

PROCESS FOR PREPARATION of (3R, 5R)-7-[2-(4-FLUOROPHENYL)-5-ISOPROPYL-3-PHENYL-4- [(4-HYDROXY METHYL PHENYL AMINO) CARBONYL]-PYRROL-1-YL]-3,5-DIHYDROXY-HEPTANOIC ACID HEMI CALCIUM SALT

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Field of the Invention

The present invention relates to processes for the preparation of (3R, 5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4- [(4-hydroxy methyl phenyl amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid hemi calcium salt.

Background of the Invention

10 (3R, 5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4- [(4-hydroxy methyl phenyl amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid hemi calcium salt acts an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, a coenzyme catalyzing the intracellular synthesis of cholesterol, and thus is useful as hypolipidemic and hypocholesterolemic agent, as discussed in PCT Publication No. 04/106299.

15 Cardiovascular disease and its associated maladies, dysfunctions and complications are a principal cause of disability and the chief cause of death. One specific factor significantly contributing to this pathophysiologic process is atherosclerosis, which has been generally recognized as the leading health care problem both with respect to mortality and health care costs.

20 Atherosclerosis is characterized by the deposition of fatty substances, primarily cholesterol, resulting in plaque formation on the inner surface of the arterial wall and degenerative change to the arteries. It is now well established that cardiovascular disorders including myocardial infarction, coronary heart disease, hypertension and hypotension, cerebrovascular disorders including stroke, cerebral thrombosis and memory loss due to stroke;
25 peripheral vascular disease and intestinal infarction are caused by blockage of arteries and arterioles by atherosclerotic plaque. Atherosclerotic plaque formation is multi-factorial in its production. Hypercholesterolemia, especially elevated levels of low-density lipoprotein cholesterol (LDL), is an important risk factor for atherosclerosis and arteriosclerosis and associated diseases.

The HMG-CoA reductase inhibitors (statins) have been used in reducing blood levels of LDL cholesterol. Cholesterol is produced via the mevalonic acid pathway. Reducing the formation of mevalonic acid, a precursor to cholesterol, leads to a corresponding decrease in hepatic cholesterol biosynthesis with a reduction in the cellular pool of cholesterol.

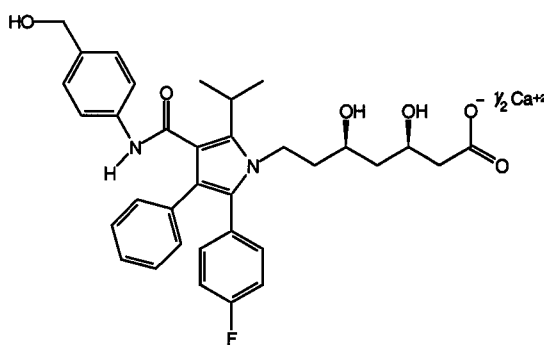
5 A synthetic procedure for preparing (3R, 5R)-7-[2-(4-fluorophenyl)-5- isopropyl-3-phenyl-4- [(4-hydroxy methyl phenyl amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid hemi calcium salt has been disclosed in PCT Publication No. WO 04/106299. The
10 aforementioned procedure involves multiple steps involving selective hydrolysis of two chemically similar functionalities e.g. hydrolysis of methyl ester in the presence of tert. -butyl ester, and reduction with sodium borohydride in the presence of iodine or with borane dimethyl
15 sulphide which are expensive reagents and are air- and moisture-sensitive, hence difficult to handle.

Summary of the Invention

Accordingly, herein are provided processes for preparing (3R, 5R)-7-[2-(4-fluorophenyl)-
15 5- isopropyl-3-phenyl-4- [(4-hydroxy methyl phenyl amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid hemi calcium salt by using synthetic procedure incorporating particular intermediates.

Further, herein are provided processes which are simple and economical, avoid the use of
20 expensive and air- and moisture-sensitive reagents, and avoid selective hydrolysis of methyl ester in the presence of tert-butyl ester.

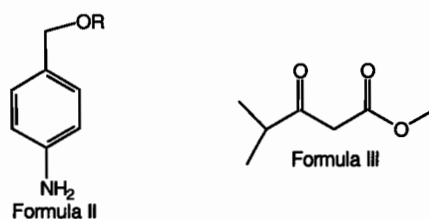
Further, herein are provided processes for the preparation of a compound of Formula I



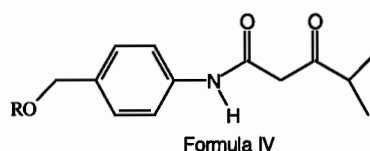
Formula I

which processes comprise:

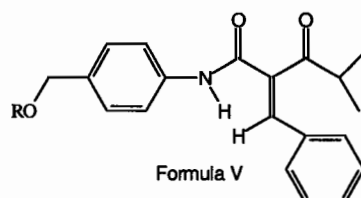
(a) reacting an amine of Formula II with methyl isobutyryl acetate of Formula III



