
Boc	tert-butyloxycarbonyl
Bs	benzenesulfonyl
10 CBz	benzyloxycarbonyl
Fmoc	9-fluorenylmethyl-oxycarbonyl
Allyloc	allyloxycarbonyl
CDI	1,1'-carbonyldiimidazole
Cp	cyclopentadienyl
15 Cs ₂ CO ₃	cesium carbonate
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIPE	diisopropyl ether
DIPEA	diisopropylethylamine
20 DMAC	N,N-dimethylacetamide
DMAP	4-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMF/DMA	N,N-dimethylformamide/dimethyl acetal
DMS	dimethylsulfide
25 DME	dimethoxyethane

	HPLC	high-performance liquid chromatography
	IPA	isopropyl alcohol
	i-PrAc	isopropyl acetate
	iPr	isopropyl
5	iPrMgCl	isopropyl magnesium chloride
	MTBE	methyl tert-butyl ether
	NHS	N-hydroxysuccinimide
	NHP	N-hydroxyphthalimide
	NHM	N-hydroxymaleimide
10	NMP	N-methyl-2-pyrrolidone
	PhMe	phenylmethyl
	CpRuCl(PPh ₃) ₂	Chloro(cyclopentadienyl)bis (triphenylphosphine) ruthenium(II)
	TBAB	tetra-n-butylammonium bromide
15	TEA	triethylamine
	THF	tetrahydrofuran
	TMG	1,1,3,3-tetramethylguanidine

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

- 20 The term “amine protecting group,” as used herein, refers to Boc, CBz, Fmoc, allyloc, methoxycarbonyl, formyl, phthaloyl, benzoyl, phenyl, methyl, ethyl, propyl, isopropyl, butyl, and tert-butyl.

- The term “deprotection,” as used herein, refers to removing a protecting group under the conditions known in the art. In a particular case, if the amine protecting group is
- 25 Boc, it is removable under acidic conditions such as aqueous hydrochloric acid, sulfuric acid, hydrobromic acid, tetrafluoroboric acid, benzenesulfonic acid, p-toluenesulfonic acid, ethanesulfonic acid, and trifluoroacetic acid in an organic solvent.

The term “transition metal catalyst,” as used herein, includes rhodium and ruthenium catalysts such as rhodium trichloride hydrate and $\text{CpRuCl}(\text{Ph}_3\text{P})_2$.

The term “acid activating agent,” as used herein, includes oxalyl chloride, triphenylphosphine/carbon tetrabromide, benzotriazol-1-yloxytris
5 (dimethylamino)phosphonium hexafluorophosphate, 1,3-dicyclohexylcarbodiimide/1-hydroxybenzotriazole, *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, alkylhaloformate, and acylhalide.

The term “non-nucleophilic base,” as used herein, includes sodium hydride, potassium hydride, lithium diisopropylamide, sodium bis(trimethylsilyl)amide, potassium
10 bis(trimethylsilyl)amide, lithium tetramethylpiperidide, triethylamine, *N,N*-diisopropylethylamine, and diisopropylamine.

The term “alkylhaloformate,” as used herein, includes methylchloroformate, ethylchloroformate, propylchloroformate, isopropylchloroformate, butylchloroformate, and tert-butylchloroformate.

15 The term “acylhalide,” as used herein, includes acetylchloride, methylacetylchloride, dimethylacetylchloride, and trimethylacetylchloride.

The term “base,” as used herein, includes methylamine, triethylamine, diisopropylamine, diisopropylethylamine, pyridine, *N*-methylpyridine, morpholine, and *N*-methylmorpholine.

20 The term “phase transfer catalyst,” as used herein, includes chloride, bromide, and iodide salts of benzyltrimethylammonium, benzyltriethylammonium, methyltricaprylammonium, methyltributylammonium, methyltrioctylammonium, and tetra-*n*-butylammonium.

The term “phosphine ligand,” as used herein, includes triphenylphosphine, tris(3-
25 fluorophenyl)phosphine, tris(3,5-difluorophenyl)phosphine, and tris(4-fluorophenyl)phosphine.

The term “cycloisomerizing agent” as used herein includes NHS, NHP, and NHM.

The term “polar aprotic solvent” as used herein includes dichloromethane, THF, DMF, acetone, ethyl acetate, isopropyl acetate, acetonitrile, DME, 1,4-dioxane, methyl
30 THF, DMA, and DMSO.

The term "non polar solvent" as used herein includes toluene, benzene, cyclohexane, and hexanes.

The compound of Formula A is reacted with 3-bromoprop-1-yne in the presence of a pulverized metal hydroxide, and optionally a phase transfer catalyst, to obtain the
5 compound of Formula II.

The metal hydroxide is selected from the group consisting of lithium hydroxide, sodium hydroxide, and potassium hydroxide. The compound of Formula II is either isolated or used as such for the next reaction.

The compound of Formula II is hydrolyzed to obtain the compound of Formula III
10 using an acid. The step of hydrolysis can be performed as described in U.S. Patent No. 7,902,376. The compound of Formula III is either isolated or used as such for the next reaction.

The compound of Formula III is protected to obtain the compound of Formula IV by using methods known in the art or as described in U.S. Patent No. 7,902,376. The
15 compound of Formula IV is either isolated or used as such for the next reaction.

The compound of Formula IV is condensed with N,O-bismethylhydroxylamine hydrochloride using an acid activating agent in the presence of a base and a polar aprotic solvent to obtain the compound of Formula V.

The acid activating agent is selected from the group consisting of alkylhaloformate
20 and acylhalide in the presence of a base.

The compound of Formula V is reacted with 2-bromo-1,4-difluorobenzene in the presence of a Grignard reagent to obtain the compound of Formula VI as described in U.S. Patent No. 7,902,376.

The reduction of the compound of Formula VI to a compound of Formula VII is
25 carried out by a method known in the art or as described in U.S. Patent No. 7,902,376. The compound of Formula VII is either isolated or used as such for the next reaction.

The compound of Formula VII is cycloisomerized using a transition metal catalyst in the presence of a sodium salt of a cycloisomerizing agent, a phosphine ligand, and tetrabutylammonium hexafluorophosphate in a solvent to obtain the compound of Formula
30 VIII. An example of a sodium salt of a cycloisomerizing agent is sodium salt NHS.

The solvent is selected from a group consisting of non polar solvents and polar aprotic solvents. Preferably, the solvent is toluene or DME. The use of sodium salt NHS is advantageous over the use of NHS in terms of increase in product formation. The use of toluene and DME reduces the reaction time and the amount of catalyst used. The
5 compound of Formula VIII is either isolated or used as such for the next reaction.

The compound of Formula VIII is converted to the compound of Formula X as described in U.S. Patent No. 7,902,376.

The compound of Formula X is reductively aminated with the compound of Formula XIV or a salt thereof to obtain omargliptin as described in U.S. Patent Nos.
10 7,902,376 and 8,143,289 or PCT Publication Nos. WO 2013/003250 and WO 2015/139859.

The compound of Formula XIV is obtained by following the process as described in U.S. Patent No. 8,143,289 or PCT Publication No. WO 2013/003250.

The compound of Formula XI is treated with an organic acid to obtain the
15 compound of Formula XII.

The organic acid is selected from the group consisting of acetic acid and trifluoroacetic acid. The use of an organic acid ensures the reduction of the compound of Formula XI with retention of the amine protected group.

The compound of Formula XI is obtained by following the process as described in
20 U.S. Patent No. 8,143,289 or PCT Publication No. WO 2013/003250.

