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(54) Title: PROCESS FOR THE PREPARATION OF ATORVASTATIN CALCIUM

(57) Abstract: The present invention relates to process for the preparation of atorvastatin calcium. The process provides the novel approach for the synthesis of an important intermediate atorvastatin protected diol chemically (4R-cis)-6-[-2-[3-phenyl-4-(phenyl-carbamoyl)-2-(4-flourophenyl)-5-(1-methyl-ethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl- [1,3]dioxane-4-yl-acetic acid-tertriay butyl ester for atorvastatin calcium i.e. [R- (R*,R*)]-2-(4-fluorophenyl-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1). The present invention relates the use of amino side chain i.e [6-(2-aminoethyl)-2,2,-dimethyl- [1,3]dioxan-4-yl]-acetic acid tert-butyl ester and stetter compound i.e. 4-(4-Fluorophenyl)-2-isobutryl-4-oxo-N-phenyl butryl amide as an important starting materials for the preparation of atorvastatin protected diol in the high yield and thereby the recovery of amino side chain with an industrially applicable process.

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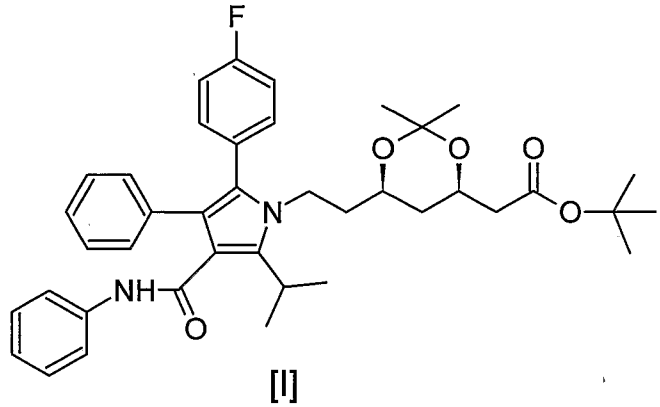
PROCESS FOR THE PREPARATION OF ATORVASTATIN CALCIUM

Field of the invention

The present invention relates to an improved process for the preparation of atorvastatin protected diol which is used to produce atorvastatin calcium i.e. [R-(R*,R*)]-2-(4-fluorophenyl-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1). Atorvastatin protected diol has the Formula-I given below. Atorvastatin Calcium is a pharmaceutical



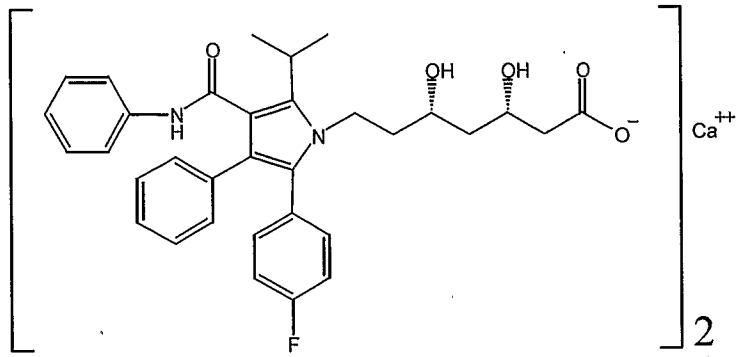
[I]

compound useful as a typical hypolipidemic or hypocholesterolemic agent.

Background of the Invention:

Statins are known as potent lipid lowering agents. Statins suppress cholesterol biosynthesis by competitively inhibiting 3-hydroxy-3-methyl-glutaryl-coenzyme a reductase, which catalyzes the conversion of HMG-CoA to mevalonate, which is the rate-determining step in the biosynthesis of cholesterol. They are currently the most therapeutically effective drugs available for the treatment of hyperlipidemia and hypercholesterolemia both of that are risk factors for arteriosclerosis and coronary heart disease.

