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(71) Applicant (for all designated States except US):
UNICHEM LABORATORIES LIMITED [IN/IN];
Unichem Bhavan, Prabhat Estate, S.V. Road, Jogeshwari
(East), Mumbai- 400 102, Maharashtra (IN).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **DESHPANDE, Pandurang, Balwant** [IN/IN]; Unichem Laboratories Limited, Unichem Bhavan, Prabhat Estate, S.V. Road, Jogeshwari (West), Mumbai 400 102, Maharashtra (IN). **RAMAKRISHNAN, Arul** [IN/IN]; Unichem Laboratories Limited, Unichem Bhavan, Prabhat Estate, S.V. Road, Jogeshwari (West), Mumbai 400 102, Maharashtra (IN). **NILESH, Balkrishna, Shrigadi** [IN/IN]; Unichem Laboratories Limited, Unichem Bhavan, Prabhat Estate, S.V. Road, Jogeshwari (West), Mumbai 400 102, Maharashtra (IN). **SANDEEP, Mukunda, Bahul** [IN/IN]; Unichem Laboratories Limited, Unichem Bhavan, Prabhat Estate, S.V. Road, Jogeshwari (West), Mumbai 400 102, Maharashtra (IN).

(74) Agent: **UNICHEM LABORATORIES LIMITED**;
Unichem Bhavan, Prabhat Estate, S.V. Road, Jogeshwari
(West), Mumbai 400 102, Maharashtra (IN).

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(54) Title: PROCESS FOR PREPARATION OF CALCIUM SALT OF ROSUVASTATIN

(57) Abstract: The invention relates to commercially viable process for the preparation of Rosuvastatin by an early introduction of correct absolute stereochemistry at C-5 (S) of Rosuvastatin side chain followed by regioselective chain extension using novel side chain building blocks and less expensive reagents. It is yet another object of the invention is to provide novel intermediates that may be used for the preparation of Calcium salt of Rosuvastatin. Formula (I).

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**Title :- PROCESS FOR PREPARATION OF CALCIUM SALT
OF ROSUVASTATIN**

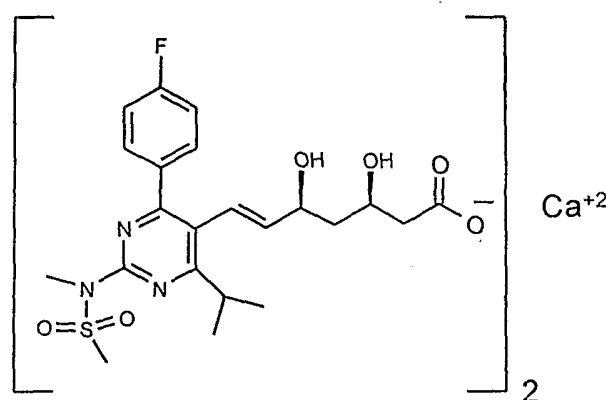
Field of Invention

The present invention relates to a process for the preparation of Rosuvastatin, a promising HMG-CoA reductase inhibitor, to process steps and novel intermediates.

Background of the invention

HMG-CoA reductase inhibitors (also called β -hydroxy- β -methylglutaryl-co-enzyme-A reductase inhibitors and also called statins) are understood to be those active agents, which may be preferably used to lower the low-density lipoprotein (LDL) particle concentration in the blood stream of patients at risk for cardiovascular disease and thus used for the prevention or treatment of hypercholesterolemia, hyperlipoproteinemia and arteriosclerosis. A high risk level of LDL in the bloodstream has been linked to the formation of coronary lesions that obstruct the flow of blood and can rupture and promote thrombosis.

Rosuvastatin, an antihypercholesterolemic drug used in the treatment of atherosclerosis is chemically (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid calcium (2:1) salt having the structural formula I.



Formula I

The prior art has been elaborated in a co-pending application number 325/MUM/2005 filed in Mumbai, India.

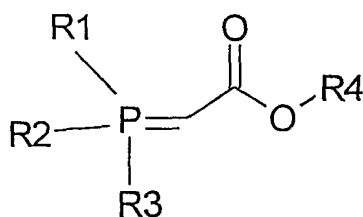
The above mentioned co-pending application discloses a commercially viable method of preparation for Rosuvastatin via novel intermediates.

In continuation of our work in this aspect, in this present invention relates another method of preparation of Rosuvastatin via novel intermediates and less expensive reagents by an early introduction of the correct absolute stereochemistry at C-5 (S) of side chain followed by regioselective chain extension using yet another side chain building blocks. The invention also relates to novel intermediates.

Detailed Description of the invention

The present invention concerns a process for the preparation of rosuvastatin comprising,

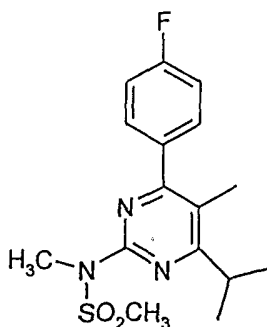
a) reacting a compound of formula (II)



Formula II

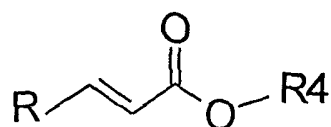
wherein, R1, R2, R3 are substituted or unsubstituted phenyl and R4 is an aliphatic residue selected from C1-C4 alkyl;

with a compound of formula R-CH(=O) (Formula III) wherein R represents the following cyclic structure (formula IV) to obtain a compound of formula (V);

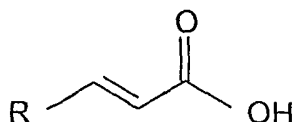


Formula IV

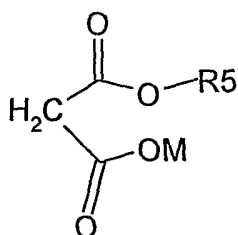
b). hydrolysing a compound of formula (V) to obtain a compound of formula (VI);

**Formula V**

c). treating a compound of formula (VI)

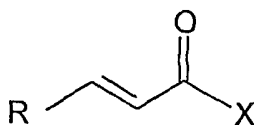
**Formula VI**

with an acid activating group and subsequently with a compound of formula VII that introduces the radical of formula $-\text{CH}_2-\text{COOR}_5$ to obtain a compound of formula VIII

**Formula VII**

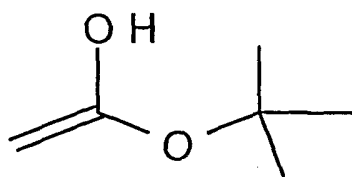
wherein, R5 represents C1-C4 alkyl; M is an alkali metal;

or in another variant of process, converting the compound of formula (VI) to its acid halide of formula (IX)

**Formula IX**

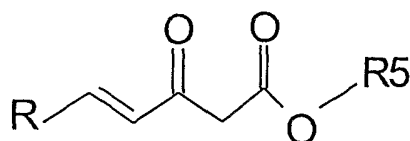
wherein, X represents a halogen

and treating a resulting compound of formula (IX) with a compound of formula (X) to obtain a compound of formula (VIII);

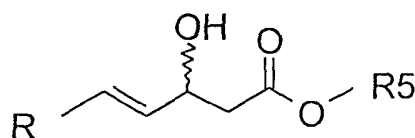
**Formula X**

or in another variant of process, treating the compound of formula (IX) with a compound of formula (VII) to obtain a compound of formula (VIII);

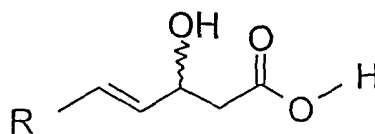
d). reducing a compound of formula (VIII) to obtain a compound of formula XI;

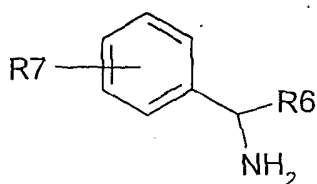
**Formula VIII**

e). hydrolyzing a compound of formula (XI) to obtain a compound of formula XII

**Formula XI**

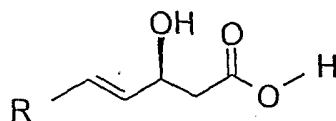
f). resolving the resulting racemic compound of formula (XII), first converting the racemic compound to its diastereomeric salt using the (+) or (-) enantiomeric amine of the formula (XIII) and separating the mixture of diastereomeric salt into the individual diastereomers by chromatography or crystallization and then neutralizing the diastereomeric salt to give the enantiomerically pure product.

