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(54) Title: PROCESS FOR THE PREPARATION OF ATORVASTATIN

(57) Abstract: The present invention relates to a process for preparing the cholesterol biosynthesis inhibitor atorvastatin, (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4- (phenylcarbamoyl)-lH-pyrrol-l-yl]-3,5-dihydroxyheptanoic acid calcium salt, which comprises a step of preparing a beta-keto ester compound using a diazoacetate compound.

【SPECIFICATION】

【Title of Invention】

PROCESS FOR THE PREPARATION OF ATORVASTATIN

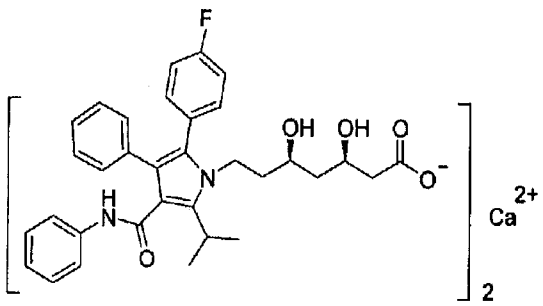
【Technical Field】

The present invention relates to a process for preparing the cholesterol biosynthesis inhibitor, atorvastatin, (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid calcium salt, which comprises a step of preparing a beta-keto ester compound using a diazoacetate compound.

【Background Art】

Atorvastatin of the following formula 1:

[Formula 1]

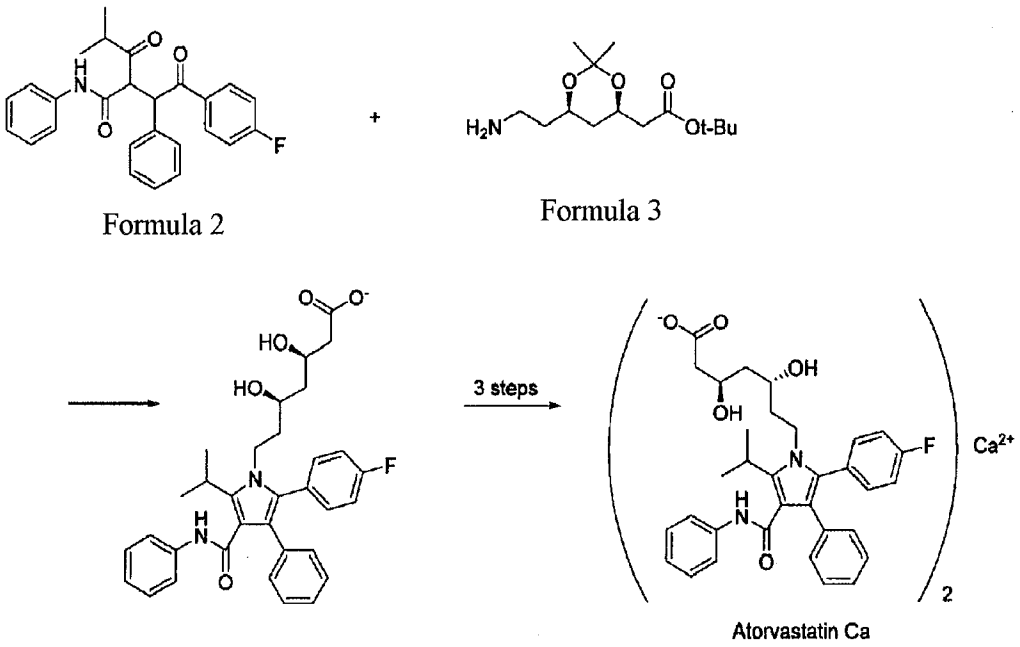


(common name: Lipito) developed by Warner-Lambert Co., and marketed by Pfizer Inc. is a drug for treating hyperlipidemia. By competitively inhibiting HMG-CoA reductase, it suppresses cholesterol biosynthesis. It's chemical name is (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid calcium salt.

Various methods for preparing atorvastatin of formula 1 have been reported, and

the method of the following Reaction Scheme 1 is typically used (see WO 89/007598, KR 132329, KR 137884, KR 132328).

Reaction Scheme 1



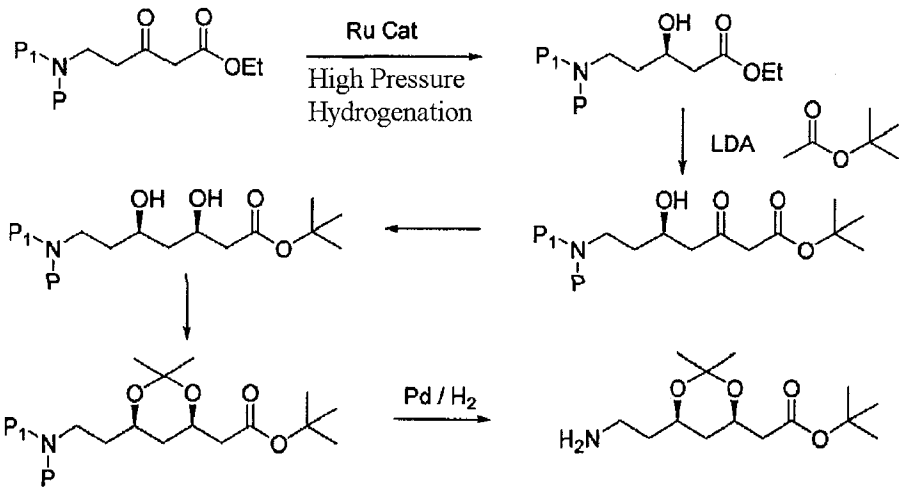
Formula 2 Formula 3

Atorvastatin Ca

In Reaction Scheme 1, 4-(4-fluorophenyl)-2-isobutyryl-3-phenyl-4-oxo-N-phenyl-butylamide of formula 2 and tert-butyl[(4R,6R)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetate of formula 3 are coupled to give a compound from which atorvastatin is prepared via three (3) steps. The stereoselectivity of atorvastatin in Reaction Scheme 1 depends on tert-butyl[(4R,6R)-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxan-4-yl]acetate of formula 3, and thus, it is important to use highly pure compound of formula 3. However, since the compound of formula 3 is in a liquid phase, its purification process (purification by silica gel) is delicate. Thus, the process of Reaction Scheme 1 cannot be readily applied to industrial production, and its yield may not be high.

