Abstract:
The present invention provides a process for the preparation of the rosuvastatin intermediates and their conversion to rosuvastatin or its pharmaceutically acceptable salts thereof.
A PROCESS FOR THE PREPARATION OF INTERMEDIATES OF ROSUVASTATIN

FIELD OF THE INVENTION

The present invention relates to a process for the preparation of intermediates of rosuvastatin. More specifically, the present invention relates to an improved process for the preparation of intermediates of rosuvastatin.

BACKGROUND OF THE INVENTION

The present invention is directed to an improved process for the preparation of compounds having formula I

(I)

and formula II

(II)

which are useful in the synthesis of rosuvastatin and its pharmaceutically acceptable salts.
Rosuvastatin calcium is chemically described as bis[(E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino] pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid] calcium salt and has the structural Formula III:

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\text{(HI)}
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Generally, rosuvastatin calcium is a synthetic lipid-lowering agent that acts as an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (HMG-CoA Reductase inhibitor). This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis. HMG-CoA reductase inhibitors are commonly referred to as "statins." Statins are therapeutically effective drugs used for reducing low density lipoprotein (LDL) particle concentration in the bloodstream of patients at risk for cardiovascular disease. Rosuvastatin calcium is used in the treatment of hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (Fredrickson Type Ha and lib). Rosuvastatin calcium is commercially available in the market under the brand name CRESTOR®.

U.S. Patent No. 5,260,440 describes pyrimidine derivatives such as rosuvastatin, its calcium salt (2:1) and its lactone form. The '440 patent discloses a process for the preparation of rosuvastatin comprising condensation of the compound of formula I with methyl (3R)-(3-(tert-butyl)dimethylsilyloxy)-5-oxo-6-triphenylphosphoranylidene hexanate followed by desilylation of the resultant product and further reduction of the obtained compound with IM diethylmethoxy borane in THF/sodium borohydride yields rosuvastatin, which is further converted to its pharmaceutically acceptable salts.

US'440 patent' also discloses a process for preparing the compound of formula I. In general, the process includes reacting ethyl isobutyryl acetate with 4-fluorobenzaldehyde to produce Ethyl-3-(4-fluorophenyl)-2-(2-methyl-l-oxopropyl)-prop-
2-enoate, which is then reacted with S-methyl isothiourea sulfate to provide ethyl-4-(4-fluoro-phenyl)-6-isopropyl-2-methylthio-3H-pyrimidine-5-carboxylate, which is then reacted with DDQ to give ethyl-4-(4-fluorophenyl)-6-isopropyl-2-methylthio-pyrimidine-5-carboxylate. This intermediate is reacted with m-chloroperbenzoic acid to yield ethyl-4-(4-fluorophenyl)-6-isopropyl-2-methylsulphonyl pyrimidine-5-carboxylate, which is then further reacted with methyl amine sulphonyl pyrimidine-5-carboxylate, which is then reacted with sodium hydride and methane sulfonyl chloride to give ethyl-4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulphonylamino) pyrimidine-5-carboxylate. This intermediate is further reduced using DIBAL-H followed by oxidation of corresponding hydroxy compound using oxidizing agent like tetrapropylammonium perruthenate (TPAP)/4-methylmorpholin-N-oxide. The oxidation with TPAP is described in Len et al. J.Chern.Soc. PTL, 1997, 3291-3292 and in Ley et al, Synthesis 1994, 639-666.

The disadvantages associated with the above processes involves tedious process, hazardous chemicals like m-chloroperbenzoic acid, sodium hydride, methane sulfonyl chloride, TPAP is an expensive and hazardous Ruthenium derivative.

There is a need in the art for processes which allow for production of highly pure rosuvastatin in a facile and cost effective manner on an industrial scale, expensive oxidizing agents like tetrapropylanmonium perruthenate and reagents that are difficult to use on a commercial scale. Intermediates are isolated by column chromatography which renders the process difficult to handle on commercial scale. The process disclosed in US'440' is schematically represented by the scheme I:
SCHEME-I

International application publication No. WO 03/0976 14A2 describes a process for preparation of rosvastatin and its pharmaceutically acceptable salts thereof. According to this patent, the compound of formula I is prepared by oxidation of corresponding hydroxy compound using hazardous and expensive chemicals like γ-manganese dioxide. The process is not industrially feasible and also is economically expensive.
Further, International application publication No. WO 2006/017357 A1 describes a process for preparation of rosvastatin and its pharmaceutically acceptable salts thereof. This patent discloses the preparation of compound of formula I by oxidation of corresponding hydroxy compound using 2, 2, 6, 6-tetramethyl piperidinyl oxy free radical (TEMPO) in the presence of sodium hypochlorite (0.7M ,pH-8.8-9.2). The process is not feasible on commercial scale as it is tedious and difficult to handle and also expensive.

U.S. Patent No. 4,970,313 describes a process for preparation of another key intermediate of rosvastatin and its related compounds. A process for the preparation of the compound of Formula II involves oxidation of its corresponding hydroxy compound by using oxalyl chloride. The process involves the hazardous and expensive chemicals like oxalyl chloride. This process is carried out at cryogenic temperatures like -78°C which is not suitable for scale-up on industrial scale and also economically not viable on commercial scale.

U.S. Patent Application Publication No. US2006/0004200 A1 describes a process for preparation of rosvastatin intermediate compounds of formula I and II which involves oxidation of corresponding hydroxy compound using 2, 2, 6, 6-tetramethyl piperidinyl oxy free radical (TEMPO) in the presence of sodium hypochlorite (10%). The process is not feasible on commercial scale as it is tedious and difficult to handle and also expensive.

Hence, there remains a need for a simple, industrially feasible, ecofriendly, inexpensive, and scaleable process for the synthesis rosvastatin intermediates that would avoid the aforementioned problems.

The present invention provides a process for the preparation of intermediates of rosvastatin with a reduced number of synthetic steps, avoids hazardous chemicals. The process of the present invention can be practiced on an industrial scale, and also can be carried out without sacrifice of overall yield.

