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(54) **Title**: METHOD OF PREPARING EZETIMIBE AND INTERMEDIATES USED THEREIN

(57) **Abstract**: Disclosed is a method for preparing ezetimibe which is effective for preventing or treating arteriosclerosis, and novel intermediates used therein. In accordance with the method which does not use expensive reagents, unwanted diastereoisomers can be easily removed by a step-by-step crystallization procedure, and the ezetimibe of formula 1 can be prepared in a high yield without the use of a hydrogenation procedure under a high pressure.

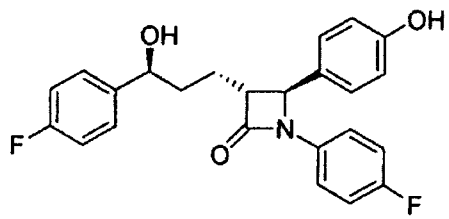
METHOD OF PREPARING EZETIMIBE AND INTERMEDIATES USED THEREIN

FIELD OF THE INVENTION

The present invention relates to an improved method for preparing ezetimibe and novel intermediates used therein.

BACKGROUND OF THE INVENTION

Ezetimibe, the azetidinone derivative of formula 1, has been used as a drug for preventing and treating arteriosclerosis, which is effective in decreasing cholesterol absorption in the intestine as well as in inhibiting cholesterol synthesis together with statins in the liver:

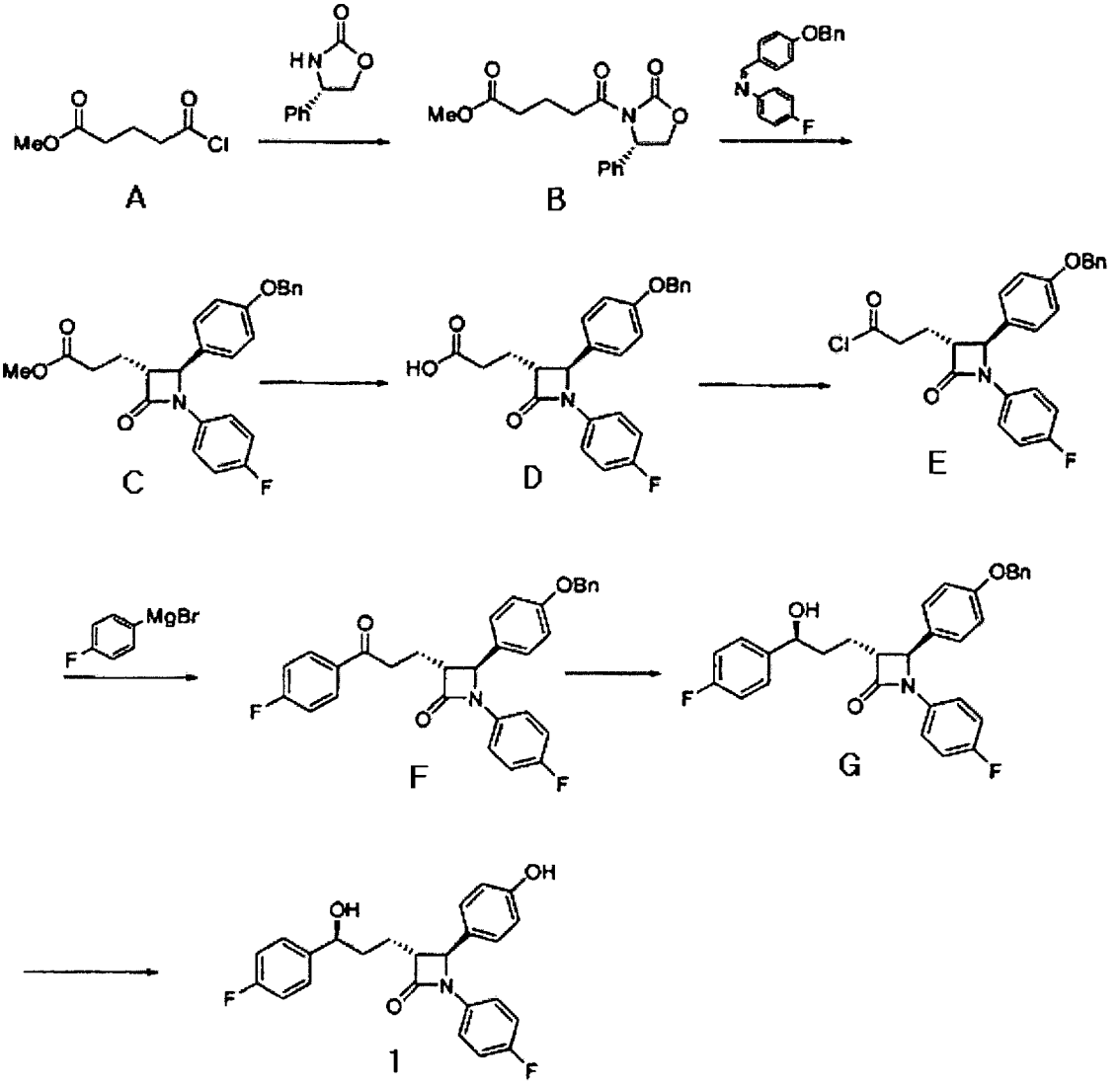


(1)

Various methods for preparing ezetimibe have been disclosed, e.g., in reissued U.S. Pat. No. 37721, U.S. Pat. No. 5,856,473, U.S. Pat. No. 6,207,822, WO 2007072088, and WO 2007120824.

The reissued U.S. Pat. No. 37721 discloses a method for preparing ezetimibe using the procedure shown in Reaction Scheme 1. However, this method have disadvantages in that the synthesis of the compound of formula F through the reaction of the carbonyl chloride of formula E with fluorophenyl magnesium bromide gives an unsatisfactorily low yield, a purification process using column chromatography is required for obtaining the compound of formula F, and a hydrogenation reaction under a high pressure is required to eliminate the benzyl protecting group of the compound of formula G.