The compound of Formula XII is reacted with methylsulfonyl chloride in the presence of a non-nucleophilic base in THF or DMF or mixtures thereof with non polar solvents and other polar aprotic solvents to obtain the compound of Formula XIII. It has been observed that selection of the solvent plays a pivotal role in determining the
25 regioselectivity of the process, and thus yielding a greater percentage of the desired regioisomer.

The compound of Formula XIII is converted to a compound of Formula XIV, and further to omargliptin, by the process as described in U.S. Patent No. 8,143,289 or PCT Publication No. WO 2013/003250.

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.

Instrument details

5 High Performance Liquid Chromatography (HPLC) purity was determined using an Alliance® HPLC System from Waters® (Separation Module 2695), detector model PDA 2996.

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

10 Examples

Example 1: Preparation of ethyl 2-[(diphenylmethylidene)amino]pent-4-ynoate (Formula II)

Pulverized potassium hydroxide (29.53 g) was added to a solution of ethyl *N*-(diphenylmethylidene)glycinate (94 g; Formula A), tetrabutylammonium bromide (11.35 g), and 3-bromoprop-1-yne (42.6 mL) in toluene (282 mL) at -5°C to 0°C. The reaction mixture was stirred for 1 hour to 2 hours at the same temperature to obtain ethyl 2-[(diphenylmethylidene)amino]pent-4-ynoate *in situ*. The reaction mixture was diluted with water (282 mL) at a temperature of -5°C to 0°C. The reaction mixture was used as such for the next reaction.

20 Example 2: Preparation of 2-[(tert-butoxycarbonyl)amino]pent-4-ynoic acid (Formula IV)

The aqueous layer (Formula II; Example 1) was treated with a solution of hydrochloric acid (50%; 94 mL) at a temperature of 2°C to 8°C. The reaction mixture was allowed to warm to a temperature of 20°C to 25°C, and was then stirred for 6 hours to 10 hours to obtain ethyl 2-aminopent-4-ynoate (Formula III). The layers were separated, and the aqueous layer was cooled to 10°C to 15°C. A solution of sodium hydroxide (50 mL; 18.5 M) was added to adjust the pH of the reaction mixture to 9.5 to 10.0. Di-tert-butylidicarbonate (84.2 g) was added to the reaction mixture. The reaction mixture was allowed to warm to 20°C to 30°C. A solution of sodium hydroxide (10 mL to 15 mL; 18.5 M) was again added to the reaction mixture to adjust the pH to 12.5 to 13. After completion of the reaction, toluene (282 mL) was added to the aqueous layer. The reaction mixture was cooled to 0°C to 5°C. An aqueous solution of hydrochloric acid (180

mL) was added to adjust the pH to 2.5 to 3.0. The mixture was stirred for 5 minutes to 10 minutes. The layers were separated. Toluene (282 mL) was added to the aqueous layer, and then the mixture was stirred for 15 minutes. The mixture was allowed to settle for 10 minutes, and the layers were separated. The organic layers were combined, and then
5 washed with a saturated solution of sodium chloride (282 mL). The reaction mixture was allowed to settle, and the layers were separated. The organic layer was concentrated under reduced pressure at 40°C to 50°C to obtain the title compound as a residue. The residue obtained was used as such in the next step.

10 Example 3: Preparation of tert-butyl {1-[methoxy(methyl)amino]-1-oxopent-4-yn-2-yl}carbamate (Formula V)

CDI (39.45 g) was added to a solution of 2-[(tert-butoxycarbonyl)amino]pent-4-ynoic acid (40 g; Formula IV, Example 2) in dimethylformamide (100 mL), and the mixture was stirred for 2 hours at 20°C to 30°C. *N*, *O*-Bismethylhydroxylamine hydrochloride (20.1 g) was added to the reaction mixture, and then the mixture was stirred
15 for 1 hour to 3 hours at 20°C to 30°C. After completion of the reaction, water (200 mL) was added to the reaction mixture, and then the mixture was stirred for 6 hours to 8 hours at 20°C to 25°C. The reaction mixture was cooled to 0°C to 5°C. MTBE (12.5 mL) was added to the reaction mixture, and then the mixture was stirred for 2 hours. The solid obtained was filtered, then washed with water (2 × 100 mL), and then dried under reduced
20 pressure at a temperature of 40°C to 50°C to obtain the title compound.

Yield: 65%

Example 4: Preparation of tert-butyl {1-[methoxy(methyl)amino]-1-oxopent-4-yn-2-yl}carbamate (Formula V)

Ethylchloroformate (6 mL) was added to a solution of 2-[(tert-butoxycarbonyl)amino]pent-4-ynoic acid (12.5 g; Formula IV, Example 2) and NMP
25 (13.50 mL) in dichloromethane (125 mL) at 0°C to -5°C, and the mixture was stirred for 2 hours to 3 hours at the same temperature. *N*, *O*-Bismethylhydroxylamine hydrochloride (5.83 g) was added to the reaction mixture, and then the mixture was stirred for 1 hour to 2 hours at 5°C to 10°C. After completion of the reaction, water (65 mL) was added to the
30 mixture, and then the mixture was stirred for 10 minutes. The reaction mixture was allowed to settle, and the layers were separated. The organic layer was washed with a saturated sodium chloride solution (65 mL). The organic layer was concentrated under

reduced pressure to obtain a residue. DIPE (25 mL) was added to the residue, and then the mixture was stirred for 15 minutes at 20°C to 30°C to obtain a solid. The solid was filtered, and then dried under reduced pressure to obtain the title compound.

Yield: 71%

5 Example 5: Preparation of tert-butyl {1-[methoxy(methyl)amino]-1-oxopent-4-yn-2-yl}carbamate (Formula V)

Trimethylacetyl chloride (24.50 mL) was added to a solution of 2-[(tert-butoxycarbonyl)amino]pent-4-ynoic acid (40 g; Formula IV, Example 2) in dichloromethane (280 mL) and DIPEA (98.50 mL) at -10°C to -5°C, and the mixture was stirred for 2 hours. *N*, *O*-Bismethylhydroxylamine hydrochloride (18.30 g) was added to the reaction mixture, and then the mixture was stirred for 3 hours to 4 hours at -10°C to -5°C. After completion of the reaction, water (200 mL) was added to the reaction mixture, and then the mixture was stirred for 30 minutes. The reaction mixture was allowed to settle, and the layers were separated. The organic layer was washed with water (200 mL), and then concentrated under reduced pressure at 40°C to 45°C to obtain a residue. MTBE (12.5 mL) was added to the residue, and then the mixture was stirred for 2 hours at 0°C to 5°C. The solid obtained was filtered, then washed with MTBE (50 mL), and then dried under reduced pressure at 40°C to 50°C to obtain the title compound.

Yield: 73%

20 Example 6: Preparation of tert-butyl [1-(2,5-difluorophenyl)-1-oxopent-4-yn-2-yl]carbamate (Formula VI)

Tert-butyl {1-[methoxy(methyl)amino]-1-oxopent-4-yn-2-yl}carbamate (5 g; Formula V; Example 3, 4, or 5) in toluene (40 mL) was added to a solution of 2-bromo-1,4-difluorobenzene (4.9 mL) and isopropyl magnesium chloride (21 mL; 2 M in THF) in toluene (15 mL) at -20°C to -10°C. The reaction mixture was allowed to warm to 25°C, and then the mixture was stirred for 2 hours. After the completion of the reaction, the reaction mixture was quenched with aqueous ammonium chloride (20%; 40 mL) to adjust the pH to 4 to 5. The reaction mixture was stirred for 10 minutes at 20°C to 25°C, and then allowed to settle. The layers were separated. The organic layer was washed with an aqueous sodium bicarbonate solution (5%; 25 mL) and then with a saturated sodium chloride solution (25 mL) at 20°C to 25°C. The organic layer was concentrated under reduced pressure at 50°C to 55°C to obtain a residue. IPA (15 mL) was added to the

residue, and then the mixture was stirred at 55°C to 60°C for 30 minutes. Water (22.5 mL) was added to the reaction mixture at 50°C to 60°C. The reaction mixture was cooled to 20°C to 25°C, and then stirred for 15 minutes. The reaction mixture was filtered, and then dried under reduced pressure at 45°C to 50°C to obtain the title compound.