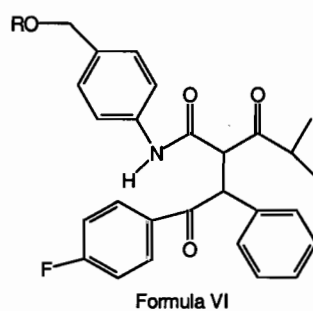
to form a compound of Formula IV (wherein R is a hydroxy protecting group, for example, acetyl, benzoyl, tetrahydropyranyl, methoxy methyl, methoxy ethoxymethyl, benzyl);



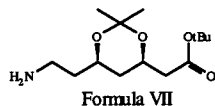
b) reacting the compound of Formula IV with benzaldehyde to form a compound of Formula V;



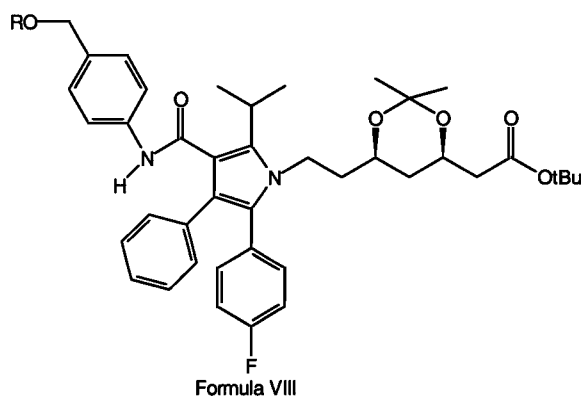
c) reacting the compound of Formula V with 4-fluorobenzaldehyde to form a compound of Formula VI;



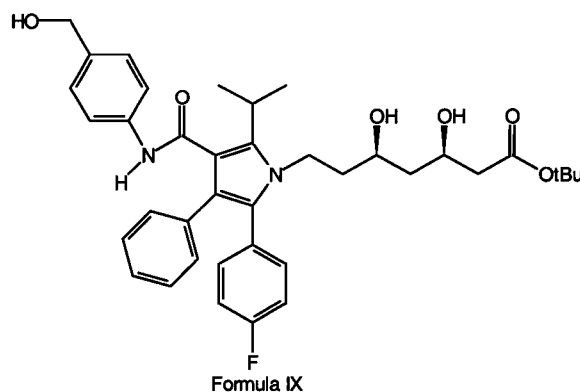
d) reacting the compound of Formula VI with a compound of Formula VII



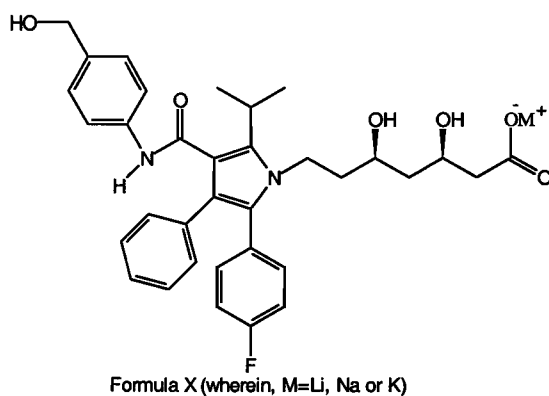
to form a compound of Formula VIII;



e) subjecting the compound of Formula VIII simultaneously to acid-catalyzed cleavage of ketal and hydroxy protecting group (when R is tetrahydropyranyl) to form a compound of Formula IX;



f) subjecting the compound of Formula IX to base-catalyzed hydrolysis to form a compound of Formula X; and



Formula X (wherein, M=Li, Na or K)