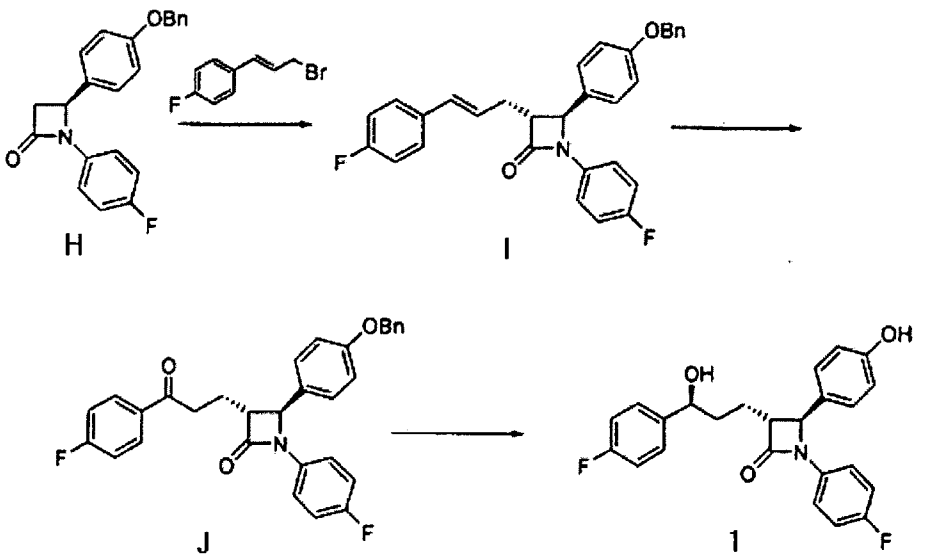
Reaction Scheme 1



wherein Me is methyl, Ph is phenyl, and Bn is Benzyl.

U.S. Pat. No. 5,856,473 discloses a method for preparing ezetimibe which involves the steps shown in Reaction Scheme 2. This method, however, has the disadvantages that the reaction to prepare the compound of formula I must be conducted at -78 ℃, a high-pressure hydrogenation reaction is required to eliminate the benzyl protecting group of the compound of formula J, and a purification process using column chromatography is required for obtaining the non-crystalline compound of formula J.

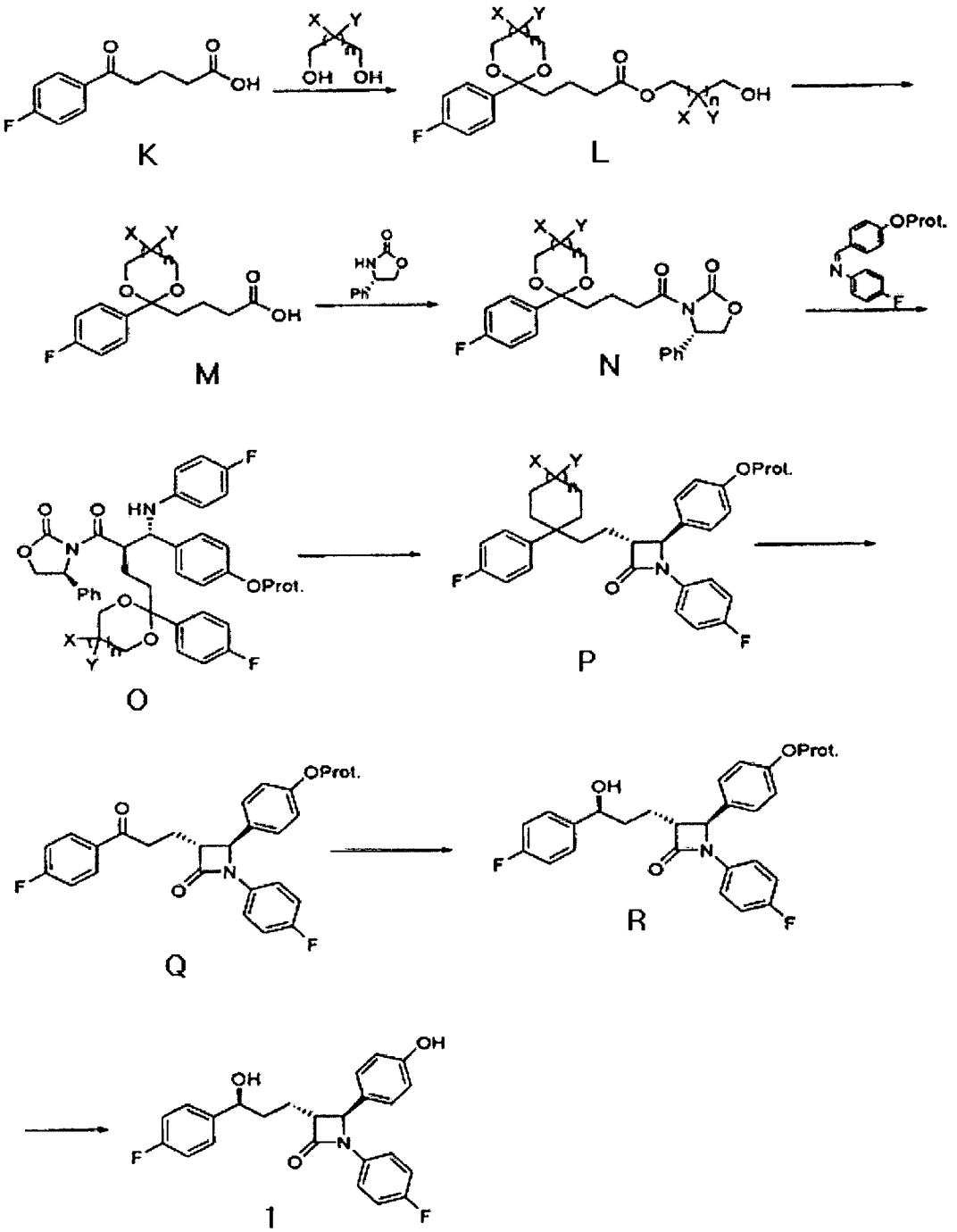
Reaction Scheme 2



wherein Bn is Benzyl.

WO 2007072088 and WO 2007120824 disclose a method for preparing ezetimibe comprising the step of introducing a ketal protecting group to the ketone of formula K, as shown in Reaction Scheme 3. However, this method has the problems that the removal of the protecting group does not precede easily and an expensive metallic catalyst is required for conducting an asymmetric reduction of the compound of formula Q to obtain the compound of formula R.

