

A NOVEL SYNTHESIS APPROACH OF ROSUVASTATIN AND THEIR INTERMEDIATES

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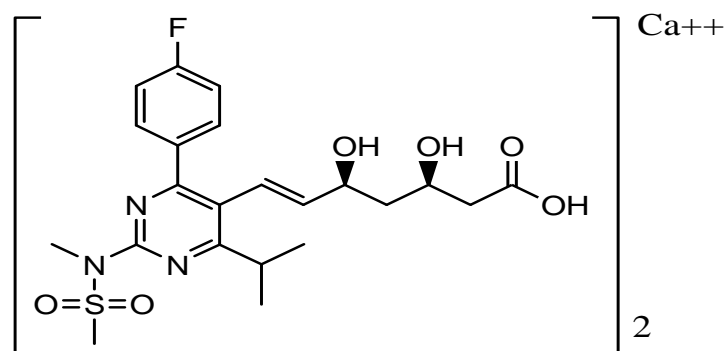
ABSTRACT

To development of novel and efficient strategies for their synthesis of Rosuvastatin and it is pharmaceutically acceptable salt. In the present exposure describe preparation of HMG-CoA reductase inhibitor, a novel process for the preparation of intermediates via Julia-modified olefination. That is describing here by the process which is suitable for large-scale up, environmentally benign synthesis & impurity free process that is capable of providing the drug in a cheaper and more convenient manner, which is extremely important and significant.

KEYWORDS: Statin; Julia-modified olefination; Eco friendly synthesis; HMG-CoA reductase.

INTRODUCTION

Rosuvastatin are helpful inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme. (HMG-CoA) reductases are the powerful lipid-lowering agents. Therefore they are known as pharmaceutical agents, they reduce cholesterol level in cardiovascular disease. So that statin drugs are useful in the treatment of hyperlipoproteinemia.^[1-2] Rosuvastatin is chemically known as (E) -7-[4-(4-fluorophenyl) -6-isopropyl-2-[methyl (methyl-sulfonyl) amino] pyrimidin-5-yl] (3R,5S)-3,5-dihydroxyhept-6-enoic acid.



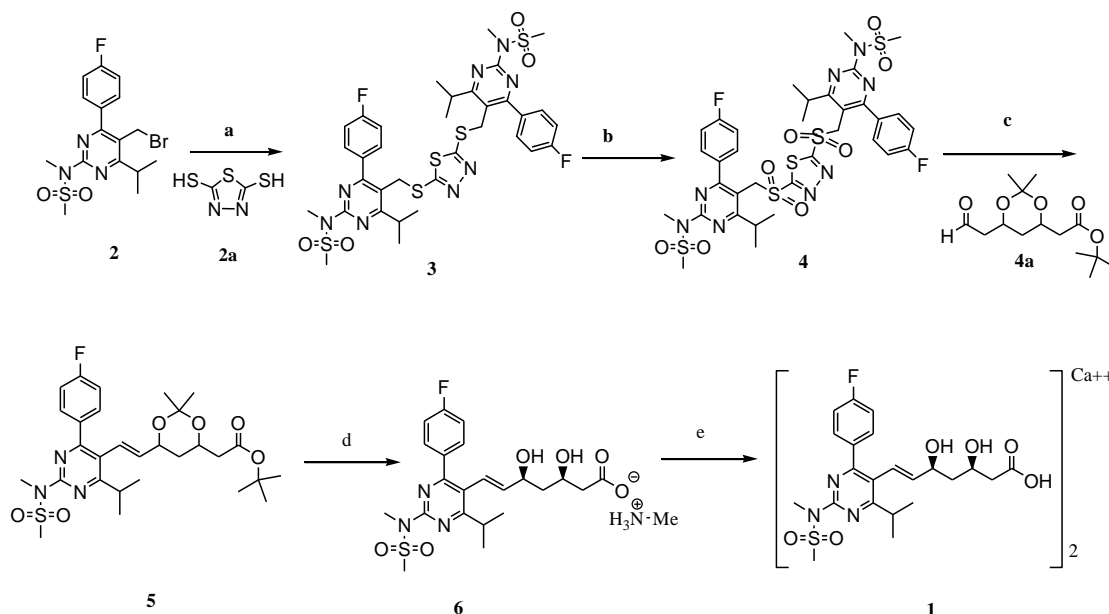
Structure of Rosuvastatin Calcium 1

RESULT AND DISCUSSION

Several pathways have been reported in literature for the preparation of Rosuvastatin.^[3-18] and their intermediates. In the manufacturing of the intermediates expensive reagents are used and it is time consuming process. Generally rosuvastatin and its intermediates are synthesized through wittig reaction and wittig horner reaction which leads to the formation of 'Z' isomer (around 20%). It also affects on yield and quality of the product and required further purifications.