**Formula XII**

**Formula XIII**

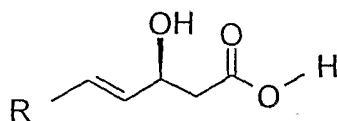
wherein, R6 represent C1-C4-alkyl which is optionally substituted by hydroxyl; R7 represent hydrogen, halogen, C1-C4 alkyl or C1-C4 alkoxy; and

g). treating the resulting compound of formula (XIV)

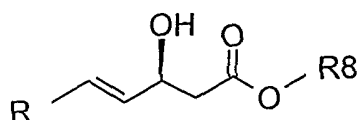
**Formula XIV**

with an acid activating group and subsequently with a compound of formula (VII) that introduces the radical of formula $-\text{CH}_2-\text{COOR}_5$ to obtain a compound of formula (XV)

or in another variant of process, esterifying a compound of formula (XIV)

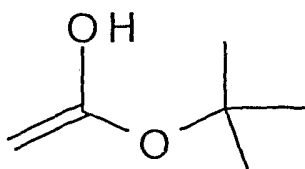
**Formula XIV**

and condensing the resulting compound of formula (XVI)

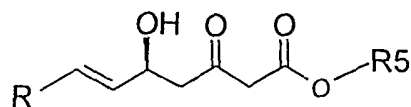
**Formula XVI**

wherein R8 is an aliphatic residue selected from C1 -C4 alkyl

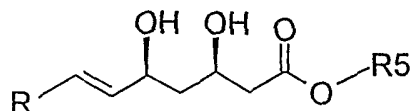
with a compound of formula (X) to obtain a compound of formula (XV)

**Formula X**

h). reducing a compound of formula (XV) to obtain a compound of formula XVII

**Formula XV**

i). hydrolyzing a compound of formula (XVII) and converting into a salt of formula I thereof

**Formula XVII**

wherein R and R5 have the meanings as defined.

In reaction step (a), the reaction of a compound of formula (II) with a compound of formula (III) is carried out in a suitable inert solvent, preferably toluene, and in a temperature range from 60°C, to the boiling point of the solvent, preferably at the boiling point of the solvent.

The saponification (step b) is carried out by treating the ester of formula (V) with a strong base, such as an alkali metal hydroxide, preferably NaOH or KOH, in aqueous aliphatic alcohol as solvent, preferably aqueous methanol, and in a temperature range from 25°C to boiling point of solvent, preferably between 25°C to 35°C and acidifying the resulting reaction mixture.

Formation of compound of formula (VIII) (step c) is carried out by treating the compound of formula (VI) with an acid activating group, especially preferred one is the use of 1,1-carbonyldiimidazole and condensing the resulting compound with alkali metal salt of monoalkyl malonate (formula VII), preferably potassium monomethylmalonate or potassium monoethylmalonate, in the presence of magnesium chloride, in an inert solvent, preferably tetrahydrofuran, at temperature between 0 – 40°C, preferably at 0 – 35°C.

In another variant of process to prepare compound of formula (VIII) is carried out by converting a compound of formula (VI) to a compound of formula (IX) in an inert solvent, preferably dichloromethane, and in temperature range from 0°C to boiling point of the solvent, preferably between 0°C to 28°C using oxalyl chloride or thionyl chloride

and subsequent treatment of a resulting of formula of (IX) with a compound of formula (X) in the presence of a suitable base and in a suitable inert solvent, especially tetrahydrofuran, and in a temperature range from -78°C , to the boiling point of the solvent, preferably at -78 to room temperature.

A suitable base is selected from an alkane alkali metal in presence of diisopropylamine, alkali alkylsilazanes like LiHMDS or NaHMDS. Especially preferred is the use of *n*-butyllithium in the presence of diisopropylamine.

In another variant of process to prepare compound of formula (VIII) is carried out by condensing a compound of formula (IX) with an alkali metal salt of monoalkyl malonate (Formula VII), preferably potassium monomethylmalonate or potassium monoethylmalonate, in the presence of magnesium chloride, in an inert solvent, preferably tetrahydrofuran, at temperature between $0 - 40^{\circ}\text{C}$, preferably at $0 - 35^{\circ}\text{C}$.

The reduction of compound of formula (VIII), is carried out in a mixture of an inert solvent, such as an ether, preferably tetrahydrofuran and lower alkanol, preferably methanol, in the ratio of 4:1 volume/volume, and at temperature range from -78°C to 0°C , preferably at -65°C to 0°C .

A preferred reduction agent is a hydride, for example, an alkalimetal borohydride, especially sodium borohydride.

The saponification step e) is carried out by treating the ester of formula (XI) with a strong base, such as an alkali metal hydroxide, preferably NaOH or KOH, in aqueous aliphatic alcohol as solvent, preferably aqueous methanol, and in a temperature range from 25°C to boiling point of solvent, preferably between 25°C to 30°C and acidifying the resulting reaction mixture.

The resolution of racemate of compound of formula (XII) (step f) in to optically pure antipodes is carried out by means of known methods for the separation of enantiomers, for example by means of preparative chromatography using chiral supports (HPLC) or by crystallization using optically pure precipitating agents. for example (+) or (-) phenylalkylamine or substituted phenylalkylamine, preferably (R)-1-phenylethylamine in alcoholic solvents such as lower alkanol, preferably ethanol and recrystallising from a

mixture of ketonic solvent and lower alkanol, preferably mixture of acetone and methanol followed by neutralization.

Formation of compound of formula (XV) is carried out by treating the compound of formula (XIV) with an acid activating group, especially preferred one is the use of 1,1-carbonyldiimidazole and condensing the resulting compound with alkali metal salt of monoalkyl malonate (Formula VII), preferably potassium monomethylmalonate or potassium monoethylmalonate, in presence of magnesium chloride, in an inert solvent, preferred one is tetrahydrofuran, at temperature between 0 – 40°C, preferably at 0 – 35°C.

In another variant of process to prepare compound of formula (XV) is carried out by converting compound of formula XIV to a compound of formula XVI by esterification and condensing the resulting compound of formula (XVI) with a compound of formula (X).

Esterification of compound of formula XIV is carried out, in lower alcoholic solvent, especially C1-C3 alkanol, preferably methanol, in presence of acidic catalyst like inorganic acids or p-toluensulphonic acid or acidic resins, and in a temperature range from 0°C to boiling point of solvent, preferably between 0°C to 30°C.

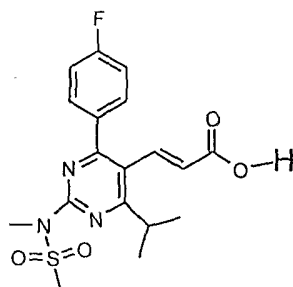
Condensation step is carried out in the presence of a suitable base and in a suitable inert solvent, especially tetrahydrofuran, and in a temperature range from –78°C to the boiling point of the solvent, preferably at room temperature. A suitable base is selected from an alkane alkalimetal in the presence of diisopropylamine, alkali alkylsilazanes like LiHMDS or NaHMDS. Preferred one is the use of n-butyllithium in the presence of diisopropylamine.