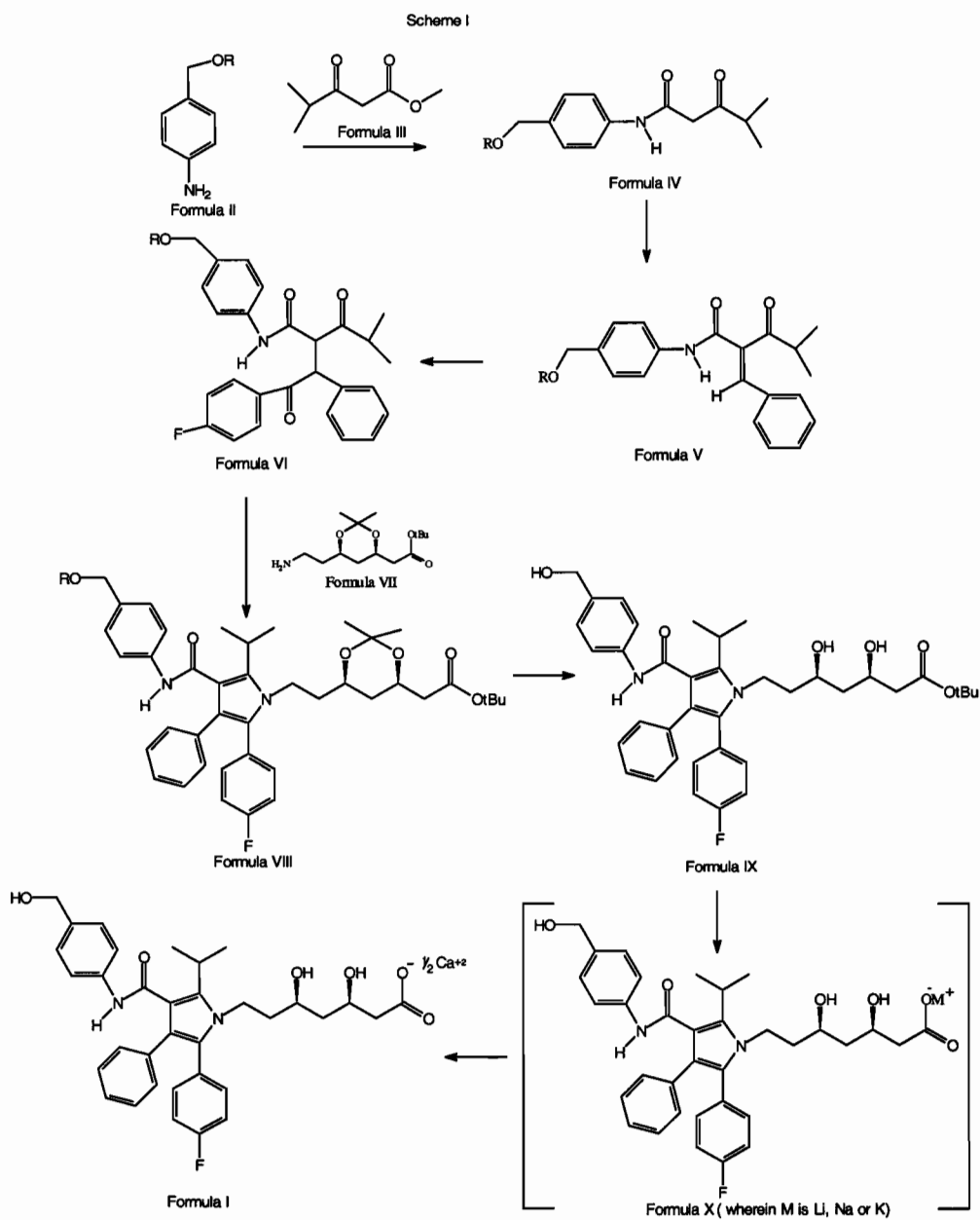
g) reacting the compound of Formula X with an aqueous solution of calcium acetate to form a compound of Formula I.

This process may involve one or more of the following features. For example, reaction of an amine of Formula II can be carried out in the presence of one or more organic bases such as, for example, triethylamine, pyridine, 1,2-ethylenediamine or mixtures thereof, in one or more aromatic solvents, for example, xylene, toluene or mixtures thereof. In another feature, the reaction of a compound of Formula IV can be carried out in the presence of one or more organic bases such as, for example, piperidine, pyridine, β -alanine or mixtures thereof, one or more organic acids such as, for example, glacial acetic acid or benzoic acid or mixture of organic bases and organic acids, in one or more solvents such as, for example, hydrocarbon solvents (*e.g.*, hexane or heptane), halogenated solvents (*e.g.*, dichloromethane, dichloroethane or chloroform), aromatic solvents (*e.g.*, toluene or xylene) or mixtures thereof. In another feature, the reaction of a compound of Formula V can be carried out in the presence of one or more catalysts such as, for example, sodium cyanide, 3-ethyl-5-(2-hydroxyethyl)-4-methyl thiazolium bromide, 3-benzyl-5-(2-hydroxyethyl)-4-methyl thiazolium chloride or mixtures thereof, one or more organic bases such as, for example, triethylamine, pyridine or mixtures thereof, in a solvent-free condition or in one or more solvents such as, for example, protic polar solvents (*e.g.*, methanol, ethanol, propanol, isopropanol or water), ethers (*e.g.*, dioxan or tetrahydrofuran) or mixtures thereof. In another feature, the reaction of a compound of Formula VI can be carried out in the presence of one or more organic acids such as, for example, pivalic acid, p-toluene sulfonic acid or mixtures thereof, in one or more solvents such as, for example, aromatic solvents (*e.g.*, xylene or toluene), hydrocarbon solvents (*e.g.*, hexane or heptane), ethers (*e.g.*, tetrahydrofuran, dioxane or diethyl ether) or mixtures thereof. In another feature, the cleavage of ketal and hydroxy protecting group of a compound of Formula VIII can be carried out in the presence of one or more mineral acids such as, for example, hydrochloric acid, hydrobromic acid, hydroiodic acid or mixtures thereof, in one or more solvents such as, for example, protic polar solvents (*e.g.*, methanol, ethanol, propanol or water), ethers (*e.g.*, tetrahydrofuran or diethyl ether) or mixtures thereof. In yet another feature, the hydrolysis of a compound of Formula IX can be carried out in the presence of one or more bases such as, for example, lithium hydroxide, sodium hydroxide, potassium hydroxide or mixtures thereof, in one or more solvents such as, for example, protic

polar solvents (*e.g.*, methanol, ethanol, propanol, isopropanol or water), ethers (*e.g.*, tetrahydrofuran or diethyl ether) or mixtures thereof.