Reaction Scheme 3

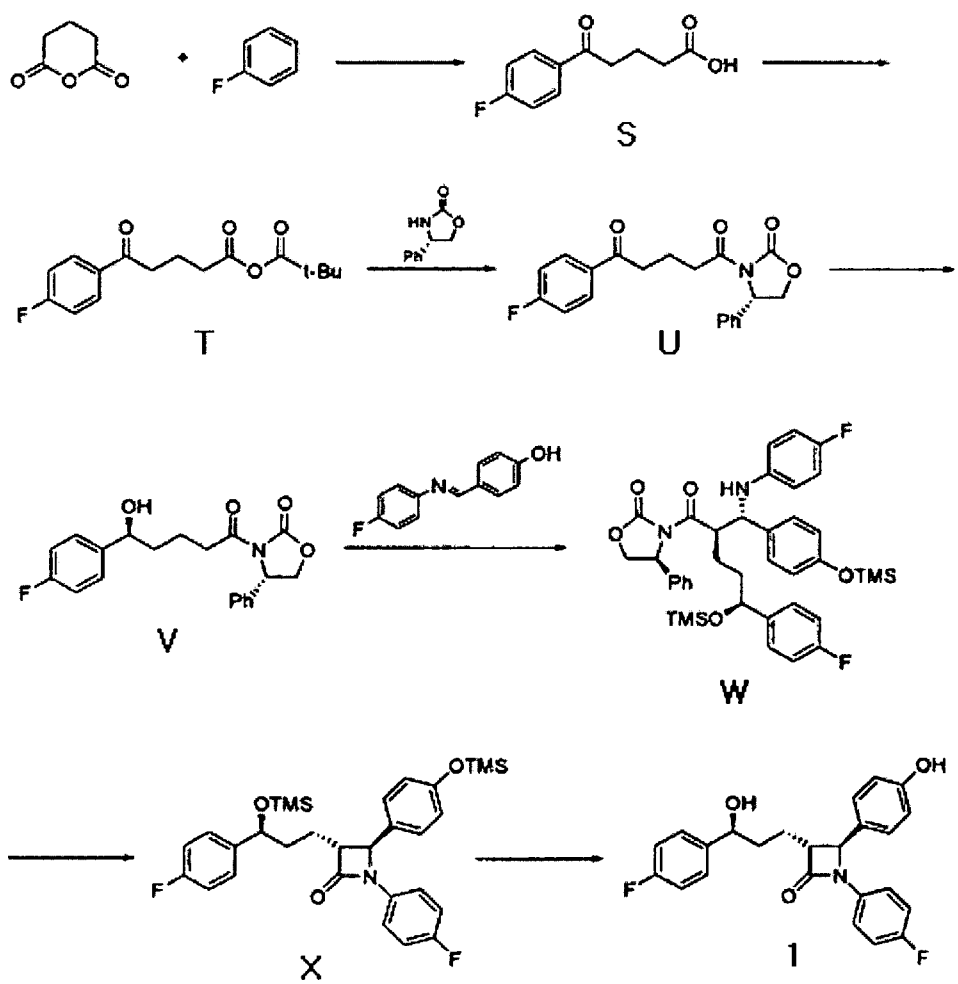


wherein X and Y are each independently hydrogen or optionally substituted alkyl, n is 0 to 3, Ph is phenyl, and Prot is a hydroxyl protecting group.

U.S. Pat. No. 6,207,822 discloses a method for preparing ezetimibe

comprising the steps of subjecting: the compound of formula U to an asymmetric reduction reaction in the presence of (R)-methyl CBS oxazaborolidine to prepare the compound of formula V; the compound of formula V and imine to hydroxyl-protecting with TMS-Cl simultaneously, then to convert into the compound of formula W through Mannich coupling reaction, and the compound of formula W to react with tetrabutylammonium fluoride/N,O-bis(trimethylsilyl)acetamide to prepare the beta-lactam compound of formula X, as shown in Reaction Scheme 4. However, this method suffers from the problem that 10 to 20 % of the compound of formula W in the above Mannich coupling reaction step is converted back to the compound of formula V due to the presence of an acid used therein for quenching the reaction.

Reaction Scheme 4



wherein t-Bu is tert-butyl, Ph is phenyl, and TMS is trimethylsilyl.

The present inventors have therefore endeavored to develop a novel method for preparing ezetimibe which is free from the above-mentioned problems associated with the conventional methods.

SUMMARY OF THE INVENTION

Accordingly, it is a primary object of the present invention to provide an improved method for preparing ezetimibe and intermediates used therein.

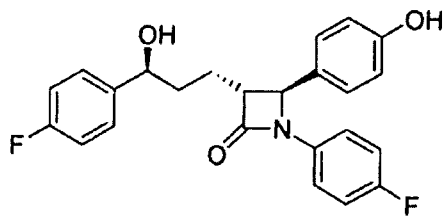
In accordance with one aspect of the present invention, there is provided a method for preparing ezetimibe of formula 1 comprising:

subjecting the compound of formula 2 to a coupling reaction with the imine of formula 6 in the presence of a Lewis acid and a base to prepare the compound of formula 3;

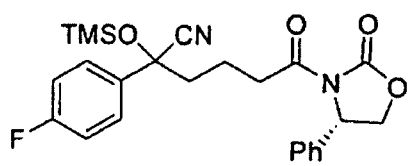
conducting a cyclization reaction of the compound of formula 3 in the presence of a base to prepare the compound of formula 4;

carrying out asymmetric reduction of the compound of formula 4 in the presence of a borane compound and a chiral catalyst to prepare the compound of formula 5; and

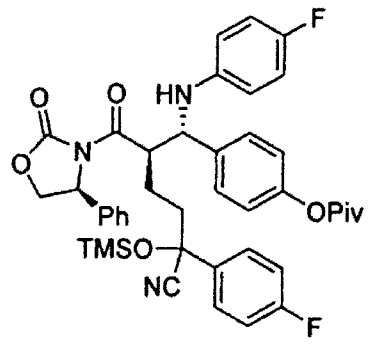
removing the hydroxyl protecting group of the compound of formula 5 in the presence of a base,



(1)



(2)



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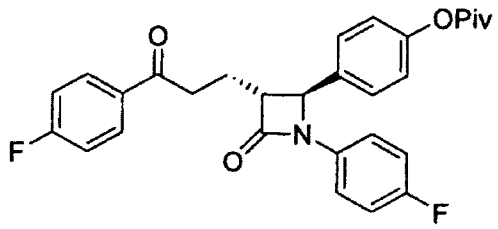

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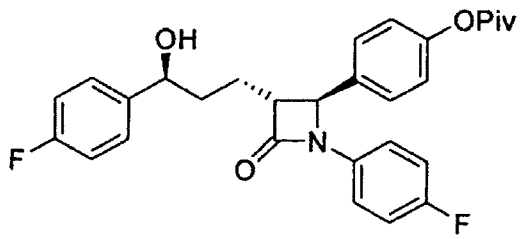

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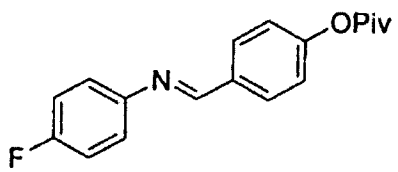


(6)

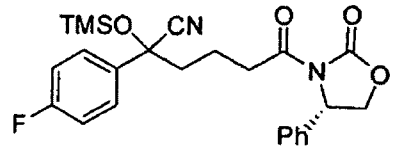
wherein,

Ph is phenyl,

TMS is trimethylsilyl, and

Piv is trimethylacetyl.

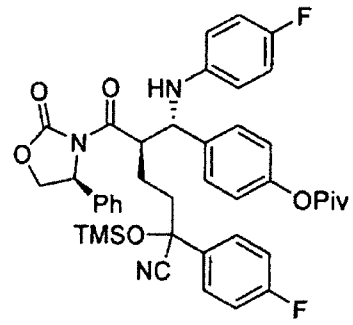
In accordance with another aspect of the present invention, there is provided the compound of formula 2 as an intermediate which is useful for preparing ezetimibe of formula 1:



(2)

wherein Ph and TMS have the same meanings as indicated above.