5 Yield: 96%

Example 7: Preparation of tert-butyl [(1R,2S)-1-(2,5-difluorophenyl)-1-hydroxypent-4-yn-2-yl]carbamate (Formula VII)

DABCO (108 g) and RuCl(R,R-FsDPEN)(p-cymene) (900 mg) were added to a solution of tert-butyl [1-(2,5-difluorophenyl)-1-oxopent-4-yn-2-yl]carbamate (100 g;
10 Formula VI; Example 6) in THF (700 mL) at ambient temperature. The reaction mixture was stirred under nitrogen for 5 minutes. Formic acid (63 mL) was added to the reaction mixture and then the mixture was stirred for 16 hours to 18 hours at 40°C to 45°C. After completion of the reaction, the reaction mixture was concentrated at 40°C to 45°C under reduced pressure to obtain a residue. Toluene (500 mL) was added to the residue, and
15 then the mixture was stirred for 5 minutes. The reaction mixture was cooled to 0°C to 5°C. Aqueous hydrochloric acid (5%; 250 mL) was added to the reaction mixture, and then the mixture was stirred at 20°C to 25°C for 30 minutes. The reaction mixture was allowed to settle, and the layers were separated. The aqueous layer was extracted with toluene (200 mL), and the layers were separated. The organic layers were washed with an
20 aqueous sodium bicarbonate solution (5%; 500 mL), and then stirred for 10 minutes. The reaction mixture was allowed to settle, and the layers were separated. The organic layer was washed with water (500 mL), and then dried under reduced pressure at 50°C to 60°C to obtain the title compound as a viscous liquid, used as such for the next reaction.

Example 8: Preparation of tert-butyl [(2R,3S)-2-(2,5-difluorophenyl)-3,4-dihydro-2H-pyran-3-yl]carbamate (Formula VIII)

Tetrabutyl ammonium hexafluorophosphate (13.8 g) and sodium salt of NHS (17.6 g) were added to a solution of tert-butyl [(1R,2S)-1-(2,5-difluorophenyl)-1-hydroxypent-4-yn-2-yl]carbamate (100 g; Formula VII; Example 7) in toluene (600 mL) under nitrogen at ambient temperature, and the mixture was stirred for 10 minutes. Triphenylphosphine (4.2
30 g) and chloro(cyclopentadienyl) bis (triphenylphosphine) ruthenium(II) ethanol (1.5 g) were added to the reaction mixture, and then the mixture was stirred for 4 hours to 5 hours at 80°C to 85°C. The reaction mixture was allowed to cool to 40°C.

Chloro(cyclopentadienyl) bis (triphenylphosphine) ruthenium(II) ethanol (1 g) was again added to the reaction mixture, and then the mixture was stirred for 16 hours to 18 hours at 80°C to 85°C. After completion of the reaction, the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was filtered to obtain a solid. The solid was washed with toluene (50 mL × 2), and then washed with a sodium bicarbonate solution (5%). The reaction mixture was stirred for 10 minutes, and then allowed to settle for 10 minutes. The layers were separated, and the aqueous layer was extracted with toluene (200 mL). The organic layers were combined, then washed with water (500 mL), and then concentrated under reduced pressure at 55°C to 60°C to obtain the title compound as a viscous liquid.

Example 9: Preparation of tert-butyl [(2R,3S)-2-(2,5-difluorophenyl)-3,4-dihydro-2H-pyran-3-yl]carbamate (Formula VIII)

Tetrabutyl ammonium hexafluorophosphate (3.4 g) and sodium salt of NHS (4.4 g) were added to a solution of tert-butyl [(1R,2S)-1-(2,5-difluorophenyl)-1-hydroxypent-4-yn-2-yl]carbamate (20 g, Formula VII; Example 7) in DME (140 mL) under nitrogen at ambient temperature, and the mixture was stirred for 10 minutes. Triphenylphosphine (1.1 g) and chloro(cyclopentadienyl) bis (triphenylphosphine) ruthenium(II) ethanol (0.6 g) were added to the reaction mixture, and then the mixture was stirred for 6 hours at 80°C to 85°C. The reaction mixture was allowed to cool to 40°C. Chloro(cyclopentadienyl) bis (triphenylphosphine) ruthenium(II) ethanol (0.2 g) was again added to the reaction mixture, and then the mixture was stirred for 20 hours at 80°C to 85°C. After completion of the reaction, the reaction mixture was allowed to cool to ambient temperature. The reaction mixture was filtered to obtain a solid. The solid was washed with DME (20 mL). Toluene (60 mL) and water (100 mL) were added to the filtrate, and then the mixture was stirred for 20 minutes. The mixture was allowed to settle, and the layers were separated. The aqueous layer was extracted with toluene (40 mL). The organic layers were combined, then washed with water (100 mL), and then washed with a saturated sodium chloride solution (100 mL). The organic layer was separated, and then concentrated under reduced pressure at 55°C to 60°C to obtain a residue. The residue was purified through column chromatography (eluent: 5% ethyl acetate in hexane; 60-120 mesh silica gel) to obtain the title compound as a viscous liquid.

Example 10: Preparation of tert-butyl[(2R,3S)-5-hydroxy-2-(2,5-difluorophenyl)tetrahydro-2H-pyran-3-yl]carbamate (Formula IX)

Borane DMS (24 mL) was added to a solution of tert-butyl [(2R,3S)-2-(2,5-difluorophenyl)-3,4-dihydro-2H-pyran-3-yl]carbamate (50 g; Formula VIII; Example 8 or 9) in MTBE (350 mL) at -10°C to -5°C. The reaction mixture was stirred for 2 hours to 3 hours at the same temperature. After completion of the reaction, the reaction mixture was
5 added to an aqueous solution of sodium hydroxide (1 N; 400 mL) while maintaining the temperature at 0°C to 10°C. Hydrogen peroxide (18 mL; 50%) was added to the reaction mixture, and then the mixture was stirred for 14 hours at 20°C to 26°C. The reaction mixture was allowed to settle, and the layers were separated. Toluene (150 mL) was added to the aqueous layer, and then the mixture was stirred at 20°C to 25°C for 10
10 minutes. The reaction mixture was allowed to settle, and the layers were separated. The organic layers were combined, then washed with water (300 mL), and then concentrated under reduced pressure at 60°C to 70°C to obtain a residue. Toluene (150 mL) was added to the residue, and then the mixture was heated at 80°C to 85°C for 45 minutes. The reaction mixture was allowed to cool to 20°C to 25°C. The reaction mixture was filtered,
15 and then dried under reduced pressure at 45°C to 50°C to obtain the title compound.