Atorvastatin calcium is currently sold as Lipitor® having the chemical name [R-(R*,R*)]-2-(4-fluorophenyl-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino) carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1). Atorvastatin and pharmaceutically acceptable salts thereof are selective, competitive inhibitors of HMG-CoA reductase. As such, Atorvastatin calcium is a potent lipid lowering compound and is thus useful as a hypolipidemic and/or hypocholesterolemic agent, as well as in the treatment of osteoporosis, Benign Prostatic Hyperplasia (BPH), and Alzheimer's disease.

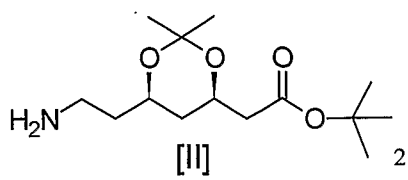


ATORVASTATIN CALCIUM

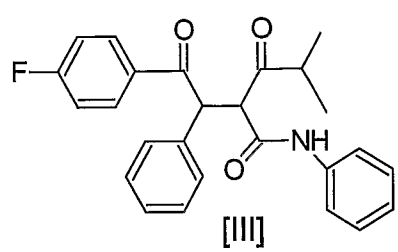
A number of patents have been issued disclosing atorvastatin, formulations of atorvastatin as well as process and key intermediates of preparing atorvastatin. These include US patent number: 4681893, 5273995, 5003080, 5097045, 5103024, 5124482, 5149837, 5155251, 5216174, 5245047, 5248793, 5280126, 5397792, 5342952, 5298627, 5446054, 5470981, 5489690, 5489691, 5510488, 5686101, 5998633, 6087511, 6126971, 6433213 and 6476235, which are herein incorporated by reference.

(4R-cis)-6-[-2-[3-phenyl-4-(phenyl-carbamoyl)-2-(4-flourophenyl)-5-(1-methyl-ethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]dioxane-4-yl-acetic acid -tertriay butyl ester of the Formula [I] (Atorvastatin protected diol) is a known and valuable pharmaceutical intermediate useful in the preparation of the HMG-CoA [R-(R*,R*)]-2-(4-fluorophenyl-β,δ-dihydroxy-5-(1-methyl ethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt having the INN (International Non-Proprietory Name) Atorvastatin.

(4R-cis)-6-[-2-[3-phenyl-4-(phenyl-carbamoyl)-2-(4-flourophenyl)-5-(1-methyl-ethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]dioxane-4-yl-acetic acid -tertriay butyl ester of Formula – I was described in EP B 330172. According to said patent [(4R-cis)-6-[-2-[3-phenyl-4-(phenyl-carbamoyl)-2-(4-flourophenyl)-5-(1-methyl-ethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3] dioxane-4-yl-acetic acid-tertriay butyl ester] of Formula – I is prepared by reacting [6-(2-aminoethyl)-2,2,-dimethyl-[1,3]dioxan-4-yl]-acetic acid tert-butyl ester [II] (amino side chain) with 4-(4-Fluorophenyl)-2-isobutryl-4-oxo-N-phenyl butryl amide Formula [III] (stetter compound)



[II]



[III]

in a 9:1 mixture of heptane and toluene under heating to boiling for 24 hours, cooling the reaction mixture, adding some 2-propanol and isolating the precipitated product by filtration.

The reference is silent in disclosing the melting point of the product and the crystal form of the product is not mentioned either.

According to U.S. Patent No.5,003,080 the reaction is carried out as described in EP-B 330172 except that a 9:1 mixture of toluene and heptane is used. The reaction mixture is then heated to boiling for 24 hours, cooled, some 2-propanol is added and the precipitated compound of the Formula I is isolated by filtration. Nothing is disclosed about the melting point and crystal form is the product.

In US Patent No. 5,155,251 the working example of EP-B 330172 is disclosed. This reference contains no teaching on the melting point and crystal form of the compound of the Formula I.