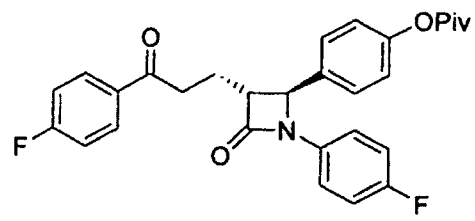
In accordance with a further aspect of the present invention, there is provided the compound of formula 3 as an intermediate which is useful for preparing ezetimibe of formula 1:



(3)

wherein Ph, TMS, and Piv have the same meanings as indicated above.

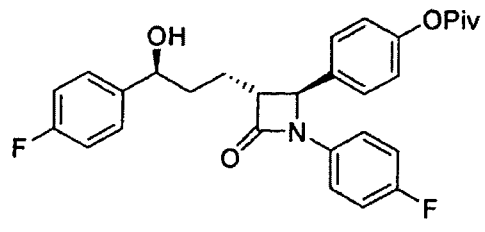
In accordance with a further aspect of the present invention, there is provided the compound of formula 4 as an intermediate which is useful for preparing ezetimibe of formula 1:



(4)

wherein Piv has the same meaning as indicated above.

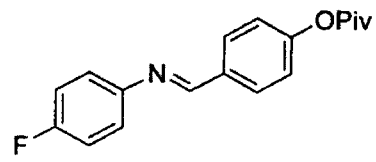
In accordance with a still further aspect of the present invention, there is provided the compound of formula 5 as an intermediate which is useful for preparing ezetimibe of formula 1:



(5)

wherein Piv has the same meaning as indicated above.

In accordance with a still yet further aspect of the present invention, there is provided the compound of formula 6 as an intermediate which is useful for preparing ezetimibe of formula 1:



(6)

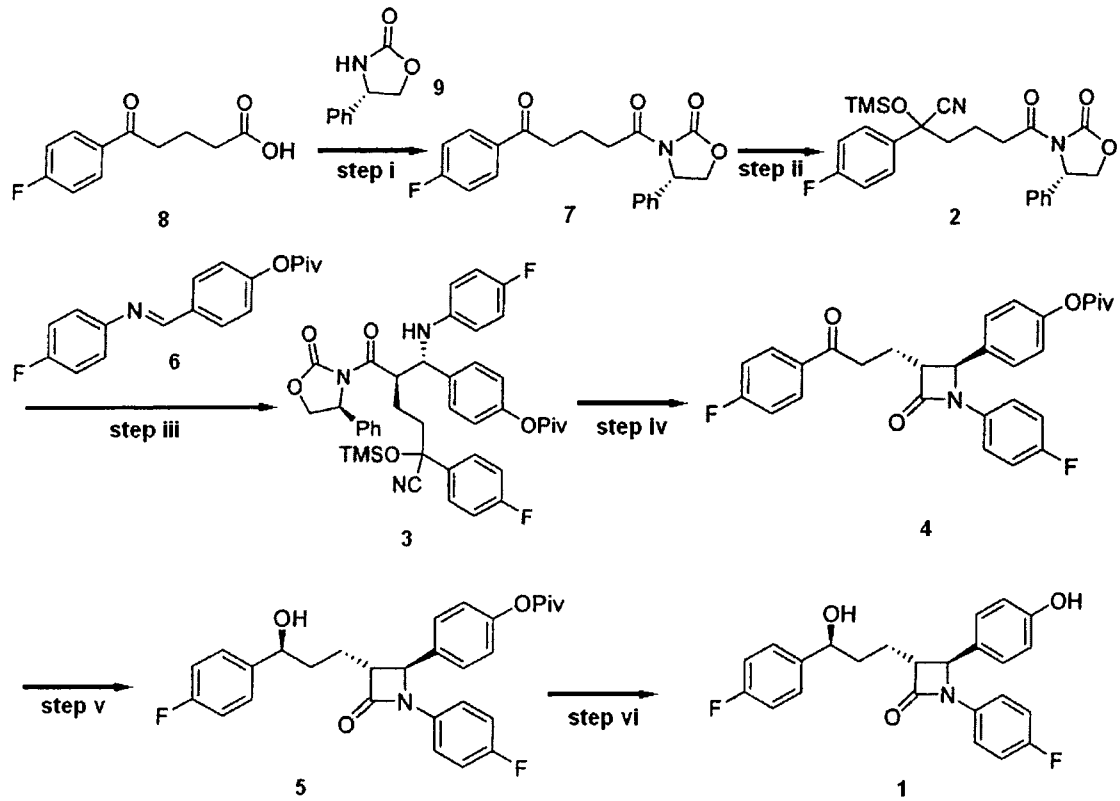
wherein Piv has the same meaning as indicated above.

DETAILED DESCRIPTION OF THE INVENTION

The preparation method according to the present invention is characterized in that the compound of formula 3 prepared by coupling the compound of formula 2 with the compound of formula 6 is cyclized to obtain the compound of formula 4 and the compound of formula 5 prepared by asymmetric reduction of the compound of formula 4 is used as an intermediate for preparing ezetimibe of formula 1, and further in that the compound of formula 2 is prepared by a reaction of the compound of formula 7 with cyanotrimethylsilane in the presence of a halogen catalyst.

In an embodiment, the ezetimibe of formula 1 according to the present invention can be prepared from the compound of formula 8 by the method illustrated in Reaction Scheme 5, but not limited thereto:

Reaction Scheme 5



wherein Ph, TMS, and Piv have the same meanings as defined above.

Step i

In this step, the ketone compound of formula 7 which is used as an intermediate in the present invention is prepared by conducting a coupling reaction of the carboxylic acid of formula 8 with the chiral auxiliary of formula 9.

The chiral auxiliary of formula 9 is used in an amount ranging from 0.9 to 1.1 molar equivalents based on the carboxylic acid of formula 8.

It is preferable that the coupling reaction is carried out in a solvent containing N,N'-dicyclohexylcarboimide and 4-dimethylaminopyridine. In this case, N,N'-dicyclohexylcarboimide is used in an amount ranging from 0.8 to 1.1 molar equivalents based on the carboxylic acid of formula 8, and 4-dimethylaminopyridine is used in an amount ranging from 0.05 to 0.5 molar equivalents, preferably 0.1 molar equivalents, based on the carboxylic acid of formula 8. Examples of the solvent include, but are not limited to,

dichloromethane, chloroform, and a mixture thereof.

Step ii

The ketal compound of formula 2, a novel intermediate for preparing ezetimibe, is prepared by treating the ketone compound of formula 7 with cyanotrimethylsilane in the presence of a halogen catalyst. The amount of cyanotrimethylsilane used is in the range of 1 to 3 molar equivalents, preferably 1.3 to 1.7 molar equivalents, based on the ketone compound of formula 7.