Yield: 53%

Example 11: Preparation of tert-butyl [(2R,3S)-2-(2,5-difluorophenyl)-5-oxotetrahydro-2H-pyran-3-yl]carbamate (Formula X)

Ruthenium chloride (45 mg) was added to a solution of tert-butyl[(2R,3S)-5-hydroxy-2-(2,5-difluorophenyl)tetrahydro-2H-pyran-3-yl]carbamate (15.0 g; Formula IX; Example 10) and acetic acid (15.0 mL) in acetonitrile (45.0 mL) and water (7.5 mL) at
20 0°C. Sodium bromate (4.0 g) was added slowly to the reaction mixture at 0°C to 5°C over 5 hours, and then the mixture was stirred for 16 hours at -5°C to 5°C. After completion of the reaction, IPA (15 mL) was added over 25 minutes at 0°C to 5°C, and then the mixture
25 was stirred for 15 minutes. Water (180 mL) was slowly added to the reaction mixture, and then the mixture was stirred for 5 hours at 0°C to 5°C. The reaction mixture was filtered, and then dried under reduced pressure at 45°C to 50°C to obtain the title compound.

Yield: 80%

Example 12: Preparation of tert-butyl 6a-hydroxy-2,4,6,6a-tetrahydropyrrolo[3,4-c]pyrazole-5(1H)-carboxylate (Formula XI)

DMF/DMA (143 mL) was added to a solution of tert-butyl 3-oxopyrrolidine-1-carboxylate (100 g) in toluene (500 mL) at 40°C to 50°C under nitrogen atmosphere. The

reaction mixture was heated to reflux, and then stirred for 2 hours. The reaction mixture was concentrated under reduced pressure at 50°C to 55°C to obtain a crude mass. Hexane (500 mL) and toluene (200 mL) were added to the crude mass, and then the mixture was stirred for 2 hours to obtain tert-butyl (3Z)-3-[(dimethylamino)methylene]-4-

- 5 oxopyrrolidine-1-carboxylate. Hydrazine hydrate (100%; 17 mL) and methanol (50 mL) were added to a solution of tert-butyl (3Z)-3-[(dimethylamino)methylene]-4-oxopyrrolidine-1-carboxylate (70 g) in toluene (350 mL). The reaction mixture was stirred at 30°C to 40°C for 4 hours. The reaction mixture was allowed to cool to 20°C to 25°C to obtain the title compound *in situ*.

- 10 Yield: 60% to 70%

Example 13: Preparation of tert-butyl 4,6-dihydropyrrolo[3,4-*c*]pyrazole-5(1*H*)-carboxylate (Formula XII)

- Trifluoroacetic acid (28.2 mL) was added to the reaction mixture (Formula XI; Example 12) at 20°C to 25°C, and the mixture was stirred for 2 hours. After completion
15 of the reaction, water (350 mL) was added to the mixture. The reaction mixture was allowed to settle, and the layers were separated. The organic layer was concentrated under vacuum to obtain a crude mass. N-heptane (210 mL) was added to the crude mass, and then the mixture was stirred for 1 hour to 3 hours at 20°C to 30°C to obtain a solid. The solid was filtered to obtain the title compound.

- 20 Yield: 98%

Example 14: Preparation of tert-butyl 2-(methylsulfonyl)hexahydropyrrolo[3,4-*c*]pyrazole-5(1*H*)-carboxylate (Formula XIII)

- A solution of tert-butyl 4,6-dihydropyrrolo[3,4-*c*]pyrazole-5(1*H*)-carboxylate (5 g; Formula XII; Example 13) in tetrahydrofuran (5 mL) and N,N-dimethylformamide (5 mL)
25 was added to a suspension of sodium hydride (60%; 1.91 g) in THF (5 mL) and DMF (10 mL) at 0°C to 5°C, and the mixture was stirred for 15 minutes. Mesyl chloride (3.2 mL) was slowly added to the reaction mixture at 0°C to 5°C, and then the mixture was stirred for 30 minutes. After completion of the reaction, water (50 mL) was added to the reaction mixture. The reaction mixture was extracted with ethyl acetate (25 mL), then dried over
30 sodium sulfate, and then concentrated under reduced pressure at 35°C to 45°C to obtain a crude mass. IPA (7.5 mL) and n-heptane (25 mL) were added to the crude mass, and then the mixture was stirred at 20°C to 30°C for 1 hour to 3 hours to obtain a solid. The solid

was filtered, and then dried under reduced pressure at 35°C to 40°C for 30 minutes to obtain the title compound.

Regioselectivity: 95%

Example 15: Preparation of tert-butyl 2-(methylsulfonyl)hexahydropyrrolo[3,4-
5 c]pyrazole-5(1H)-carboxylate (Formula XIII)

A solution of tert-butyl 4,6-dihydropyrrolo[3,4-*c*]pyrazole-5(1H)-carboxylate (2 g; Formula XII; Example 13) was added to a suspension of sodium hydride (60%; 0.46 g) in tetrahydrofuran (30 mL) at 30°C to 40°C, and the mixture was stirred for 2 hours. Mesyl chloride (3.2 mL in 20 mL of tetrahydrofuran) was slowly added to the reaction mixture at
10 30°C to 40°C, and then the mixture was stirred for 2 hours. After completion of the reaction, water (20 mL) and ethyl acetate (50 mL) were added to the reaction mixture. The reaction mixture was allowed to settle, and the layers were separated. The organic layer was washed with a saturated sodium chloride solution (25 mL). The organic layer was concentrated under reduced pressure at 35°C to 45°C to obtain a crude mass. IPA
15 (7.5 mL) and n-heptane (25 mL) were added to the crude mass, and then the mixture was stirred at 20°C to 30°C for 1 hour to 3 hours to obtain a solid. The solid was filtered, and then dried under reduced pressure at 35°C to 40°C for 30 minutes to obtain the title compound.

Regioselectivity: 82%

Example 16: Preparation of tert-butyl 2-(methylsulfonyl)hexahydropyrrolo[3,4-
20 c]pyrazole-5(1H)-carboxylate (Formula XIII)

Triethylamine (1.15 mL) was added to a solution of tert-butyl 4,6-dihydropyrrolo[3,4-*c*]pyrazole-5(1H)-carboxylate (1 g; Formula XII; Example 13) in tetrahydrofuran (10 mL) at ambient temperature. Mesyl chloride (0.49 mL) was slowly
25 added to the reaction mixture at 0°C to 5°C, and then the mixture was stirred for 30 minutes. The temperature was allowed to rise to ambient temperature, and then the mixture was stirred for 3 hours. After completion of the reaction, water (25 mL) and ethyl acetate (25 mL) were added to the reaction mixture. The reaction mixture was allowed to settle, and the layers were separated. The organic layer was concentrated under reduced
30 pressure at 30°C to 35°C to obtain a crude mass. IPA (7.5 mL) and n-heptane (25 mL) were added to the crude mass, and then the mixture was stirred at 30°C to 35°C for 30

minutes to obtain a solid. The solid was filtered, and then dried under reduced pressure 30°C to 35°C for 30 minutes to obtain the title compound.