**SUMMARY OF THE INVENTION**

The present invention relates to a process for the preparation of intermediates of Rosuvastatin.
In one aspect, the present invention relates to a process for the preparation of compound 4-((4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-5-pyrimidine carboxaldehyde of Formula I, which the process comprises:

a) oxidation of compound [4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulphonyl amino) pyridin-5-yl] methanol of Formula V

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\begin{align*}
\text{V} & \\
\text{I} & 
\end{align*}
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using pyridine sulfur trioxide complex as an oxidizing agent under suitable conditions to afford the compound 4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-5-pyrimidine carboxaldehyde of Formula I

In another aspect, the present invention relates to a process for the preparation of compound tertiary butyl-2-[(4R,6S)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl] acetate of Formula II, which the process comprises:

a) oxidation of compound (4R-cis)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester of Formula IV

\[
\begin{align*}
\text{I} & \\
\end{align*}
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using pyridine sulfur trioxide complex as an oxidizing agent under suitable conditions to afford the compound tertiary butyl-2-[((R,6S)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl] acetate of Formula II.

The advantages of the process of present invention include:

1. Economical process at commercial scale because of the use of inexpensive raw materials.
2. Less reaction steps,
3. Simple reaction conditions provide easier and more economical production.
4. Cryogenic temperatures are eliminated.
5. Hazardous chemicals avoided.
6. Higher yields and purity of key intermediates are achieved.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides an efficient, cost effective and ecofriendly process for the preparation of compounds of Formula I and II.

In one aspect of the present invention provides an improved process for the preparation of key intermediates of Rosuvastatin i.e. compounds of Formula I and II on commercial scale.

In another aspect of present invention provides a process for the preparation of 4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)-5-pyrimidine carboxaldehyde, compound of Formula I. The reaction sequence of an embodiment can also be represented by scheme II:
This process generally includes the steps of:

A) Condensation of methyl isobutyryl acetate of compound Formula X and 4-fluorobenzaldehyde of compound Formula IX in presence of suitable catalyst in organic solvent followed by reacting condensed product with S-Methylisothiourea sulfate and suitable oxidative dehydrogenating agent to yield Methyl-4-(4-fluorophenyl)-6-isopropyl-2-methylthio-pyrimidine-5-carboxylate of compound Formula VIII;

B) Oxidation of the compound 2-methylthiopyrimidine of Formula VIII to give the compound Methyl-4-(4-fluorophenyl)-6-isopropyl-2-methylsulfonyl pyrimidine-5-carboxylate of Formula VII;

C) Reacting the 2-methylsulfonylpyrimidine of compound Formula VII with N-methyl methane sulfonamide to give Methyl-4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulphonylamino) pyrimidine-5-carboxylate of compound Formula VI,
D) Reducing the compound of Formula VI with reducing agent to yield [4-(4-flourophenyl)-6-isopropyl-2-(N-methyl-N-methylsulphonylamino)pyridin-5-yl] methanol of compound Formula V;

E) Oxidation of [4-(4-flourophenyl)-6-isopropyl-2-(N-methyl-N-methylsulphonyl amino) pyridin-5-yl] methanol of compound Formula V with pyridine-sulfur trioxide complex in the presence of dimethyl sulfoxide/diisopropylethyl amine to give 4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonyl amino)-5-pyrimidine carboxaldehyde, compound of Formula I.

Step A) of the foregoing process may be carried out in a suitable solvent, for example toluene, cyclohexane, benzene, dichloroethane and mixture of thereof at a reflux temperature in the presence of basic catalysts like cyclic secondary amines, beta-alanine, DL-alanine, glycine esters and acidic catalyst like pyridyl carboxylic acids, acetic acid or mixture thereof. The time of reaction may vary from about 15 to about 25 hours. The product can be isolated by conventional method followed by drying or used as is in the next step without purification.

The cyclization process may be carried out in a suitable solvent such as hexamethylphosphoric acid triamide, N,N-dimethyl formamide (DMF), dimethyl sulfoxide (DMSO), dimethyl acetamid e and mixture thereof using S-methylisothiourea sulfate. The reaction temperature may vary from about 20°C to about 130°C. The time for the reaction may vary from about 18 hour to about 25 hours. The product can be isolated by conventional process.

This process can be carried out as per disclosed in prior art. The oxidation process can be carried out in suitable solvent such as toluene, cyclohexane, ethanol, methanol, aliphatic and aromatic halogenated hydrocarbons and mixture thereof. The oxidative dehydrogenating agents can be selected from DDQ, Copper chloride / K₂CO₃ / TBHP, Ceric Ammonium Nitrate, Nitric acid and Pd/C. The reaction temperature may vary from about 20°C to about 50°C. The time may vary from about 1 hours to about 10 hours. The product can be isolated by conventional techniques known in the art followed by drying.

Step (B) of the foregoing process may be carried out in the presence of a suitable solvent such as aromatic hydrocarbons, e.g., toluene, xylene and the like; halogenated solvents, e.g., dichloromethane, 1, 2-dichloroethane, chloroform and the like; and mixtures thereof. A suitable oxidizing agent includes ammonium heptamolybdate.
tetrahydrate, sodium tungstate, hydrogen peroxide, oxone, sodium metaperiodate, vanadium pentoxide or mixture thereof. The transformation can be carried out in presence of phase transfer catalyst or absence of catalyst. The temperature of the reaction may vary from about 20°C to about 50°C. The time of reaction varies from about 15 to about 20 hours. The product can be isolated by conventional method followed by drying or used as is in the next step without purification.

Step (C) of the foregoing process can be carried out by reacting the compound of formula VII with N-methyl methane sulfonamide using a suitable base such as sodium tert-pentoxide, potassium tert-butoxide, sodium hydride, sodium amide, lithium hexamethyl disilazide (LiHMDS), lithium diisopropyl amide (LDA), potassium carbonate, cesium carbonate and the like in a suitable solvent such as methanol, 2-propanol, dimethylsulfoxide (DMSO), tetrahydrofuran (THF), toluene, tert-butyl acetate, n-butyl acetate and the like and mixture thereof.

The reaction temperature can vary from room temperature to about 110°C and the time for the reaction can range from about 2 to about 8 hours. The product can be isolated by conventional methods known in the art followed by drying or used as is in the next step without purification.

Step (D) of the foregoing process can be carried out in the presence of a suitable solvent such as toluene, xylene, mesitylene, dichloromethane, tetrahydrofuran, cyclohexane and the like and mixtures thereof.