Therefore, many researches have been performed to increase the stereoselectivity of atorvastatin. According to a method of KR2004/57450 among them, the compound of formula 3 may be effectively prepared by pressurized hydrogenation reaction using a metal catalyst, as depicted in the following Reaction Scheme 2:

Reaction Scheme 2

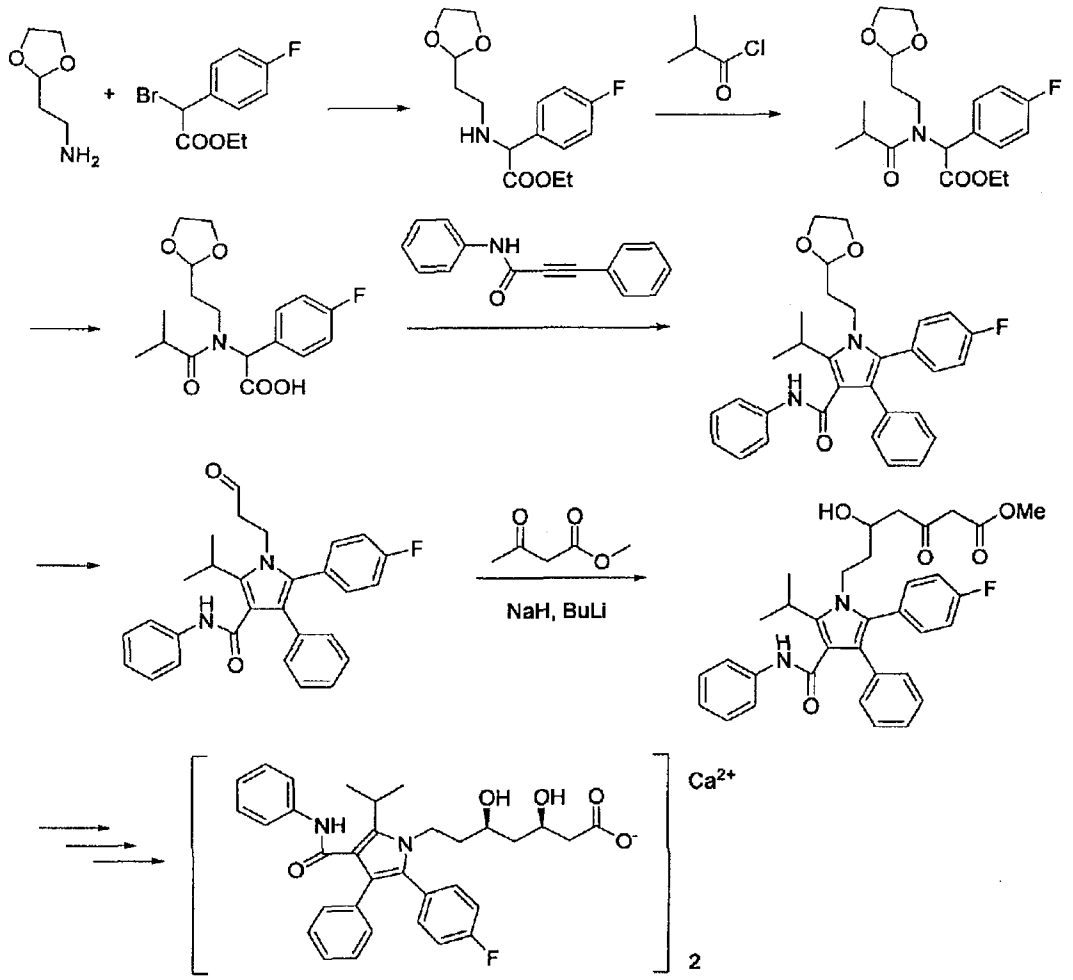


in the Reaction Scheme 2, P and P_1 each represent amino-protecting group.

However, the hydrogenation reaction requires high pressure, and thus, is dangerous in the industrial use.

On the other hand, US 4,681,893 describes another process for preparing atorvastatin, which is summarized in the following Reaction Scheme 3:

Reaction Scheme 3



The process of Reaction Scheme 3 comprises the steps of reacting an aldehyde compound with an ester compound to introduce stereoselectivity, and synthesizing the stereoselective beta-keto ester compound using butyl lithium. However, butyl lithium is highly explosive as well as requires extremely low temperature, and thus, it is not easy to be used industrially.

【Detailed Description of the Invention】

【Technical Subject to be Solved】

Thus, the present inventors have extensively studied to prepare atorvastatin

having good stereoselectivity using a process that is economical as well as easy to be applied industrially.

【Means for Solving the Technical Subject】

As a result, the present inventors have developed a process for preparing atorvastatin having the desired stereoselectivity to be applied economically and safely in an industrial production, which comprises the step of preparing a beta-keto ester compound using a diazoacetate compound.

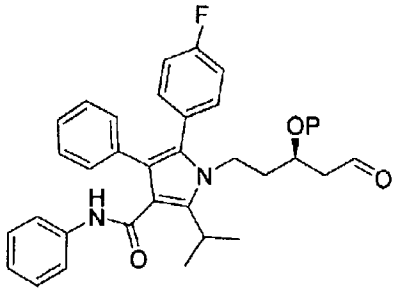
【Effect】

That is, the present invention provides a new, meaningful process for effectively preparing atorvastatin that can be advantageously used in an industrial production. Hereinafter, the present invention will be explained more specifically.

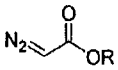
【Best Mode for Carrying Out the Invention】

The present invention provides a process for preparing atorvastatin of formula 1, which comprises the steps of (a) reacting an alkyl aldehyde compound of formula 4 with a diazoacetate of formula 5 in the presence of a catalyst to give a beta-keto ester compound of formula 6, (b) deprotecting the compound of formula 6 to give a compound of formula 7, (c) reducing the compound of formula 7 to give a compound of formula 8, (d) converting the compound of formula 8 to a lactone compound of formula 9 which is then converted to a calcium salt.

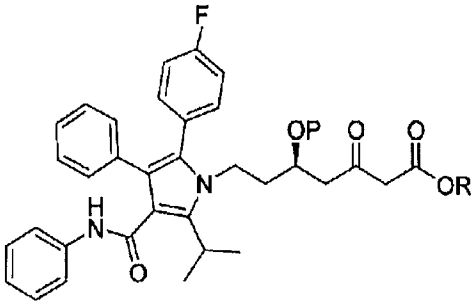
[Formula 4]



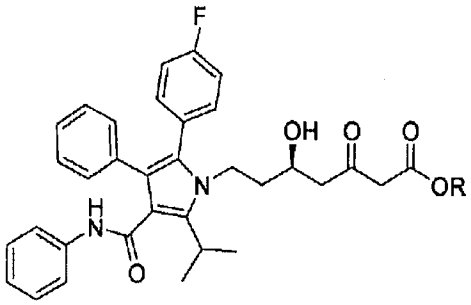
[Formula 5]



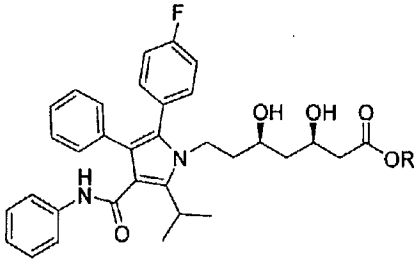
[Formula 6]



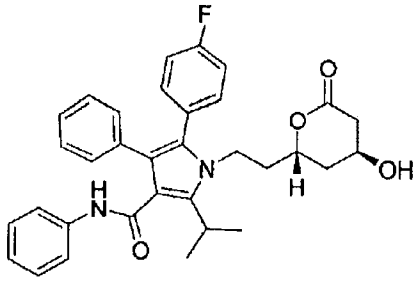
[Formula 7]



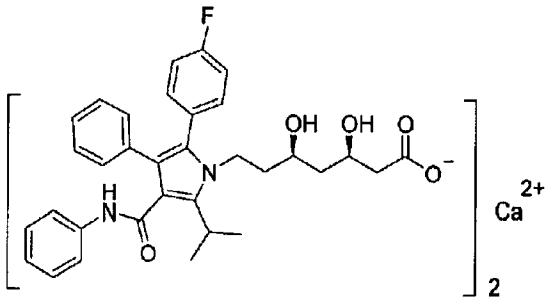
[Formula 8]



[Formula 9]



[Formula 1]



