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(54) **Title**: METHOD FOR PREPARING SITAGLIPTIN AND AMINE SALT INTERMEDIATES USED THEREIN

(57) **Abstract**: The present invention relates to a method for preparing sitagliptin by using an amine salt of (3R)-3-azido-4-(2,4,5-trifluorophenyl)-butyric acid (formula (V)) in a high yield and purity, and amine salt intermediates used therein.

Description

Title of Invention

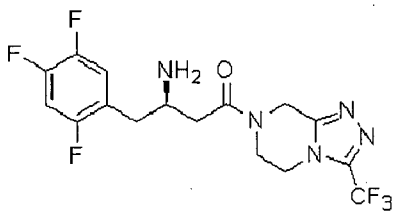
METHOD FOR PREPARING SITAGLIPTIN AND AMINE SALT INTERMEDIATES USED THEREIN

Technical Field

The present invention relates to a method for preparing sitagliptin in a high yield and purity, which is used as adjurvants for diet and exercise therapies of II-type protein patients, and amine salt intermediates used therein.

Background Art

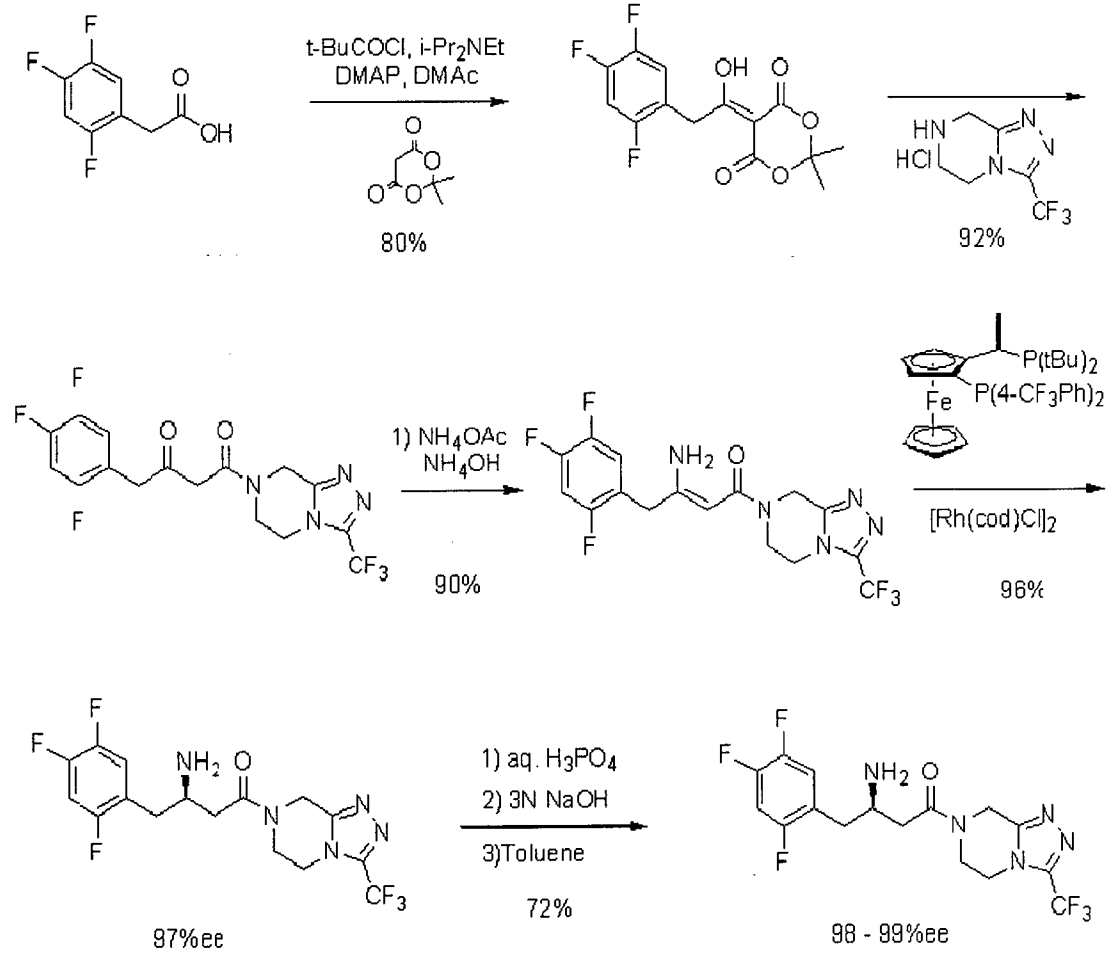
Sitagliptin of formula (I) is a drug which selectively inhibits second generation dipeptidyl peptidase IV (DPP-4), making an incretin level in the body constant. A phosphate monohydrate form of sitagliptin has been approved as adjurvants for diet and exercise therapies of II-type protein patients by FDA dated October, 2006, and it is currently commercially marketable as a trade name of Januvia™ (single preparation) or Janumet™ (oral complex preparation with metformine) in Korea or United States of America.



(I)

Various methods of preparing sitagliptin are hitherto reported. For example, International Publication No. WO 2005/097733 discloses a method of preparing sitagliptin by way of stereoselectively reducing an enamine intermediate using a rodium catalyst of $[Rh(cod)Cl]_2$ and a chiral diphosphine ligand, as shown in Reaction Scheme A.

[Reaction Scheme A]



However, this method has problems in that it requires a further purification of sitagliptin in the final step to control a stereoselectivity and highten an optical purity, and that a yield in the purification process is very low, i.e., 72%.

Disclosure of Invention

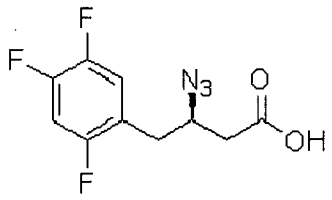
Accordingly, it is an object of the present invention to provide an effective method for preparing sitagliptin in a high yield and purity, and intermediates used therein.