Regioselectivity: 90%

Example 17: Preparation of tert-butyl 2-(methylsulfonyl)hexahydropyrrolo[3,4-c]pyrazole-5(1H)-carboxylate (Formula XIII)

- Triethylamine (1.15 mL) was added to a solution of tert-butyl 4,6-dihydropyrrolo[3,4-c]pyrazole-5(1H)-carboxylate (1 g; Formula XII; Example 13) in 2-methyltetrahydrofuran (10 mL) at 0°C to 5°C, and the mixture was stirred for 15 minutes. Mesyl chloride (0.49 mL) was slowly added to the reaction mixture at 0°C to 5°C, and then the mixture was stirred for 30 minutes. The reaction mixture was allowed to rise to ambient temperature, and was then stirred at the same temperature for 2 hours. Triethylamine (0.2 mL) was added to the reaction mixture, and then the mixture was stirred for 30 minutes at 30°C to 35°C. After completion of the reaction, water (15 mL) was added. The reaction mixture was allowed to settle, and the layers were separated. The organic layer was washed with a saturated sodium chloride solution (25 mL). The organic layer was concentrated under reduced pressure to obtain a crude mass. IPA (7.5 mL) and n-heptane (25 mL) were added to the crude mass, and then the mixture was stirred at 30°C to 35°C for 30 minutes to obtain a solid. The solid was filtered, and then dried under reduced pressure at 30°C to 35°C for 8 hours to obtain the title compound.
- Regioselectivity: 90%

Example 18: Preparation of tert-butyl 2-(methylsulfonyl)hexahydropyrrolo[3,4-c]pyrazole-5(1H)-carboxylate (Formula XIII)

- Triethylamine (1.6 mL) was added to a solution of tert-butyl 4,6-dihydropyrrolo[3,4-c]pyrazole-5(1H)-carboxylate (2 g; Formula XII; Example 13) in N,N-dimethylformamide (20 mL) at ambient temperature, and the mixture was stirred for 2 hours. Mesyl chloride (1.1 mL in 10 mL of N,N-dimethylformamide) was slowly added to the reaction mixture at 0°C to 5°C, and then the mixture was stirred for 2 hours. Triethylamine (3 mL) was added to the reaction mixture, and then the mixture was stirred for 2 hours at 0°C to 5°C. After completion of the reaction, water (50 mL) and dichloromethane (50 mL) were added. The reaction mixture was allowed to settle, and the layers were separated. The organic layer was washed with a saturated sodium chloride solution (25 mL). The organic layer was concentrated under reduced pressure to obtain a crude mass. IPA (7.5 mL) and

n-heptane (25 mL) were added to the crude mass, and then the mixture was stirred at 30°C to 35°C for 30 minutes to obtain a solid. The solid was filtered, and then dried under reduced pressure at 30°C to 35°C for 8 hours to obtain the title compound.

Regioselectivity: 95%

5 Example 19: Preparation of tert-butyl 2-(methylsulfonyl)hexahydropyrrolo[3,4-c]pyrazole-5(1H)-carboxylate (Formula XIII)

Tert-butyl 4,6-dihydropyrrolo[3,4-c]pyrazole-5(1H)-carboxylate (5 g; Formula XII; Example 13) was added to a suspension of sodium hydride (1.14 g; 60%) in acetonitrile (150 mL) at 20°C to 30°C, and the mixture was stirred for 2 hours. Mesyl chloride (4.6
10 mL in 35 mL of acetonitrile) was slowly added to the reaction mixture at 20°C to 30°C, and then the mixture was stirred for 2 hours. After completion of the reaction, water (50 mL) and dichloromethane (50 mL) were added to the reaction mixture. The reaction mixture was allowed to settle, and the layers were separated. The organic layer was washed with a saturated sodium chloride solution (25 mL). The organic layer was
15 concentrated under reduced pressure to obtain a crude mass. IPA (7.5 mL) and n-heptane (25 mL) were added to the crude mass, and then the mixture was stirred at 30°C to 35°C for 30 minutes to obtain a solid. The solid was filtered, and then dried under reduced pressure at 30°C to 35°C for 8 hours to obtain the title compound.

Regioselectivity: 50%

20 Example 20: Preparation of tert-butyl 2-(methylsulfonyl)hexahydropyrrolo[3,4-c]pyrazole-5(1H)-carboxylate (Formula XIII)

A solution of tert-butyl 4,6-dihydropyrrolo[3,4-c]pyrazole-5(1H)-carboxylate (5 g; Formula XII; Example 13) in N,N-dimethylformamide (15 mL) was added to a suspension of sodium hydride (1.91 g in 10 mL of THF; 60%) at 0°C to 5°C, and the mixture was
25 stirred for 15 minutes. Mesyl chloride (3.8 mL) was slowly added to the reaction mixture at -10°C to 0°C, and then the mixture was stirred for 30 minutes. After completion of the reaction, water (50 mL) was added to the reaction mixture. The reaction mixture was extracted in ethyl acetate (20 mL), then dried over sodium sulfate, and then concentrated under reduced pressure to obtain a crude mass. IPA (7.5 mL) and n-heptane (25 mL) were
30 added to the crude mass, and then the mixture was stirred at 30°C to 35°C for 30 minutes to obtain a solid. The solid was filtered, and then dried under reduced pressure at 30°C to 35°C for 8 hours to obtain the title compound.

Regioselectivity: 95%

Example 21: Preparation of tert-butyl 2-(methylsulfonyl)hexahydropyrrolo[3,4-c]pyrazole-5(1H)-carboxylate (Formula XIII)

A solution of tert-butyl 4,6-dihydropyrrolo[3,4-c]pyrazole-5(1H)-carboxylate (5 g; Formula XII; Example 13) in N,N-dimethylformamide (15 mL) was added to a suspension of sodium hydride (60%; 1.91 g in 10 mL of DMF) at 0°C to 5°C, and the mixture was stirred for 15 minutes. Mesyl chloride (3.8 mL) was slowly added to the reaction mixture at -10°C to 0°C, and then the mixture was stirred for 30 minutes. After completion of the reaction, water (50 mL) was added to the reaction mixture. The reaction mixture was extracted in ethyl acetate (20 mL), then dried over sodium sulfate, and then concentrated under reduced pressure to obtain a crude mass. IPA (7.5 mL) and n-heptane (25 mL) were added to the crude mass, and then the mixture was stirred at 30°C to 35°C for 8 hours to obtain a solid. The solid was filtered, and then dried under reduced pressure at 30°C to 35°C for 30 minutes to obtain the title compound.

Regioselectivity: 95%

Example 22: Preparation of p-toluenesulfonate salt of tert-butyl 2-(methylsulfonyl)-2,6-dihydropyrrolo[3,4-c]pyrazole-5-(4H)-carboxylate (Formula XIV)

P-toluenesulfonic acid (42.3 g dissolved in 96 mL of IPA) was added to a solution of tert-butyl 2-(methylsulfonyl)hexahydropyrrolo[3,4-c]pyrazole-5(1H)-carboxylate (32 g; Formula XIII) in isopropyl acetate (160 mL). The reaction mixture was stirred for 8 hours to 12 hours at ambient temperature. After completion of the reaction, the reaction mixture was filtered, then washed with isopropyl acetate (50 mL), and then dried under reduced pressure at 45°C to 50°C to obtain the title compound.

Yield: 78%

Example 23: Preparation of tert-butyl {(2R,3S,5R)-2-(2,5-difluorophenyl)-5-[2-(methylsulfonyl)-2,6-dihydropyrrolo[3,4-c]pyrazol-5(4H)-yl]tetrahydro-2H-pyran-3-yl}carbamate (Formula XV)

Dimethylacetamide (12.5 mL) was added to a solution of p-toluenesulfonate salt of tert-butyl 2-(methylsulfonyl)-2,6-dihydropyrrolo[3,4-c]pyrazole-5-(4H)-carboxylate (0.55 g; Formula XIV; Example 22) and tert-butyl [(2R,3S)-2-(2,5-difluorophenyl)-5-oxotetrahydro-2H-pyran-3-yl]carbamate (0.5 g; Formula X; Example 11) at -10°C.