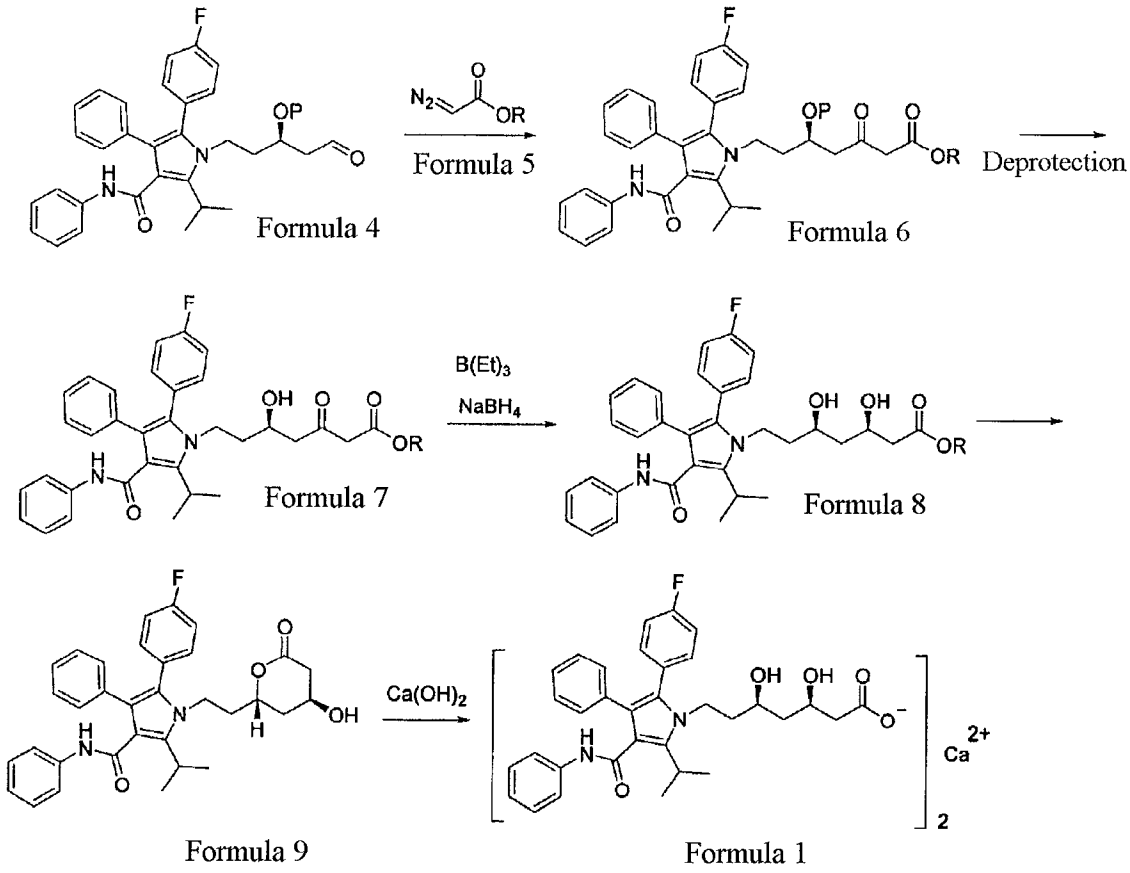
in which

R represents C_1-C_4-alkyl, and

P represents a silyl-containing protecting group.

The above process can be depicted as in the following Reaction Scheme 4.

Reaction Scheme 4



Each step of the Reaction Scheme 4 for effectively synthesizing atorvastatin is explained more in detail below.

In the step (a) reaction wherein the alkyl aldehyde of formula 4 reacts with the alkyl diazoacetate compound of formula 5 to give the beta-keto ester compound of formula 6, the catalyst may include a Lewis acid and montmorillonite K-10. As the Lewis acid, boron trifluoride, tin chloride (II) or (IV), aluminum chloride (III), etc. may be used (Bandgar. B. P. Green Chemistry, 2001, 3, 247-249), preferably tin chloride is used. Particularly preferably, montmorillonite K-10 is used. It is a kind of zeolite, and most appropriate in an industrial production since it is environmentally friendly.

Ethyl diazoacetate among the starting compounds alkyl diazoacetate of formula 5 is commercially available (Aldrich, Cas. No: 623-73-4), and thus, easy to be applied in a mass production. Another starting compound of formula 4 may be prepared as separately explained below.

In the step (b) reaction, the silyl-containing protecting group of the beta-keto ester compound prepared in step (a) is removed. The deprotection reaction may be carried out by the conventional method to remove the silyl-containing protecting group, i.e., using hydrochloric acid solution or fluoride ion. Here, since a lactone may be formed under strong acid or strong base condition, pH is adjusted to neutral to weak acidic (pH 6.0~7.0) during the reaction. As the reaction solvent, a typical polar solvent, such as for example, ethyl acetate, tetrahydrofuran, acetone, 1,4-dioxane, dimethylformamide, dimethylsulfoxide, etc. may be used, among which acetone and tetrahydrofuran are most appropriate in the aspects of reactivity and process application.

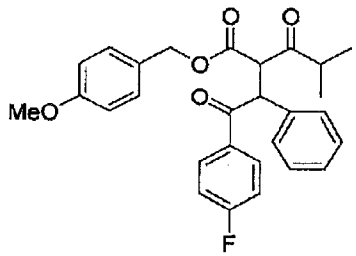
In the step (c) reaction, as US 5,273,995 describes, the compound of formula 7 is reduced with triethylborane and sodium borohydride so that it may have a stereoselectivity to give the compound of formula 8.

In the step (d) reaction, the atorvastatin lactone of formula 9 is prepared from the compound of formula 8, and the compound of formula 9 is converted to its calcium salt to give the desired compound of formula 1. The detailed reaction conditions may refer to US 4,681,893, US 5,273,995, KR-A-2003-59253, WO 2005/033078, etc.

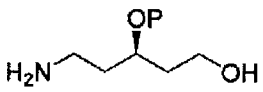
On the other hand, the compound of formula 4, the starting material in the process

of Reaction Scheme 4, can be prepared by a process which comprises the steps of (i) reacting a compound of formula 10 with a compound of formula 11 to give a pyrrole compound of formula 12, (ii) removing the carboxyl-protecting group of the compound of formula 12 to give a compound of formula 13, (iii) subjecting the compound of formula 13 to an amidation reaction to give a compound of formula 14, and (iv) oxidizing the alcohol group of the compound of formula 14 to an aldehyde group.