In accordance with one aspect of the present invention, there is provided

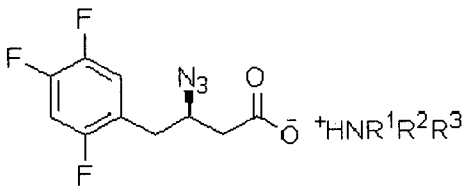
a method for preparing sitagliptin, which comprises the steps of:

(a) subjecting the compound of formula (IV) to a reaction with an amine of $NR^1R^2R^3$ to obtain an amine salt of formula (V); and

(b) subjecting the amine salt of formula (V) to a condensation reaction with 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine (TFT), followed by reduction of the azido group in the resulting compound:



(IV)

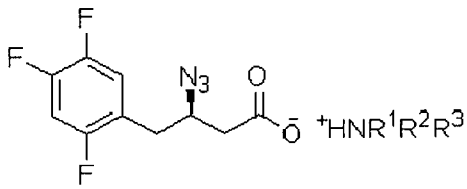


(V)

wherein,

R^1, R^2 and R^3 are each independently H, C_{1-5} alkyl, benzyl, 1-phenylethyl, or 2,2-diphenylethyl; or linked together with the adjacent nitrogen atom to form a pyridine, piperidine, morpholine, pyrrolidine, or piperazine ring.

In accordance with another aspect of the present invention, there is provided a compound of formula (V) used as an intermediate in preparing sitagliptin:



(V)

wherein,

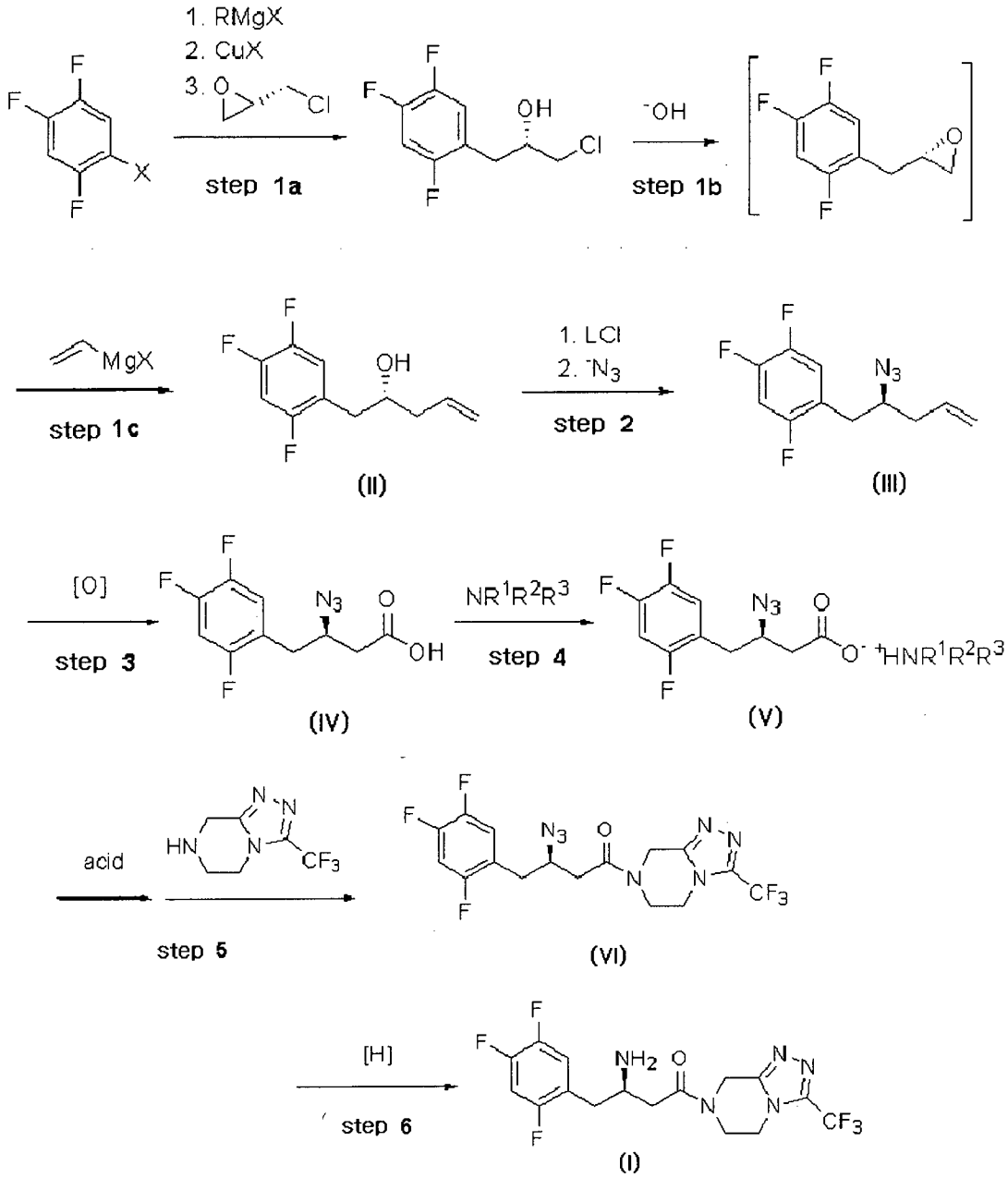
R^1, R^2 and R^3 have the same meanings as defined above.

Best Mode for Carrying Out the Invention

The method for preparing sitagliptin according to the present invention is characterized by the use of an amine salt of (3R)-3-azido-4-(2,4,5-trifluorophenyl)-butyric acid (formula (V)), which can be formed in high compound and optical purities, as an intermediate.

The sitagliptin of formula (I) of the present invention may be prepared by the procedure shown in Reaction Scheme B, which is explained below in more detail.

[Reaction Scheme B]



wherein,

X is halogen;

L is mesyl, tosyl, benzenesulfonyl or trifluoromethanesulfonyl;

R is linear or branched C_{1-5} alkyl; and

R^1, R^2 and R^3 have the same meanings as defined above.