Detailed Description of the Invention

(3R, 5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-[(4-hydroxy methyl phenyl amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid hemi calcium salt described herein may be prepared by following, for example, reaction sequences as depicted in Scheme I.



(3R, 5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4- [(4-hydroxy methyl phenyl amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid hemi calcium salt of Formula I can be prepared, for example, according to Scheme I. Thus, an amine of Formula I can be reacted with methyl isobutyryl acetate of Formula III to form a compound of Formula of IV (wherein R is the same as defined earlier). The compound of Formula IV can be reacted with benzaldehyde to form a compound of Formula V. The compound of Formula V can be reacted with 4-fluorobenzaldehyde to form a compound of Formula VI. The compound of Formula VI can be reacted with a compound of Formula VII to form a compound of Formula VIII. The compound of Formula VIII can be simultaneously subject to acid catalyzed cleavage of ketal and hydroxy protecting group (when R is tetrahydropyranyl) to form a compound of Formula IX. The compound of Formula IX can be subject to alkali base catalyzed hydrolysis to form a compound of Formula X. The compound of Formula X can be further converted to hemi calcium salt of Formula I by following procedures known to those of skill in the art.

The reaction of an amine of Formula II can be carried out in one or more aromatic solvents, for example, xylene, toluene or mixtures thereof. The reaction can also be carried out in the presence of one or more organic bases, for example, triethylamine, pyridine, 1,2-ethylenediamine or mixtures thereof.

The reaction of a compound of Formula IV can be carried out in one or more solvents, for example, hydrocarbon solvents (*e.g.*, hexane or heptane), or halogenated solvents (*e.g.*, dichloromethane, dichloroethane or chloroform), aromatic solvents (*e.g.*, toluene or xylene) or mixtures thereof. The reaction can also be carried out in the presence of one or more organic bases, for example, piperidine, pyridine or β -alanine, one or more organic acids, for example, glacial acetic acid or benzoic acid or mixtures of organic bases and organic acids.

The reaction of a compound of Formula V can be carried out in the presence of one or more catalysts, for example, sodium cyanide, 3-ethyl-5- (2-hydroxyethyl)-4-methyl thiazolium bromide, 3-benzyl-5- (2-hydroxyethyl)-4-methyl thiazolium chloride or mixtures thereof. The reaction can also be carried out in the presence of one or more organic bases, for example, triethylamine, pyridine or mixture thereof, in a solvent-free condition or in one or more solvents,

for example, protic polar solvents (*e.g.*, methanol, ethanol, propanol, isopropanol or water), ethers (*e.g.*, dioxan or tetrahydrofuran) or mixtures thereof.

The reaction of a compound of Formula VI can be carried out in one or more solvents, for example, aromatic solvents (*e.g.*, xylene or toluene), hydrocarbon solvents (*e.g.*, hexane or heptane), ethers (*e.g.*, tetrahydrofuran, dioxane or diethyl ether) or mixtures thereof. The reaction can also be carried out in the presence of one or more organic acids, for example, pivalic acid, p-toluene sulfonic acid or mixtures thereof.

The cleavage of ketal and hydroxy protecting group of a compound of Formula VIII can be carried out in the presence of one or more mineral acids, for example, hydrochloric acid, hydrobromic acid, hydroiodic acid or mixtures thereof. The reaction can also be carried out in one or more solvents, for example, protic polar solvents (*e.g.*, methanol, ethanol, propanol or water), ethers (*e.g.*, tetrahydrofuran or diethyl ether) or mixtures thereof. The cleavage of ketal and hydroxy protecting group can also be carried out by any other cleavage method known to those of skill in the art.

The hydrolysis of a compound of Formula IX can be carried out in the presence of one or more bases, for example, lithium hydroxide, sodium hydroxide, potassium hydroxide or mixtures thereof. The reaction can also be carried out in one or more solvents, for example, protic polar solvents (*e.g.*, methanol, ethanol, propanol, isopropanol or water), ethers (*e.g.*, tetrahydrofuran or diethyl ether) or mixtures thereof.

The compound of Formula X can be converted into its corresponding hemi calcium salt of Formula I by following procedure known to those of skill in the art.