The reduction of compound of formula XV (step h), is carried out in a mixture of an inert solvent, preferably tetrahydrofuran and a lower alkanol, preferably methanol, in the ratio of 4:1 volume/volume, and at temperatures from –78°C to 0°C, preferably at –78°C to –70°C. To split the corresponding boronic ester the reaction mixture is then treated with methanol, and in a temperature range from 0°C to the boiling point of solvent, preferably in range of 0°C to 40°C.

A preferred reduction agent is an alkalimetal borohydride in the presence of a di-C1-C7-alkyl-C1-C4 alkoxy-borane, especially sodium borohydride in the presence of diethylmethoxyborane.

The isolation of compound of formula I (step i), is carried out by saponification of a compound of formula XVII using a base, such as an alkali metal hydroxide, preferably NaOH and followed by treatment with aqueous calcium chloride solution.

The present invention also relates to a novel compound of formula VI or its acid chloride and process of making it.



Formula VI

The starting material of formula III may be prepared, for example, as described in Bioorganic & Medicinal Chemistry 1997, 437.

In the following examples, the preferred embodiments of the present invention are described only by way of illustrating the process of the invention. However, these are not intended to limit the scope of the present invention in any way.

Example 1. Preparation of ethyl (2E)-3-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}acrylate

To a solution of N-[4-(4-fluorophenyl)-5-formyl-6-isopropylpyrimidin-2-yl]-N-methylmethylsulfonamide (55g; 156mmol) in 700ml of toluene, 60.2g of (carbethoxymethylene)triphenylphosphorane (172mmol) was added at 25 – 29°C. The reaction mixture was refluxed for 6 hours. After completion of reaction (TLC; disappearance of starting material), reaction mixture was cooled between 25 – 28°C and 500ml of n-hexane was added and stirrer for 15 minutes. The separated solid was removed by filtration and the filtrate was distilled under reduced pressure to remove the solvents. The oily mass obtained after removal of solvents was purified through silica gel column to obtain ethyl (2E)-3-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}acrylate as a solid.

^1H NMR (400MHz, CDCl_3): 1.27-1.3 (9H, m, $-\text{CH}(\text{CH}_3)_2$, $-\text{CH}_2\text{CH}_3$), 3.33-3.4 (1H, m, $-\text{CH}(\text{CH}_3)_2$, 3.49 (3H, s, $-\text{NCH}_3$), 3.55 (3H, s, $-\text{SO}_2\text{CH}_3$), 4.19 (2H, q, $-\text{OCH}_2\text{CH}_3$), 5.81 (1H, d, $J=16.10$), 5.81 (1H, d, $\text{C}=\text{CHCOOCH}_2$), 7.10 (2H, t, Ar-H), 7.59 (2H, dd, Ar-H), 7.68 (1H, d, $J=16.10$, $-\text{CH}=\text{CHCOOCH}_2$).

^{13}C NMR (400MHz, CDCl_3): 14.32, 21.97, 30.01, 32.29, 42.44, 60.76, 115.45, 115.67, 118.81, 125.71, 132.04, 132.73, 133.67, 133.71, 139.17, 157.97, 162.51, 164.33, 165.01, 165.50, 175.15

Example 2. Preparation of (2E)-3-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}acrylic acid

A solution of ethyl (2E)-3-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}acrylate 20g (47.5 mmol) in methanol (200ml). To this solution, NaOH (2.09g; 52.25mmol) in 50ml of water was added in drop wise over the period of approximately 15 minutes at temperature between 25°C to 29°C . After stirring at this temperature for further 8 hours, to the reaction mixture 200 ml of tert-butyl methyl ether was added followed by 50ml of water. The aqueous layer was separated and the organic layer was washed with 50ml of water. The aqueous layers were combined and the pH was adjusted to approximately 3-4 by acidification and extracted twice to 200ml of dichloromethane. The combined organic layers were washed with 100 ml saturated NaCl solution, dried over anhydrous Na_2SO_4 and filtered. The filtrate obtained was evaporate to dryness under vacuum to obtain (2E)-3-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}acrylic acid as a white solid. The structure of the product has been conformed by NMR, Mass.

^1H NMR (400MHz, CDCl_3) δ = 1.23 (6H, d, $-\text{CH}(\text{CH}_3)_2$); 3.33-3.4 (1H, m, $-\text{CH}(\text{CH}_3)_2$); 3.45 (3H, s, $-\text{NCH}_3$); 3.52 (3H, s, $-\text{SO}_2\text{CH}_3$); 5.8 (1H, d, $J=16.34$, $=\text{CH}-\text{COOH}$); 7.06 (2H, t, Ar-H), 7.53 (2H, dd, Ar-H); 7.75 (1H, d, $J=16.10$, $-\text{CH}=\text{CH}-\text{COOH}$); 9.8 (1H, br. s, COOH).

Example 3 Preparation of methyl (4E)-5-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3-oxo-4-pentenoate

Method 1:

To a solution of (2E)-3-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}acrylic acid (2.0g; 5.06mmol) in 8 ml of tetrahydrofuran (THF), 1,1-carbonyldiimidazole (0.98g; 6.07mmol) was added in portions over a period of 5 minutes and stirred between 25°C and 29°C under nitrogen atmosphere. After stirring for 2 hours, this solution was added to a preformed mixture of monomethyl malonate potassium salt (0.79g; 5.06mmol), magnesium chloride (0.482g; 5.06mmol and triethylamine which was stirred for further 2 hours at 25 –28°C. The resulted reaction mixture was stirred for 24 hours at 35°C. The reaction mixture was cooled to approximately to 27°C and filtered. The residue was washed twice with 25ml of THF and combined with the filtrate. The combined filtrate was concentrated under vacuum and the residue obtained was dissolved in 60ml of ethyl acetate, washed with 30ml of 1 N hydrochloric acid, thrice with 40ml of saturated NaHCO₃ followed by saturated NaCl solution, dried over anhydrous Na₂SO₄. The filtrate obtained after the filtration was concentrated under reduced pressure to obtain methyl (4E)-5-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3-oxo-4-pentenoate as a yellow colored solid.

¹H NMR (400MHz, CDCl₃): 1.26 (6H, d, -CH(CH₃)₃); 3.3-3.38 (1H, m, -CH(CH₃)₃); 3.49 (3H, s, -NCH₃); 3.55 (3H, s, -SO₂CH₃); 3.7 (3H, s, OCH₃); 4.94 (1H, s); 5.72 (1H, d, J=15.85, Ar-CH=CH-); 7.08 (2H, t, Ar-H); 7.42 (1H, d, J=15.85' Ar-CH=CH-); 7.61 (2H, dd, Ar-H), 11.79 (1H, s, enol-OH).

Method 2:

a). Preparation of (2E)-3-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-2-propenoyl chloride

To a solution of (2E)-3-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}acrylic acid (2.0g; 5.06mmol) in 20ml of dichloromethane oxalyl chloride (0.77g ; 6.07mmol) was added in drop wise over a period of 5 minutes at 0 -5°C with stirring under nitrogen atmosphere. The reaction mixture was allowed to warm up and stirred at 25°C to 29°C. After stirring for 2 hours, the reaction mixture was concentrated under reduced pressure and swapped trice with 20ml dichloromethane to

obtained (2E)-3-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-2-propenoyl chloride as a solid.

b). Preparation of methyl (4E)-5-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3-oxo-4-pentenoate

To a solution of monomethyl malonate potassium salt (0.79g; 5.06mmol), magnesium chloride (0.482g; 5.06mmol) was added followed by triethylamine (0.51g) and the suspension was stirred for 2 hours at 25 –28°C. To this, solution of (2E)-3-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-2-propenoyl chloride (2.06g, 5.0mmol) in 10ml of THF was added and stirred for 24 hours at 30-35°C. The reaction mixture was cooled, filtered and then residue was washed twice with 25ml of THF. The filtrate was concentrated by evaporation, taken up in 60ml of ethyl acetate, washed with 30ml of 1N hydrochloric acid, thrice with 40ml of saturated NaHCO₃ solution followed by saturated NaCl solution and dried over anhydrous Na₂SO₄. The filtrate after filtration was concentrated under reduced pressure to obtain methyl (4E)-5-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3-oxo-4-pentenoate as yellow colored solid.