<Step 1>

In step 1, (2R)-1-(2,4,5-trifluorophenyl)-4-penten-2-ol of formula (II) may be prepared from a 2,4,5-trifluorobenzyl halide by sequentially performing a Grignard reaction, a reaction with (S)-epichlorohydrin, epoxidation, and vinylation.

—<Step 1a>

First, a 2,4,5-trifluorobenzyl halide is subjected to organic metallization (a Grignard reaction) to obtain an organic metalide, which is sequentially subjected to respective reactions with a copper halide (CuX, a catalyst content) and (S)-epichlorohydrin, to obtain (2S)-3-(2,4,5-trifluorophenyl)-1-chloro-2-propanol.

The organic metallization (the Grignard reaction) may be performed by subjecting a 2,4,5-trifluorobenzyl halide to a reaction with magnesium (Mg) and an organic alkyl halide such as 1,2-dibromoethane, a reaction with magnesium (Mg) and iodine (I_2), or a reaction with isopropyl magnesium chloride (*i*-PrMgCl). The 2,4,5-trifluorobenzyl halide may be 2,4,5-trifluorobenzyl bromide, 2,4,5-trifluorobenzyl chloride, or a mixture thereof.

The copper halide used in this reaction may be CuI, CuBr, $CuBrS(CH_3)_2$, or a mixture thereof.

<Step 1b>

Then, (2S)-3-(2,4,5-trifluorophenyl)-1-chloro-2-propanol obtained in step 1a is subjected to an epoxidation reaction using a strong base in an organic solvent to obtain (2S)-2-(2,4,5-trifluorobenzyl)-oxylane.

The organic solvent used in this reaction may be tetrahydrofuran, diethyl ether, or a mixture thereof, and the strong base used in this reaction may be a hydroxide of an alkali metal such as sodium hydroxide, potassium hydroxide, lithium hydroxide, and a mixture thereof, preferably sodium hydroxide.

<Step 1c>

Then, (2S)-2-(2,4,5-trifluorobenzyl)-oxylane obtained in step 1b is subjected to a vinylation reaction with a vinyl magnesium halide to obtain (2R)-1-(2,4,5-trifluorophenyl)-4-penten-2-ol of formula (II) having the vinyl group at its end.

The vinyl magnesium halide may be vinyl magnesium bromide, vinyl magnesium chloride, or a mixture thereof. Preferably, the vinylation reaction may be performed in an organic solvent such as tetrahydrofuran, diethyl ether, and a mixture thereof, and in the presence of a copper halide catalyst such as CuI, CuBr, $CuBrS(CH_3)_2$, and a mixture thereof.

The reaction in step 1c may be conducted after or without removing an organic solvent from the resulting solution generated in step 1b. Preferably, it may be continuously conducted without removal of the organic solvent used in step 1b due to high volatility of (2S)-2-(2,4,5-trifluorobenzyl)-oxylane, which leads to reproducible formation of (2R)-1-(2,4,5-trifluorophenyl)-4-penten-2-ol of formula (II).

<Step 2>

In step 2, (2S)-1-(2-azido-4-pentenyl)-2,4,5-trifluorobenzene of formula (III) having an azido group may be prepared by subjecting (2R)-1-(2,4,5-trifluorophenyl)-4-penten-2-ol of formula (II) obtained in step 1 to a reaction with an activating agent to activate its hydroxy group, followed by an azidation reaction.

The activating agent used in this reaction may be mesyl chloride, *p*-tosyl chloride, benzenesulfonyl chloride, trifluoromethanesulfonyl chloride, or a mixture thereof.

The azidation reaction may be carried out by using a compound having an azido group such as sodium azide.

<Step 3>

In step 3, (3R)-3-azido-4-(2,4,5-trifluorophenyl)-butyric acid of formula (IV) having a carboxy group may be prepared by subjecting (2S)-1-(2-azido-4-

pentenyl)-2,4,5-trifluorobenzene of formula (III) obtained in step 2 to an oxidation reaction with an oxidizing agent to oxidize the alkenyl group therein.

The oxidizing agent used in this reaction may be $NaIO_4$, $NaMnO_4$, $KMnO_4$, H_2CrO_4, OsO_4, NaOCl, or a mixture thereof. The oxidizing agent may be preferably used in an amount ranging from 1 to 5 mole equivalents based on the amount of the compound of formula (III).

It is preferred that the reaction in step 3 is conducted in the presence of a catalyst, wherein suitable for use as the catalyst is $RuCl_3$, RuO_4, OsO_4, $KMnO_4$, or a mixture thereof. The catalyst may be preferably used in an amount ranging from 0.0001 to 0.1 mole equivalents based on the amount of the compound of formula (III).

<Step 4>

In step 4, an amine salt of (3R)-3-azido-4-(2,4,5-trifluorophenyl)-butyric acid of formula (V) may be prepared by subjecting (3R)-3-azido-4-(2,4,5-trifluorophenyl)-butyric acid of formula (IV) obtained in step 3 to a reaction with an amine, i.e., $NR^1R^2R^3$.

The amine, $NR^1R^2R^3$, may be a first, secondary or tertiary amine, and representative examples thereof include benzylamine, (R) or (S)-methylbenzylamine, 2,2-diphenylethylamine, dibenzylamine, dicyclohexylamine, diisopropylamine, diisopropylethylamine, diphenylamine, triethylamine, pyridine, and morpholine. It may be preferably used in an amount ranging from 0.8 to 10 mole equivalents based on the amount of the compound of formula (IV).

After the reaction with the amine, induction of crystallization may be performed. The crystallization may be carried out in an organic solvent selected from the group consisting of toluene, ethyl acetate, n-hexane, methylbutylether, heptane, and a mixture thereof.

<Step 5>

In step 5, (3R)-3-azido-1-(3-trifluoromethyl-5,6-dihydro-8H-

[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-4-(2,4,5-trifluorophenyl)-butan-1-one of formula (VI) may be prepared by subjecting the amine salt of (3R)-3-azido-4-(2,4,5-trifluorophenyl)-butyric acid of formula (V) obtained in step 4 to a condensation reaction with 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine (TFT).