Suitable reducing agents include, but are not limited to, lithium aluminum hydride, diisobutylaluminum hydride, sodium borohydride/Nickel chloride, lithium triethylborohydride and the like and mixtures thereof. The reaction temperature may vary from about -70°C to about -5°C. The time may vary from about 1 hour to about 5 hours. The product can be isolated by conventional techniques followed by drying or used in the next step without further purification.

Step (E) of the foregoing process can be carried out in the presence of a suitable solvent include but are not limited to halocarbonated solvents such as dichloromethane, and the like; aprotic polar solvents such as dimethylsulfoxide (DMSO), N,N-dimethylformamide (DMF), dimethyl acetamide (DMA) and the like; esters such ethyl acetate and the like; hydrocarbon solvents such as toluene, xylene, mesitylene,
cyclohexane and the like; ethers such as tetrahydrofuran (THF) and the like; and mixtures thereof in various proportions without limitation.

Suitable oxidizing agent is pyridine sulfur trioxide complex.

Suitable bases include, but are not limited to diisopropyl ethyl amine, pyridine, triethyl amine, triisopropyl amine and the like.

The reaction temperature can range from about -10°C to about 10°C.

The time may vary from about 1 hour to about 5 hours, product can be isolated by conventional method followed by drying under reduced pressure at 40°C to about 45°C to afford desired product, 4-(4-fluorophenyl)-6-isopropyl-2- (N-methyl-N-methylsulfonylamino)-5-pyrimidine carboxaldehyde, compound of Formula I.

The reaction mixture is maintained for a time sufficient for oxidation of compound of Formula V. The time necessary for oxidation of compound of Formula V may depend on reaction scale and mixing procedures, and may easily be determined by one skilled in the art. Preferably, the reaction mixture is maintained for about 30 minutes to about 5 hours. More preferably, the reaction mixture is maintained for about two hours.

Preferably, at least about 90%, more preferably at least about 95% (by weight or mole) conversion of compound of Formula V to compound of Formula I is achieved during the reaction.

The process of the present invention is performed at a temperature of about -10°C to about 10°C; more preferably, the temperature is in the range of about 0°C to about -5°C.

The molar ratio of pyridine sulfur trioxide complex to the compound of Formula V can be from about 1 to about 0.8 or more.

Thus resultant compound of Formula I can be optionally purified by recrystallization using suitable solvent, for example alcohol solvents like ethanol, methanol, isopropanol and the like and further converted into rosuvastatin or its pharmaceutically acceptable salts by any process known in the art, for example as described in United states Patent No. 5,260,440 incorporated here for reference.

In another aspect of present invention also provides a process for the preparation of tertiary butyl-2-[(4R,6S)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl] acetate, compound of Formula II comprising oxidation of corresponding hydroxy compound, (4R-cis)-6-
(hydroxymethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester of Formula IV using pyridine-sulfur trioxide complex. Advantageously the oxidation may be carried out in a solvent under basic conditions for example in the presence of dimethyl sulfoxide as solvent and diisopropylethyl amine as a base at temperature less than about 0°C. An embodiment of the above reaction sequence can be represented by following synthetic scheme III:

**SCHEME-III**

This process generally includes the steps of:

(a) oxidation (4R-cis)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester of Formula IV using pyridine-sulfur trioxide complex in the presence of suitable base such as diisopropylethylamine and dimethyl sulfoxide as a solvent under suitable conditions;

(b) Quenching of reaction mass by addition of water;

(c) Organic layer separation and washing with water;

(d) drying organic layer over sodium sulfate and evaporation of organic layer.

Step (a) of the foregoing process can be carried out in the presence of a suitable solvent include but are not limited to halocarbonated solvents such as dichloromethane, and the like; aprotic polar solvents such as dimethylsulfoxide (DMSO), N,N-dimethylformamide (DMF), dimethyl acetamide (DMA) and the like; esters such ethylacetate and the like; hydrocarbon solvents such as toluene, xylene, mesitylene, cyclohexane and the like; ethers such as tetrahydrofuran (THF) and the like; and mixtures thereof in various proportions without limitation.

Suitable oxidizing agent is pyridine sulfur trioxide complex.

Suitable bases include, but are not limited to organic bases such as diisopropyl ethyl amine, pyridine, triethyl amine, triisopropyl amine and the like. The reaction
temperature may vary from about 10°C to about -10°C. The time may vary from about 1 hour to about 5 hours.

Step (b) of the foregoing process can be carried out by adding water at about 0°C to about 20°C.

Step (c) can be carried out by separating organic layer followed by extraction of aqueous layer with reaction solvent and water washing to organic layer to make pH neutral. The temperature may vary from about 20°C to about 25°C.

Step (d) of the foregoing process can be carried out by adding sodium sulfate at about 20°C to about 25°C and solvent may be distilled at about 40°C to about 45°C under reduced pressure to afford the desired compound, tertiary butyl-2-[(4R,6S)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl] acetate, compound of Formula II.

Pyridine sulfur trioxide complex is prepared by the reaction of pyridine and sulfur trioxide in the ratio of 1:1.

The reaction mixture is maintained for a time sufficient for oxidation of compound of Formula IV. The time necessary for oxidation of compound of Formula IV may depend on reaction scale and mixing procedures, and may easily be determined by one skilled in the art. Preferably, the reaction mixture is maintained for about 1 hour to about 5 hours. More preferably, the reaction mixture is maintained for about two hours.

Preferably, at least about 90%, more preferably at least about 95% (by weight or mole) conversion of compound of Formula IV to compound of Formula II is achieved during the reaction.

The process of the present invention is performed at a temperature of about -10°C to about 5°C; more preferably, the temperature is in the range of about 0°C to about -5°C.

The molar ratio of pyridine sulfur trioxide complex to the compound of Formula IV can be from about 1 to about 0.5 or more.

The amount of solvents used depends upon the solubility of the reagents and the intermediates used.

Thus, obtained compound of Formula II can be further used as a key intermediate in the preparation of rosuvastatin or pharmaceutically acceptable salt.

It will be understood that various modifications may be made to the embodiments disclosed herein. Therefore the above description should not be construed as limiting,
but merely as exemplifications of preferred embodiments. For example, the functions described above and implemented as the best mode for operating the present invention are for illustration purposes only. Other arrangements and methods may be implemented by those skilled in the art without departing from the scope and spirit of this invention.