In the above schemes, where specific reducing agents, solvents, bases, catalysts, acids etc., are mentioned, it is to be understood that other reducing agents, solvents, bases, catalysts, acids etc., known to those skilled in the art may be used. Similarly, the reaction temperature and duration may be adjusted.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are within the scope of the present invention.

Examples

Example 1: Preparation of 4-methyl-3-oxo-pentanoic acid [4-(tetrahydropyran-2-yloxymethyl) phenyl] amide

A mixture of 4-(tetrahydropyran-2-yloxymethyl) phenyl amine (70 g, 0.34 mol, 1 equiv.)
 5 (prepared following the procedure mentioned in *J.Med.Chem.*, **41**, 26, (1998), 5297-5309; and
Tetrahedron Lett., **43**, 30, (2002), 5353), methyl isobutyryl acetate (49 g, 0.34 mol, 1 equiv.),
 toluene (600 mL) and 1,2-ethylenediamine (2.0 g, 0.034 mol, 0.1 equiv.) was placed in a 2-
 necked round bottom flask and the reaction mixture was refluxed under a Dean-Stark set up.
 After completion of the reaction, the solvent was removed under vacuum. The crude product
 10 was taken as such for next step. Yield: 116g (crude)

MS (+ion mode): m/z 320.16 (M+ 1); ¹H NMR(CDCl₃, 300Hz): δ 1.27(d, J=6Hz, 6H); 1.33(s, 2H); 1.54-1.72(m, 7H); 2.74(sep, J=6Hz, 1H); 3.52-3.56(m, 1H); 3.61(s, 2H); 3.87-3.95(m, 1H); 4.47(d, J=12Hz, 1H); 4.68(m, 1H); 4.74(d, J=12Hz, 1H); 7.32(d, J=9Hz, 2H); 7.53(d, J=6Hz, 2H); 9.22(brs, 1H).

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Example 2: Preparation of 2-benzylidene-4-methyl-3-oxo-pentanoic acid [4-(tetrahydro-pyran-2-yloxy methyl) phenyl] amide

A mixture of crude 4-methyl-3-oxo-pentanoic acid [4-(tetrahydropyran-2-yloxy methyl)
 phenyl] amide (100 g, 0.31 mol, 1 equiv.), β-alanine (5.6 g, 0.063 mol, 0.2 equiv.), benzaldehyde
 20 (30.5 mL, 0.31 mol, 1 equiv.), glacial acetic acid (10.6 mL, 0.19 mol, 0.6 equiv.) and hexane
 (500 mL) was placed in a 2 necked-flask equipped with a Dean-Stark setup. The reaction
 mixture was refluxed with azeotropic removal of water. At the end of the reaction (TLC
 monitoring) the solvent was evaporated under reduced pressure to give solid, which was washed
 with hot hexane, and the solid was collected on a Buchner funnel. The crude compound was
 25 purified on column (silica gel, 100-200 mesh, 15% ethyl acetate/hexane) to afford the pure
 product. Yield: 66.81 g (52.36%).

MS (+ion mode): m/z 408.12 ($M+1$); $^1\text{H NMR}$ (CDCl_3 , 300Hz): δ 1.22(d, $J=6.0\text{Hz}$, 6H); 1.52-1.85(m, 8H); 3.35(sep, $J=6\text{Hz}$, 1H); 3.52-3.56(m, 1H); 3.87-3.91(m, 1H); 4.47(d, $J=12\text{Hz}$, 1H); 4.68-4.7(m, 1H); 4.75(d, $J=12\text{Hz}$, 1H); 7.32-7.64(m, 11H).

Example 3: Preparation of 2-[2-(4-fluorophenyl)-2-oxo-1-phenylethyl]-4-methyl-3-oxo-pentanoic acid [4-(tetrahydropyran-2-yloxy methyl phenyl) amide]

A mixture of 2-benzylidene-4-methyl-3-oxo-pentanoic acid [4-(tetrahydropyran-2-yloxy methyl phenyl) amide] (5.0 g, 0.012 mol, 1 equiv.), 4-fluorobenzaldehyde (1.5 mL, 0.0013 mol, 1.1 equiv.), 3-ethyl-5-(2-hydroxyethyl)-4-methyl thiazolium bromide (0.77 g, 0.0003 mol, 0.25 equiv.), triethyl amine (dry, 10 mL, 0.0072 mol, 5.8 equiv.) were placed in round bottom flask, and purged with nitrogen gas. The reaction mixture was refluxed at 90°C for about 6 hours. After the reaction was over, the reaction mixture was extracted with ethyl acetate and washed with water, and dried over anhydrous sodium sulphate. Organic layer was concentrated and the crude mixture was purified on column (silica gel, 100-200 mesh, 17% ethyl acetate/hexane) to afford the pure product. Yield: 2.52g (38.6%)

MS (+ion mode): m/z 532.17 ($M+1$); $^1\text{H NMR}$ (CDCl_3 , 300Hz): δ 1.15(d, $J=6.0\text{Hz}$, 3H); 1.23(d, $J=6.0\text{Hz}$, 3H); 1.45-1.851(m, 6 H); 2.85-3.05(m, 1H); 3.20-3.55(m, 1H); 3.70-3.95(m, 1H); 4.40-4.53(m, 2H); 4.67-4.72(m, 2H); 5.34(d, $J=9.0\text{Hz}$, 1H); 7.01-7.28(m, 12H); 7.95-8.00(m, 2H).