It is preferred that prior to the condensation reaction with TFT, the compound of formula (V) is further allowed to be kept in the presence of an inorganic or organic acid to remove the amine salt therefrom, and then the resulting compound is subjected to a reaction with a carboxy group-activating agent to activate the carboxy group therein.

The inorganic acid may be hydrochloride, nitric acid, sulfuric acid, phosphoric acid, or a mixture thereof, and the organic acid may be formic acid, acetic acid, tartaric acid, benzenesulfonic acid, toluenesulfonic acid, or a mixture thereof. In addition, exemplary carboxy group-activating agents include thionylchloride, oxalylchloride, phosphoryloxychloride, N-ethyl-N'-(3-dimethylaminopropyl)carbodiimide (EDC), N,N'-dicyclohexylcarbodiimide (DCC), 1,1'-carbonyldiimidazole (CDI), a mixture of DCC and 1-hydroxybenzotriazole (HOBt), a mixture of DCC and 1-hydroxysuccinimide, and a mixture thereof.

<Step 6>

In step 6, sitagliptin of formula (I) may be prepared by subjecting (3R)-3-azido-1-(3-trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-4-(2,4,5-trifluorophenyl)-butan-1-one of formula (VI) obtained in step 5 to a reduction reaction with a reducing agent to reduce the azido group therein.

The reducing agent used in this reaction may be PPh_3/H_2O, PPh_3/HCl, PPh_3/NH_4OH, PPh_3/H_2S, or a mixture thereof. Also, under the condition of the presence of a metal catalyst including Ranie-Ni, Pd, Pt, Pd/C, Pd/Al_2O_3, $Pd(OH)_2/C$, and a mixture thereof, it may be used as the reducing agent hydrogen, HCOOH, $(NH_4)O_2H$, NH_2NH_2, BH_3, $NaBH_4$, Zn, HCl, or a mixture thereof.

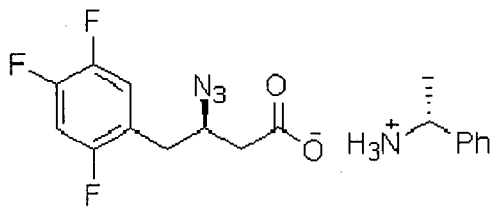
The title compound, sitagliptin, thus obtained may be converted to a

form of phosphate through a further reaction with phosphoric acid.

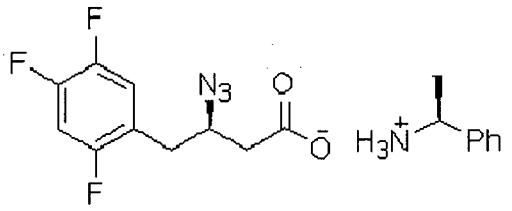
A conventional sitagliptin preparation method requires a further purification of sitagliptin in order to improve both compound purity and optical purity, which disadvantageously causes a significant decrease of a yield. Unlike the conventional method, the inventive method employs as an intermediate an amine salt of (3R)-3-azido-4-(2,4,5-trifluorophenyl)-butyric acid (formula (V)), which can be formed in a high compound purity (e.g., 98%) and a high optical purity (e.g., 99.8% ee), thereby simply and economically generating desired sitagliptin in a high yield and purity without an additional purification.

Further, the amine salt of formula (V) used as an intermediate in the preparation of sitagliptin according to the present invention is a novel compound.

Preferred amine salt intermediates include (R)-methylbenzylamine salt of (3R)-3-azido-4-(2,4,5-trifluorophenyl)-butyric acid of formula (Va) and (S)-methylbenzylamine salt of (3R)-3-azido-4-(2,4,5-trifluorophenyl)-butyric acid of formula (Vb):



(Va)

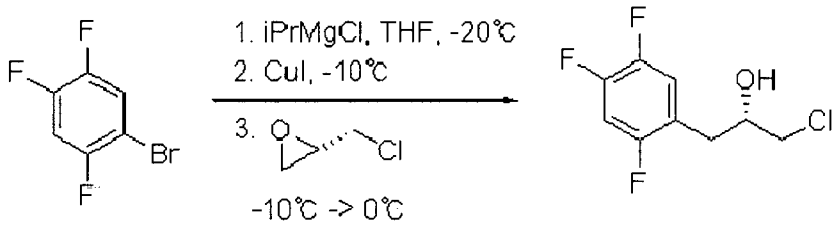


(Vb)

In accordance with the method of the present invention, sitagliptin can be easily prepared in a high yield and purity.

The following Examples are intended to further illustrate the present invention without limiting its scope.

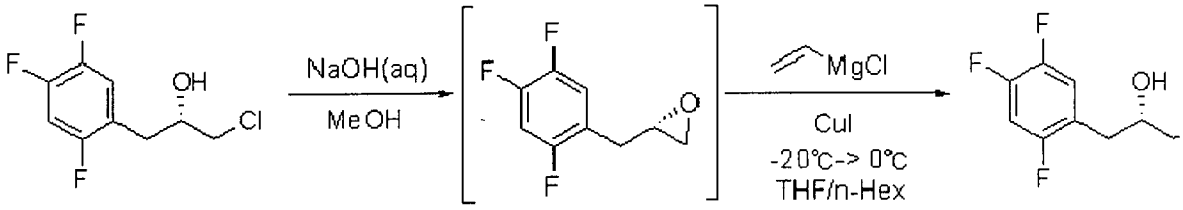
Example 1: Preparation of 1-chloro-3-(2,4,5-trifluorophenyl)-(2S)-propanol



25g of 2,4,5-trifluorobenzene bromide was added dropwise to 75mL of tetrahydrofuran (THF) under a nitrogen atmosphere. The mixture was cooled to -20℃ and 60.4mL of 2M i-PrMgCl (in THF) was added thereto over 10 min while keeping the temperature of the mixture at 0~3℃. The resulting solution was cooled to -10℃ for 1 hr with stirring and 1.81g of Cu(I)I was added thereto, which was further stirred at the same temperature for 30 min. Then, 13.9mL of (S)-epichlorohydrin diluted with 13.9mL of THF was added dropwise to the resulting solution for 30 min and stirred at -10℃ for 1.5 hrs, which was heated to 0℃ and further stirred for 1 hr. 250mL of 2N HCl was added thereto and stirred at room temperature for 30 min. 125mL of dichloromethane (MC) was added to the resulting solution. The organic layer was separated, washed twice with 250mL of water, dried over anhydrous magnesium sulfate, and filtered. The organic solvent was removed from the filtrate under a reduced pressure to obtain 26.6g of the title compound (yield: 100%).