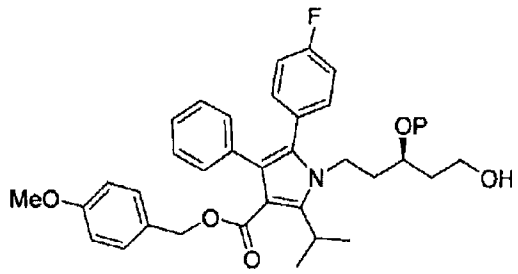
[Formula 10]



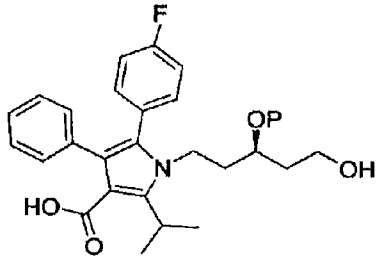
[Formula 11]



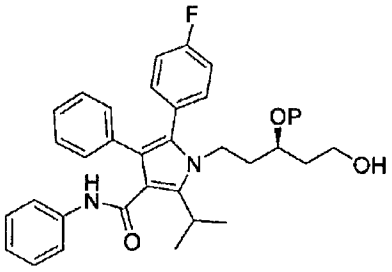
[Formula 12]



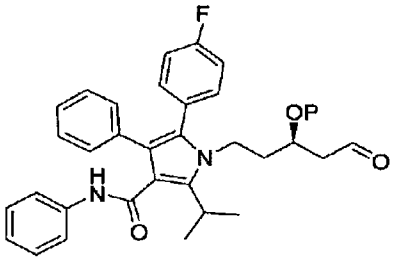
[Formula 13]



[Formula 14]

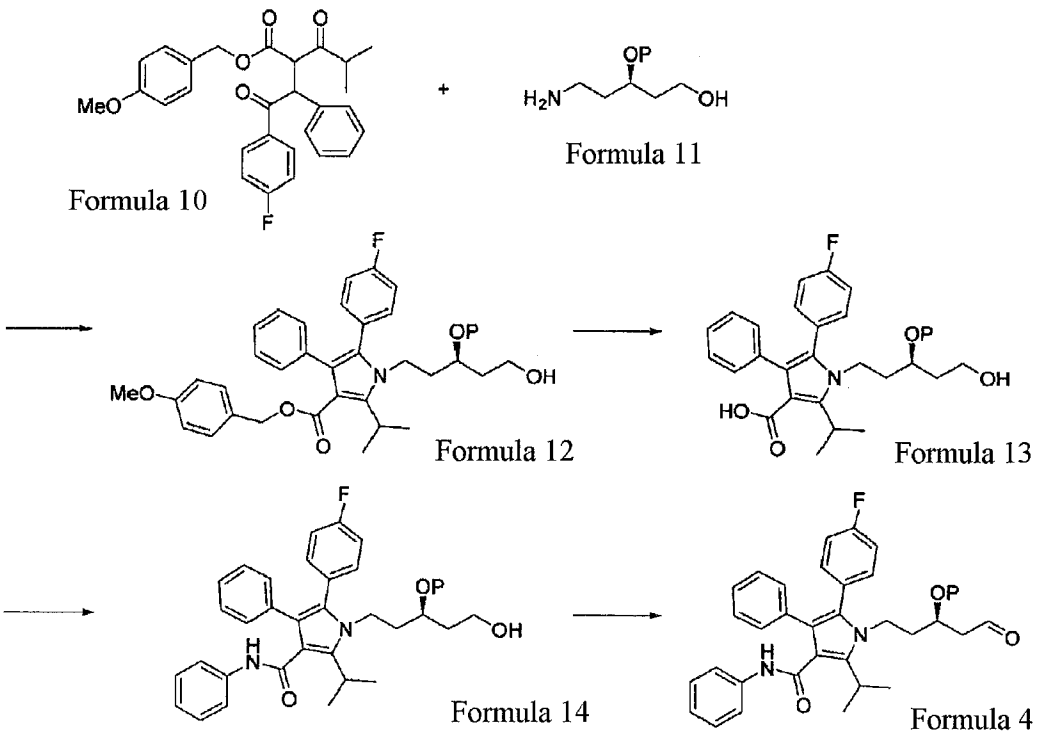


[Formula 4]



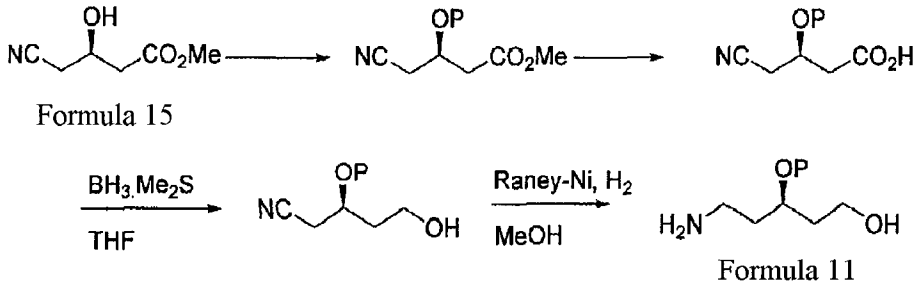
The above process is depicted in the following Reaction Scheme 5.

Reaction Scheme 5



The starting compound of formula 11 in the above reaction may be easily prepared by a process of the following Reaction Scheme 6.

Reaction Scheme 6



Formula 15

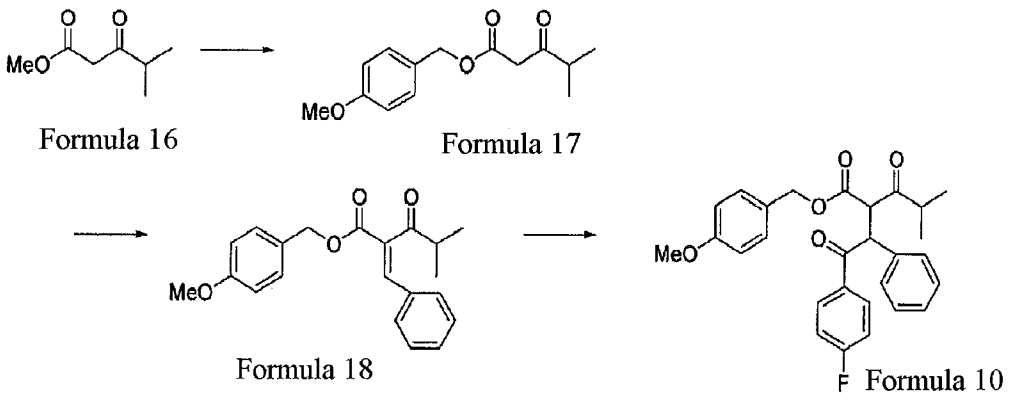
Formula 11

In the above Reaction Scheme 6, first, the secondary alcohol group of the compound of formula 15 that is commercially available and has a high ee% value (Aldrich, cas: 141942-85-0) is protected. Here, the protecting group should be selected in view of the stability of the compound. That is, a strong base such as sodium hydroxide, etc. is used in the hydrolysis of the methyl ester group of the compound of formula 15, and thus, a protecting group that is stable under a base condition should be selected. For this purpose, typical silyl-containing protecting groups, such as for example, trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylethoxysilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl, tribenzylsilyl, etc. may be used, among which tert-butyldimethylsilyl group is most appropriate since it shows considerable stability under a base condition and is easily available. As the solvent that can be used, tetrahydrofuran, ethyl acetate, dimethylsulfoxide, dimethylformamide, 1,4-dioxane, etc. may be mentioned. Dimethylformamide is most appropriate since hydrochloride of imidazole, the side product that results during the

reaction, can be dissolved and easily removed. The protected comound is hydrolyzed by sodium hydroxide at room temperature, and then reduced by boron dimethylsulfide. Subsequently, the nickel catalyst, preferably Raney-nickel catalyst, may be used in the hydrogenation reduction reaction to give the compound of formula 11. The typical hydrogenation reduction reaction usually requires high pressure and temperature, but the present process that uses Raney-nickel catalyst has the advantage of preparing the compound of formula 11 with considerably high yield under mild conditions (relatively low hydrogen pressure and temperature).