Further K.L. Baumann et al. describes in tetrahedron Lett. 1992, 33, 2283-84 the preparation of dimethyl ketol of the atorvastatin tertiary butyl ester (I) by a Paal-Knorr pyrrole synthesis using a ternary solvent mixture of toluene-heptane-tetrahydrofuran (1:4:1) with catalysis by pivalic acid and conversion of (I) to atorvastatin hemi-calcium without isolating any intermediates. A similar procedure was reported by Peter. 25°C to 35°C temperature. K. Woo et al. in J. Zabel. Compound. Ratiopharm, 1999, vol.42, part II, 135-145 and by B.C. chen. et. al. in J. Label. Compd. Ratiopharm, 2000, vol. 43, part III, 261-270.

Moreover, WO 03/024959 discloses the process for the preparation of intermediate polymorph Form – I and Form – II. Paal-Knoor synthesis i.e. condensation of compound of Formula – II and Formula – III in the solvent ratio 1:4:1 of toluene, heptane and THF in presence of pivalic acid as a catalyst which is a known prior art to obtain compound of Formula – I.

Additionally, a number of published international patent applications and patents have disclosed crystalline forms of atorvastatin, as well as process for preparing. These include US6121461 US6605759 WO01/36384 WO02/41834 WO02/43667 WO02/43732 WO02/051804 WO02/057228 WO02/057229 WO02/057274 WO059087 WO02/083637 WO02/083638 WO03/011826 WO03/050085 WO03/07072 WO04/022053 and US 5969156.

Preparation of atorvastatin calcium as disclosed in U.S. Patent No. 5,273,995 which involves alkylation of aldehyde with the ester side chain forms the chiral ester which on transesterification gives methylester and removable side chain by the use of sodium methoxide. Further, methylester is reacted with lithium enolate of tert-butylacetate to form the β-ketoester, which is then further reacted over a series of steps to form atorvastatin calcium.

An improved process is disclosed in WO 2005/087723 which involves chiral β-ketoester as the starting substrate, which on reduction (using metal hydroxide base in aqueous media) and further hydrolysis of the formed compound by reduction, gives the intermediate β-hydroxy carboxylic acid and removable side chain. This formed intermediate in the presence of 1,1'- carbonyldimidazole (CDI), mono-tert-butyl malonate and magnesium ethoxide gives β-ketoester. Finally β-ketoester is converted to atorvastatin calcium based on the procedures known in the art.

Objects of the invention

It is one of the important objects of the present invention to provide an improved process for the preparation of atorvastatin protected diol, an important intermediate for the preparation of atorvastatin calcium.

Another object of the present invention is to use the reagents *i.e.*, amino side chain and stetter compound as the starting material in the mole ratio of 4:1 in order to obtain high yield of atorvastatin protected diol, thereby developing an industrially important process for the recovery of excess amino side chain. Finally the present invention provides pure atovastatin calcium in high yield by using atorvastatin protected diol.

Summary of the Invention

The present invention shows an improved process for the synthesis of Atorvastatin Calcium. The invention further discloses the use of Stetter Compound and Amino side chain as the starting substrates for the route of synthesis. The reaction between Stetter Compound and amino side chain in the presence of cyclohexane, THF and Pivalic acid forms Atorvastatin protected diol, which is further, converted to final API, Atorvastatin Calcium.