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.17~7.08 (1H, m), 6.96~6.88 (1H, m), 4.11~4.01 (1H, m), 3.66 (1H, dd, J=7.6, 11.3), 3.49 (1H, dd, J=7.6, 11.3), 2.93~2.78 (2H, m), 2.39 (1H, d, J=5.3)

Example 2: Preparation of (2R)-1-(2,4,5-trifluorophenyl)-4-penten-2-ol



(Step 2-1)

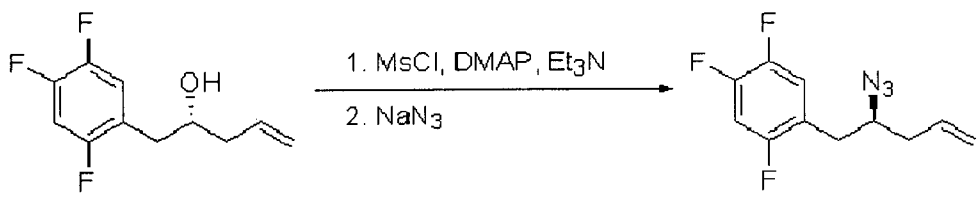
26.6g of 1-chloro-3-(2,4,5-trifluorophenyl)-(2S)-propanol prepared in Example 1 and 53.2mL of methanol were mixed in a reactor with stirring. 35.6mL of 5N NaOH was slowly added thereto over 20 min and stirred for 15 min. After the completion of the reaction was confirmed by TLC, 266mL of H_2O and 79.8mL of n-hexane were added thereto. The water layer was further extracted with 53.2mL of n-hexane. The combined organic layer was washed three times with 106mL of water, dried over anhydrous magnesium sulfate, and filtered using 133mL of n-hexane.

(Step 2-2)

66.5mL of THF was added to the filtrate obtained in Step 2-1 and cooled to -20℃ under a nitrogen atmosphere. 1.13g of Cu(I)I was added thereto, and 1.6M vinyl magnesium bromide (in THF) was slowly added to the resulting solution for 1 hr and further stirred for 30 min. After the completion of the reaction was confirmed by TLC, the reaction solution was heated to 0℃. 266mL of 2N HCl was added thereto and stirred at room temperature for 30 min. The organic layer was separated, washed three times with 266mL of water, dried over anhydrous magnesium sulfate, and filtered. The organic solvent was removed from the filtrate under a reduced pressure to obtain 23.8g of the title compound (yield: 93%, purity: 95%, optical purity: 99.2% ee).

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.15~7.06 (1H, m), 6.94~6.86 (1H, m), 5.85~5.79 (1H, m), 5.20~5.14 (2H, m), 3.90~3.85 (1H, m), 3.82 (1H, dd, J=4.6, 18.5), 2.69 (1H, dd, J=7.9, 14.0), 2.37~2.32 (1H, m), 2.24~2.17 (1H, m), 1.86(1H, Br)

Example 3: Preparation of (2S)-1-(2-azido-4-pentenyl)-2,4,5-trifluorobenzene



(Step 3-1)

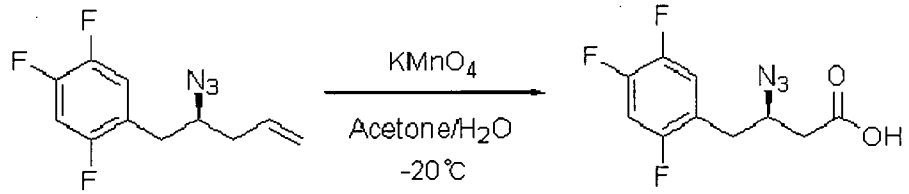
23.98g of (2R)-1-(2,4,5-trifluorophenyl)-4-penten-2-ol prepared in Example 2 and 150mL of ethyl acetate were mixed in a reactor under a nitrogen atmosphere and cooled to 0℃. 16.59mL of triethylamine and 1.39g of 4-dimethylamino pyridine (DMAP) were sequentially added to the mixture, and 9.21mL of methanesulfonic acid was slowly added thereto over 15 min. After the completion of the reaction was confirmed by TLC, 240mL of water was added thereto. The organic layer was separated, sequentially washed with 24mL of 1N HCl and 120mL of water, washed twice with 240mL of brine, dried over anhydrous magnesium sulfate, and filtered. The organic solvent was removed from the filtrate under a reduced pressure.

(Step 3-2)

The residue obtained in Step 3-1 was dissolved in 120mL of DMF, which was mixed with 9.58g of NaN_3 dissolved in 36mL of water. The mixture was heated to 75℃ and stirred for 2 hrs. After the completion of the reaction was confirmed by TLC, the reaction solution was cooled to room temperature. 240mL of water and 120mL of n-hexane were added to the resulting solution. The organic layer was separated, washed twice with 240mL of water, dried over anhydrous magnesium sulfate, and filtered. The organic solvent was removed from the filtrate under a reduced pressure to obtain 25.3g of the title compound (yield: 94%).