Examples of the halogen catalyst include bromine, iodine, etc, preferably iodine. The halogen catalyst is used in an amount ranging from 0.01 to 0.1 molar equivalents based on the ketone compound of formula 7.

It is preferable that the reaction is carried out at a temperature of -10 to 25 ℃.

Examples of the solvent used in this step include, but are not limited to, dichloromethane, chloroform, toluene, tetrahydrofuran, N,N-dimethylformamide, dimethylsulfoxide, and a mixture thereof.

Step iii

In this step, the compound of formula 3 is prepared by conducting a coupling reaction of the ketal compound of formula 2 obtained in step ii with the imine compound of formula 6 having the protected hydroxyl group in the presence of a Lewis acid and a base.

The amount of the compound of formula 6 used in this step is in the range of 1 to 3 molar equivalents, preferably 1.2 molar equivalents, based on the ketal compound of formula 2.

Examples of the Lewis acid include, but are not limited to, titanium tetrachloride, dibutylboron triplate, and a mixture thereof, and the amount of the Lewis acid used in this step is in the range of 1 to 3 molar equivalents, preferably 1 to 1.5 molar equivalents, based on the ketal compound of formula 2.

Examples of the base include, but are not limited to, amine having C_{1-6} alkyl such as triethylamine, diisopropylethylamine, and tributylamine, and the

amount of the base used in this step is in the range of 1 to 3 molar equivalents, preferably 1.3 to 1.7 molar equivalents, based on the ketal compound of formula 2.

It is preferable that the reaction is carried out at a temperature of -75 ℃ to 25 ℃, preferably -45 ℃ to -30 ℃. Examples of the solvent used in this step include, but are not limited to, dichloromethane, chloroform, toluene, tetrahydrofuran, ethyl acetate, and a mixture thereof.

Step iv

In this step, the beta-lactam cyclic compound of formula 4 is prepared by the cyclization of the compound of formula 3 obtained in step iii in the presence of a base.

Examples of the base include, but are not limited to, n-butyl lithium, lithium t-butoxide, lithium hexamethyldisilyl amide, and a mixture thereof, and the amount of the base used in this step is in the range of 1 to 3 molar equivalents based on the compound of formula 3.

It is preferable that the reaction is carried out at a temperature of -20 ℃ to 25 ℃, preferably -5 ℃ to 5 ℃.

Examples of the solvent used in this step include, but are not limited to, dichloromethane, chloroform, tetrahydrofuran, and a mixture thereof.

Step v

In this step, the compound of formula 5 is prepared by carrying out asymmetric reduction of the beta-lactam cyclic compound of formula 4 obtained in step iv in the presence of a borane compound and a chiral catalyst.

As used herein, the term "chiral catalyst" which is also called an asymmetric catalysis, refers to a material which allows a non-chiral compound to convert into a chiral compound having an optical activity by asymmetric reduction of the carbonyl group of the non-chiral compound. Examples of the chiral catalyst as used herein include, but are not limited to (R)-methyl-CBS oxazaborolidine, (R)-propyl-CBS oxazaborolidine, (R)-butyl-CBS

oxazaborolidine, (R)-o-tollyl-CBS oxazaborolidine, and a mixture thereof. The amount of the chiral catalyst used in this step is in the range of 0.05 to 0.3 molar equivalents, preferably 0.09 to 0.11 molar equivalents, based on the compound of formula 4.

Examples of the borane compound include, but are not limited to, borane-dimethylsulfide, borane-tetrahydrofuran, catecholborane and a mixture thereof. The amount of the borane compound used in this step is in the range of 1 to 3 molar equivalents, preferably 1.3 to 1.7 molar equivalents, based on the compound of formula 4.

It is preferable that the reaction is carried out at a temperature of -30 ℃ to 0 ℃.

Examples of the solvent used in this step include, but are not limited to, dichloromethane, chloroform, tetrahydrofuran, diethyl ether, toluene, and a mixture thereof, preferably tetrahydrofuran.

Step vi

In this step, the compound of formula 1 is prepared by removing the hydroxyl protecting group of the compound of formula 5 obtained in step v in the presence of a base.

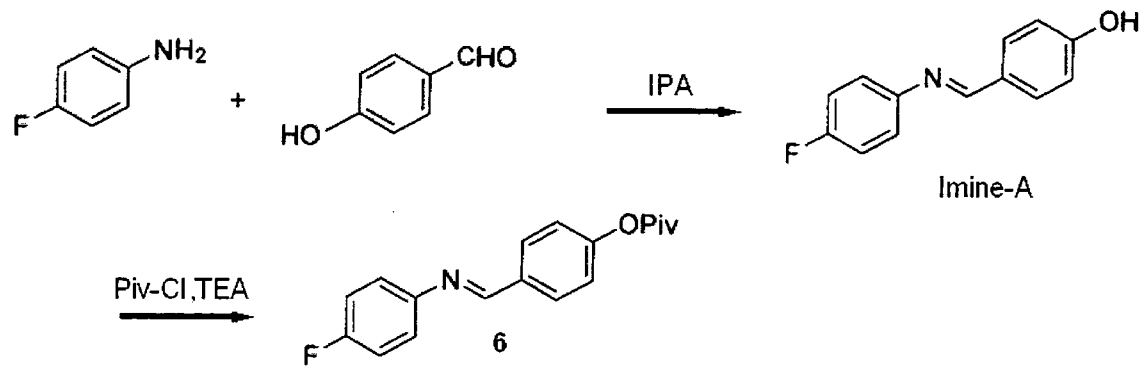
Examples of the base include, but are not limited to, lithium hydroxide, sodium hydroxide, potassium hydroxide, tetrabutylammonium fluoride, tetrabutylammonium chloride, tetrabutylammonium bromide, and a mixture thereof. The amount of the base used in this step is in the range of 1 to 4 molar equivalents, preferably 1.5 to 2 molar equivalents, based on the compound of formula 5.

It is preferable that the reaction is carried out at a temperature of -20 ℃ to 0 ℃.

Examples of the solvent used in this step include, but are not limited to, methanol, ethanol, propanol, isopropanol, butanol, acetonitril, 1,4-dioxane, acetone, tetrahydrofuran, dichloromethane, chloroform, and a mixture thereof.

Further, the hydroxyl-protected imine compound of formula 6 obtained in step iii is prepared by the method illustrated in Reaction Scheme 6, but not limited thereto:

Reaction Scheme 6



wherein Piv is trimethylacetyl radical, TEA is triethylamine.

The novel compound of formula 6 is prepared by allowing 4-[(4-fluorophenylimino)-methyl]phenol (Imine-A) to react with trimethylacetylchloride in the presence of triethylamine.

Imine-A is prepared by the method disclosed in U.S. Pat. No. 6,207,822.