Example 4: Preparation of [(4R,6R)-6-(2-{2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-[4-(tetrahydropyran-2-yloxy methyl) phenyl amino)carbonyl]pyrrol-1-yl}ethyl)-2,2-dimethyl-[1,3]dioxan-4-yl]-acetic acid tert-butyl ester

A mixture of 2-[2-(4-fluorophenyl)-2-oxo-1-phenylethyl]-4-methyl-3-oxo-pentanoic acid [4-(tetrahydropyran-2-yloxy methyl)phenyl] amide (2.0 g, 0.004 mol, 1 equiv.), an amine of Formula IX (1.5 g, 0.006 mol, 1.5 equiv.), pivalic acid (0.45 mL, 0.004 mol, 1.03 equiv.), and heptane:toluene:tetrahydrofuran (4:1:1, 24 ml) was placed in a round bottom flask equipped with a Dean-Stark setup. The reaction mixture was refluxed at with azeotropic removal of water. After the completion of reaction (TLC monitoring), the solvents were removed on a rotary evaporator. The residue was diluted with ethyl acetate and a saturated solution of sodium bicarbonate was added to this solution. The aqueous layer was extracted with ethyl acetate and

the organic layer was washed with water, brine, dried over anhydrous sodium sulphate and concentrated. The crude mixture was purified on column (silica gel, 100-200 mesh, 15% ethyl acetate/hexane) to obtain the pure product. Yield: 1.0 g (34.6%).

MS (+ion mode): m/z 769.45 (M+ 1); ¹H NMR (CDCl₃, 300Hz): δ 0.9-1.1(m, 2H); 1.30(s, 1H),
 1.36(s, 3H); 1.43(s, 9H); 1.50-1.77(m, 14 6H); 2.20-2.40(m, 2H); 3.52-3.70(m, 3H); 3.85-3.89(m,
 2H); 4.05-4.25(m, 2H); 4.40(d, J=12 Hz, 1H); 4.64-4.70(m, 2H); 6.86-7.25(m, 14H).

Example 5: Preparation of (3R,5R)-7-[2-(4-fluorophenyl)-4-(4-hydroxymethyl- phenylamino) carbonyl]-5-isopropyl-3-phenylpyrrol-1-yl]-3,5-dihydroxy heptanoic acid tert-butyl ester

A mixture of [(4R, 6R)-6-(2-{2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4- [4-(tetrahydro-
 pyran-2-yloxy methyl) phenyl amino) carbonyl]-pyrrol-1-yl}ethyl)-2,2-dimethyl- [1,3] dioxan-4-
 yl]-acetic acid tert-butyl ester (0.8 g, 0.0015 mol, 1 equiv.) and a mixture of 1N hydrochloric
 acid:methanol:tetrahydrofuran in the ratio 2:5:5 (24 mL) was placed in a single neck flask. The
 reaction mixture was stirred at room temperature. Reaction mixture was concentrated by
 evaporating solvent under reduced pressure. The crude compound was extracted with ethyl
 acetate and the ethyl acetate layer was washed with brine, dried over anhydrous sodium sulphate
 and concentrated. The crude mixture was purified on column (silica gel, 100-200 mesh, 60%
 ethyl acetate/hexane) to obtain the pure product. Yield: 446 mg (66.56%).

MS (+ion mode): m/z 645.32 (M+ 1); ¹H NMR(CDCl₃, 300Hz): δ 1.15-1.30(m, 2H); 1.45(s,
 9H); 1.47-1.62(m, 8H); 2.32(d, J=6.0Hz, 2H); 3.53-3.60(m, 2H); 3.69-3.92(m, 1H); 4.08-4.13(m,
 2H); 4.58(s, 2H); 6.87(s, 1H); 6.97-7.25(m, 13H).