Example 4 Preparation of racemic methyl (4E)-5-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3-hydroxy-4-pentenoate

To a solution of methyl (4E)-5-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3-oxo-4-pentenoate (1.5g; 3.325mmol) in 15ml of THF/methanol (4:1) was cooled to -65°C under nitrogen atmosphere with stirring. To this stirred solution, NaBH₄ (0.154g; 3.99mmol) was added in portion and solution was stirred for further 1-2 hours at -65°C. To this 1ml of acetic acid in 15ml water followed by 15ml ethyl acetate was added and stirred for 5min. The layers were separated and aqueous layer was extracted twice with 30ml of ethyl acetate. The combined organic phases are washed twice with 30ml saturated NaHCO₃ solution and then with 30ml saturated NaCl solution, dried over anhydrous Na₂SO₄, filtered. The filtrate was concentrated under reduced pressure to obtained methyl (4E)-5-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl) amino]pyrimidin-5-yl}-3-hydroxy-4-pentenoate as solid.

¹H NMR (400MHz, CDCl₃): 1.21 (6H, d, -CH(CH₃)₃), 2.3-2.5 (2H, m, CH₂-COO); 3.27-3.34 (1H, m, -CH(CH₃)₃), 3.49 (3H, s, -NCH₃), 3.54 (3H, s, -SO₂CH₃); 3.68 (3H, s, -OCH₃); 4.52-5.56 (1H, m, >CH-OH); 5.45 (1H, d, J=16.10, =CHCOO), 6.64 (1H, d, J=16.10, CH=CHCOO); 7.07 (2H, t, Ar-H), 7.6 (2H, dd, Ar-H),

Example 5 Preparation of racemic (4E)-5-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3-hydroxy-4-pentenoic acid

To a stirred solution of racemic methyl (4E)-5-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3-hydroxy-4-pentenoate (12g; 26.6 mmol) in 120ml of methanol, a solution of aqueous sodium hydroxide (1.17g; 29.3mmol in 25ml water) was added slowly at temperature between 27-29°C and stirred for further 1-2 hours. After completion of reaction (TLC; disappearance of starting material), 25ml of water and 120ml *tert*-butyl methyl ether were added. The organic layer was separated and washed with 25ml water. The aqueous layers were combined and the pH was adjusted to approximately 3-4 by acidification and extracted twice to 100ml of dichloromethane. The combined organic layers were washed with 50 ml saturated NaCl solution, dried over anhydrous Na₂SO₄, filtered. The filtrate obtained was evaporated to dryness under vacuum to obtain racemic (4E)-5-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3-hydroxy-4-pentenoic acid as off-white solid. The structure of the product has been conformed by NMR.

¹H NMR (400MHz, CDCl₃): 1.3 (6H, d, -CH(CH₃)₃), 3.34-3.41 (1H, m, -CH(CH₃)₃), 3.47 (3H, s, -NCH₃), 3.56 (3H, s, -SO₂CH₃), 5.85 (1H, d, J=16.34, =CHCOOH), 7.12 (2H, t, J=8.29, Ar-H), 7.59 (2H, dd, J=8.05, 5.51, Ar-H), 7.8 (1H, d, J=16.34, -CH=CHCOOH), 10.79 (1H, br., -COOH).

¹³C NMR (400MHz, CDCl₃): 21.96, 32.37, 33.03, 42.45, 115.56, 115.77, 118.39, 124.88, 132.04, 132.13, 133.60, 133.59, 141.59, 158.13, 162.57, 164.60, 165.07, 170.91, 175.23.

Example 6. Preparation of (4E)-5-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}(3S)-3-hydroxy-4-pentenoic acid

To a solution of racemic (4E)-5-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3-hydroxy-4-pentenoic acid in ethanol, (R)-1-phenyl

ethylamine was added at 25-29°C. The reaction mixture was cooled to 0°C and stirred for another 3 hours. The solid precipitated was filtered and washed with tert-butyl methyl ether, dried under vacuum. The solid obtained after drying was recrystallised from 5 volumes of methanol - acetone mixture (1:4 ratio by v/v) to get (R)-1-phenylethylamine salt of (4E)-5-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}(3S)-3-hydroxy-4-pentenoic acid.

The crystallised salt was taken in methanol and treated with aqueous sodium hydroxide solution at 25 -28°C with stirring. After stirring for 1 hour, water was added followed by tert-butyl methyl ether. The organic layer was separated and the aqueous layer was acidified (pH of 3-4) and extracted with dichloromethane. After removal of solvent under vacuum, (4E)-5-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}(3S)-3-hydroxy-4-pentenoic acid was obtained as a solid.

¹H NMR (400MHz, CDCl₃): 1.3 (6H, d, -CH(CH₃)₃), 3.34-3.41 (1H, m, -CH(CH₃)₃), 3.47 (3H, s, -NCH₃), 3.56 (3H, s, -SO₂CH₃), 5.85 (1H, d, J=16.34, =CHCOOH), 7.12 (2H, t, J=8.29, Ar-H), 7.59 (2H, dd, J=8.05, 5.51, Ar-H), 7.8 (1H, d, J=16.34, -CH=CHCOOH), 10.79 (1H, br s, -COOH).

¹³C NMR (400MHz, CDCl₃): 21.96, 32.37, 33.03, 42.45, 115.56, 115.77, 118.39, 124.88, 132.04, 132.13, 133.60, 133.59, 141.59, 158.13, 162.57, 164.60, 165.07, 170.91, 175.23.

Example 7 Preparation of methyl (6E)-7-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}(5S)-5-hydroxy-3-oxo-6-heptenoate

To a solution of (4E)-5-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}(3S)-3-hydroxy-4-pentenoic acid (2.0g; 4.57mmol) in 8ml of THF, 1,1-carbonyldiimidazole (0.885g, 5.48mmol) was added in portions over a period of 5 minutes and stirred between 25°C and 29°C under nitrogen atmosphere. After stirring for 2 hours, this solution was added to a preformed mixture of monomethyl malonate potassium salt (0.71g; 4.57mmol), magnesium chloride (0.435g; 4.57mmol) and triethylamine (0.46g; 4.57mmol) which was stirred for further 2 hours at 25 -28°C. The resulted reaction mixture was stirred for 24 hours at 30 - 35°C. The reaction mixture was cooled and filtered and then residue is washed twice with 25ml of THF. The filtrate was concentrated by evaporation, taken up in 60ml of ethyl acetate, washed with 30ml of 1N

hydrochloric acid, thrice with 40ml of saturated NaHCO_3 solution followed by saturated NaCl solution, dried over anhydrous Na_2SO_4 . The filtrate obtained after filtration was concentrated under reduced pressure to obtain yellow colored oily mass, which was purified through column to obtain methyl (6E)-7-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl) amino]pyrimidin-5-yl}(5S)-5-hydroxy-3-oxo-6-heptenoate.