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.11~7.02 (1H, m), 7.97~6.87 (1H, m), 5.89~5.80 (1H, m), 5.23~5.17 (1H, m), 3.63~3.59 (1H, m), 2.87 (1H, dd, J=4.7, 18.7), 2.68 (1H, dd, J=7.9, 13.7), 2.38~2.17 (2H, m)

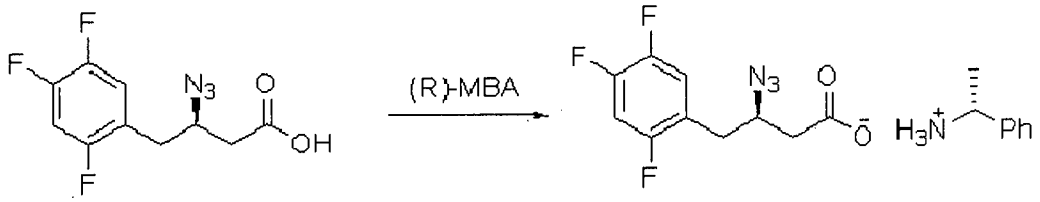
Example 4: Preparation of (3R)-3-azido-4-(2,4,5-trifluorophenyl)-butyric acid



65.26g of potassium permanganate and 149mL of water were mixed in a reactor with stirring at room temperature. 149mL of acetone was added thereto, stirred for 30 min, and cooled to -20℃. 24.9g of (2S)-1-(2-azido-4-pentenyl)-2,4,5-trifluorobenzene prepared in Example 3 dissolved in 74.5mL of acetone was slowly added to the mixture over 1 hr while keeping the temperature of the mixture at below -10℃, which was stirred at -20℃ for 2 hrs. 500mL of 6N HCl and 250mL of ethyl acetate (EA) were added to the resulting solution, and stirred for 1.5 hrs. The organic layer was separated and extracted with 100mL of EA. The organic solvent was removed from the extract under a reduced pressure. The resulting resiude was dissolved in 250mL of EA, which was washed three times with 250mL of water. The organic layer was dried over anhydrous magnesium sulfate, and filtered. The organic solvent was removed from the filtrate under a reduced pressure to obtain 26.2g of the title compound (yield: 98%, purity: 82%, optical purity: 96.6% ee).

^{1}H-NMR (300MHz, $CDCl_3$): δ 10.5 (1H, br), 7.17~7.05 (1H, m), 7.02~6.87 (1H, m), 4.14~4.03 (1H, m), 2.94~2.78 (2H, m), 2.65~2.51 (2H, m)

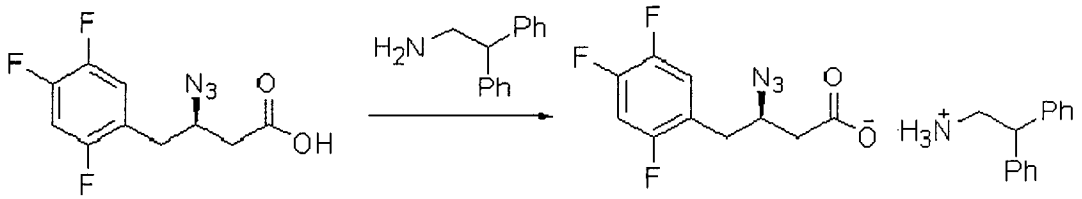
Example 5: Preparation of (3R)-3-azido-4-(2,4,5-trifluorophenyl)-butyric acid (R)-methylbenzylamine salt



20g of (3R)-3-azido-4-(2,4,5-trifluorophenyl)-butyric acid prepared in Example 4 was added dropwise to 66.9mL of EA. 13.2mL of (R)-methylbenzylamine (MBA) was slowly added thereto over 15 min and stirred for 10 min. 214mL of n-hexane was slowly added to the resulting solution to generate a solid precipitate. After 1 hr, the precipitate was separated by filtration and dried with a warm breeze in a 40℃ oven for 12 hrs to obtain 22.0g of the title compound (yield: 75%, purity: 98%, optical purity: 99.8% ee).

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.61 (COOH, br), 7.39~7.28 (5H, m), 7.01~6.90 (2H, m), 4.25~4.18 (1H, m), 3.81~3.72 (1H, m), 2.69 (1H, dd, J=14.0, 4.8), 2.48 (1H, dd, J=14.0, 5.6), 2.08 (2H, d , J=6.7), 1.52 (3H, d, J=6.8)

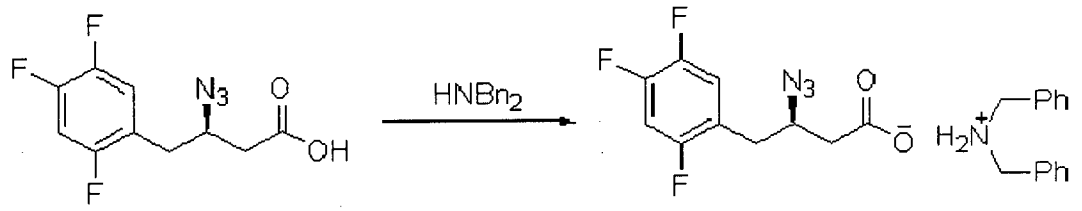
Example 6: Preparation of (3R)-3-azido-4-(2,4,5-trifluorophenyl)-butyric acid 2,2-diphenylethylamine salt



3.0g of (3R)-3-azido-4-(2,4,5-trifluorophenyl)-butyric acid (purity: 82%, optical purity: 96.6% ee) prepared in Example 4 was added dropwise to 21mL of EA. 2.28g of 2,2-diphenylethylamine was added thereto and stirred for 1 hr. The solid precipitate generated was separated by filtration and dried with a warm breeze in a 40℃ oven for 12 hrs to obtain 4.17g of the title compound (yield: 60%, purity: 98.8%, optical purity: 99.7% ee).