Sodium triacetoxyborohydride (0.97 g) was added to the reaction mixture at the same temperature, and then the mixture was stirred for 1 hour to 2 hours. After completion of the reaction, water (12.5 mL at 0°C to 5°C) was added to the reaction mixture at 0°C to 5°C over 30 minutes to obtain a solid. The solid was filtered, then washed with
5 dimethylacetamide (5 mL), water (10 mL), and n-heptane (7.5 mL), and then dried at 55°C to 60°C to obtain the title compound.

Yield: 80%

Example 24: Preparation of omarigliptin (Formula I)

Trifluoroacetic acid (73.3 g) was added to a solution of tert-butyl {(2R,3S,5R)-2-
10 (2,5-difluorophenyl)-5-[2-(methylsulfonyl)-2,6-dihydropyrrolo[3,4-c]pyrazol-5(4H)-yl]tetrahydro-2H-pyran-3-yl} carbamate (8.2 g; Formula XV; Example 23) in dichloromethane (123 mL) at 0°C. The reaction mixture was allowed to warm to the ambient temperature, and was then stirred at the same temperature for 30 minutes. After completion of the reaction, water (99 mL at 0°C to 5°C) was added to the reaction mixture
15 at 0°C to 5°C. An aqueous ammonia solution (25%) was added to the reaction mixture to adjust the pH to 9.6. The reaction mixture was allowed to settle, and the layers were separated. The organic layer was washed with water (85 mL). The organic layer was separated, and then concentrated under vacuum at 30°C to 35°C to obtain a crude mass. Dichloromethane (95 mL) was added to the crude mass to obtain a solution. Charcoal (0.8
20 g) was added to the solution, and then the solution was filtered to obtain the organic layer. The organic layer was concentrated to obtain a solid mass. The solid mass was dissolved in dichloromethane (30 mL) at 40°C to obtain a clear solution. Isopropyl acetate (15 mL) was added to the clear solution, and then the mixture was stirred for 2 hours at ambient temperature until a solid started to appear. Isopropyl acetate (55 mL) was again added to
25 the solution, and then the reaction mass was stirred for 2 hours at ambient temperature to obtain a solid. The solid was filtered, then washed with n-heptane (45 mL), and then dried under vacuum at 40°C to 45°C to obtain omarigliptin.

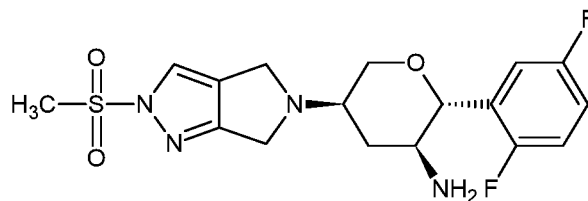
Yield: 84%

HPLC Purity: 99.76%

30

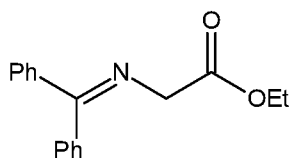
We claim:

1. A process for the preparation of omarigliptin of Formula I,

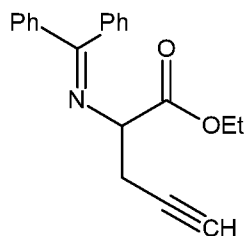
**Formula I**

wherein the process comprises the steps of:

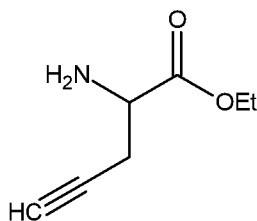
- a) reacting ethyl *N*-(diphenylmethylidene)glycinate of Formula A

**Formula A**

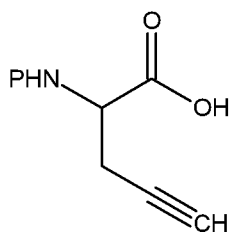
with 3-bromoprop-1-yne using a pulverized metal hydroxide to obtain a compound of Formula II;

**Formula II**

- b) hydrolyzing the compound of Formula II to obtain a compound of Formula III;

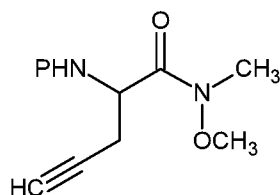
**Formula III**

- c) protecting the compound of Formula III to obtain a compound of Formula IV,

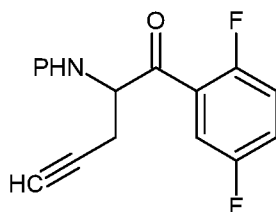
**Formula IV**

wherein P is an amine protecting group;

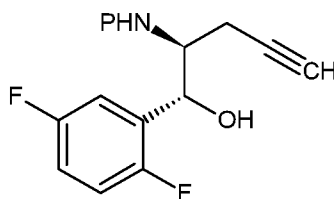
- d) condensing the compound of Formula IV with N,O-bisdimethylhydroxylamine hydrochloride using an acid activating agent in the presence of a base to obtain a compound of Formula V;

**Formula V**

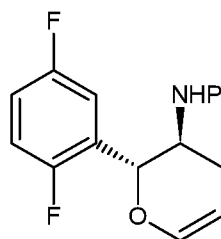
- e) reacting the compound of Formula V with 2-bromo-1,4-difluorobenzene in the presence of a Grignard reagent to obtain a compound of Formula VI;

**Formula VI**

- f) reducing the compound of Formula VI to obtain a compound of Formula VII;

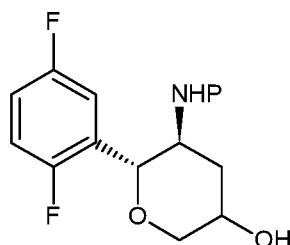
**Formula VII**

- g) cycloisomerizing the compound of Formula VII in the presence of a sodium salt of a cycloisomerizing agent in a solvent to obtain a compound of Formula VIII;



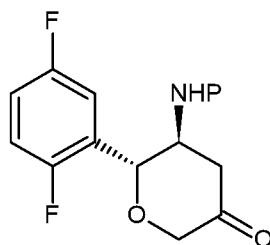
Formula VIII

- h) converting the compound of Formula VIII to a compound of Formula IX;



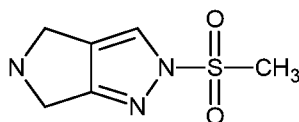
Formula IX

- i) oxidizing the compound of Formula IX to a compound of Formula X;



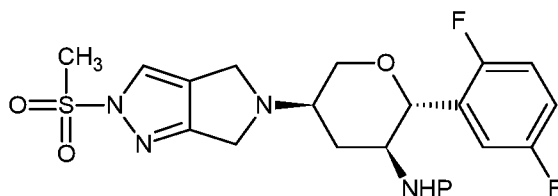
Formula X

- j) reductive amination of the compound of Formula X with a compound of Formula XIV or its salts



Formula XIV

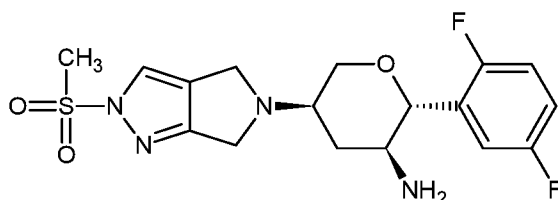
to obtain a compound of Formula XV; and



Formula XV

k) deprotecting the compound of Formula XV to obtain omarigliptin of Formula I.