EXAMPLES

EXAMPLE-I: PREPARATION OF 4-(4-FLUOROPHENYL)-O-ISOPROPYL-(N-METHYL-N-METHYL SULFONYLAMINO)-5-PYRIMIDINE CARBOXYALDEHYDE

Step -A: PREPARATION OF METHYL-4-(4-FLUOROPHENYL)-6-ISOPROPYL-2-METHYLTHIO- PYRIMIDINE-5-CARBOXYLATE (FORMULA VIII)

To a four neck clean RB flask, charged cyclohexane (1600.0 ml), acetic acid (50.0 gm, 0.832 moles) and β-alanine (25.0 gm, 0.404 moles) were stirred for 15 min at room temperature. This was followed by addition of 4-fluorobenzaldehyde (174.0 gm, 1.40 moles) and methylisobutyryl acetate (200.0 g, 1.386 moles) at room temperature. The reaction mixture was heated to reflux with azeotropic water removal for 20 to 24 hours. After the completion of reaction, the mixture was cooled and washed with water (400.0 ml), 5% sodium carbonate solution (400.0 ml) and water (2 x 500.0 ml). The evaporation of the solvent furnished olefin as a oil. The obtained residue was taken for next step without purification.

Hexamethylphosphoric acid triamide (1640.0 ml) and S-Methylisothiourea sulfate (218.0 gm, 0.782 moles) added to the above resulted oil at room temperature. This was followed by heating at 100 to H O°C under stirring for 24 hrs. The reaction mass was cooled after the completion of reaction at room temperature. This was followed by addition of toluene (1400.0 ml) and purified water (1400.0 ml) under stirring. The reaction mixture was further stirred for 20 min. This was followed by layer separation. The aqueous layer was extracted with toluene (2 x 350.0 ml toluene) followed by washing, combined toluene layers with 2.5% sodium carbonate solution (700.0 ml) and 25% sodium chloride solution (2 x 700.0 ml). Toluene layer was dried over sodium sulfate (100.0 gm).
To the above dried toluene layer charged slowly 2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone (184.0 gm, 0.81 moles) over period of 1 hr at 25 to 45 °C under stirring.

The reaction mass was stirred for 2 hrs at 25 to 30°C followed by filtration of reaction mass and washing with 400.0 ml toluene followed by washing with water (3 x 500.0 ml) at 25 to 30°C. Toluene was distilled under reduced pressure at 50 to 55°C and Degassed mass for 1 hr under reduced pressure at 50 to 55°C. This was followed by addition of 400 ml isopropyl alcohol and distilled out completely under reduced pressure at 50 to 55 °C. This was further followed by addition of 400.0 ml isopropyl alcohol and reaction mass was heated to 60 to 65 °C get clear solution. The reaction mass was cooled to 25 to 30 °C and stirred for 8 hrs at 25 to 30 °C, cooled to 0 to 5 °C and stirred for 2 to 3 hrs at 0 to 5 °C. Filtered and washed with chilled (0 °C) isopropyl alcohol (2 x 100.0 ml). The wet product was dried at 40 to 450°C under reduced pressure to obtain Methyl-4-(4-fluorophenyl)-6-isopropyl-2-methylthio-pyrimidine-5-carboxylate, compound of formula VIII (174.0 g, 39.15%).

Step -B: PREPARATION OF METHYL-4-(4-FLUOROPHENYL)-6-ISOPROPYL-2-METHYL SULFONYL PYRIMIDINE-5-CARBOXYLATE (FORMULA VII)

To a four neck clean RB flask, charged dichloromethane (1500.0 ml), Methyl-4-(4-fluorophenyl)-6-isopropyl-2-methylthio-pyrimidine-5-carboxylate (150.0gm,0.468 moles), ammonium heptamolybdate tetrahydrate (8.62 gm,0.00697 moles) and tricaprylylmethyl ammonium chloride (Aliquat®336) (21.0 gm,0.047 moles) were stirred at 25 to 30°C. This was followed by the slow addition of 50 % hydrogen peroxide solution (96.5 gm, 1.42 moles) at 20 to 35°C over period of 1 to 1.5 hrs. Reaction mass were further stirred at 25 to 30°C for 18 to 20 hours. After the completion of reaction charged water (450.0 ml) and continued stirring for 10 min. This was followed by layer separation. The aqueous layer was extracted with 130.0 ml dichloromethane. Combined all organic layers and Washed with water (2 x 500.0 ml). Dichloromethane was distilled under reduced pressure at 40 to 45°C and followed by degassing for 30 min at 50 to 55°C under reduced pressure. Isopropyl alcohol (175.0 ml) was added and distilled out under vacuum at 50 to 55 °C, followed by the addition of isopropyl alcohol (350.0 ml) and heat to 60 to 65°C to get clear solution. Cooled solution to 25 to 30°C and stirred for 2.0 hrs at 25 to 30°C. Further cooled to 0 to 5 °C and stirred for 2.0 hrs at 0 to 5 °C. Filtered and washed with chilled (0 °C) isopropyl alcohol (100.0 ml). The wet product was dried at 40 to 45°C
under reduced pressure to obtain Methyl-4-(4-fluorophenyl)-6-isopropyl-2-methylsulfonyl pyrimidine-5-carboxylate (150.0 g, 90.92%).

Step -C: PREPARATION OF METHYL-4-(4-FLUOROPHENYL)-6-ISOPROPYL-2-(N-METHYL-N-METHYLSULPHONYLAMINO) PYRIMIDINE-5-CARBOXYLATE (FORMULA VI)