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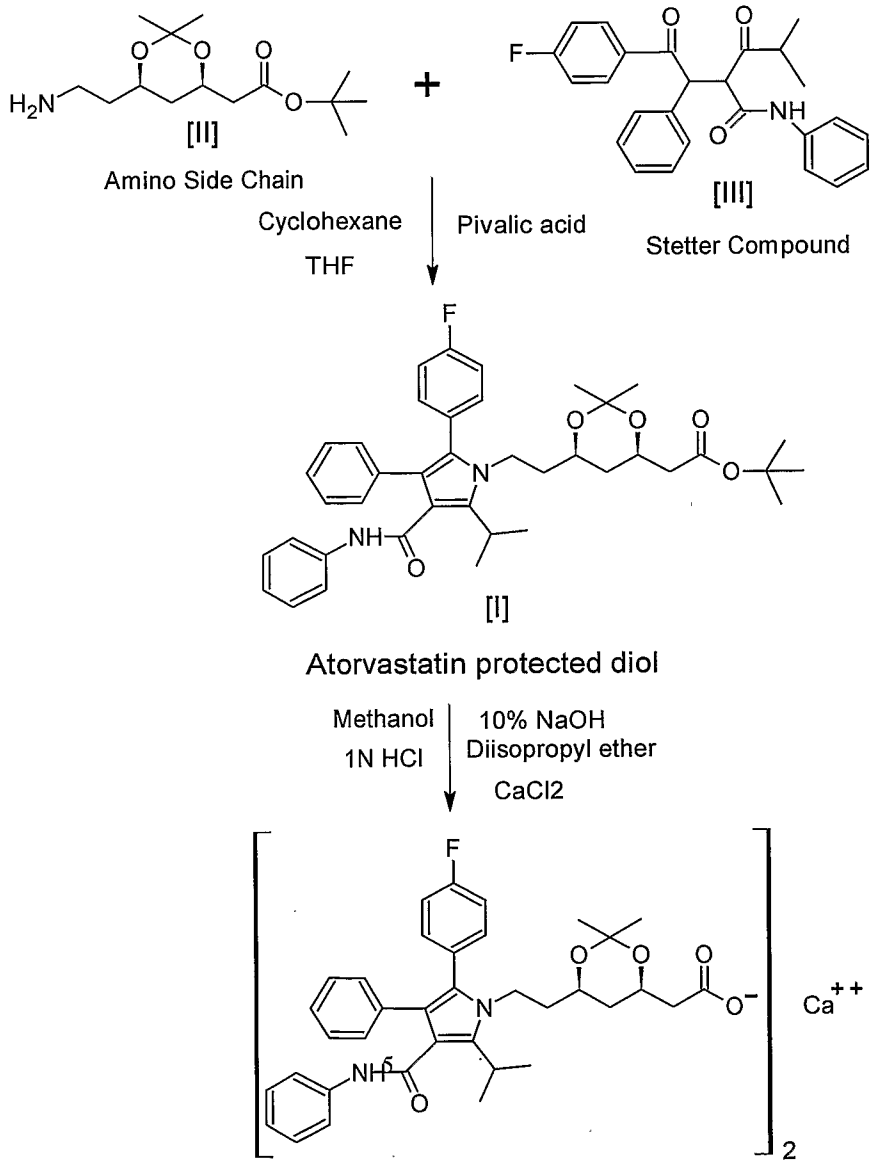
Detailed Description:

This present invention provides process for the preparation of atorvastation protected diol by reacting amino side chain and stetter compound in the mole ratio of



4:1 in presence of pivalic acid as catalyst.

Scheme (I)

The reaction can be preferably carried out in presence of inert organic solvent like cyclohexane, THF, and the like or mixtures there of. This reaction is also carried out in inert solvent like toluene, heptane, THF, and the like or mixtures there of in an appropriate mole ratio.

This reaction is carried out in presence of catalytic amount of pivalic acid. After the completion of reaction the pH of the reaction mixture is adjusted by using liquor ammonia and the aqueous layer is extracted with the help of MDC. Finally the reaction mixture is crystallized with mixture of IPA and water.

The present invention discloses the use of amino side chain and stetter intermediate in the improved mole ratio to get high yield and recovery of excess of amino side chain by an industrially useful procedure.

The process described in the present invention is demonstrated in examples illustrated below. These examples are provided as illustration only and therefore should not be constructed as limitation of the scope of the invention.