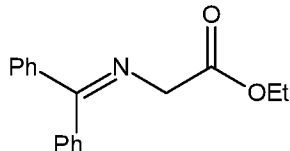
2. A process for the preparation of omarigliptin of Formula I,



Formula I

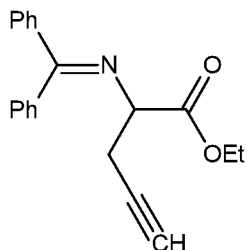
comprising the steps of:

a) reacting ethyl *N*-(diphenylmethylidene)glycinate of Formula A



Formula A

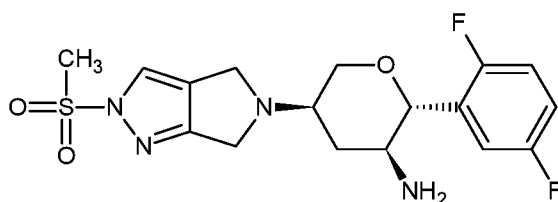
with 3-bromoprop-1-yne in the presence of a pulverized metal hydroxide to obtain a compound of Formula II; and



Formula II

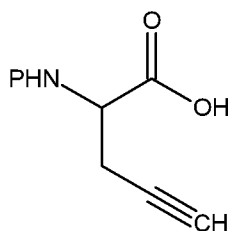
b) converting the compound of Formula II to omarigliptin of Formula I.

3. A process for the preparation of omarigliptin of Formula I,

**Formula I**

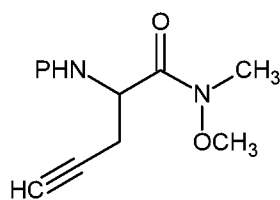
wherein the process comprises the steps of:

- a) condensing a compound of Formula IV,

**Formula IV**

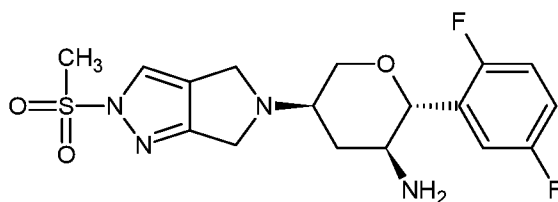
wherein P is an amine protecting group,

with N,O-bisdimethylhydroxylamine hydrochloride using an acid activating agent in the presence of a base to obtain a compound of Formula V; and

**Formula V**

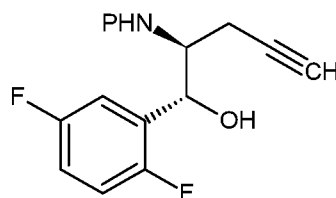
- b) converting the compound of Formula V to omarigliptin of Formula I.

4. A process for the preparation of omarigliptin of Formula I,

**Formula I**

wherein the process comprises the steps of:

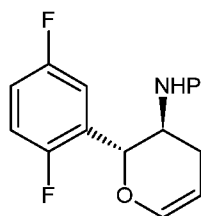
5 a) cycloisomerizing the compound of Formula VII,



6
7 **Formula VII**

8 wherein P is an amine protecting group,

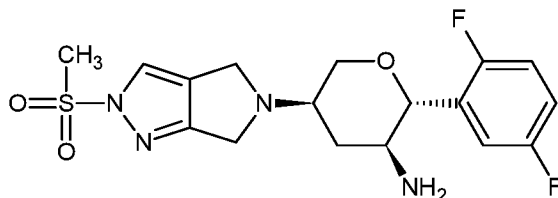
9 in the presence of a sodium salt of a cycloisomerizing agent in a solvent to
10 obtain a compound of Formula VIII; and



11
12 **Formula VIII**

13 b) converting the compound of Formula VIII to omarigliptin of Formula I.

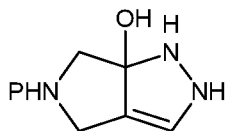
1 5. A process for the preparation of omarigliptin of Formula I,



2
3 **Formula I**

4 wherein the process comprises the steps of:

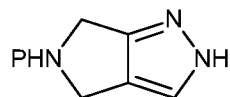
5 a) treating a compound of Formula XI,



6
7 **Formula XI**

8 wherein P is an amine protecting group,

9 with an organic acid to obtain a compound of Formula XII; and



10

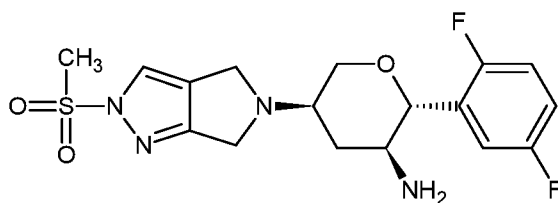
11

Formula XII

12

b) converting the compound of Formula XII to omarigliptin of Formula I.

1 6. A process for the preparation of omarigliptin of Formula I,



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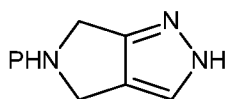
Formula I

4

wherein the process comprises the steps of:

5

a) reacting a compound of Formula XII



6

7

Formula XII

8

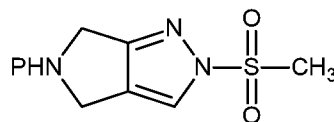
with methylsulfonyl chloride in the presence of a non-nucleophilic base in THF

9

or DMF or mixtures thereof with non polar solvents and other polar aprotic

10

solvents to obtain a compound of Formula XIII; and



11

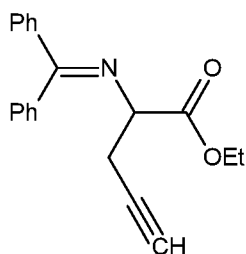
12

Formula XIII

13

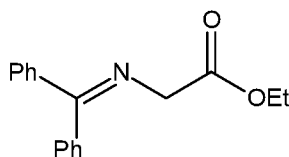
b) converting the compound of Formula XIII to omarigliptin of Formula I.

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



2
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4
5
Formula II

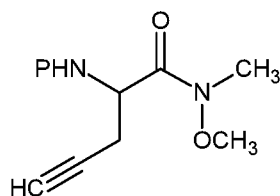
wherein the process comprises reacting ethyl *N*-(diphenylmethylidene) glycinate of
Formula A



6
7
Formula A

with 3-bromoprop-1-yne in the presence of a pulverized metal hydroxide to obtain the
compound of Formula II.

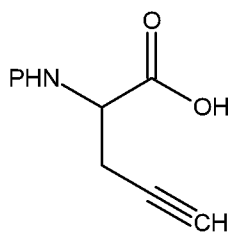
8. A process for the preparation of a compound of Formula V,



2
3
Formula V

wherein P is an amine protecting group;

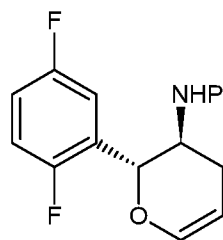
comprising condensing a compound of Formula IV



6
7
Formula IV

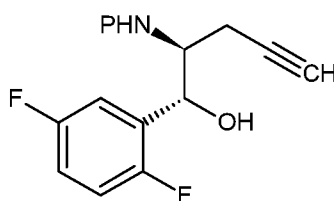
8 with N,O-bisdimethylhydroxylamine hydrochloride using an acid activating agent in
 9 the presence of a base to obtain the compound of Formula V.

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



2
 3 **Formula VIII**

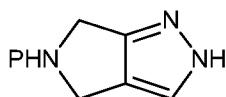
4 wherein P is an amine protecting group,
 5 comprising cycloisomerizing a compound of Formula VII



6
 7 **Formula VII**

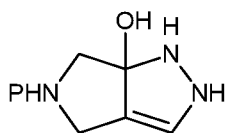
8 in the presence of a sodium salt of a cycloisomerizing agent in a solvent to obtain the
 9 compound of Formula VIII.