^1H NMR (400MHz, CDCl_3): δ =1.2 (6H, d, $-\text{CH}(\text{CH}_3)_2$); 2.6 (2H, d, $(\text{OH})\text{CH}-\text{CH}_2-\text{C}(\text{O})$); 3.3 (1H, m, $-\text{CH}(\text{CH}_3)_2$); 3.43 (2H, s, $(\text{O})\text{C}-\text{CH}_2-\text{COO}-$); 3.47 (3H, s $-\text{NCH}_3$); 3.52 (3H, s, $-\text{SO}_2\text{CH}_3$); 3.7, (3H, s, $-\text{COOCH}_3$); 4.61 (1H, m, $>\text{CH}-\text{OH}$); 5.4 (1H, dd, $J=16$, $=\text{CH}-\text{CH}(\text{OH})$); 6.6 (1H, d, 15.85, $\text{Ar}-\text{CH}=\text{CH}$); 7.1 (2H, t, $\text{Ar}-\text{H}$); 7.6 (2H, dd, $\text{Ar}-\text{H}$).

Example 8 Preparation of methyl (6E)-7-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}(3R,5S)-3,5-dihydroxyhept-6-enoate

Methyl (6E)-7-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}(5S)-5-hydroxy-3-oxo-6-heptenoate (1g; 2.03mmol) was taken in 10ml dry THF/methanol (4:1) and cooled to -78°C under nitrogen atmosphere. To this stirred solution, diethylmethoxyborane (1 M in THF; 0.223g; 2.23mmol) was added drop wise over a period of ~5 minutes. After stirring at that temperature for 30 minutes, NaBH_4 (0.076g; 2.23mmol) was added at -78°C and stirred at -78°C for 3-4 hours. To this reaction mixture, 1ml of acetic acid was added in drop wise followed by 10ml of ethyl acetate and 10ml of water. After stirring for 10 minutes at -78°C , the reaction mixture allowed reach $25-28^\circ\text{C}$. The layers were separated and the aqueous layer was extracted twice with 30ml of ethyl acetate. The combined organic layers were washed twice with 30ml saturated NaHCO_3 solution and then with saturated NaCl solution, dried over anhydrous Na_2SO_4 . The reaction mixture was filtered and the solvents were removed by distillation under vacuum. The oily product thus obtained was swapped thrice with 30ml of methanol to remove borate complex and concentrated to obtained oily mass, which after column purified provided methyl (6E)-7-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}(3R,5S)-3,5-dihydroxyhept-6-enoate.

^1H NMR (400MHz, CDCl_3): δ =1.2 (6H, d, $-\text{CH}(\text{CH}_3)_2$); 1.39 -1.56 (2H, m, $>\text{CH}_2$); 2.4 (2H, $\text{CH}-\text{CH}_2-\text{COO}$); 3.3 (1H, m, $-\text{CH}(\text{CH}_3)_2$); 3.48 (3H, s $-\text{NCH}_3$); 3.53 (3H, s, $-\text{SO}_2\text{CH}_3$); 3.7, (3H, s, $-\text{COOCH}_3$); 4.16 (1H, m, $>\text{CH}-\text{OH}$); 4.42 (1H, m, $>\text{CH}-\text{OH}$); 5.4

(1H, dd, $J=16$, $=\underline{\text{CH}}-\text{CH}(\text{OH})$); 6.6 (1H, d, 15.85, $\text{Ar}-\underline{\text{CH}}=\text{CH}$); 7.1 (2H, t, Ar-H); 7.6 (2H, dd, Ar-H).

Example 9 Preparation of calcium salt of (2:1)-(+)-7-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}(3R,5S)-3,5-dihydroxy-(E)-hept-6-enoic acid

To a solution of methyl (6E)-7-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}(3R,5S)-3,5-dihydroxyhept-6-enoate (2g, 4.04mmol) in 30ml of acetonitrile, 0.25N solution of NaOH (17.7ml; 4.44mmol) was added over a period of 5 minutes at temperature between 26-29°C with stirring. After stirring for 3-4 hours, 30ml tert-butyl methyl ether was added followed by 10ml of water. The layers were separated and organic layer was extracted with 20ml of water. The combined aqueous layers were concentrated by evaporation under reduced pressure to its half volume. To the concentrated aqueous layer, a 1 M solution of $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ (2.02ml, 2.02mmol) was added drop wise with stirring at 25-28°C. After stirred for 45 minutes, the precipitate formed was filtered and washed with water to get Rosuvastatin Calcium as a white solid.

Example 10 Preparation of *tert*-butyl (4E)-5-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3-oxo-4-pentenoate

Diisopropylamine (7.4g; 73.2mmol) was taken in 100ml of dry THF and cooled to -5°C to 0°C with stirring under nitrogen atmosphere. To this stirred solution *n*-butyllithium (1.6M in hexane; 47ml; 73.2mmol) was added in drop wise manner over a period of approximately 30 minutes at temperature between -5°C to +5°C under nitrogen atmosphere. The reaction mixture was then allowed to reach +10°C (in the course of 10 minutes) and maintained at that temperature for 30 min. Again the reaction mixture was cooled to around -65°C, *tert*-butyl acetate (8.5g; 73.2mmol) was added in drop wise over a period of 20 minutes and stirred out at that temperature for 40 min. To this, a solution of (2E)-3-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-2-propenoyl chloride (25.1g; 61mmol) in 100ml of dry THF was added in one lot at -65°C. The reaction mixture was stirred out at temperature between -60°C and -65°C, the

reaction mixture allowed to warm up to -5°C (in time interval of ~ 45 minutes) and stirred at that temperature for further 30 minutes. The reaction mixture quenched with drop wise addition of acetic acid (50ml) and stirred for ~ 10 minutes. To this 200ml of ethyl acetate was added followed by 200ml of water and stirring is carried out for ~ 10 minutes. The layers were separated and the aqueous layer was extracted twice with 200ml of ethyl acetate. The combined organic layers were washed twice with 300ml saturated NaHCO_3 solution and then with saturated NaCl solution, dried over anhydrous Na_2SO_4 , filtered. The filtrate was distilled under reduced pressure to obtained *tert*-butyl (4E)-5-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3-oxo-4-pentenoate as an oily mass.

Example 11 Preparation of racemic (4E)-5-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3-hydroxy-4-pentenoic acid

To a stirred solution of *tert*-butyl (4E)-5-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3-hydroxy-4-pentenoate (28.5g; 57mmol) in 200ml of methanol, a solution of aqueous sodium hydroxide (2.54g; 63.5mmol in 50ml water) was added slowly at temperature between $27-29^{\circ}\text{C}$. The reaction mixture was heated and refluxed for 6-10 hours. After completion of reaction (completion of reaction was monitored by TLC, ethyl acetate: hexane 3:7), 50ml of water and 200ml of *tert*-butyl methyl ether were added. The organic layer was separated and washed with 100ml water. The aqueous layers were combined and the pH was adjusted to approximately between 3-4 by acidification and extracted twice with 200ml of dichloromethane. The combined organic layers were washed with 100ml saturated NaCl solution, dried over anhydrous Na_2SO_4 . The filtrate obtained after filtration was evaporated to dryness under vacuum to obtain racemic (4E)-5-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3-hydroxy-4-pentenoic acid as white solid. The structure of the product has been conformed by NMR.

^1H NMR (400MHz, CDCl_3): 1.2 (6H, d, $-\text{CH}(\text{CH}_3)_3$), 2.5 (1H, m, $-\text{CH}_2-\text{COOH}$), 3.3 (1H, m, $-\text{CH}(\text{CH}_3)_3$), 3.49 (3H, s, $-\text{NCH}_3$), 3.54 (3H, s, $-\text{SO}_2\text{CH}_3$), 4.58 (1h, s, $>\text{CH}-\text{OH}$), 5.46 (1H, d, $J=15.98$, $=\text{CHCOOH}$), 6.7 (1H, d, $J=15.85$, $-\text{CH}=\text{CHCOOH}$), 7.1 (2H, t, Ar-H), 7.59 (2H, dd, Ar-H).

