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# A NOVEL STRATEGY SYNTHESIS OF ROSUVASTATIN AND THEIR INTERMEDIATES

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## ABSTRACT

The present disclosure provides a novel process for the preparation of intermediates of the statin via Julia-modified olefnation. This can be effectively used for the preparation of HMG-CoA reductase inhibitors such as Rosuvastatin and its pharmaceutically acceptable salt, which is suitable for large-scale up, environmentally benign synthesis, cost-effective & improved impurity free process is described here by addressing various scales up.

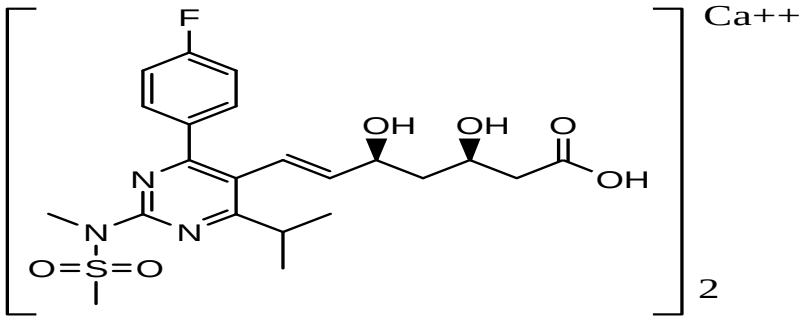
**KEYWORDS:** Statin, Cost-effective, Julia-modified olefnation, Environmentally benign synthesis.

## INTRODUCTION

The compounds of the present invention inhibit the HMG CoA reductase[1], which plays a main role in the synthesis of cholesterol, and subsequently they suppress the biosynthesis of cholesterol. Therefore, they are useful in the treatment of, hyperlipoproteinemia.[2] Rosuvastatin is chemically (E) -7-[4-(4-fluorophenyl) -6-isopropyl-2-[methyl (methyl-sulfonyl) amino] pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid.

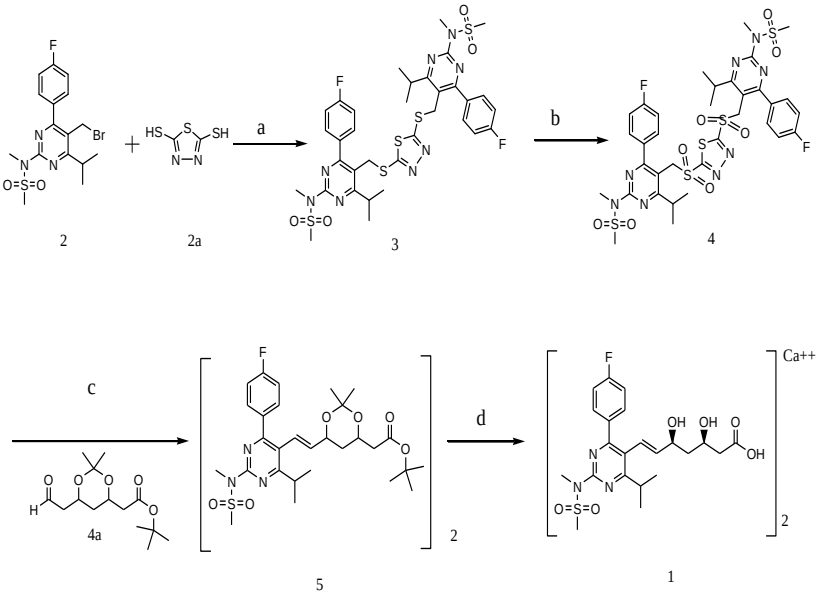
Several processes have been reported in literature for the preparation of Rosuvastatin.[3-11] The most of these processes use hazardous reagents like phosphorous trihalides or phosphorous oxyhalides, strong base like LDA, Triethyl Borane, Sodium hydrate, n-Butyl Lithium which are highly pyrophoric in nature, Critical, subzero reaction, high temperature

reaction, use a mixture of solvents, distillation of water for removing of alkyl amine and weak solubility of calcium salt (1) in an aqueous methanol. Hence these are not recommended for commercial scale up. Thus, there remains a need for a modified commercial scale process for preparing statins and its novel intermediates.




**Structure of Rosuvastatin Calcium (1)**

Therefore, in the present research work, an attempt has been made to overcome the above mentioned drawbacks of existing processes for intermediates of Rosuvastatin calcium by developing a feasible process using Julia-modified olefnation instead of witting reaction in scheme-1.




**Scheme1 - An Improved Scalable Synthesis of Rosuvastatin Calcium**

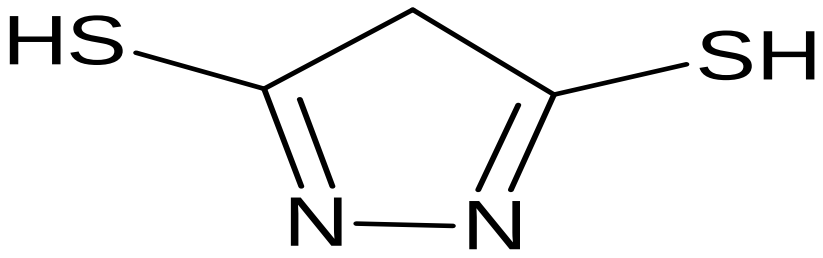
***Reagent and Condition: a) Sodium hydroxide, acetone at 25-30°C, b) Meta chloroperbenzoic acid, MDC at 25-30°C, c) Sodium Methoxide, THF ethyl acetate at 25-30°C, d) Dilute hydrochloric Acid, Sodium hydroxide, calcium chloride dehydrate, DM water at 20-25°C.***