Example – 1

Step-1: Preparation of (4R-cis)-6-[-2-[3-phenyl-4-(phenyl-carbamoyl)-2-(4-flouro phenyl)-5-(1-methyl-ethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]dioxane-4-yl-acetic acid-tertriay butyl ester

In a 2 L round bottom flask equipped with a mechanical stirrer and temperature monitoring facility, Stetter compound i.e. 4-(4-Fluorophenyl)-2-isobutryl-4-oxo-N-phenyl butryl amide (100 g, 0.24 mole) and Amino side chain i.e. [6-(2-aminoethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid tert-butyl ester (261.9 g, 0.96 mole) was added at 25-35 °C. To this reaction vessel 2 L cyclohexane,100 ml THF and Pivalic acid (11.0 g, 0.11 mole) were added under same temperature condition. The reaction mixture was heated up to reflux temperature 70-85 °C and the reflux was maintained for 18 hrs. After cooling the reaction mixture to room temperature (25-35 °C), 500 ml water was added and stirred for 20 min. To this reaction mixture Liq. Ammonia was added to adjust the pH between 8.5-9.5 and stirred for 30 min. at room temperature. Now for separating the layers, aq. layer is extracted with 2 x 500 ml MDC. From the combined MDC and cyclohexane layer, MDC and cyclohexane were distilled out. At

this stage weight of the residue was 389.0 g. Now 720 ml IPA was added in to reaction mixture and the temperature raised up to 50-60 °C within 1 hr. Stirred for 30 min. at 50-60 °C. Slowly 327 ml water was added at 50-60 °C within 1 hour and then cooled down to room temperature 25-35 °C. Further stirred for 5 hrs at the same temperature and then filtered and washed with 50 ml x 2 mixture of IPA and water (11:5). Finally dried for 12 hrs at 50-55°C to obtain 117.3 g dry cake of (4R-cis)-6-[-2-[3-phenyl-4-(phenyl-carbamoyl)-2-(4-flourophenyl)-5-(1-methyl-ethyl)-pyrrol-1-yl]-ethyl]-2,2-di methyl-[1,3]dioxane-4-yl-acetic acid-tertriay butyl ester (Atorvastatin protected diol).

Step – 2: Recovery of [6-(2-aminoethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid tert-butyl ester (Amino Side Chain)

In a 2 L round bottom flask equipped with a mechanical stirrer and temperature as well as pH monitoring facility mother liquor (step – 1) and 429 ml water at 25 to 35°C temperature were taken. 100 ml of acetic acid was added at 25 to 35°C temperature. The reaction mixture was washed with 2 x 400 ml of toluene at room temperature. Organic layer was washed with 2 x 100 ml of 20% acetic acid solution at room temperature. The organic layer was discarded. Liquid ammonia was added by combining all the aqueous layer to adjust the pH 9 to 9.5 at 10 to 20°C. The reaction mixture was extracted with 3 x 400 ml of MDC. Combining all the MDC layer, MDC v/v at 45 to 50°C was distilled out. Oily residue was obtained. Weight 200 g. Yield: 79.12% (considering the recovery of the amino side chain).

Example-2:

Step-1: Preparation of [R-(R*,R*)]-2-(4-fluorophenyl-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyrrole-1-heptanoic acid calcium salt (2:1) [Atorvastatin Calcium]

In a 2 L round bottom flask equipped with a mechanical stirrer and temperature monitoring facility, 50 g of atorvastatin protected diol and 500 ml methanol were added at 25-35 °C. The temperature of the reaction mixture was raised up to 50-55 °C. 1 N HCl solution was added into the reaction mixture at 50-55 °C and stirred for 2 hrs at the same temperature. 10 ml 10% NaOH solution was added in to reaction mixture at 50-55 °C. The reaction mixture was stirred for ½ hrs at 50-55 °C. The reaction mixture was cooled to 25 – 35 °C and 250 ml water was added into reaction mixture. The pH of the reaction mass was adjusted to 8 to 8.5 by using 1N HCl solution. 500 ml of diisopropyl ether was added into reaction mixture and stirred for 30 mins at 25 – 35 °C. Aqueous layer and organic layer are separated thereby collecting the aqueous layer and