It is preferable that the reaction is carried out in a solvent at a temperature of 0 ℃ to 25 ℃. Examples of the solvent include, but are not limited to, dichloromethane, chloroform, tetrahydrofuran, and a mixture thereof.

In accordance with the inventive preparation method which does not use expensive reagents, unwanted diastereoisomers can be easily removed by a step-by-step crystallization procedure, and the ezetimibe of formula 1 can be prepared in a high yield without the use of a hydrogenation procedure under a high pressure.

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

Example 1: Preparation of ezetimibe

(1-1) Preparation of 3-[5-(fluorophenyl)-1,5-dioxapentyl]-4(S)-phenyl-2-oxazolidinone (Formula 7)

200 g of 5-(4-fluorophenyl)-5-oxopentanoic acid of formula 8, 160 g of (S)-4-phenyloxazolidine-2-one of formula 9, and 11.6 g of 4-dimethylaminopyridine were dissolved in 600 mℓ of dichloromethane to prepare a reaction mixture. A solution which was prepared by dissolving 157 g of N,N'-dicyclohexylcarboimide in 200 mℓ of dichloromethane was added to the reaction mixture and stirred for 2 hours. After completion of the reaction, the resulting reaction mixture was filtered to remove by-products. The filtrate thus obtained was washed successively with 1 ℓ of 6N HCl, 1 ℓ of water, and 1 ℓ of saturated sodium chloride, dried over anhydrous magnesium sulfate, filtered, and distilled under a reduced pressure to remove the solvent. The residue thus obtained was dissolved in 2 ℓ of methanol by heating and cooled to induce crystallization. 2 ℓ of water was added thereto and stirred for 30 min. The solid thus obtained was isolated by filtering to obtain 289 g of the title compound as a white solid (yield: 86%).

^{1}H NMR(300MHz, $CDCl_3$) : δ 7.92 (2H, M), 7.35-7.13 (5H, m), 7.04 (2H, m), 5.43 (1H, q), 4.75(1H, t), 4.22 (1H, q), 3.05-2.93 (4H, m), 2.03 (2H, m)

(1-2) Preparation of 2-(4-fluorophenyl)-6-oxo-6-(2-oxo-4-phenyl oxazolidine-3-yl)-2-trimethylsilyloxy hexane nitrile (Formula 2)

100 g of 3-[5-(fluorophenyl)-1,5-dioxapentyl]-4(S)-phenyl-2-oxazolidinone obtained in (1-1) was dissolved in 1 ℓ of dichloromethane and cooled to 0 ℃. 3.55 g of iodine was added thereto, followed by adding thereto 53 mℓ of cyanotrimethylsilane over 20 min. After 2 hrs, the reaction mixture was washed twice with 500 mℓ of aqueous $Na_2S_2O_3$ and the organic layer was isolated. The organic layer was dried over anhydrous magnesium sulfate and distilled under a reduced pressure to obtain 127.9 g of the title compound (yield: 100 %).

^{1}H NMR (300MHz, $CDCl_3$) : δ 7.35-7.14 (7H, m), 6.94 (2H, t), 5.26 (2H, dd), 4.56 (1H, t), 4.15 (2H, dd), 2.83 (2H, t), 1.90-1.48 (4H, m), 0.02 (9H, s)

(1-3) Preparation of 2,2-dimethyl-propionic acid 4-[(4-fluorophenyl imino)-methyl]-phenyl ester (Formula 6)

180 g of 4-[(4-fluorophenylimino)-methyl]-phenol, which had been prepared by the reaction of 4-hydroxybenzaldehyde with 4-fluoroaniline according to the method described in U.S. Pat. No. 6,207,822, was dissolved in 1.26 ℓ of dichloromethane and stirred to obtain a slurry. 354 mℓ of triethylamine and 113 mℓ of trimethylacetyl chloride were added to the slurry and stirred for 30 min. The reaction mixture thus obtained was combined with 630 mℓ of water to obtain an separated organic layer, which was further washed with 1 ℓ of water. The washed organic layer was dried over anhydrous magnesium sulfate and distilled under a reduced pressure to remove the solvent. The residue thus obtained was dissolved in 540 mℓ of n-hexane and stirred at 0 ℃ for 1 hour to induce the precipitation of a solid. The solid was filtered to obtain 233 g of the title compound as a white solid (yield: 93 %).

^{1}H NMR (300MHz, $CDCl_3$) : δ 8.42 (1H, s), 7.91(2H, d), 7.22-67.16 (4H, m), 7.07 (2H, t), 1.38 (9H, s)

(1-4) Preparation of 2,2-dimethylpropionic acid 4-[5-cyano -5-(4-fluorophenyl)-1-(4-fluorophenylamino)-2-(2-oxo-4-phenyl-oxazolidine-3 -carbonyl) -5-trimethylsilyloxypentyl]-phenyl ester (Formula 3)

127.9 g of the compound of formula 2 obtained in (1-2) and 101.08 g of the imine compound of formula 6 obtained in (1-3) were dissolved in 1.02 ℓ of dichloromethane and cooled at -40 ℃. 73.69 mℓ of diisopropylethylamine was added thereto and maintained for 10 min. 0.31 ℓ of titanium tetrachloride (1M solution in CH_2Cl_2) was added thereto over 30 min and stirred for 30 min. After completion of the reaction, isopropyl alcohol/dichloromethane (256 mℓ/128 mℓ) were added to the reaction mixture thus obtained while maintaining at the temperature of -25 ℃ or less, and then heated to 0 ℃. The reaction mixture was washed successively with 640 mℓ of water at 0 ℃ and 640 mℓ of saturated sodium chloride, and the organic layer was isolated. The organic layer was dried

over anhydrous magnesium sulfate and distilled under a reduced pressure to remove the solvent. The residue thus obtained was dissolved in 256 ml of ethyl acetate with heating, and then cooled to room temperature to induce the precipitation of a solid. 768 ml of n-hexane was added to the solid and stirred for 1 hour to obtain 123 g of the title compound as a white solid (yield: 58%).