The present invention provides following advantages over the existing processes for preparation of Rosuvastatin calcium and its intermediates

- No Synthesis of ammonium salts.
- No Distillation of water for the removing of alkyl amine
- No use mixture of solvents
- No Critical subzero reaction processing
- No High temperature reaction processing
- No methylation of sulfone compound.
- No usage of pyrophoric reagents like LDL, Triethyl borane, Sodium hydrate and n-Butyl Lithium.
- No usage of hazardous reagents like phosphorous trihalides or phosphorous oxyhalides.
- Use of simple bases like Sodium Hydroxide, potassium carbonate and sodium Methoxide.
- Sulfone compounds are stable.
- The yields are above 70%
- The calcium salt (1) is freely soluble in an aqueous methanol.

Besides this newly developed method is environmentally benign, commercial scalable, cost effective and impurity free for the synthesis of Rosuvastatin calcium.

The present invention provides an improved process for the preparation of Rosuvastatin calcium and its intermediates by paying Julia-modified olefnation using 1,3,4-thiadiazole-2,5-dithiol[12].




**(2a)**

**EXPERIMENTAL**

**Example-1: Preparation of pyrimidine sulfide compound (3)**

Pyrimidine Bromo compound (2) was treated with 1,3,4-thiadiazole-2,5-dithiol (2a) in the presence of base to get pyrimidine sulfide compound (3). **Yield: 25 gm; The Mass shows m/z 821 (base peak), 1H NMR (DMSO-d6) δ 1.20 (d,6H), 3.35 (s,3H), 3.46 (s, 3H), 3.54**

**(hept, 1H), 4.56 (s, 2H), 7.29- 7.68 (m,4H).**

**Example-2: Preparation of pyrimidine sulfone compound (4)**

Then sulfide compound was then oxidized with a suitable oxidizing agent Meta chloroperbenzoic acid, in MDC to get pyrimidine sulfone compound (4). **Yield: 33.0 gms**

**The Mass shows m/z 885 (base peak), 1H NMR (DMSO-d6) δ 1.14 (d,6H), 3.30 (s,3), 3.50 (s, 3H), 4.0 (hept, 1H), 5.39 (s, 2H), 7.20- 7.90 (m,4H), Example-3: Preparation tert-butyl 6-[(1e)- 2-(4-(4-fluorophenyl)-6-(1-methylethyl)-2-(methyl (methylsulfonyl) amino)-5-pyrimidinyl) ethenyl]-2,2-dimethyl-1,3- dioxane-4-acetate (5).**

The sulfone compound (4) was further condensed via Julia-modified reaction with tertiary butyl 2-[(4R,6S) -6-formyl-2,2-dimethyl-1,3-dioxane-4-yl] acetate in the presence of sodium methoxide with THF at 25-30°C for 5-7h. After completion of the reaction the compound was extracted and organic solvent was distilled out completely. Then the yellowish colored semisolid residual material, thus obtained was tert-butyl 6-[(1e) - 2-(4-(4-fluorophenyl) -6-(1-methylethyl) -2-(methyl (methylsulfonyl) amino) -5-pyrimidinyl) ethenyl] -2,2-dimethyl-1,3-dioxane-4-acetate (5). **The Mass shows m/z 578 (base peak),1H NMR (DMSO-d6) δ 1.30 (d,6H), 1.50 (s,9H), 2.40 (dd, 2H), 3.40 (hept, 1H), 3.48 (s, 3H), 3.55 (s, 3H), 3.72 (dd, 1H), 3.81 (dd, 1H), 4.40 (dd, 1H), 4.48 (dd, 1H), 5.50 (dd,1H), 6.60 (dd,1H), 7.20- 7.80 (m,4H), IR (KBR) ν cm-1: 3111, 2908, 1720, 1604, 1155, 965. Cm-1**

**Example-4: Preparation of Rosuvastatin Calcium (1)**

From example -3 the pyrimidine tert butyl ester (5) was deprotected in the presence of dilute acid with solvent at 10-15°C to get pyrimidine free diol, which was subsequently hydrolyzed by base in a mixture of water and solvent at 25-30°C to get Rosuvastatin sodium salt. The solvent was recovered and water to residual mass, then filter the reaction mass to remove the extraneous material. Rosuvastatin sodium salts get suspended in water, then added aqueous calcium chloride solution to precipitate Rosuvastatin calcium salt, filtered, washed with water and dried to get pure Rosuvastatin calcium salt (1). **Yield: 15.0 gms. HPLC: >99%. The Mass shows m/z 480 (base peak), 1H NMR (DMSO-d6) δ 1.20 (d,6H), 1.80 (t,2H), 2.00 (s, 2H), 2.10 (d, 1H), 2.20 (d, 1H), 3.50 (s, 3H), 3.50 (t, 1H), 3.55 (s, 3H), 3.80 (m, 1H), 3.95 (t, 1H), 6.40 (t, 1H), 6.70 (d,1H), 7.45- 7.80 (m,4H), IR (KBR) ν cm-1: 3411, 2968, 2933, 1604, 1549, 1381, 1155, 965. Cm-1**

## CONCLUSION

We have developed an improved and industrially feasible manufacturing novel process for the synthesis of rosuvastatin calcium **1** and its intermediates, which is free from impurities and meets the pharmaceutical norms. The present scalable, cost effective and impurity free process allowed us to prepare pure rosuvastatin calcium with more than 99% purity with more than 70% yield.

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