Another important starting material in the synthesis of atorvastatin, 4-methoxybenzyl 2-(2-(4-fluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxopentanoate of formula 10, can be prepared by a process of the following Reaction Scheme 7 that is similar to the process disclosed in KR 137884.

Reaction Scheme 7



Formula 16 Formula 17 Formula 18 Formula 10

In the earlier processes for preparing atorvastatin (US 4,681,893 and US-A- 2007-0043221), the pyrrole formation reaction is carried out using a compound having methyl ester group, like the compound of formula 16. According to our experimental result, it

has been confirmed that such compound having methyl ester group is less selective in the pyrrole formation reaction to induce many side reactions. Thus, the present inventors have prepared a compound having 4-methoxybenzyl ester group, i.e., the compound of formula 17, instead of the compound having methyl ester group, which decreases the production of side products in the subsequent pyrrole formation reaction.

The pyrrole formation is achieved by reacing the compound of formula 10 having 4-methoxybenzyl ester group with the compound of formula 11. This reaction is performed by adding pivalic acid and removing water by using Dean-Stack apparatus in a solvent mixture of heptane, tetrahydrofuran and toluene to give the compound of formula 12. The compound of formula 13 is obtained by removing 4-methoxybenzyl group using $Pd(OH)_2/C$ catalyst, the compound of formula 14 is obtained by substituting with phenylamide group, and the compound of formula 4 is obtained by oxidizing the alcohol group to an aldehyde group using Dess-Martin periodinane reagent. Oxidation of the alcohol group may be achieved when conventional oxidizing agents such as N-bromosuccinimide (NBS), chromic acid, Oxone, sodium hyperchloride, etc. are used. However, Dess-Martin periodinane reagent is most appropriate since it shows high selectivity and yield in the synthesis of aldehyde from alcohol. Dess-Martin periodinane reagent is preferably used in the amount of 1 to 1.5 eq. with respect to the compound of formula 14, and as the solvent nonpolar solvents such as methylene chloride, chloroform, carbon tetrachloride, etc., preferably methylene chloride is used.

The present invention will be more specifically explained by the following examples. However, it should be understood that they are intended to illustrate the present invention but not in any manner to limit the scope of the present invention.

Example 1

Preparation of (R)-methyl-3-(tert-butyldimethylsilyloxy)-4-cyanobutanoate

To a 1000㎖ reactor equipped with a stirrer and a thermometer was introduced 50g of (R)-methyl-3-hydroxy-4-cyanobutanoate, which was dissolved in 150㎖ of dimethylformamide. 32.5g of imidazole was added thereto. The reaction temperature was maintained at 20~25℃, and 55g of tert-butyldimethylchlorosilane was added. The mixture was stirred at room temperature for 12 h. 250㎖ of ethyl acetate and 250㎖ of water were added to separate the layers from which the aqueous layer was removed. The organic layer was dried over magnesium sulfate, and ethyl acetate was removed by concentration under reduced pressure. The residue was purified by column chromatography (ethyl acetate:hexane = 1:3) to give the title compound (R)-methyl-3-(tert-butyldimethylsilyloxy)-4-cyanobutanoate (70.8g, Yield 87%).

Example 2

Preparation of (R)-3-(tert-butyldimethylsilyloxy)-4-cyanobutanoic acid

In a 1000㎖ reactor equipped with a stirrer and a thermometer, 70g of (R)-methyl-3-(tert-butyldimethylsilyloxy)-4-cyanobutanoate was dissolved in 280㎖ of methanol. The reaction temperature was maintained at 20~25℃, during which 70㎖ of water and 14g of sodium hydroxide were added, and stirred for 3 h. After completion of the reaction, the mixture was concentrated under reduced pressure to remove methanol. 350㎖ of ethyl acetate was added. 1N aqueous hydrochloric acid solution was added in drops to adjust the pH of the reaction solution to 6~7. The aqueous layer was removed by phase separation. The organic layer was dried over magnesium sulfate, and ethyl acetate was removed by concentration under reduced pressure. The residue was purified

by column chromatography (ethyl acetate: hexane = 1:1) to give the title compound (R)-3-(tert-butyldimethylsilyloxy)-4-cyanobutanoic acid (57.7g, Yield 87%).

Example 3

Preparation of (R)-3-(tert-butyldimethylsilyloxy)-5-hydroxypentanenitrile

To a 1000㎖ reactor equipped with a stirrer and thermometer was introduced 57g of (R)-3-(tert-butyldimethylsilyloxy)-4-cyanobutanoic acid, which was dissolved in 600㎖ of tetrahydrofuran. The reaction temperature was maintained at 20~25℃, during which 300㎖ of 2M tetrahydrofuran solution of borane.dimethylsulfide complex was added in drops thereto. The mixture was reacted at room temperature for 12 h, and 70㎖ of methanol was added. The mixture was concentrated under reduced pressure to remove tetrahydrofuran and methanol. 300㎖ of ethyl acetate and 400㎖ of water were added. The resulting mixture was stirred, and subjected to phase separation to remove water. Ethyl acetate was removed by concentration under reduced pressure, and the residue was purified by column chromatography (ethyl acetate: hexane = 1:2) to give the title compound (R)-3-(tert-butyldimethylsilyloxy)-5-hydroxypentanenitrile (40.1g, Yield 74.5%).

Example 4

Preparation of (R)-5-amino-3-(tert-butyldimethylsilyloxy)pentan-1-ol

In a 1000㎖ reactor equipped with a stirrer and a thermometer, 50g of (R)-3-(tert-butyldimethylsilyloxy)-5-hydroxypentanenitrile was dissolved in 600㎖ of methanol. 10g of Raney-Ni was added thereto. The mixture was stirred for 5 h under hydrogen atmosphere (1 atm.) in a water bath of 45~50℃. After completion of the reaction, Raney-Ni was removed by filtration. Methanol was removed by concentration under

reduced pressure to give the title compound (R)-5-amino-3-(tert-butyldimethylsilyloxy)pentan-1-ol (41.5g, Yield 81.5%).

Example 5

Preparation of 4-methoxybenzyl 4-methyl-3-oxopentanoate

To a 1000㎖ reactor equipped with a stirrer and a thermometer were introduced 50g of methyl isobutyrylacetate and 52.7g of 4-methoxybenzyl alcohol, which were dissolved in 500㎖ of toluene. 0.5g of acetic acid was added, and the mixture was heated under reflux for 15 h. 500㎖ of 5% sodium hydrogen carbonate solution was added to separate the organic layer, which was then concentrated under reduced pressure to give the title compound 4-methoxybenzyl 4-methyl-3-oxopentanoate (78g, Yield 90%).

Example 6

Preparation of 4-methoxybenzyl 2-benzylidene-4-methyl-3-oxopentanoate

To a 1000㎖ reactor equipped with a stirrer and a thermometer was introduced 50g of 4-methoxybenzyl 4-methyl-3-oxopentanoate, which was dissolved in 500㎖ of toluene. 40.5g of benzaldehyde, 4.1㎖ of acetic acid and 1.72㎖ pf piperidine were added thereto, and the mixture was heated under reflux for 24 h. After cooling, 300㎖ of water was added to separate the phases from which the aqueous layer was removed. 300㎖ of 1N aqueous hydrochloric acid solution was added, and the aqueous layer was removed by phase separation. The organic layer was dried over magnesium sulfate, and concentrated to remove toluene. The residue was purified by column chromatography (ethyl acetate: hexane = 1:10) to give the title compound 4-methoxybenzyl 2-benzylidene-4-methyl-3-oxopentanoate (56g, Yield 82.8%).