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.34~7.03(10H, m), 7.17~7.01 (1H, m), 6.94~6.88(1H, m), 4.18 (1H, t), 3.95 (1H, m), 3.38 (2H, d, J=8.0), 2.83 (1H, dd, J=14.2, 5.1), 2.71 (1H, dd, J=14.2, 8.3), 2.33 (2H, m)

Example 7: Preparation of (3R)-3-azido-4-(2,4,5-trifluorophenyl)-butyric acid dibenzylamine salt

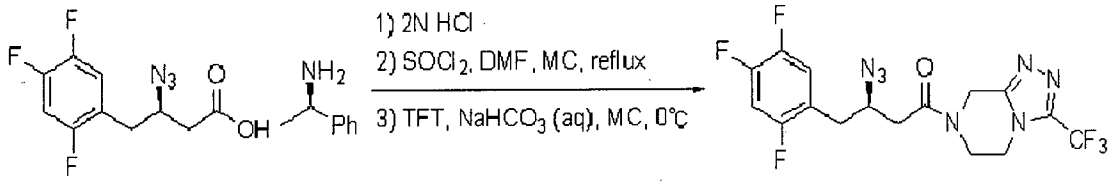


3.0g of (3R)-3-azido-4-(2,4,5-trifluorophenyl)-butyric acid (purity: 82%, optical purity: 96.6% ee) prepared in Example 4 was added dropwise to 7.5mL of EA. 2.24mL of dibenzylamine was slowly added thereto over 15 min and stirred for 10 min. 22.5mL of n-hexane was slowly added to the resulting

solution to generate a solid precipitate. After 1 hr, the precipitate was separated by filtration and dried with a warm breeze in a 40℃ oven for 12 hrs to obtain 4.1g of the title compound (yield: 78%, purity: 98.5%, optical purity: 98.0% ee).

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.38~7.26 (10H, m), 7.17~7.01 (1H, m), 6.94~6.88 (1H, m), 4.00 (1H, m), 3.87 (4H, S), 2.85 (1H, dd, J=14.2, 5.2), 2.72 (1H, dd, J=14.2, 8.3), 2.42 (2H, d, J=7.1)

Example 8: Preparation of (3R)-3-azido-1-(3-trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl)-4-(2,4,5-trifluorophenyl)-butan-1-one



(Step 8-1)

31.2g of (3R)-3-azido-4-(2,4,5-trifluorophenyl)-butyric acid (R)-methylbenzylamine salt prepared in Example 5 was dissolved in 218mL of dichloromethane, and 156mL of 2N HCl was added thereto and stirred. The organic layer was separated, washed three times with 312mL of water, dried over anhydrous magnesium sulfate, and filtered.

(Step 8-2)

12.0mL of thionyl chloride and 0.64mL of DMF were added to the resulting solution obtained in Step 8-1, which was refluxed for 3 hrs. After the completion of the reaction was confirmed by NMR, the remaining amouts of thionyl chloride and the organic solvent were removed from the resulting solution under a reduced pressure.

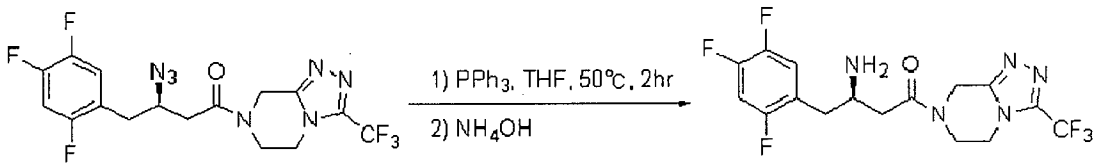
(Step 8-3)

The residue obtained in Step 8-2 was dissolved in 100mL of MC, which was slowly added dropwise to 100ml of a saturated sodium bicarbonate solution

containing 11.4g of 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine hydrochloride at below 10℃, and stirred at room temperature for 1 hr. The water layer was removed from the resulting solution. The organic layer was dried over anhydrous magnesium sulfate and filtered. The organic solvent was removed from the filtrate under a reduced pressure to obtain 33.8g of the title compound (yield: 95%).

^{1}H-NMR (300MHz, $CDCl_3$): δ7.20~7.11 (1H, m), 6.99~6.90(1H, m), 5.20~4.96 (2H, m), 4.28~4.05 (5H, m), 2.98~2.67 (4H, m)

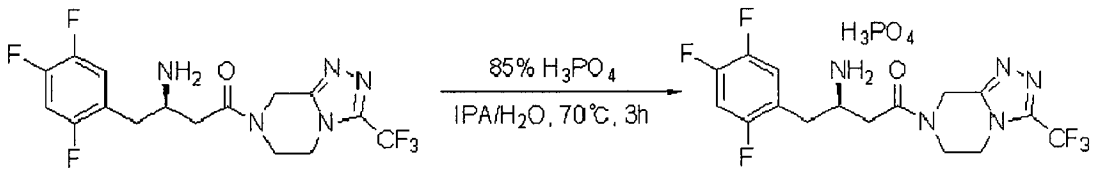
Example 9: Preparation of sitagliptin



22.4g of triphenylphosphine and 336mL of THF were added to 33.6g of (3R)-3-azido-1-(3-trifluoromethyl-5,6-dihydro-8H-[1,2,4]triazolo[4,3-a] pyrazin-7-yl)-4-(2,4,5-trifluorophenyl)-butan-1-one prepared in Example 8, which was heated to 50℃ and stirred for 2 hrs. 101mL of ammonia was added thereto and stirred for 10 hrs. THF was removed from the resulting solution under a reduced pressure. 168mL of 2N HCl and 336mL of a mixed solvent of EA/n-hexane (5:3) were added to the resulting solution, and stirred, followed by layer separation. The water layer was washed three times with 336mL of a mixed solvent of EA/n-hexane (5:3). 16.8mL of ammonia was added to the water layer to neutralize it, which was extracted three times with 168mL of EA. The organic layer was dried over anhydrous magnesium sulfate and filtered. The organic solvent was removed from the filtrate under a reduced pressure to obtain 37.3g of the title compound (yield: 90%, purity: 99.7%, optical purity: 99.8% ee).