Acetonitrile (1000ml), Methyl-4-(4-fluorophenyl)-6-isopropyl-2-methylsulfonylpyrimidine-5-carboxylate (145.0 g, 0.411 moles), freshly dried powdered potassium carbonate (85.45 gm, 0.618 moles) and N-methyl methane sulfonamide (58.40 gm, 0.535 moles) at 25 to 30°C added in four neck round bottom flask. The reaction mass was reflux under stirring under at 80 to 85°C for 2.5 to 3 hours. The reaction mass was cooled at 25 to 30°C after the completion of reaction, which is then followed by filtration and washing with acetonitrile (245.0 ml). Acetonitrile was distilled under reduced pressure at 50 to 55°C followed by degassing for 30 min at 55 to 60°C under reduced pressure. This was followed by addition of isopropyl alcohol (165.0 ml) and distillation under reduced pressure at 50 to 55°C. Isopropyl alcohol (575.0 ml) was again added and reaction mass was heated to 65 to 70°C to get clear solution. The reaction mixture was cooled to 25 to 30°C followed by stirring for about 4.0 hrs at 25 to 30°C. The reaction mixture was cooled to 0 to 5°C and stirred for 2.0 hrs at 0 to 5°C. The reaction mass was filtered and washed with chilled (0°C) isopropyl alcohol (100.0 ml). The wet product was dried at 40 to 45°C under reduced pressure to obtain Methyl-4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulphonylamino) pyrimidine-5-carboxylate, (138.0 gm, 87.93%)

Step-D: PREPARATION OF [4-(4-FLUROPHENYL)-6-ISOPROPYL-2-(N-METHYL-N-METHYLSULPHONYLAMINO) PYRIDIN-5-YL] METHANOL (FORMULA V)

Dissolved Methyl-4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methyl sulphonylamino) pyrimidine-5-carboxylate (130.0 g, 0.340 moles) in toluene (1300.0 ml) under nitrogen at 25 to 30°C. The reaction mass was cooled to -10 to -15°C followed by the addition of diisobutyl aluminum hydride (730.0 ml, 20% wt in toluene, 1.0266 moles) over period of 1 to 1.5 hrs at -10 to -15.0°C under stirring for 1 hrs at -5 to -10°C. After the completion of reaction, diluted HCl (137.0 ml in 1370.0 ml water) was
added over a period of 30 to 40 minutes, maintaining temperature below -10 °C and followed by stirring at 35 to 40 °C for 30 to 40 min. This was followed by addition of ethyl acetate (1000.0 ml) and purified water (1000.0 ml) under stirring to the reaction mass and continued stirring for 10 minutes. This was followed by layer separation.

Aqueous layer was extracted with ethyl acetate (2 x 500.0 ml). Ethyl acetate layer was washed with 5% sodium bicarbonate solution (1000.0 ml) and 25% sodium chloride solution (1000.0 ml) followed by the distillation of solvents under reduced pressure at 50 to 55 °C after drying over sodium sulfate followed by degassing mass for 30 min at 50 to 55 °C under vacuum. This was followed by addition of cyclohexane (650.0 ml), heating the reaction mass at 60 to 65 °C to get uniform slurry. The reaction mass was cooled at 25 to 30 °C and stirred for 2 hrs at 25 to 30 °C. The resulted mass was filtered and washed with cyclohexane (200.0 ml). The wet product was dried at 40 to 45 °C under reduced pressure to afford [4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulphonylamino) pyrimidin-5-yl] methanol (112.0 gm, 93.0%).

Step-E: PREPARATION OF 4-(4-FLUOROPHENYL)-6-ISOPROPYL-2-(N-METHYL-N-METHYL SULFONYLAMINO)-5-PYRIMIDINE CARBOXALDEHYDE, COMPOUND OF FORMULA I

[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulphonylamino) pyrimidin-5-yl] methanol (100.0 gm, 0.282 moles) was dissolved in dimethyl sulfoxide (110.0 gm, 1.41 moles) and dichloromethane (1000 ml). The reaction mass was cooled to 0 to -5 °C and stirred for 15 min at 0 to -5 °C. This was followed by addition of Diisopropylethyl amine (127.56 gm, 0.987 moles) at 0 to -5 °C and stirring continued for 15 min at 0 to -5 °C.

In another flask, pyridine-sulfur trioxide complex (90.0 g, 0.44 moles), pyridine (44.6 g, 0.44 moles) and dimethyl sulfoxide (110.0 g, 1.41 moles) were charged at room temperature and stirred for 10 min at room temperature. The resulting suspension was added to the above alcohol solution in dichloromethane at 0 to -5 °C and stirring was continued for 1 hr at 0 to -5 °C. After the completion of reaction, water (400.0 ml) was added and under stirring for 10 min. This was followed by layer separation. The aqueous layer was extracted with dichloromethane (2 x 200 ml). Dichloromethane layers washed with water (3 x 600.0 ml) followed by drying over sodium sulfate. Dichloromethane was
distilled under vacuum at 40 to 45.0 °C and followed by degassed mass for 30 min at 40
to 45.0 °C. Isopropyl alcohol (100.0 ml) was added to the reaction mass and distilled out
under reduced pressure at 50 to 55 °C. Isopropyl alcohol (250.0 ml) was again added to
the reaction mass and heated the reaction mass at 60 to 65 °C to get clear solution. The
solution was cooled to 25 to 30 °C and stirred for 4 hrs at 25 to 30 °C. The reaction
mixture was further cooled to 0 to 5 °C and stirred for 2 hrs at 0 to 5 °C. The solid mass
and washed with chilled (0 °C) isopropyl alcohol (50.0 ml). The wet product was dried at
40 to 45 °C under reduced pressure to obtain. The wet product was dried at 40 to 45 °C
under reduced pressure to obtain 4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methyl
sulfonylamino)-5-pyrimidine carboxaldehyde, compound of formula I (90.0 gm, 90.5%).

EXAMPLE-2: PREPARATION OF TERTIARY BUTYL-2-[(4R,6S)-6-FORMYL-2,2-
DIMETHYL-1,3-DIOXAN-4-YL] ACETATE, COMPOUND OF
FORMULA II

(4R-cis)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethyl
ethyl ester (10.0 g, 0.0385 mol) mol) was dissolved in dimethyl sulfoxide (15.0 g, 0.192
mol) and dichloromethane (100 ml) followed by cooling at 0 to -5 °C. The reaction mass
was cooled for 15 min at 0 to -5 °C followed by addition of Diisopropylethyl amine (17.42 g, 0.1347 mol) at 0 to -5 °C and continued stirring for 15 min at 0 to -5 °C.