discarding the organic layer. Freshly prepared solution of calcium chloride fine was filtered. The filtrate was transferred into 3 L round bottom flask at 25 – 35 °C. The temperature of calcium chloride solution was raised up to 50 – 55 °C. Aqueous layer collected before was added into the calcium chloride solution at same temperature within 2 to 3 hrs. The temperature of the reaction was maintained at the same temperature for next 1 hour. The reaction mixture was cooled to room temperature 25 – 35 °C and stirred for 1 hour. It was further cooled down to 10 – 15 °C and stirred for 2 hrs. The reaction mass was filtered and washed with water 50 ml x 3. The material was dried till constant weight was obtained at 50 – 55 °C. The yield of crude atorvastatin calcium obtained was 45.5g.

Step – 2: Purification of Atorvastatin calcium: -

In a 1 L round bottom flask 43g of crude atorvastatin calcium and 344 ml of methanol was taken at 25 – 35°C. Reaction mixture was stirred for 30 min at 25 – 35 °C till clear solution was obtained. 2.1g of activated charcoal was added and reaction mixture was stirred for 1 hr at 25 – 35 °C. The reaction mixture was fine filtered with high-flow bed and bed was washed with methanol 43 ml x 2. 860 ml of water was added into round bottom flask at 25 – 35 °C and the temperature was increased to 50 – 55 °C. The above fine filtered solution was added into water at same temperature. The reaction mixture was cooled to 25 – 35 °C and stirred for 1 hr at 25 – 35 °C. It was further cooled to 10 – 15 °C. The product was filtered washed with water 43 ml x 2. The yield of pure atorvastatin calcium was 41g.

Advantages of the Invention:

1) The present invention provides an improved process for the synthesis of (4R-cis)-6-[-2-[3-phenyl-4-(phenyl-carbamoyl)-2-(4-flourophenyl)-5-(1-methyl-ethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]dioxane-4-yl-acetic acid-tert-butyl ester (Atorvastatin protected diol) with high yield as an important intermediate for preparation of atorvastatin calcium.
2) 4-(4-Fluorophenyl)-2-isobutryl-4-oxo-N-phenyl butryl amide (stetter compound) and [6-(2-aminoethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid tert-butyl ester (amino side chain) used to obtain atorvastatin protected diol in the range of 1:1 to 1:10 of molar ratio to improve the yield.
3) The mole ratio of 4-(4-Fluorophenyl)-2-isobutryl-4-oxo-N-phenyl butryl amide (stetter compound) and [6-(2-aminoethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic

acid tert-butyl ester (amino side chain) used to obtain atorvastatin protected diol is preferably 1:4.

4) The recovery of [6-(2-aminoethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid tert-butyl ester (amino side chain) is an industrial applicable process.

5) The process for the preparation of highly pure atorvastatin calcium from atorvastatin protected diol.

Claims:

1. A process for preparing atorvastatin calcium which comprises

a) reacting 4-(4-Fluorophenyl)-2-isobutryl-4-oxo-N-phenyl butyl amide (stetter compound) and [6-(2-aminoethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid tert-butyl ester (amino side chain) in the range of 1:1 to 1:10 of molar ratio to obtain (4R-cis)-6-[-2-[3-phenyl-4-(phenyl-carbamoyl)-2-(4-flourophenyl)-5-(1-methyl-ethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3] dioxane-4-yl-acetic acid-tert-butyl ester (Atorvastatin protected diol);

b) converting said (4R-cis)-6-[-2-[3-phenyl-4-(phenyl-carbamoyl)-2-(4-flouro phenyl)-5-(1-methyl-ethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]dioxan -4-yl-acetic acid-tert-butyl ester (Atorvastatin protected diol) to atorvastatin calcium.

c) purifying said atorvastatin calcium.