^{1}H-NMR (300MHz, $CDCl_3$): δ 7.14~7.06 (1H, m), 7.00~6.88 (1H, m), 5.13~4.88 (2H, m), 4.24~3.80 (4H, m), 3.58 (1H, m), 2.85~2.66 (2H, m), 2.61~2.46 (2H, m), 2.11 (3H, br)

Example 10: Preparation of sitagliptin phosphate



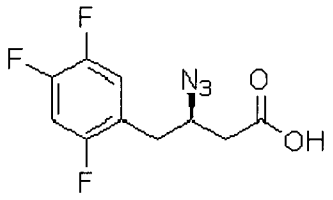
17.5g of sitagliptin prepared in Example 9 was dissolved in a mixture of 220mL of IPA and 18mL of H_2O. 5.6mL of phosphoric acid was slowly added to the resulting mixture, heated to 70℃, stirred for 3 hrs, cooled to room temperature, and further stirred for 10 hrs. The solid precipitate generated was separated by filtration and dried with a warm breeze in a 40℃ oven for 12 hrs to obtain 20.3g of the title compound (yield: 95%).

^{1}H-NMR (300MHz, D_2O): δ 7.23~7.10 (1H, m), 7.08~7.00 (1H, m), 4.88~4.78 (2H, m), 4.25~4.17 (2H, m), 3.97~3.89 (3H, m), 3.02~2.77 (4H, m)

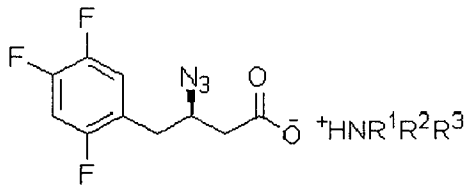
While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes of the invention also fall within the scope of the present invention defined by the claims that follow.

Claims

1. A method for preparing sitagliptin, which comprises the steps of:
(a) subjecting the compound of formula (IV) to a reaction with an amine of $NR^1R^2R^3$ to obtain an amine salt of formula (V); and
(b) subjecting the amine salt of formula (V) to a condensation reaction with 3-trifluoromethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine (TFT), followed by reduction of the azido group in the resulting compound:



(IV)



(V)

wherein,

R^1, R^2 and R^3 are each independently H, C_{1-5} alkyl, benzyl, 1-phenylethyl, or 2,2-diphenylethyl; or linked together with the adjacent nitrogen atom to form a pyridine, piperidine, morpholine, pyrrolidine, or piperazine ring.

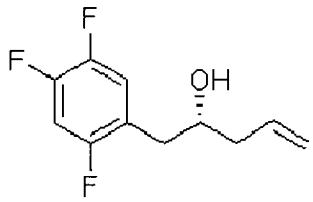
2. The method of claim 1, wherein the amine of $NR^1R^2R^3$ used in step (a) is selected from the group consisting of benzylamine, (R)-methylbenzylamine, (S)-methylbenzylamine, 2,2-diphenylethylamine, dibenzylamine, dicyclohexylamine, diisopropylamine, diisopropylethylamine, diphenylamine, triethylamine, pyridine, and morpholine.

3. The method of claim 1, wherein in step (a), the amine of $NR^1R^2R^3$ is used in an amount ranging from 0.8 to 10 mole equivalents based on the amount of the compound of formula (IV).

4. The method of claim 1, wherein in step (a), after the reaction with the amine, crystallization is performed in an organic solvent selected from the group consisting of toluene, ethylacetate, n-hexane, methylbutylether, heptane, and a mixture thereof.

5. The method of claim 1, wherein in step (b), the reduction is performed using a reducing agent selected from the group consisting of PPh_3/H_2O, PPh_3/HCl, PPh_3/NH_4OH, PPh_3/H_2S, and a mixture thereof.

6. The method of claim 1, wherein the compound of formula (IV) is prepared by activating the hydroxy group of the compound of formula (II) and converting it to the azido group, followed by oxidation of the resulting compound.



(II)

7. The method of claim 6, wherein the activation of the hydroxy group of the compound of formula (II) is performed using an activating agent selected from the group consisting of mesyl chloride, *p*-tosyl chloride, benzenesulfonyl chloride, trifluoromethanesulfonyl chloride, and a mixture thereof.

8. The method of claim 6, wherein the oxidation is performed using an oxidizing agent selected from the group consisting of $NaIO_4$, $NaMnO_4$, $KMnO_4$, H_2CrO_4, OsO_4, NaOCl, and a mixture thereof.

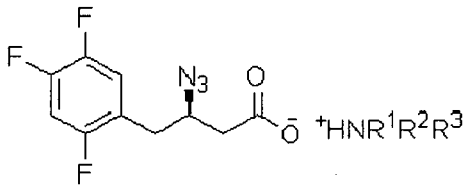
9. The method of claim 6, wherein the compound of formula (II) is prepared by a method comprising the steps of:
(i) subjecting a 2,4,5-trifluorobenzene halide to organic metallization to obtain an organic metalide, and sequentially subjecting the organic metalide to respective reactions with a copper halide and (S)-epichlorohydrin;

(ii) subjecting the resulting compound obtained in step (i) to an epoxidation reaction using a strong base in an organic solvent; and
(iii) subjecting the resulting compound obtained in step (ii) to a vinylation reaction with a vinyl magnesium halide.

10. The method of claim 9, wherein the reaction in step (iii) is conducted without removing the organic solvent used in step (ii).

11. The method of claim 9, wherein the strong base used in step (ii) is selected from the group consisting of sodium hydroxide, potassium hydroxide, lithium hydroxide, and a mixture thereof; the copper halide used in step (i) is selected from the group consisting of CuI, CuBr, $CuBrS(CH_3)_2$, and a mixture thereof; and the vinyl magnesium halide used in step (iii) is selected from the group consisting of vinyl magnesium bromide, vinyl magnesium chloride, and a mixture thereof.

12. A compound of formula (V):



(V)

wherein,

R^1, R^2 and R^3 are each independently H, C_{1-5} alkyl, benzyl, 1-phenylethyl, or 2,2-diphenylethyl; or linked together with the adjacent nitrogen atom to form a pyridine, piperidine, morpholine, pyrrolidine, or piperazine ring.

13. The compound of claim 12, which is (R)-methylbenzylamine salt or (S)-methylbenzylamine salt.