In another flask, charged pyridine-sulfur trioxide complex (12.25 g, 0.077 mol),
pyridine (6.09 g, 0.077 mol) and dimethyl sulfoxide (15.0 g, 0.192 mol) at room
temperature followed by stirring for 10 min. Resulting suspension was added to the
above alcohol solution in dichloromethane at 0 to -5 °C and continued stirring for 1 hr at
0 to -5 °C. After the completion of reaction, water (50.0 ml) was added and stirred for 10
min. This was followed by layer separation. Aqueous layer was extracted with
dichloromethane (2 x 20 ml). Dichloromethane layer was washed with water (3 x 100.0
ml) followed by drying over sodium sulfate and distilled dichloromethane under vacuum
at 40 to 45.0 °C. Degased mass for 1 hr at 40 to 45.0 °C under reduced pressure to obtain
tertiary butyl-2-[(4R,6S)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl] acetate, compound of
formula II (9.22 g, 93.0%).

EXAMPLE-3: PREPARATION OF 4-(4-FLUOROPHENYL)-O-ISOPROPYL-(N-
METHYL-N-METHYL SULFONYLAMINO)-5-PYRIMIDINE CARBOXYLATE (FORMULA I)

Step -A: PREPARATION OF METHYL-4- (4-FLUOROPHENYL)-6-ISOPROPYL-2-
METHYLTHIO- PYRIMIDINE-5-CARBOXYLATE (FORMULA VIII)

To a four neck clean RB flask, charged cyclohexane (2400.0 ml), acetic acid (75.0 gm, 1.25 moles) and β-alanine (37.5 gm, 0.420 moles) were stirred for 15 min at room temperature. This was followed by addition of 4-fluorobenzaldehyde (261.00 gm, 2.078 moles) and methylisobutryl acetate (300.0 g, 2.080 moles) at room temperature. The reaction mixture was heated to reflux with azeotropic water removal for 20 to 24 hours. After the completion of reaction, the mixture was cooled and washed with water (400.0 ml), 5% sodium carbonate solution (600.0 ml) and water (2 x 600.0 ml). The evaporation of the solvent furnished olefin as oil. The obtained residue was taken for next step without purification.

Hexamethylphosphoric acid triamide (1579.0 ml) and S-Methylisothiourea sulfate (313.08 gm, 1.12 moles) added to the above resulted oil at room temperature. This was followed by heating at 100 to 105 °C under stirring for 24 hrs. The reaction mass was cooled after the completion of reaction at room temperature. This was followed by addition of toluene (2010.00 ml) and purified water (2010.00 ml) under stirring. The reaction mixture was further stirred for 20 min. This was followed by layer separation. The aqueous layer was extracted with toluene (2 x 1000 ml toluene) followed by washing, combined toluene layers with 2.5% sodium carbonate solution (1000.0 ml) and 25% sodium chloride solution (2 x 1000 ml). Toluene layer was dried over sodium sulfate (143.0 gm).

To the above dried toluene layer charged slowly 2, 3-dichloro-5, 6-dicyano-1, 4-
benzoquinone (264.0 gm, 1.164 moles) over period of 1 hr at 25 to 45 °C under stirring. The reaction mass was stirred for 2 hrs at 25 to 30 °C followed by filtration of reaction mass and washing with 400.0 ml toluene followed by washing with water (3 x 500.0 ml) at 25 to 30 °C. Toluene was distilled under reduced pressure at 50 to 55 °C and Degassed mass for 1 hr under reduced pressure at 50 to 55 °C. This was followed by addition of 550.0 ml isopropyl alcohol and distilled out completely under reduced pressure at 50 to 55 °C. This was further followed by addition of 550.0 ml isopropyl alcohol and reaction
mass was heated to 60 to 65 °C get clear solution. The reaction mass was cooled to 25 to
30 °C and stirred for 8 hrs at 25 to 30 °C, cooled to 0 to 5 °C and stirred for 2 to 3 hrs at 0
to 5 °C. Filtered and washed with chilled (0 °C) isopropyl alcohol (2 x 100.0 ml). The wet
product was dried at 40 to 45°C under reduced pressure to obtain 236.0 gm. Methyl-4- (4-
fluorophenyl)-6-isopropyl-2-methylthio-pyrimidine-5-carboxylate, compound of formula
VIII.

Purity by HPLC : 99.22%
Melting point : 86.0°C to 87.5°C

Step -B: PREPARATION OF METHYL-4- (4-FLUOROPHENYL)-6-ISOPROPYL-2-
METHYL SULFONYL PYRIMIDINE-5-CARBOXYLATE (FORMULA VII)

To a four neck clean RB flask, charged dichloromethane (2530.0ml), Methyl-4-
(4-fluorophenyl)-6-isopropyl-2-methylthio-pyrimidine-5-carboxylate (225.0gm, 0.7022
moles), ammonium heptamolybdate tetrahydrate (12.93 gm, 0.01046 moles) and tricapryl
methyl ammonium chloride (Aliquat®336) (28.44 gm, 0.0703 moles) were stirred at 25 to
30°C. This was followed by the slow addition of 50% hydrogen peroxide solution
(145.15 gm, 2.1393 moles) at 20 tq 35°C over period of 1 to 1.5 hrs. Reaction mass were
further stirred at 25 to 30°C for 18 to 20 hours. After the completion of reaction charged
water (700.0ml) and continued stirring for 10 min. This was followed by layer separation.

The aqueous layer was extracted with 330.0 ml dichloromethane. Combined all organic
layers and Washed with water (2 x 750.0 ml). Dichloromethane was distilled under
reduced pressure at 40 to 45°C and followed by degassing for 30 min at 50 to 55°C under
reduced pressure. Isopropyl alcohol (225.0 ml) was added and distilled out under vacuum
at 50 to 55 °C, followed by the addition of isopropyl alcohol (900.0 ml) and heat to 60 to
65°C to get clear solution. Cooled solution to 25 to 30°C and stirred for 2.0 hrs at 25 to
30°C. Further cooled to 0 to 5 °C and stirred for 2.0 hrs at 0 to 5 °C. Filtered and washed
with chilled (0 °C) isopropyl alcohol (110.0 ml). The wet product was dried at 40 to 45°C
under reduced pressure to obtain 213.0 gm Methyl-4- (4-fluorophenyl)-6-isopropyl-2-
methylsulfonyl pyrimidine-5-carboxylate.