2. A process for preparing (4R-cis)-6-[-2-[3-phenyl-4-(phenyl-carbamoyl)-2-(4-flourophenyl)-5-(1-methyl-ethyl)-pyrrol-1-yl]-ethyl]-2,2-dimethyl-[1,3]dioxane-4-yl-acetic acid-tert-butyl ester (Atorvastatin protected diol) which comprises reacting 4-(4-Fluorophenyl)-2-isobutryl-4-oxo-N-phenyl butyl amide (stetter compound) and [6-(2-aminoethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid tert-butyl ester (amino side chain) in the range of 1:1 to 1:10 of molar ratio.
3. A process as claimed in claim 1 wherein [6-(2-aminoethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid tert-butyl ester (amino side chain) is recovered.
4. A process as claimed in claim 1 or 3 wherein step (a) is carried out in the presence of a hydrocarbon solvent, preferably cyclohexane.
5. A process as claimed in claim 1 or 3 wherein step (a) is carried out in the presence of a etheral solvent preferably, tetrahydrofuran.
6. A process as claimed in claim 1 or 3 wherein step (a) is carried out in the presence of an organic acid, preferably, pivalic acid.
7. A process as claimed in claim 1 or 3 wherein step (a) is carried out after a pH adjustment of 8.5 to 9.5 by treatment with base preferably, liquid ammonia.
8. A process as claimed in any preceding claim wherein the product of step (a) is filtered and washed with a mixture of organic solvent and water, preferably, isopropyl alcohol and water in a ratio of 11:5.
9. A process as claimed in any one of claims 1 and 3 to 9 wherein step (b) is performed with alcoholic solvent preferably, methanol.

10 A process as claimed in any one of claims 1 and 3 to 9 wherein step (b) is performed with alkali preferably sodium hydroxide.

11. A process as claimed in any one of claims 1 and 3 to 9 wherein step (b) is performed with mineral acid preferably, hydrochloric acid.

12. A process as claimed in any one of claims 1 and 3 to 10 wherein step (b) is carried out after a pH adjustment of 8 to 8.5 by treatment with mineral acid preferably hydrochloric acid.

13. A process as claimed in any one of claims 1 and 3 to 10 wherein step (b) is carried out in the presence of an ethereal solvent preferably isopropyl ether.

14. A process as claimed in any one of claims 1 and 3 to 10 wherein step (b) is carried out in the presence of calcium chloride.

15. A process as claimed in any one of claims 1 and 3 to 10 wherein the product of step (b) is filtered and washed with polar solvent preferably, water.

16. A process as claimed in any one of claims 1 and 3 to 15 wherein in step (c) purification is performed with organic solvent preferably methanol.

17. A process as claimed in any one of claims 1 and 3 to 16 wherein the product of step (c) is further washed with polar solvent, preferably water.

18. A highly pure atorvastatin protected diol having purity 99% and above.

19. A highly pure atorvastatin calcium having purity 99% and above.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2007/000426

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D405/06 A61K31/4015

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	K. L. BAUMANN ET AL: "The convergent synthesis of CI-981, an optically active, highly potent, tissue selective inhibitor of HMG-CoA reductase" TETRAHEDRON LETTERS, vol. 33, no. 17, 1992, pages 2283-2284, XP002443772 cited in the application Schema on pages 2283-2284.	1-19
X	US 5 273 995 A (ROTH BRUCE D [US]) 28 December 1993 (1993-12-28) cited in the application Example 10, columns 14-16.	19
X	EP 0 330 172 A2 (WARNER LAMBERT CO [US]) 30 August 1989 (1989-08-30) cited in the application Step f, pages 43-44.	2,4,18

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
24 July 2007	09/08/2007

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