Example 6: Preparation of (3R,5R)-7-[2-(4-fluorophenyl)-4-(4-hydroxy methyl- phenyl amino) carbonyl]-5-isopropyl-3-phenylpyrrol-1-yl]-3,5-dihydroxy-heptanoic acid hemi calcium salt

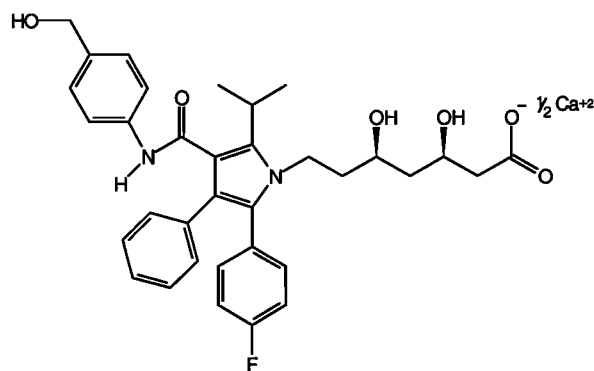
Step 1: (3R, 5R)-7-[2-(4-fluorophenyl)-4-(4-hydroxy methyl phenyl amino) carbonyl]-5-
 isopropyl-3-phenylpyrrol-1-yl]-3,5-dihydroxyheptanoic acid tert-butyl ester in a mixture of
 methanol-tetrahydrofuran (1:1) was cooled to 0°C and sodium hydroxide pellets were added.
 The reaction mixture was then stirred at an ambient temperature. At the end of ester hydrolysis,
 solvents were removed and the residue was dissolved in water, and the aqueous layer was
 washed with ether.

Step 2: To an aqueous solution of sodium salt of (3R,5R)-7-[2-(4-fluorophenyl)-4-(4-hydroxy methyl- pheny lamino) carbonyl)-5-isopropyl-3-phenyl-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid was added drop wise an aqueous solution (1M) of calcium acetate (0.55 equiv.). White precipitate was obtained, which was filtered off, washed with copious amount of water, and dried in vacuo. Yield = 63.4%

MS (positive ion mode): m/z 589 (Acid+1); m.p. = 189-204°C; ¹H NMR (DMSO-d₆): δ 1.22-1.62 (m, 11H), 1.98 (dd, J=15 & 8.1Hz, 1H), 2.06-2.16 (m, 1H), 3.25-3.37 (m, 2H), 3.57 (brs, 2H), 3.80 (brs, 1H), 4.43 (s, 2H), 7.03-7.28 (m, 12H), 7.50 (d, J=6H, 2H), 9.80 (s, 1H)

We Claim:

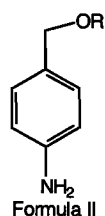
1. A method for the preparation of (3R, 5R)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-[(4-hydroxy methyl phenyl amino) carbonyl]-pyrrol-1-yl]-3,5-dihydroxy-heptanoic acid hemi calcium salt of Formula I,



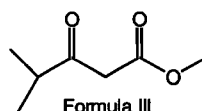
Formula I

comprising:

(a) reacting an amine of Formula II with methyl isobutyryl acetate of Formula III

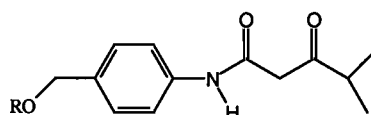


Formula II



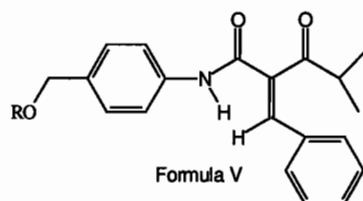
Formula III

to form a compound of Formula of IV, wherein R is a hydroxy protecting group selected from the group consisting of acetyl, benzoyl, tetrahydropyranyl, methoxy methyl, methoxy ethoxymethyl, and benzyl;

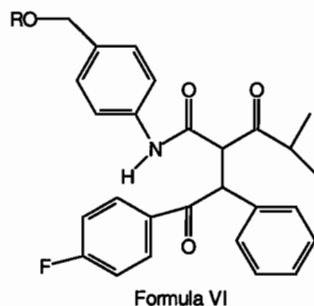


Formula IV

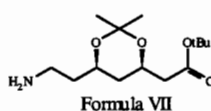
- b) reacting the compound of Formula IV with benzaldehyde to form a compound of Formula V;



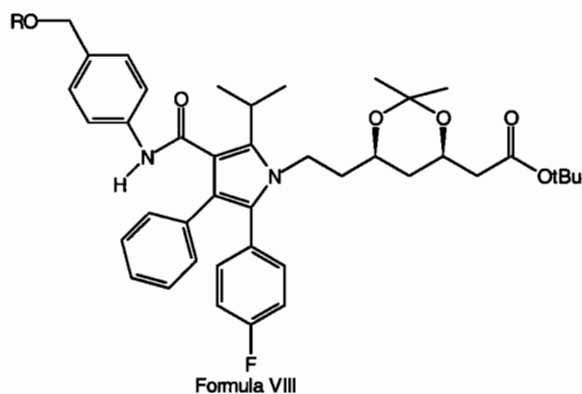
- c) reacting the compound of Formula V with 4-fluorobenzaldehyde to form a compound of Formula VI;