Purity by HPLC: 98.34%
Melting point: 115.9.0°C to 117.5°C

Step -C: PREPARATION OF METHYL-4- (4-FLUOROPHENYL)-6-ISOPROPYL-2-
(N-METHYL-N-METHYLSULPHONYLAMINO) PYRIMIDINE-S-
CARBOXYLATE (FORMULA VI)

Acetonitrile (1500ml), Methyl-4-(4-fluorophenyl)-6-isopropyl-2-
methylsulfonylpyrimidine-5-carboxylate (200.0 g, 0.567 moles), freshly dried powdered
potassium carbonate (117.8 gm, 0.852 moles) and N-methyl methane sulfonamide (80.52
gm, 0.738 moles) at 25 to 30°C added in four neck round bottom flask. The reaction mass
was reflux under stirring under at 80 to 85°C for 2.5 to 3 hours. The reaction mass was
cooled at 25 to 30°C after the completion of reaction, which is then followed by filtration
and washing with acetonitrile (300.0ml). Acetonitrile was distilled under reduced
pressure at 50 to 55°C followed by degassing for 30 min at 55 to 60°C under reduced
pressure. This was followed by addition of isopropyl alcohol (200.0 ml) and distillation
under reduced pressure at 50 to 55°C. Isopropyl alcohol (630.0 ml) was again added and
reaction mass was heated to 65 to 70°C to get clear solution. The reaction mixture was
cooled to 25 to 30°C followed by stirring for about 3.0 hrs at 25 to 30°C. The reaction
mixture was cooled to 0 to 5°C and stirred for 2.0 hrs at 0 to 5°C. The reaction mass was
filtered and washed with chilled (0°C) isopropyl alcohol (150.0 ml). The wet product
was dried at 40 to 45°C under reduced pressure to obtain 193.0 gm Methyl-4-(4-
fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulphonylamino) pyrimidine-5-
carboxylate.

Purity by HPLC : 99.7%

Melting point : 130.0°C to 132.5°C

^H NMR (CDC13): 1.30 (d, 6H); 3.15 -3.22 (m, IH); 3.52 (S, 3H); 3.60 (S, 3H); 3.71 (S,
3H); 7.14 (dd, 2H); 7.68 (dd, 2H);

Step-D: PREPARATION OF [4-(4-FLOUROPHENYL)-6-ISOPROPYL-2-(N-
METHYL-N-METHYL-SULPHONYLAMINO) PYRIMIDIN-S-YL]

METHANOL (FORMULA V)

Dissolved Methyl-4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methyl
sulphonylamino) pyrimidine-5-carboxylate (185.0 g, 0.485 moles) in toluene (1800.0 ml)
under nitrogen at 25 to 30°C. The reaction mass was cooled to -10 to -15°C followed by
the addition of diisobutyl aluminum hydride (1034.0 ml, 20% wt in toluene, 1.455
moles) over period of 1 to 1.5 hrs at -10 to -15.0°C under stirring for 1 hrs at -5 to -10
°C. After the completion of reaction, diluted HCl (200.0 ml in 2000.0ml water) was
added over a period of 30 to 40 minutes, maintaining temperature below -10°C and
followed by stirring at 35 to 40 °C for 30 to 40 min. This was followed by addition of ethyl acetate (660.0 ml) under stirring to the reaction mass and continued stirring for 10 minutes. This was followed by layer separation. Aqueous layer was extracted with ethyl acetate (374.0 ml). Ethyl acetate layer was washed with 5% sodium bicarbonate solution (1000.0 ml) and 25% sodium chloride solution (1000.0 ml) followed by the distillation of solvents under reduced pressure at 50 to 55 °C after drying over sodium sulfate followed by degassing mass for 30 min at 50 to 55 °C under vacuum. This was followed by addition of isopropyl alcohol (185.0 ml) and distilled out completely, followed by addition of isopropyl alcohol (555.00 ml) heating the reaction mass at 60 to 65 °C to get clear solution. The reaction mass was cooled at 25 to 30 °C and stirred for 2 hrs at 25 to 30 °C then to 0 °C-5 °C for 3 hrs. The resulted mass was filtered and washed with isopropyl alcohol (185.0 ml). The wet product was dried at 40 to 45 °C under reduced pressure to obtain 165.0 gm [4-(4-flourophenyl)-6-isopropyl-2-(N-methyl-N-methylsulphonylamino) pyrimidin-5-yl] methanol.

Purity by HPLC : 99.87%
Melting point : 138.90 °C to 142 °C

Step-E: PREPARATION OF 4-(4-FLUOROPHENYL)-6-ISOPROPYL-2-(N-METHYL-N-METHYL SULFONYLAMINO)-5-PYRIMIDINE CARBOXALDEHYDE (FORMULA I)
[4-(4-flourophenyl)-6-isopropyl-2-(N-methyl-N-methylsulphonylamino) pyridine-5-yl] methanol (150.0 gm, 0.4244 moles) was dissolved in dimethyl sulfoxide (165.0 ml, and dichloromethane (1500 ml). The reaction mass was cooled to 0 to -5 °C and stirred for 15 min at 0 to -5 °C. This was followed by addition of Diisopropylethyl amine (190.8 gm, 1.477 moles) at 0 to -5 °C and stirring continued for 15 min at 0 to -5 °C. In another flask, pyridine-sulfur trioxide complex (148.6 g, 0.9337 moles), pyridine (73.7 g, 0.9337 moles) and dimethyl sulfoxide (165 ml) were charged at room temperature and stirred for 10 min at room temperature. The resulting suspension was added to the above alcohol solution in dichloromethane at 0 to -5 °C and stirring was continued for 1 hr at 0 to -5 °C. After the completion of reaction, water (600.0 ml) was added and under stirring for 10 min. This was followed by layer separation. The aqueous layer was extracted with dichloromethane (2 x 300 ml). Dichloromethane layers washed with water (3 x 850.0 ml) followed by drying over sodium sulfate. Dichloromethane was distilled under vacuum at
40 to 45.0 °C and followed by degassed mass for 30 min at 40 to 45.0 °C. Isopropyl alcohol (150.0 ml) was added to the reaction mass and distilled out under reduced pressure at 50 to 55 °C. Isopropyl alcohol (750.0 ml) was again added to the reaction mass and heated the reaction mass at 60 to 65°C. The reaction mass was cooled to 25 to 30°C and stirred for 4 hrs at 25 to 30°C. The reaction mixture was further cooled to 0 to 5 °C and stirred for 2 hrs at 0 to 5 °C. The solid mass and washed with chilled (0 °C) isopropyl alcohol (150.0 ml). The wet product was dried at 40 to 45°C under reduced pressure to obtain 134.0 gm 4-(4-fluorophenyl)-6-isopropyl-2- (N-methyl-N-methyl sulfonlamino)-5-pyridine carboxaldehyde, compound of formula I.