^{1}H NMR (300MHz, $CDCl_3$) : δ 7.25-6.84 (13H, m), 6.66-6.62 (2H, m), 6.27-6.25 (2H, m), 5.31 (1H, m), 4.84 (1H, d), 4.58 (1H, m), 4.39 (1H, m), 4.27 (1H, m), 4.10 (2H, dd), 1.97-1.43 (4H, m), 1.28 (9H, m) 0.02 (9H, s)

(1-5) Preparation of 2,2-dimethyl-propionic acid 4-{1-(4-fluorophenyl) -3-[3-(4-fluorophenyl)-3-oxopropyl]-4-oxoazetidine-2-yl}-phenyl ester (Formula 4)

15.9 ml of lithium hexamethyldisilylamide (1M solution in Toluene) was added to a solution which was prepared by dissolving 10 g of the compound of formula 3 obtained in (1-4) in 50 ml of dichloromethane and cooling at 0 ℃, and stirred for 30 min. 20 ml of methanol was added thereto and further stirred for 15 min to obtain a reaction mixture. 50 ml of dichloromethane, 50 ml of water, and 50 ml of 3N hydrochloric acid were added successively to the reaction mixture and stirred to isolate an aqueous layer. The aqueous layer was extracted with 50 ml dichloromethane and the organic layer was isolated. The organic layer was washed with 100 ml of saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and distilled under a reduced pressure to remove the solvent. 50 ml of dichloromethane and 0.92 ml of triethylamine were added to the residue thus obtained. 0.82 ml of trimethylacetyl chloride was added thereto and stirred. The reaction mixture thus obtained was extracted with 50 ml of water and 10 ml of 3N hydrochloric acid, and the organic layer was isolated. The organic layer was washed successively with 50 ml of sodium bicarbonate and 50 ml of saturated sodium chloride, dried over anhydrous magnesium sulfate, and distilled under a reduced pressure. The residue thus obtained was dissolved in 60 ml of methanol. 20 ml of water was added thereto and stirred for 1 hour to induce the precipitation of a solid. The solid

was isolated by filtering to obtain 5.2 g of the title compound as a pale yellow solid (yield: 80 %).

^{1}H NMR (300MHz, $CDCl_3$) : δ 8.01-7.96 (2H, m), 7.35-6.90 (10H, m), 4.75 (1H, s), 3.29-3.11 (3H, m), 2.42-2.27 (2H, m), 1.34 (9H, s)

(1-6) Preparation of 4-((2S,3R)-1-(4-fluorophenyl)-3-((S)-3-(4-fluoro phenyl)-3-hydroxypropyl)-4-oxoazetidine-2-yl)-phenyl pivalate (Formula 5)

30 mℓ of tetrahydrofuran was placed in a reactor and cooled to -25 ℃. 2.89 mℓ of BMS (Borane-dimethylsulfide complex) and 2 mℓ of (R)-(+)-2-methyl-CBS-oxazaborolidine(1M solution in Toluene) were added thereto and stirred for 15 min. The reaction mixture thus obtained was added to a solution which was prepared by dissolving 10 g of the compound of formula 4 obtained in (1-5) in 30 mℓ of tetrahydrofuran over 30 min, and stirred for 1.5 hour. After completion of the reaction, 30 mℓ of 10% hydrogen-peroxide was added thereto and stirred for 10 min to quench. The reaction mixture thus obtained was extracted with 30 mℓ of ethyl acetate and 30 mℓ of water, and the organic layer was isolated. The organic layer was washed successively with 20 mℓ of 2 N sulfuric acid and 20 mℓ of saturated sodium chloride, dried over anhydrous magnesium sulfate, and distilled under a reduced pressure to remove the solvent. The residue thus obtained was dissolved in 50 mℓ of methanol, and 20 mℓ of water was added thereto and stirred for 1 hour to induce the precipitation of a solid. The solid was isolated by filtering to obtain 8.82 g of the title compound as a pale yellow solid (yield: 88%).

^{1}H NMR (300MHz, $CDCl_3$) : δ 7.33-6.82(12H, m), 4.70 (1H, t), 4.61 (1H, d), 3.08 (1H, q), 2.19(1H, s), 2.07-1.84 (4H, m), 1.30 (9H, m)

(1-7) Preparation of 1-(4-fluorophenyl)-3-[3-(4-fluorophenyl)-3-hydroxypropyl] -4-(4-hydroxyphenyl)-azetidine-2-one (Formula 1)

10 g of the compound of formula 5 obtained in (1-6) was dissolved in 70 mℓ of tetrahydrofuran and cooled to -15 ℃. The reaction solution thus obtained was added to a solution which was prepared by dissolving 1.6 g of sodium

hydroxide in 30 ㎖ of methanol, and stirred for 30 min. The reaction mixture thus obtained was extracted with 100 ㎖ of 1N hydrochloric acid and 50 ㎖ of ethyl acetate, and the aqueous layer was isolated. The aqueous layer was extracted with 30 ㎖ of ethyl acetate and the organic layer was isolated. The organic layer was washed three times with 50 ㎖ of water, dried over anhydrous magnesium sulfate, and distilled under a reduced pressure to remove the solvent. The residue thus obtained was dissolved in 50 ㎖ of methanol. 37.5 ㎖ of water was added thereto and stirred for 1 hour to induce the precipitation of a solid. The solid was isolated by filtering to obtain 7.63 g of the title compound as a white solid (yield: 92%).

^{1}H NMR (300MHz, DMSO-d_6) : δ9.53 (1H, s), 7.46-7.09 (10H, m), 6.78 (2H, d), 5.29 (1H, d), 4.89 (1H, s), 4.51 (1H, d), 3.09 (1H, m), 1.88-1.73 (4H, m)

(1-8) Purification of ezetimibe

10 g of ezetimibe obtained in (1-7) was dissolved in 60 ㎖ of acetonitrile at 40 ℃ and cooled to room temperature. 60 ㎖ of water was added thereto and stirred for 1 hour to induce the precipitation of a solid. The solid was isolated by filtering to obtain 9.0 g of the title compound as a white solid (yield: 90 %).

While the invention has been described with respect to the above specific embodiments, it should be recognized that various modifications and changes may be made to the invention by those skilled in the art which also fall within the scope of the invention as defined by the appended claims.

WHAT IS CLAIMED IS:

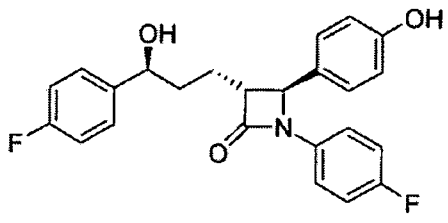
1. A method for preparing ezetimibe of formula 1, comprising:

(i) subjecting the compound of formula 2 to a coupling reaction with the imine of formula 6 in the presence of a Lewis acid and a base to prepare the compound of formula 3;

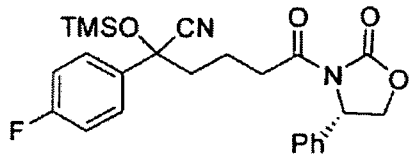
(ii) conducting a cyclization reaction of the compound of formula 3 in the presence of a base to prepare the compound of formula 4;

(iii) carrying out asymmetric reduction of the compound of formula 4 in the presence of a borane compound and a chiral catalyst to prepare the compound of formula 5; and

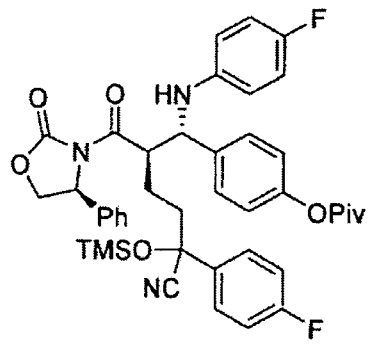
(iv) removing the hydroxyl protecting group of the compound of formula 5 in the presence of a base:



(1)



(2)



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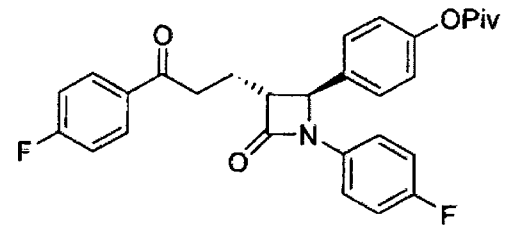
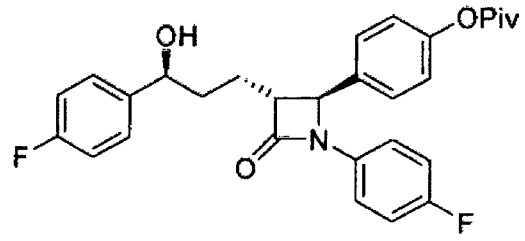
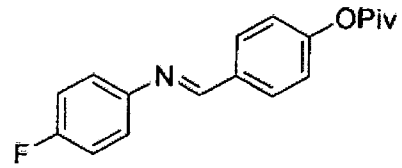


(4)



(5)



(6)

wherein,

Ph is phenyl,

TMS is trimethylsilyl, and

Piv is trimethylacetyl.

2. The method of claim 1, wherein the amount of the compound of formula 6 used in step i is in the range of 1 to 3 molar equivalents based on the compound of formula 2.

3. The method of claim 1, wherein the Lewis acid used in step i is selected from the group consisting of titanium tetrachloride, dibutylboron triplate, and a mixture thereof, and used in an amount ranging from 1 to 3 molar equivalents based on the compound of formula 2.

4. The method of claim 1, wherein the base used in step i is selected from the group consisting of triethylamine, diisopropylethylamine, tributylamine, and a mixture thereof, and used in an amount ranging from 1 to 3 molar equivalents

based on the compound of formula 2.

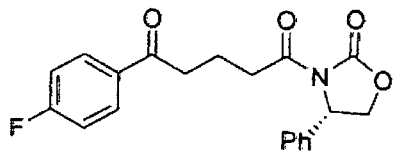
5. The method of claim 1, wherein the base used in step ii is selected from the group consisting of lithium hexamethyldisilyl amide, n-butyl lithium, lithium t-butoxide, and a mixture thereof, and used in an amount ranging from 1 to 3 molar equivalents based on the compound of formula 3.

6. The method of claim 1, wherein the chiral catalyst used in step iii is selected from the group consisting of (R)-methyl-CBS oxazaborolidine, (R)-propyl-CBS oxazaborolidine, (R)-butyl-CBS oxazaborolidine, (R)-o-tollyl-CBS oxazaborolidine, and a mixture thereof, and used in an amount ranging from 0.05 to 0.3 molar equivalents based on the compound of formula 4.

7. The method of claim 1, wherein the amount of the borane compound used in step iii is in the range of 1 to 3 molar equivalents based on the compound of formula 4.

8. The method of claim 1, wherein the base used in step iv is selected from the group consisting of lithium hydroxide, sodium hydroxide, potassium hydroxide, tetrabutylammonium fluoride, tetrabutylammonium chloride, tetrabutylammonium bromide, and a mixture thereof, and used in an amount ranging from 1 to 4 molar equivalents based on the compound of formula 7.

9. The method of claim 1, wherein the compound of formula 2 is prepared by subjecting the compound of the formula 7 to a reaction with cyanotrimethylsilane in the presence of a halogen catalyst:



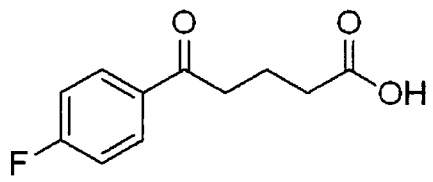
(7)

wherein Ph is phenyl.

10. The method of claim 9, wherein the cyanotrimethylsilane is used in an amount ranging from 1 to 3 molar equivalents based on the compound of formula 7.

11. The method of claim 9, wherein the halogen catalyst is used in an amount ranging from 0.01 to 0.1 molar equivalents based on the compound of formula 7.

12. The method of claim 9, wherein the compound of formula 7 is prepared by conducting a coupling reaction of the compound of formula 8 with the compound of formula 9 in the presence of N,N'-dicyclohexylcarboimide and 4-dimethylaminopyridine:



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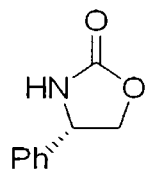
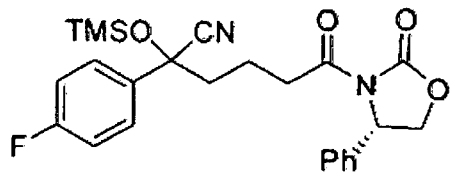


(9)

wherein Ph is phenyl.

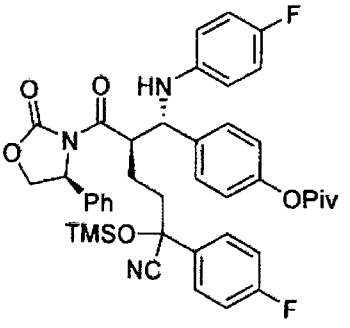
13. The compound of formula 2:



(2)

wherein Ph and TMS have the same meanings as defined in claim 1.

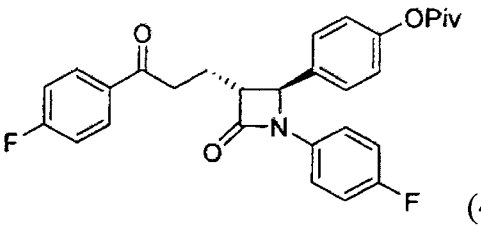
14. The compound of formula 3:



(3)

wherein Ph, TMS, and Piv have the same meanings as defined in claim 1.

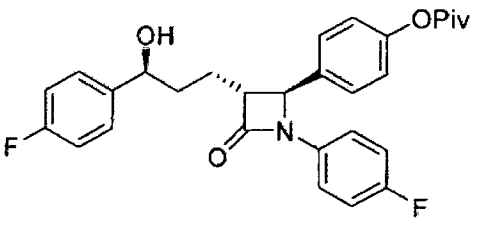
15. The compound of formula 4:



(4)

wherein Piv has the same meaning as defined in claim 1.

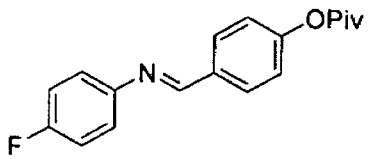
16. The compound of formula 5:



(5)

wherein Piv has the same meaning as defined in claim 1.

17. The compound of formula 6:



(6)

wherein Piv has the same meaning as defined in claim 1.