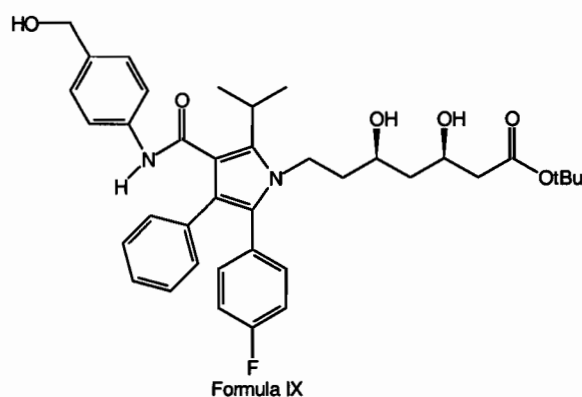
- d) reacting the compound of Formula VI with a compound of Formula VII



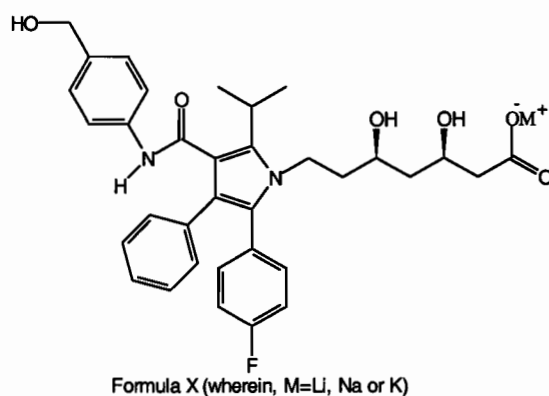
to form a compound of Formula VIII;



- e) subjecting the compound of Formula VIII with a mineral acid simultaneously to induce acid-catalyzed cleavage of ketal and the hydroxy protecting groups to form a crude compound of Formula IX;



- f) purifying the crude compound of Formula IX to form a purified compound of Formula IX;
- g) subjecting the purified compound of Formula IX with a base to induce base-catalyzed hydrolysis to form a compound of Formula X; and



- h) reacting the compound of Formula X with aqueous solution of calcium acetate to form a compound of Formula I.

2. The process of claim 1, wherein the reaction of the amine of Formula II is carried out

- i) in the presence of one or more organic bases; and

3 ii) in one or more aromatic solvents.

1 3. The process of claim 1, wherein the reaction of the compound of Formula IV is carried
2 out

3 i) in the presence of one or more organic bases selected from the group consisting of
4 piperidine, pyridine, and β -alanine; or in the presence off one or more organic
5 acids selected from the group consisting of glacial acetic acid and benzoic acid; or
6 in the presence of a mixture of organic bases or organic acids; and

7 ii) in one or more solvents selected from the group consisting of hexane, heptane,
8 dichloromethane, dichloroethane, chloroform, toluene, xylene, and mixtures
9 thereof.

1 4. The process of claim 1, wherein the reaction of the compound of Formula V is carried out

2 i) in the presence of one or more catalysts selected from the group consisting of
3 sodium cyanide, 3-ethyl-5- (2-hydroxyethyl)-4-methyl thiazolium bromide, 3-
4 benzyl-5- (2-hydroxyethyl)-4-methyl thiazolium chloride and mixtures thereof;

5 ii) in the presence of one or more organic bases selected from the group consisting of
6 triethylamine, pyridine and mixtures thereof; and

7 iii) in a solvent-free condition or in one or more solvents selected from the group
8 consisting of methanol, ethanol, propanol, isopropanol, water, dioxin,
9 tetrahydrofuran, and mixtures thereof.

1 5. The process of claim 1, wherein the reaction of a compound of Formula VI is carried out

2 i) in the presence of one or more organic acids selected from the group consisting of
3 pivalic acid, p-toluene sulfonic acid, and mixtures thereof; and

4 ii) in the presence of one or more solvents selected from the group consisting of
5 xylene, toluene, hexane, and heptanes, tetrahydrofuran, dioxane, diethyl ether, and
6 mixtures thereof.

1 6. The process of claim 1, wherein the cleavage of ketal and hydroxy protecting groups of
2 the compound of Formula VIII is carried out

i) in the presence of one or more mineral acids selected from the group consisting of hydrochloric acid, hydrobromic acid, hydroiodic acid, and mixtures thereof; and

ii) in the presence of one or more solvents selected from the group consisting of methanol, ethanol, propanol, water, tetrahydrofuran, diethyl ether, and mixtures thereof.

7. The process of claim 1, wherein the hydrolysis of a compound of Formula IX is carried out

i) in the presence of one or more bases selected from the group consisting of lithium hydroxide, sodium hydroxide, potassium hydroxide and mixtures thereof; and

ii) in the presence of one or more solvents selected from the group consisting of methanol, ethanol, propanol, isopropanol, water, tetrahydrofuran, diethyl ether, and mixtures thereof.

8. The process of claim 1, wherein the crude compound of Formula IX is purified by a column.