^{13}C NMR (400MHz, CDCl_3): 21.55, 32.11, 33.10, 40.40, 42.73, 68.09, 114.96, 115.16, 120.86, 124.22, 131.99, 132.08, 134.27, 134.30, 137.32, 157.34, 161.99, 163.53, 164.47, 174.82, 176.81.

Example 12 preparation of methyl (4E)-5-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl) amino]pyrimidin-5-yl}(3S)-3-hydroxy-4-pentenoate

Methanol (25ml) was taken in a 100ml three necked round bottomed flask and cooled to -5°C with stirring. To this acetyl chloride (0.588g; 7.488mmol) was added drop wise in such a way that the temperature remains between -5°C to $+5^\circ\text{C}$ over a period of approximately 10 minutes. After stirring for 30 minutes at 0°C , a solution of (4E)-5-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}(3S)-3-hydroxy-4-pentenoic acid (4.2g; 9.6mmol) in 15ml of methanol was added drop wise over a period of ~10 minutes at 0°C and stirred at that temperature for further 30 minutes. Then the reaction mixture was allowed to reach $20 - 25^\circ\text{C}$ and stirred for 3-4 hours at $25 - 29^\circ\text{C}$. Again the reaction mixture was cooled to 0°C and 3g of powdered NaHCO_3 was added in portions. The reaction mixture was filtered and to the filtrate 50ml of ethyl acetate and 30ml of water were added. The layers were separated and the aqueous layer was extracted twice with 30ml of ethyl acetate. The combined organic layers were washed with 50ml of saturated NaHCO_3 solution, 50 ml of saturated NaCl solution and dried over anhydrous Na_2SO_4 . Methyl (4E)-5-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl (methylsulfonyl)amino]pyrimidin-5-yl}(3S)-3-hydroxy-4-pentenoate was obtained as solid after complete removal of solvent by distillation under vacuum.

^1H NMR (400MHz, CDCl_3): 1.2 (6H, d, $-\text{CH}(\text{CH}_3)_3$), 2.4-2.5 (2H, m, $-\text{CH}_2\text{COOMe}$), 3.1 (1H, d, $>\text{CH}-\text{OH}$), 3.34-3.41 (1H, m, $-\text{CH}(\text{CH}_3)_3$), 3.48 (3H, s, $-\text{NCH}_3$), 3.54 (3H, s, $-\text{SO}_2\text{CH}_3$), 3.7 (3H, s, $-\text{COOCH}_3$), 4.6 (1H, s, $>\text{CH}-\text{OH}$), 5.5 (1H, dd, $J=16.10$, $=\text{CHCOOCH}_3$), 5.12 (1H, dd, $J=16.10$, $-\text{CH}=\text{CHCOOMe}$), 7.1 (2H, t, Ar-H), 7.6 (2H, dd, Ar-H).

^{13}C NMR (400MHz, CDCl_3): 21.54, 32.03, 33.04, 40.31, 51.85, 68.15, 114.89, 115.10, 121.00, 123.73, 132.00, 132.09, 134.32, 137.71, 157.27, 161.94, 164.42, 172.38, and 174.79.

Example 13 Preparation of tert-butyl (6E)-7-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl) amino]pyrimidin-5-yl}(5S)-5-hydroxy-3-oxo-6-heptenoate

To a solution of diisopropylamine (0.9g; 8.87mmol) in 10ml of dry tetrahydrofuran, n-butyllithium (1.6M in hexane; 6ml; 8.87mmol) was added at 0°C under nitrogen atmosphere, with stirring in drop wise over a period of ~10 minutes. The reaction mixture was then allowed to warm up to $+10^\circ\text{C}$ (in time interval of ~10 minutes) and maintained at that temperature for 30 minutes. Again the reaction mixture was cooled to -65°C and tert-butyl acetate (1.03g; 8.87mmol) was added drop wise over a period of ~5 minutes. After stirred for another 40 minutes, the resulting solution was transferred to a solution of methyl (4E)-5-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}(3S)-3-hydroxy-4-pentenoate (1g; 2.2 mmol) in 5ml of dry THF at 0°C . The reaction mixture was allowed to reach to 20°C and stirred at that temperature for ~4 hours. 1ml of acetic acid was added in drop wise to the reaction mixture followed by 10ml of ethyl acetate and 10ml of water. After stirring for 10 minutes, the layers were separated and the aqueous phase was extracted twice with 30ml of ethyl acetate. The combined organic layers were washed twice with 30ml saturated NaHCO_3 solution and then with saturated NaCl solution, dried over anhydrous Na_2SO_4 . The filtrate obtained after filtration was distilled under vacuum to remove the solvent completely. tert-butyl (6E)-7-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-(5R)-5-hydroxy-3-oxo-6-heptenoate was obtained as an orange oily mass and was taken as it is for next step.

Example 14 Preparation of tert-butyl (6E)-7-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methyl sulfonyl) amino]pyrimidin-5-yl}(3R,5S)-3,5-dihydroxyhept-6-enoate
tert-butyl (6E)-7-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}(5S)-5-hydroxy-3-oxo-6-heptenoate (1g; 1.87mmol) was taken in 10ml of

dry THF/methanol (4:1 v/v) and cooled to -78°C under nitrogen atmosphere with stirring. To this stirred solution, diethylmethoxyborane (1 M in THF; 2.1g; 2.05mmol) was added drop wise over a period of ~5 minutes. After stirring for at that temperature for further 30 minutes, NaBH_4 (0.08g; 2.05mmol) was added at -78°C . The reaction mixture was stirred at -78°C for 3-4 hours. To the reaction mixture 1ml of acetic acid was added in drop wise followed by 10ml of ethyl acetate and 10ml of water. After stirring for 10 minutes at -78°C the reaction mixture was allowed reach $25 - 28^{\circ}\text{C}$. The layers were separated and the aqueous layer was extracted twice with 30ml of ethyl acetate. The combined organic phases were washed twice with 30ml saturated NaHCO_3 solution and then with saturated NaCl solution, dried over anhydrous Na_2SO_4 . The reaction mixture was filtered and the solvent was removed by distillation under vacuum. The oily product thus obtained was swapped thrice with 30ml of methanol to remove borate complex and concentrated to obtain an oily mass, which after column purification provided tert-butyl (6E)-7-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}(3R,5S)-3,5-dihydroxyhept-6-enoate as a solid.

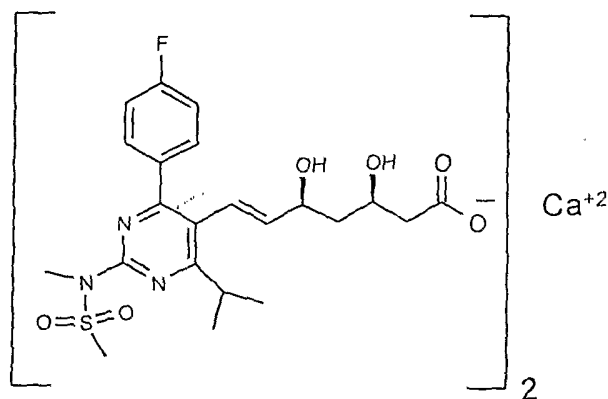
^1H NMR (400MHz, CDCl_3): 1.23 (6H, d, $-\text{CH}(\text{CH}_3)_3$), 1.40–1.50 (11H, m, $-\text{C}(\text{CH}_3)_3$, $-\text{CH}_2$), 2.34 (2H, d, $-\text{CH}_2\text{COO}$), 3.35 (1H, d, $>\text{CH}-\text{OH}$), 3.31-3.38 (1H, m, $-\text{CH}(\text{CH}_3)_3$), 3.49 (3H, s, $-\text{NCH}_3$), 3.54 (3H, s, $-\text{SO}_2\text{CH}_3$), 3.76 (H, s, $-\text{OH}$), 3.86 (H, s, $-\text{OH}$), 4.41 (1H, d, $>\text{CH}-\text{OH}$), 4.42 (1H, t, $>\text{CH}-\text{OH}$), 5.42 (1H, dd, $J=115.98$ $=\text{CHCOO}$), 6.6 (1H, d, $J=16.10$, $-\text{CH}=\text{CHCOO}$), 7.06 (2H, t, Ar-H), 7.6 (2H, dd, Ar-H).