Example 7

Preparation of 4-methoxybenzyl 2-(2-(4-fluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxopentanoate

To a 1000㎖ reactor equipped with a stirrer and a thermometer was introduced 60g of 4-methoxybenzyl 2-benzylidene-4-methyl-3-oxopentanoate, which was dissolved in 600㎖ of absolute ethanol. 10.2g of 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazonium bromide, 24㎖ of 4-fluorobenzaldehyde and 31.7㎖ of triethylamine were added thereto. After heating under reflux for 36 h, the mixture was concentrated to remove ethanol. 300㎖ of ethyl acetate was added to dissolve the residue. 300㎖ of water was added to separate the phases from which the aqueous layer was removed. 300㎖ of 1N aqueous hydrochloric acid solution was added, and the aqueous layer was removed by phase separation. The organic layer was dried over magnesium sulfate, and concentrated under reduced pressure to remove ethyl acetate. The residue was purified by column chromatography (ethyl acetate: hexane = 1:5) to give the title compound 4-methoxybenzyl 2-(2-(4-fluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxopentanoate (71.8g, Yield 87.5%).

Example 8

Preparation of (R)-4-methoxybenzyl-1-(3-(tert-butyldimethylsilyloxy)-5-hydroxypentyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1H-pyrrole-3-carboxylate

To a 1000㎖ reactor equipped with a stirrer and a thermometer were introduced 30g of 4-methoxybenzyl 2-(2-(4-fluorophenyl)-2-oxo-1-phenylethyl)-4-methyl-3-oxopentanoate and 24.7g of (R)-5-amino-3-(tert-butyldimethylsilyloxy)pentan-1-ol, which were dissolved in 300㎖ of a solvent mixture of heptane:toluene: tetrahydrofuran=9:1:1. 6g of pivalic acid was added thereto. The mixture was reacted by heating under reflux

for 50 h from which the resulting water was removed using a Dean-stark apparatus. After completion of the reaction, the reaction mixture was cooled, and subjected to phase separation by adding 120㎖ of ethyl acetate and 150㎖ of water. The aqueous layer was removed. 300㎖ of 1N aqueous hydrochloric acid solution was added to separate the phases from which the aqueous layer was removed. The organic layer was dried over magnesium sulfate, and concentrated under reduced pressure to remove ethyl acetate. The residue was purified by column chromatography (ethyl acetate: hexane = 1:5) to give the title compound (R)-4-methoxybenzyl-1-(3-(tert-butyldimethylsilyloxy)-5-hydroxypentyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1H-pyrrole-3-carboxylate (25g, Yield 58.4%).

Example 9

Preparation of (R)-1-(3-(tert-butyldimethylsilyloxy)-5-hydroxypentyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1H-pyrrole-3-carboxylic acid

To a 500㎖ reactor equipped with a stirrer and a thermometer was introduced 20g of (R)-4-methoxybenzyl-1-(3-(tert-butyldimethylsilyloxy)-5-hydroxypentyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1H-pyrrole-3-carboxylate, which was dissolved in 200㎖ of methanol. 2g of $Pd(OH)_2/C$ was added, and the mixture was reacted under hydrogen atmosphere at room temperature. After 1 h, the catalyst was filtered off using diatomaceous earth. The reaction solution was concentrated, and the residue was purified by column chromatography (ethyl acetate:hexane=1:1) to give the title compound (R)-1-(3-(tert-butyldimethylsilyloxy)-5-hydroxypentyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1H-pyrrole-3-carboxylic acid (12.3g, Yield 75.5%).

Example 10

Preparation of (R)-1-(3-(tert-butyldimethylsilyloxy)-5-hydroxypentyl)-5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide

To a 500㎖ reactor equipped with a stirrer and a thermometer was introduced 10g of (R)-1-(3-(tert-butyldimethylsilyloxy)-5-hydroxypentyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1H-pyrrole-3-carboxylic acid, which was dissolved in 100㎖ of tetrahydrofuran. 1.9g of triethylamine and 2.6g of isobutylchloroformate were added thereto, and the mixture was stirred for about 15 min at -15℃. 1.8g of aniline and 0.1g of p-toluenesulfonic acid were diluted in 10㎖ of tetrahydrofuran, which was then added to the reaction solution. The reaction solution was heated at 60℃ for 15 h, and extracted with 100㎖ of distilled water and 100㎖ of methylene chloride. The organic layer was dried over magnesium sulfate, and concentrated. The residue was purified by column chromatography (ethyl acetate: hexane = 1:2) to give the title compound (R)-1-(3-(tert-butyldimethylsilyloxy)-5-hydroxypentyl)-5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide (9g, Yield 79%).

Example 11

Preparation of (R)-1-(3-(tert-butyldimethylsilyloxy)-5-oxopentyl)-5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide

To a 250㎖ reactor equipped with a stirrer and a thermometer was introduced 10g of (R)-1-(3-(tert-butyldimethylsilyloxy)-5-hydroxypentyl)-5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide, which was dissolved in 50㎖ of methylene chloride. The reaction temperature was maintained at 20~25℃, during which 8.1g of Dess-Martin periodinane reagent was slowly added thereto. After reacting for 5 h, the reaction mixture was filtered to remove the solid. 50㎖ of water was added to separate

the phases from which the aqueous layer was removed. 50㎖ of 1% aqueous sodium bicarbonate solution was added to separate the phases from which the aqueous layer was removed. The organic layer was dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography (ethyl acetate: hexane = 1:5) to give the title compound (R)-1-(3-(tert-butyldimethylsilyloxy)-5-oxopentyl)-5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide (8.6g, Yield 86.2%).

Example 12

Preparation of (R)-ethyl 5-(tert-butyldimethylsilyloxy)-7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-1H-pyrrol-1-yl)-3-oxoheptanoate [tin chloride (II) was used]

To a 250㎖ reactor equipped with a stirrer and a thermometer was introduced 9g of (R)-1-(3-(tert-butyldimethylsilyloxy)-5-oxopentyl)-5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide, which was dissolved in 90㎖ of methylene chloride. 1.6g of ethyldiazoacetate and 200mg of tin chloride (II) were added, and the mixture was stirred for 12 h. After completion of the reaction, the mixture was filtered to remove tin chloride (II). 50㎖ of water was added to separate the phases from which the aqueous layer was removed. The organic layer was concentrated under reduced pressure to remove methylene chloride. The residue was purified by column chromatography (ethyl acetate: hexane = 1:5) to give the title compound (R)-ethyl 5-(tert-butyldimethylsilyloxy)-7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-1H-pyrrol-1-yl)-3-oxoheptanoate (7.5g, Yield 73%).