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



2
 3 **Formula XII**

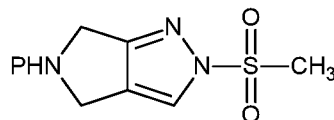
4 wherein P is an amine protecting group,
 5 comprising treating a compound of Formula XI



6
 7 **Formula XI**

8 with an organic acid to obtain the compound of Formula XII.

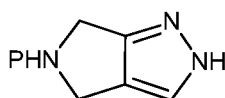
1 11. A process for the preparation of a compound of Formula XIII,



3 **Formula XIII**

4 wherein P is an amine protecting group,

5 comprising reacting a compound of Formula XII



7 **Formula XII**

8 with methylsulfonyl chloride in the presence of a non-nucleophilic base in THF or
9 DMF or mixtures thereof with non polar solvents and other polar aprotic solvents.

1 12. The process according to claim 1, 2, or 7, wherein the compound of Formula A is
2 reacted with 3-bromoprop-1-yne in the presence of a pulverized metal hydroxide, and
3 optionally a phase transfer catalyst, to obtain the compound of Formula II.

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

1 14. The process according to claim 12, wherein the phase transfer catalyst is selected from
2 the group consisting of chloride, bromide, and iodide salts of
3 benzyltrimethylammonium, benzyltriethylammonium, methyltricaprylammonium,
4 methyltributylammonium, methyltrioctylammonium, and tetra-n-butylammonium.

1 15. The process according to claim 1, 3, or 8, wherein the compound of Formula IV is
2 condensed with N,O-bismethylhydroxylamine hydrochloride using an acid activating
3 agent in the presence of a base and a polar aprotic solvent to obtain the compound of
4 Formula V.

1 16. The process according to claim 15, wherein the acid activating agent is selected from
2 the group consisting of alkylhaloformates and acylhalides.

- 1 17. The process according to claim 16, wherein the alkylhaloformate is selected from the
2 group consisting of methylchloroformate, ethylchloroformate, propylchloroformate,
3 isopropylchloroformate, butylchloroformate, and tert-butylchloroformate.
- 1 18. The process according to claim 16, wherein the acylhalide is selected from the group
2 consisting of acetylchloride, methylacetylchloride, dimethylacetylchloride, and
3 trimethylacetylchloride.
- 1 19. The process according to claim 15, wherein the base is selected from the group
2 consisting of methylamine, triethylamine, diisopropylamine, diisopropylethylamine,
3 pyridine, N-methylpyridine, morpholine, and N-methylmorpholine.
- 1 20. The process according to claim 15, wherein the polar aprotic solvent is selected from
2 the group consisting of dichloromethane, THF, DMF, acetone, ethyl acetate, isopropyl
3 acetate, acetonitrile, DME, 1,4-dioxane, methyl THF, DMA, and DMSO.
- 1 21. The process according to claim 1, 4, or 9, wherein the compound of Formula VII is
2 cycloisomerized using a transition metal catalyst in the presence of a sodium salt of a
3 cycloisomerizing agent, a phosphine ligand, and tetrabutylammonium
4 hexafluorophosphate in a solvent to obtain the compound of Formula VIII.
- 1 22. The process according to claim 21, wherein the transition metal catalyst is selected
2 from the group consisting of rhodium and ruthenium.
- 1 23. The process according to claim 22, wherein the transition metal catalyst is rhodium
2 trichloride hydrate or $\text{CpRuCl}(\text{Ph}_3\text{P})_2$.
- 1 24. The process according to claim 21, wherein the cycloisomerizing agent is selected
2 from the group consisting of NHS, NHP, and NHM.
- 1 25. The process according to claim 21, wherein the phosphine ligand is selected from the
2 group consisting of triphenylphosphine, tris(3-fluorophenyl)phosphine, tris(3,5-
3 difluorophenyl)phosphine, and tris(4-fluorophenyl)phosphine.
- 1 26. The process according to claim 21, wherein the solvent is selected from the group
2 consisting of non polar solvents and polar aprotic solvents.
- 1 27. The process according to claim 21, wherein the solvent is toluene or DME.
- 1 28. The process according to claim 5 or 10, wherein the compound of Formula XI is
2 treated with an organic acid to obtain the compound of Formula XII.

- 1 29. The process according to claim 28, wherein the organic acid is selected from the group
2 consisting of acetic acid and trifluoroacetic acid.
- 1 30. The process according to claim 6 or 11, wherein the compound of Formula XII is
2 reacted with methylsulfonyl chloride in the presence of a non-nucleophilic base in
3 THF or DMF or mixtures thereof with nonpolar solvents and polar aprotic solvents to
4 obtain the compound of Formula XIII.
- 1 31. The process according to claim 30, wherein the non-nucleophilic base is selected from
2 the group consisting of sodium hydride, potassium hydride, lithium diisopropylamide,
3 sodium bis(trimethylsilyl)amide, potassium bis(trimethylsilyl)amide, lithium
4 tetramethylpiperidide, triethylamine, N,N-diisopropylethylamine, and
5 diisopropylamine.
- 1 32. The process according to claim 30, wherein the nonpolar solvent is selected from the
2 group consisting of toluene, benzene, cyclohexane, and hexanes.
- 1 33. The process according to claim 30, wherein the polar aprotic solvent is selected from
2 the group consisting of dichloromethane, THF, DMF, acetone, ethyl acetate, isopropyl
3 acetate, acetonitrile, DME, 1,4-dioxane, methyl THF, DMA, and DMSO.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2016/056656

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - A61K 31/4162; A61K 31/4439; A61K 31/4985; C07C 215/30; C07C 225/10; C07C 225/16 (2017.01)

CPC - A61K 31/4162; A61K 31/4439; A61K 31/4985; C07C 215/30; C07C 225/10; C07C 225/16 (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)

IPC(8) - A61K 31/4162; A61K 31/4439; A61K 31/4985; C07C 215/30; C07C 225/10; C07C 225/16 (2017.01)

CPC - A61K 31/4162; A61K 31/4439; A61K 31/4985; C07C 215/30; C07C 225/10; C07C 225/16 (2017.01)

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

USPC - 514/407; 514/338; IPC(8) - A61K 31/4162; A61K 31/4439; A61K 31/4985; C07C 215/30; C07C 225/10; C07C 225/16 (2017.01);

CPC - A61K 31/4162; A61K 31/4439; A61K 31/4985; C07C 215/30; C07C 225/10; C07C 225/16 (2017.01) (keyword delimited)

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

PatBase, STN, PubChem, Google Patents, Google Scholar

Search terms used: Preparation omarigliptin metal hydroxide weinreb amide cyclizing agent

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Xu et al. Asymmetric Synthesis of Highly Functionalized Tetrahydropyran DPP-4 Inhibitor. Organic Letters, 16, 5422-5425, 2014. [retrieved on 17 January 2017]. Retrieved from the Internet. < http://pubs.acs.org/doi/abs/10.1021/ol502661g > entire document	9, 21-26
X	US 2012/0277240 A1 (WILKENING et al) 01 November 2012 (01.11.2012) entire document	11, 30, 31, 33
A	WO 2015/139859 A1 (FIS FABBRICA ITALIANA SINTETICI SPA) 24 September 2015 (24.09.2015) entire document	1-33
A	WO 2013/003249 A1 (MERCK SHARP & DOHME CORP) 03 January 2013 (03.01.2013) entire document	1-33
A	US 7,902,376 B2 (XU et al) 08 March 2011 (08.03.2011) entire document	1-33

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

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"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

18 January 2017

Date of mailing of the international search report

23 MAR 2017

Name and mailing address of the ISA/US

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