Purity by HPLC : 97.77%
Melting point : 176.3°C to 178.7°C

EXAMPLE-4: PREPARATION OF TERTIARY BUTYL-2-[(4R,6S)-6-FORMYL-2,2-DIMETHYL-1,3-DIOXAN-4-YL] ACETATE (FORMULA II)

(4R-cis)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethyl ethyl ester (10.0 g ,0.0385 mol) mol) was dissolved in dimethyl sulfoxide (15.0 g , 0.192 mol) and dichloromethane (100 ml) followed by cooling at 0 to -5 °C. The reaction mass was cooled for 15 min at 0 to -5 °C followed by addition of diisopropylethyl amine ( 17.42 g ,0.1347 mol) at 0 to -5 °C and continued stirring for 15 min at 0 to -5 °C.

In another flask, charged pyridine-sulfur trioxide complex (12.25 g, 0.077 mol), pyridine (6.09 g, 0.077 mol) and dimethyl sulfoxide (15.0 g, 0.192 mol) at room temperature followed by stirring for 10 min. Resulting suspension was added to the above alcohol solution in dichloromethane at 0 to -5 °C and continued stirring for 1 hr at 0 to -5 °C. After the completion of reaction, water (50.0 ml) was added and stirred for 10 min. This was followed by layer separation. Aqueous layer was extracted with dichloromethane (2 x 20 ml). Dichloromethane layer was washed with water ( 3 x 100.0 ml ) followed by drying over sodium sulfate and distilled dichloromethane under vacuum at 40 to 45.0 °C. Degased mass for 1 hr at 40 to 45.0 °C under reduced pressure to obtain tertiary butyl-2-[(4R,6S)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl] acetate, compound of formula II (9.22 g, 93.0%).
EXAMPLE-5: PURIFICATION OF COMPOUND OF FORMULA I USING DILUTE HYDROCHLORIDE

Dissolved 114.0 gm compound of formula I into 1026 ml dichloromethane at R.T. Added dil. HCL solution (23.0 ml Cone. HCL into 456 ml water ) . Reaction mass stirred for 15 mins. Layers separated. Organic layer washed with 228.0 ml brine solution and dried over sodium sulphate. Concentrated mass under reduced pressure. Stripping using 120.0 ml isopropyl alcohol given. Dissolved solid into 570.0 ml isopropyl alcohol. Cooled to R.T. stirred for 2 hrs. Filtered and wash with isopropyl alcohol. Dried at 45°C to obtain 111.0 gm compound of formula I.
Claims:

1. A process for preparing a compound 4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulphonylamino)-5-pyrimidine carboxaldehyde of Formula I

![Formula I]

comprising oxidation of compound [4-(4-flourophenyl)-6-isopropyl-2-(N-methyl-N-methylsulphonylamino) pyridine-5-yl] methanol of Formula V

![Formula V]

using pyridine sulfur trioxide complex as an oxidizing agent.

2. The process of claim 1 wherein oxidation is carried out in a solvent selected from the group comprising of methylenechloride, dimethylsulfoxide, N,N-dimethylformamide, and N,N-dimethylacetamide.

3. The process of claim 1, wherein the base is selected from the group consisting of: an organic amine such as triethylamine, diisopropylethylamine.

4. The process of claim 1 wherein the oxidation is carried out at temperatures of about -10 °C to about 10° C.
5. The process of claim 1, wherein the molar ratio of pyridine sulfur trioxide complex to the compound [4-(4-flourophenyl)-6-isopropyl-2-(N-methyl-N-methylsulphonylamino) pyridine-5-yl] methanol of Formula V is about 1 to about 0.8.

6. The process of claim 1, wherein the reaction mixture is maintained for a period of about 30 minutes to about 5 hours.

7. The process of claim 1, wherein the reaction is conducted at a pH of about 8 to about 12.

8. The process of claim 1, wherein the step of recovering compound of Formula I is carried out by extraction.

9. The process of claim 1, further comprising recrystallizing the compound of Formula I from alcohol solvent.

10. The process of claim 1, further comprising the step of drying the recovered compound of Formula I.

11. The process of claim 1, wherein the starting compound of Formula V is prepared according to the process comprising:
condensation of 4-fluorobenzaldehyde of Formula IX

\[
\text{OH}_2C\begin{array}{c} F \\ \text{OHC} \end{array}
\]

IX

with a compound methylisobutyryl acetate of Formula X

\[
\text{H}_3\text{CO}\begin{array}{c} \text{C} \\ \text{O} \end{array}
\]

X

using beta-alanine as a catalyst to obtain a compound of Formula VIII.
and conversion of the compound of Formula VIII to the compound of Formula V.

12. A process for preparing a compound tertiary butyl-2-[(4R,6S)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl] acetate of Formula II

comprising oxidation of compound (4R-cis)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethyl ethyl ester of Formula IV

using pyridine sulfur trioxide complex as an oxidizing agent.

13. The process of claim 12 wherein oxidation is carried out in a solvent selected from the group comprising of methylenechloride, dimethylsulfoxide, N,N-dimethylformamide and N,N-dimethylacetamide.

14. The process of claim 12 wherein the oxidation is conducted at temperatures less
than about 5° C.

15. The process of claim 12 wherein reaction is conducted for a period of about 1 to 5 hours.

16. The process of claim 12, wherein the molar ratio of pyridine sulfur trioxide complex to the compound (4R-cis)-6-(hydroxymethyl)-2,2-dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethyl ester of Formula IV is about 1 to about 0.5.

17. A process of preparing rosuvastatin or a pharmaceutically acceptable salt of rosuvastatin comprising: (a) preparing compound 4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulphonylamino)-5-pyrimidine carboxaldehyde of Formula I according to claim 1; and (b) converting the prepared 4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulphonylamino)-5-pyrimidine carboxaldehyde of Formula I into rosuvastatin or a pharmaceutically acceptable salt of rosuvastatin.