Example 13

Preparation of (R)-ethyl 5-(tert-butyldimethylsilyloxy)-7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-1H-pyrrol-1-yl)-3-oxoheptanoate [montmorillonite K-10 was used]

To a 250㎖ reactor equipped with a stirrer and a thermometer was introduced 9g of (R)-1-(3-(tert-butyldimethylsilyloxy)-5-oxopentyl)-5-(4-fluorophenyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide, which was dissolved in 90㎖ of methylene chloride. 1.6g of ethyldiazoacetate and 200mg of montmorillonite K-10 were added, and the mixture was stirred for 8 h. After completion of the reaction, the mixture was filtered to remove montmorillonite K-10, and washed with 30㎖ of methylene chloride. 90㎖ of water was added to separate the phases from which the aqueous layer was removed. The organic layer was concentrated under reduced pressure to remove methylene chloride. The residue was purified by column chromatography (ethyl acetate: hexane = 1:5) to give the title compound (R)-ethyl 5-(tert-butyldimethylsilyloxy)-7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-1H-pyrrol-1-yl)-3-oxoheptanoate (7.1g, Yield 69%).

Example 14

Preparation of (R)-ethyl-7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-1H-pyrrol-1-yl)-5-hydroxy-3-oxoheptanoate

In a 250㎖ reactor equipped with a stirrer and a thermometer, 9g of (R)-ethyl 5-(tert-butyldimethylsilyloxy)-7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-1H-pyrrol-1-yl)-3-oxoheptanoate was dissolved in 50㎖ of tetrahydrofuran. 5g of tetrabutylammonium fluoride adjusted to pH 7 using anhydrous acetic acid and dissolved in tetrahydrofuran was added thereto, and the mixture was reacted for 24 h. After completion of the reaction, the reaction mixture was concentrated

under reduced pressure to remove tetrahydrofuran. 50㎖ of ethyl acetate and 50㎖ of water were added to separate the phases from which the aqueous layer was removed. The residue was purified by column chromatography (ethyl acetate: hexane = 1:1) to give the title compound (R)-ethyl-7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-1H-pyrrol-1-yl)-5-hydroxy-3-oxoheptanoate (6.8g, Yield 90.3%).

Example 15

Preparation of (3R,5R)-ethyl 7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-1H-pyrrol-1-yl)-3,5-dihydroxyheptanoate

In a 100㎖ reactor equipped with a stirrer and a thermometer, 6g of (R)-ethyl-7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-1H-pyrrol-1-yl)-5-hydroxy-3-oxoheptanoate was dissolved in 60㎖ of tetrahydrofuran and 12㎖ of methanol. 15㎖ of triethylborane 1M tetrahydrofuran solution was added thereto, and the mixture was stirred for 1 h at room temperature. After cooling the mixture to -40℃, 600mg of sodium borohydride was slowly added thereto for 30 min. After stirring for 3 h to complete the reaction, 50㎖ of MeOH and 3㎖ of acetic acid were added to quench the reaction. The reaction mixture was stirred for 1 h at room temperature, and concentrated to remove tetrahydrofuran and methanol. 60㎖ of ethyl acetate and 100㎖ of water were added to separate the phases from which the aqueous layer was removed. The organic layer was concentrated, and the residue was purified by column chromatography (ethyl acetate: hexane = 1:2) to give the title compound (3R,5R)-ethyl 7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-1H-pyrrol-1-yl)-3,5-dihydroxyheptanoate (4.1g, Yield 68%).

Example 16

Preparation of 5-(4-fluorophenyl)-1-(2-(2S,4S)-4-hydroxy-6-oxo-tetrahydro-2H-pyran-2-yl)ethyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide (atorvastatin lactone)

To a 100㎖ reactor equipped with a stirrer and a thermometer was introduced 5g of (3R,5R)-ethyl 7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-phenylcarbamoyl-1H-pyrrol-1-yl)-3,5-dihydroxyheptanoate, which was dissolved in 10㎖ of tetrahydrofuran. 50㎖ of 2N aqueous sodium hydroxide solution was added, and the mixture was stirred for 5 h. After completion of the reaction, the mixture was concentrated under reduced pressure to remove tetrahydrofuran. 50㎖ of ethyl acetate and 20㎖ of water were added, and then 30㎖ of 6N hydrochloric acid was added to separate the phases from which the aqueous layer was removed. The organic layer was concentrated to thoroughly remove ethyl acetate. 30㎖ of toluene was added, and the mixture was heated under reflux for 3 h. The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography (ethyl acetate: hexane = 1:2) to give the title compound 5-(4-fluorophenyl)-1-(2-(2S,4S)-4-hydroxy-6-oxo-tetrahydro-2H-pyran-2-yl)ethyl)-2-isopropyl-N,4-diphenyl-1H-pyrrol-3-carboxamide (atorvastatin lactone) (3.6g, Yield 78%).

Example 17

Preparation of (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid hemicalcium salt (atorvastatin calcium)

In a 100㎖ reactor equipped with a stirrer and a thermometer, 3.6g of 5-(4-fluorophenyl)-1-(2-(2S,4S)-4-hydroxy-6-oxo-tetrahydro-2H-pyran-2-yl)ethyl)-2-isopropyl-N,4-diphenyl-1H-pyrrole-3-carboxamide (atorvastatin lactone) was dissolved in

30㎖ of methanol and 10㎖ of distilled water. 2.7g of calcium hydroxide and 180mg of tetrabutylammonium bromide were added thereto, and the mixture was reacted for 5 h at 50℃. After the reaction, the reaction mixture was filtered to remove the excess calcium hydroxide, and cooled to room temperature. To this solution was added 2㎖ of distilled water while stirring. The resulting solution was stirred for 12 h at room temperature to produce crystal which was then filtered under vacuum. The crystal was washed with aqueous methanol solution (mixture of 5㎖ of methanol and 20㎖ of distilled water), and dried under vacuum at 65℃ to give 615mg of the title compound (3R,5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid hemicalcium salt (atorvastatin calcium).

【Industrial Applicability】

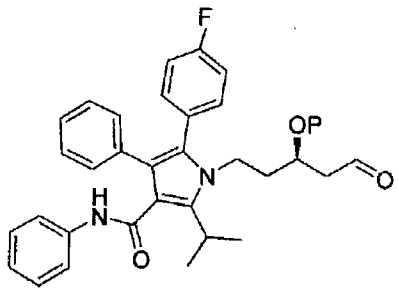
As explained above, the present invention provides a process which can prepare atorvastatin having stereoselectivity economically and safely in the industrial scale production.

【CLAIMS】

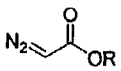
【Claim 1】

A process for preparing atorvastatin of formula 1, which comprises the steps of (a) reacting an alkyl aldehyde compound of formula 4 with a diazoacetate of formula 5 in the presence of a catalyst to give a beta-keto ester compound of formula 6, (b) deprotecting the compound of formula 6 to give a compound of formula 7, (c) reducing the compound of formula 7 to give a compound of formula 8, (d) converting the compound of formula 8 to a lactone compound of formula 9 which is then converted to a calcium salt:

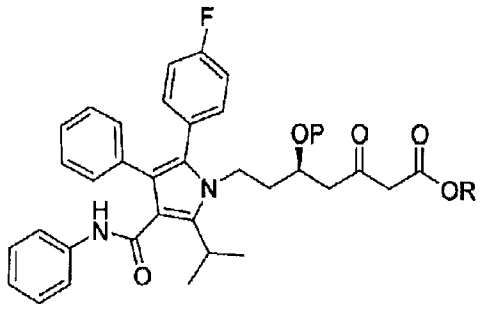
[Formula 4]