Example 15 Preparation of Calcium (2:1)-(+)-7-[4-(4-fluorophenyl)-6-isopropyl-2[N-methyl-N-methylsulfonylamino]pyrimidin-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoic acid
A solution of tert-butyl (6E)-7-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}(3R,5S)-3,5-dihydroxyhept-6-enoate (2g; 3.72 mmol) in 30ml of acetonitrile of 0.25 M solution of NaOH (14.9ml; 3.72 mmol) was added over a period of 5 minutes at temperature between $26 - 29^{\circ}\text{C}$ with stirring. After stirred for 3-4 hours, 30 ml of tert-butyl methyl ether was added followed by 10ml of water. The layers were separated and the organic layer was extracted with 20ml of water. The combined aqueous layers were concentrated by evaporation under reduced pressure to its

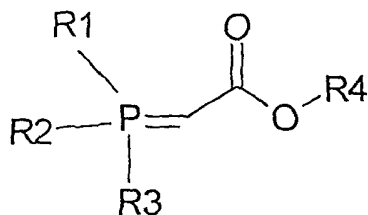
half volume. To the concentrated aqueous layer, 1 M solution of $\text{CaCl}_2 \cdot 2\text{H}_2\text{O}$ (1.86ml: 1.86 mmol) was added drop wise with stirring at 25 - 28°C. After stirred for 45 minutes, the precipitate formed was filtered and washed with water to get Rosuvastatin Calcium as a white solid.

Claims :-

1. A process for the manufacture of Rosuvastatin of formula I, according to the present invention, comprising



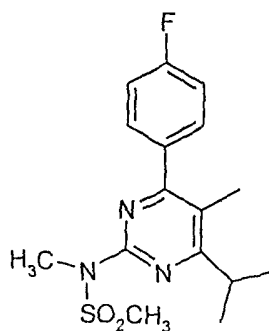
a) reacting a compound of formula (II)



Formula II

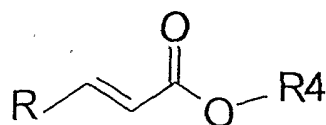
wherein, R1, R2, R3 are substituted or unsubstituted phenyl and R4 is an aliphatic residue selected from C1-C4 alkyl;

with a compound of formula R-CH(=O) (Formula III) wherein R represents the following cyclic structure (formula IV) to obtain a compound of formula (V);



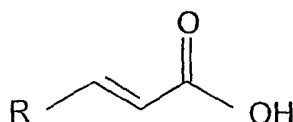
Formula IV

b) hydrolysing a compound of formula (V) to obtain a compound of formula (VI);



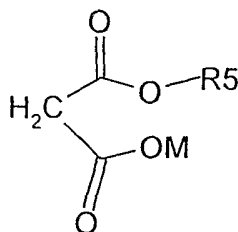
Formula V

c). treating a compound of formula (VI)



Formula VI

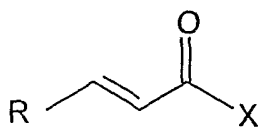
with an acid activating group and subsequently with a compound of formula VII that introduces the radical of formula $-\text{CH}_2-\text{COOR}_5$ to obtain a compound of formula VIII



Formula VII

wherein, R5 represents C1-C4 alkyl; M is an alkali metal;

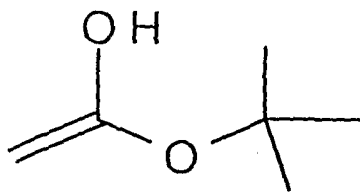
or in another variant of process, converting the compound of formula (VI) to its acid halide of formula (IX)



Formula IX

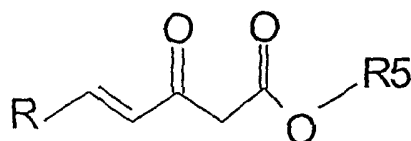
wherein, X represents a halogen

and treating a resulting compound of formula (IX) with a compound of formula (X) to obtain a compound of formula (VIII);

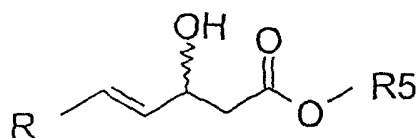
**Formula X**

or in another variant of process, treating the compound of formula (IX) with a compound of formula (VII) to obtain a compound of formula (VIII);

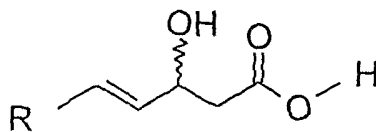
d). reducing a compound of formula (VIII) to obtain a compound of formula XI;

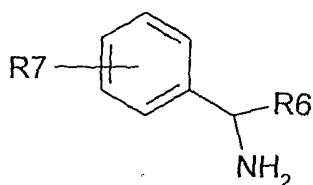
**Formula VIII**

e). hydrolyzing a compound of formula (XI) to obtain a compound of formula XII

**Formula XI**

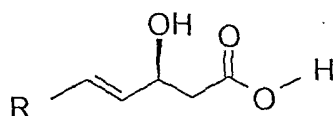
f). resolving the resulting racemic compound of formula (XII), first converting the racemic compound to its diastereomeric salt using the (+) or (-) enantiomeric amine of the formula (XIII) and separating the mixture of diastereomeric salt into the individual diastereomers by chromatography or crystallization and then neutralizing the diastereomeric salt to give the enantiomerically pure product.

**Formula XII**

**Formula XIII**

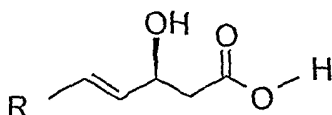
wherein, R6 represent C1-C4-alkyl which is optionally substituted by hydroxyl; R7 represent hydrogen, halogen, C1-C4 alkyl or C1-C4 alkoxy; and

g). treating the resulting compound of formula (XIV)

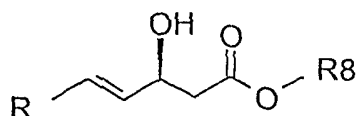
**Formula XIV**

with an acid activating group and subsequently with a compound of formula (VII) that introduces the radical of formula $-\text{CH}_2-\text{COOR}_5$ to obtain a compound of formula (XV)

or in another variant of process, esterifying a compound of formula (XIV)

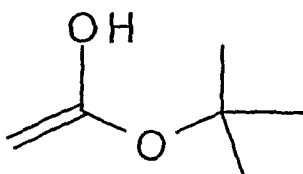
**Formula XIV**

and condensing the resulting compound of formula (XVI)

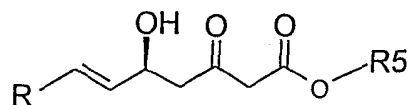
**Formula XVI**

wherein R8 is an aliphatic residue selected from C1 -C4 alkyl

with a compound of formula (X) to obtain a compound of formula (XV)

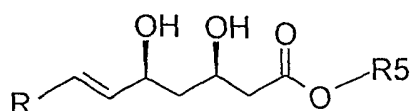
**Formula X**

h) reducing a compound of formula (XV) to obtain a compound of formula XVII



Formula XV

i). hydrolyzing a compound of formula (XVII) and converting into a salt of formula I thereof



Formula XVII

wherein R and R5 have the meanings as defined.

2. A process according to claim 1, wherein the compound of formula II, V, VII, VIII, XI, XV and XVII is used, wherein R4 or R5, respectively, represent C1-C4 alkyl, especially methyl or ethyl or C1-C4 alkyl, especially methyl or ethyl or tert-butyl.
3. A process according to claim 1, wherein the compound of formula XVI is used, wherein R8 represent C1-C4 alkyl, especially methyl or ethyl.
4. A compound of formula VI.
5. A process according to claim 1, the preparation of compound of formula (V) is carried out in a suitable inert solvent, preferably toluene, and in a temperature range from 60°C to the boiling point of the solvent, preferably at the boiling point of the solvent.
6. A process according to claim 1, the specification of compound of formula (V) is carried out by treating the ester of formula (V) with a strong base, such as an alkali metal hydroxide, preferably NaOH or KOH, in aqueous aliphatic alcohol as solvent, preferably aqueous methanol, and in a temperature range from 25°C to boiling point of solvent, preferably between 25°C to 35°C and acidifying the resulting reaction mixture.

7. A process according to claim 1, formation of compound of formula VIII (step c) is carried out by treating the compound of formula (VI) with an acid activating group, especially preferred one is the use of 1,1-carbonyldiimidazole and condensing the resulting compound with alkali metal salt of monoalkylmalonate (formula VII), preferably potassium monomethylmalonate or potassium monoethylmalonate, in presence of magnesium chloride, in an inert organic solvent, preferably tetrahydrofuran, at temperature between 0 – 40°C, preferably at 0 – 35°C.

8. A process according to claim 1, in another variant of process to prepare compound of formula VIII is carried out by first converting compound of formula VI to a compound of formula (IX) in an inert solvent, preferably dichloromethane, and in temperature range from 0°C to boiling point of the solvent, preferably between 0°C to 28°C using oxalyl chloride or thionyl chloride and subsequent treatment of a resulting compound of formula (IX) with compound of formula (X) in the presence of a suitable base and in a suitable inert solvent, especially tetrahydrofuran, and in a temperature range from –78°C, to the boiling point of the solvent, preferably at –78 to room temperature.

A suitable base is selected from an alkane alkali metal in presence of diisopropylamine, alkali alkylsilazanes like LiHMDS or NaHMDS. Especially preferred is the use of *n*-butyllithium in the presence of diisopropylamine.

9. A process according to claim 1, in another variant of process to prepare compound of formula VIII is carried out by condensing a compound of formula (IX) with an alkali metal salt of monoalkylmalonate (formula VII), preferably potassium monomethylmalonate or potassium monoethylmalonate, in presence of magnesium chloride, in an inert organic solvent, preferably tetrahydrofuran, at temperature between 0 – 40°C, preferably at 0 – 35°C.

10. A process according to claim 1, reduction of compound of formula VIII (step d), is carried out in a mixture of an inert solvent, such as an ether, preferably tetrahydrofuran

and a lower alkanol, preferably methanol, in the ratio of 4:1 volume/volume, and at temperature range from -78°C to 0°C , preferably at -65°C to 0°C .

A preferred reduction agent is a hydride, for example, an alkalimetal borohydride, especially sodium borohydride.

11. A process according to claim 1, saponification of compound of formula XI (step e) is carried out by treating the ester of formula (XI) with a strong base, such as an alkali metal hydroxide, preferably NaOH or KOH, in aqueous aliphatic alcohol as solvent, preferably aqueous methanol, and in a temperature range from 25°C to boiling point of solvent, preferably between 25°C to 30°C and acidifying the resulting reaction mixture.

12. A process according to claim 1, resolution of racemate of compound of formula XII (step f), in to optically pure antipodes is carried out by means of preparative chromatography using chiral supports (HPLC) or by crystallization using optically pure precipitating agents, for example (+) or (-) phenylalkylamine or substituted phenylalkylamine, preferably (R)-1-phenylethylamine in alcoholic solvents such as lower alkanol, preferably ethanol and recrystallising from a mixture of ketonic solvent and lower alkanol, preferably mixture of acetone and methanol followed by neutralization.

13. A process according to claim 1, formation of compound of formula XV (step g) is carried out by treating the compound of formula XIV with an acid activating group, especially preferred one is the use of 1,1-carbonyldiimidazole and condensing the resulting compound with an alkali metal salt of monoalkyl malonate (formula VII), preferably potassium monomethylmalonate or potassium monoethylmalonate, in presence of magnesium chloride, in an inert solvent, preferred one is tetrahydrofuran, at temperature between $0 - 40^{\circ}\text{C}$, preferably at $0 - 35^{\circ}\text{C}$.

14. A process according to claim 1, in another variant of process to prepare compound of formula XV is carried out by converting compound of formula XIV to a compound of

formula XVI by esterification and condensing the resulting compound of formula XVI with a compound of formula X.

Esterification of compound of formula XIV is carried out, in lower alcoholic solvent, especially C1-C3 alkanol, preferably methanol, in presence of acid catalyst like inorganic acids or p-toluensulphonic acid or acidic resins, and in a temperature range from 0°C to boiling point of solvent, preferably between 0°C to 30°C.

Condensation step is carried out in the presence of a suitable base and in a suitable inert solvent, especially tetrahydrofuran, and in a temperature range from -78°C to the boiling point of the solvent, preferably at room temperature. A suitable base is selected from an alkane alkalimetal in the presence of diisopropylamine, alkali alkylsilazanes like LiHMDS or NaHMDS. Preferred one is the use of n-butyllithium in the presence of diisopropylamine.

15. A process according to claim 1, reduction of compound of formula XV (step h), is carried out in a mixture of an inert solvent, preferably tetrahydrofuran and lower alkanol, preferably methanol, in the ratio of 4:1 volume/volume, and at temperature from -78°C to 0°C, preferably at -78°C to -70°C. To split the corresponding boronic ester the reaction mixture is then treated with methanol, and in a temperature range from 0°C to the boiling point of solvent, preferably in range of 0°C to 40°C.

A preferred reduction agent is an alkali metal borohydride in the presence of a di-C1-C7-alkyl-C1-C4 alkoxy-borane, preferably sodium borohydride in presence of diethylmethoxyborane.

16. A process according to claim 1, formation of compound of formula I (step i), is carried out first saponification of compound of formula XVII using a base, such as an alkali metal hydroxide, preferably NaOH followed by treatment with aqueous calcium chloride solution.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2005/000265

A. CLASSIFICATION OF SUBJECT MATTER

C07D239/42

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

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, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	WO 2004/052867 A (RANBAXY LABORATORIES LIMITED; KUMAR, YATENDRA; MEERAN, HASHIM, NIZAR,) 24 June 2004 (2004-06-24) scheme 1	1-16
A	WO 00/49014 A (ASTRAZENECA UK LIMITED; SHIONOGI & CO. LTD; KOIKE, HARUO; KABAKI, MIKI) 24 August 2000 (2000-08-24) claim 1	1-16
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☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search

22 February 2006

Date of mailing of the international search report

04/04/2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Bakboord, J

INTERNATIONAL SEARCH REPORT

International application No

PCT/IN2005/000265

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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A	WO 03/097614 A (RANBAXY LABORATORIES LIMITED; KUMAR, YATENDRA; DE, SHANTANU; RAFEEQ, M) 27 November 2003 (2003-11-27) scheme 1 -----	1-16
A	HIYAMA T ET AL: "SYNTHESIS OF ARTIFICIAL HMG-COA REDUCTASE INHIBITORS BASED ON THE OLEFINATION STRATEGY" BULLETIN OF THE CHEMICAL SOCIETY OF JAPAN, CHEMICAL SOCIETY OF JAPAN, TOKYO, JP, vol. 68, no. 1, 1995, pages 364-372, XP009013246 ISSN: 0009-2673 page 368, second column, final paragraph -----	1-16

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IN2005/000265

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