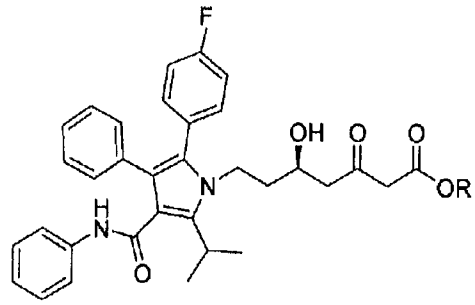
[Formula 5]



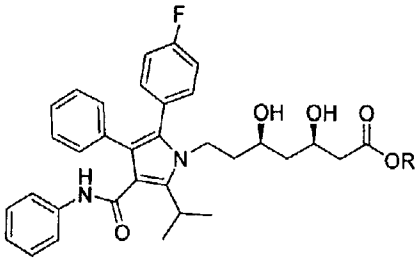
[Formula 6]



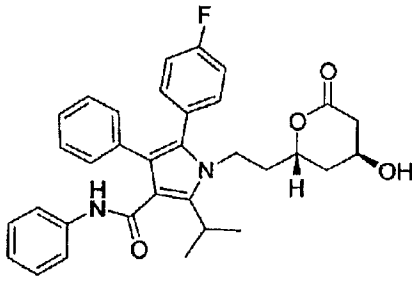
[Formula 7]



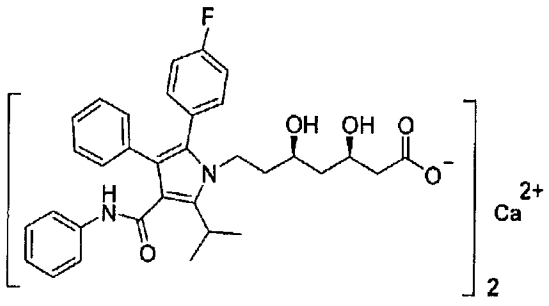
[Formula 8]



[Formula 9]



[Formula 1]



in which

R represents C_1-C_4-alkyl, and

P represents a silyl-containing protecting group.

【Claim 2】

The process of Claim 1 wherein a Lewis acid or montmorillonite K-10 is used as the catalyst in the step (a) reaction.

【Claim 3】

The process of Claim 2 wherein the Lewis acid is selected from tin chloride (II), tin chloride (IV) and aluminum chloride (III).

【Claim 4】

The process of Claim 1 wherein the compound of formula 5 is ethyl diazoacetate in the step (a) reaction.

【Claim 5】

The process of Claim 1 wherein the reaction solution is adjusted to neutral to weak acidic of pH 6.0~7.0 in the step (b) reaction.

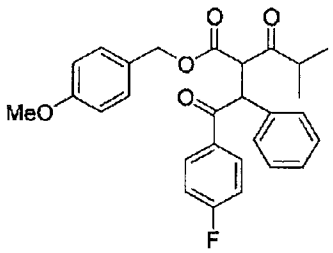
【Claim 6】

The process of Claim 1 wherein P is selected from trimethylsilyl, triethylsilyl, triisopropylsilyl, dimethylisopropylsilyl, diethylisopropylsilyl, dimethylethoxysilyl, tert-butyldimethylsilyl, tert-butyldiphenylsilyl and tribenzylsilyl.

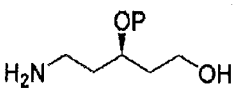
【Claim 7】

The process of Claim 1 wherein the compound of formula 4 is prepared by a process which comprises the steps of (i) reacting a compound of formula 10 with a compound of formula 11 to give a pyrrole compound of formula 12, (ii) removing the carboxyl-protecting group of the compound of formula 12 to give a compound of formula 13, (iii) subjecting the compound of formula 13 to an amidation reaction to give a compound of formula 14, and (iv) oxidizing the alcohol group of the compound of formula 14 to an aldehyde group:

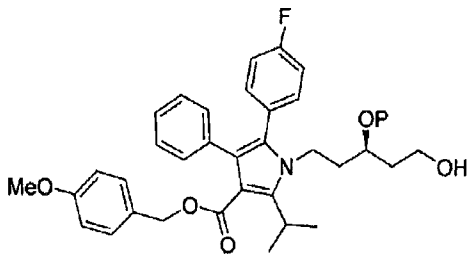
[Formula 10]



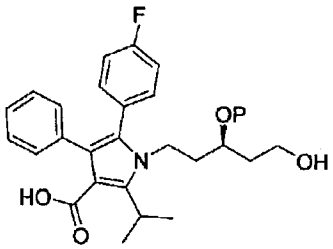
[Formula 11]



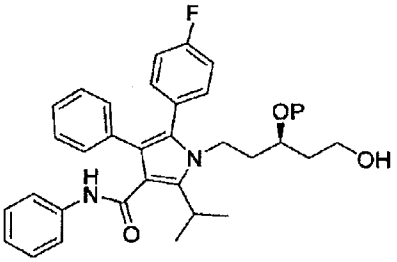
[Formula 12]



[Formula 13]



[Formula 14]



in which P represents a silyl-containing protecting group.

【Claim 8】

The process of Claim 7 wherein the preparation of the pyrrole compound is performed by adding pivalic acid and removing water by Dean-Stack apparatus in the step

(i) reaction.

【Claim 9】

The process of Claim 7 wherein the oxidation is performed by using Dess-Martin periodinane reagent in the step (iv) reaction.

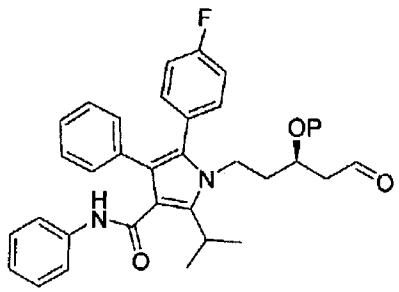
【Claim 10】

The process of Claim 9 wherein Dess-Martin periodinane reagent is used in the amount of 1 to 1.5 eq. with respect to the compound of formula 14.

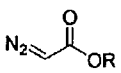
【Claim 11】

A process for preparing a beta-keto ester compound of formula 6, which comprises the step of reacting an alkyl aldehyde compound of formula 4 with a diazoacetate of formula 5 in the presence of a catalyst:

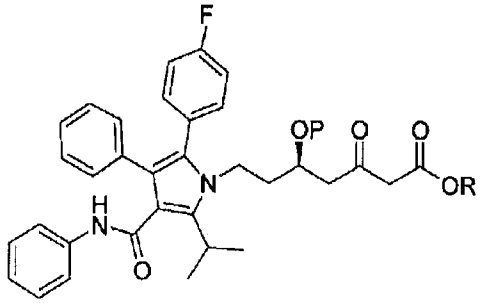
[Formula 4]



[Formula 5]



[Formula 6]



in which

R represents C_1-C_4-alkyl, and

P represents a silyl-containing protecting group.

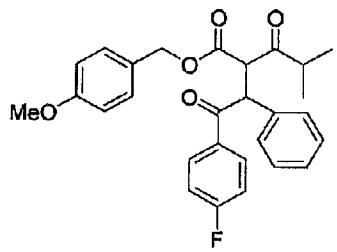
【Claim 12】

The process of Claim 11 wherein the catalyst is selected from tin chloride and montmorillonite K-10.

【Claim 13】

Compound of formula 10:

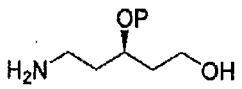
[Formula 10]



【Claim 14】

Compound of formula 11:

[Formula 11]



in which P represents a silyl-containing protecting group.