In reported processes for synthesis of rosuvastatin, reagents like phosphorous trihalides or phosphorous oxyhalides, LDA, Triethyl Borane, Sodium hydrate and n-Butyl Lithium are used. Which are hazardous and highly pyrophoric in nature. Critical subzero reaction (i.e. -5 to 0^o C) reported in synthesis of rosuvastatin ammonium salt. High temperature reaction and use of mixture of solvents for synthesis of wittig salt of rosuvastatin. Solubility of calcium salt (1) is weak in an aqueous methanol. Hence these are not recommended for commercial scale up. Thus, a modified commercial scale up process for preparation of rosuvastatin and its intermediates is needed.

Therefore, in the present research work our attempt is to modify overcomes the above mentioned drawbacks of existing processes. It is strategic synthesis for the intermediates of rosuvastatin by developing a feasible process with Julia-Modified olefination reaction. Where the Pyrimidine bromo compound (2) couple with 1, 3, 4-thiadiazole-2,5-dithiol in the presence of base (2) to get sulfide intermediates (3). Further it is oxidized with oxidizing agent to obtained pure sulfone intermediate (4). It is then coupled with olefinic aldehyde (4a) to obtain the desired olefin. That is to be isolated rosuvastatin tert butyl ester (5). Finally it is converted to the optically pure HMG CoA reductase inhibitor via rosuvastatin ammonium salt (6) in scheme-1.



Scheme 1 – New Synthesis Approach 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 at 25-30°C, d) Dilute hydrochloric Acid, Sodium hydroxide, 40% mono methyl amine solution, MDC at 0- 5°C, e) Sodium hydroxide, calcium chloride, DM water at 20-25°C.

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

- Mixture of solvents, critical subzero reaction processing and high temperature reaction processing is avoided.
- In the present invention pyrophoric and hazardous reagents not required.
- Use of simple bases like Sodium Hydroxide, potassium carbonate and sodium Methoxide.
- As per the present invention synthesize Sulfone compounds are stable.
- The yields are above 70% for all stages of the present invention.
- The calcium salt (1) is freely soluble in an aqueous methanol.

Along with this newly developed for the synthesis of Rosuvastatin calcium is eco-friendly, commercial scalable, cost effective and impurity free.

EXPERIMENTAL

Step-1: Preparation of pyrimidine sulfide compound(3)

Pyrimidine Bromo compound (2) was coupled with 1, 3, 4-thiadiazole-2, 5-dithiol in the

presence of aqueous sodium hydroxide solution to get pyrimidine sulfide compound (3). Yield: 90% w/w; The $^1\text{H-NMR}$ (DMSO- d_6) shows the following signal δ 7.29- 7.68 (4H, m), 4.56 (2H, s), 3.54 (1H, hept), 3.46 (3H, s), 3.35 (3H, s), 1.20 (6H, d). The Mass shows m/z 821 (base peak).

Step-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: 85%. The $^1\text{H-NMR}$ (DMSO- d_6) shows the following signal δ 7.20- 7.90 (4H, m), 5.39 (2H, s), 4.0 (1H, hept), 3.50 (3H, s), 3.30 (3H, s), 1.14 (6H, d). The Mass shows m/z 885 (base peak).

Step-3: Preparation Rosuvastatin tert. butyl salt (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, then it is crystallizes by using alcohol and Heptane. Thus after drying at 50-55°C in a vacuum drying cupboard to get 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). Yield: 80%, HPLC: >99%. The $^1\text{H-NMR}$ (DMSO- d_6) shows the following signal δ 7.20- 7.80 (4H,m), 6.60 (1H,dd), 5.50 (1H, dd), 4.48 (1H, dd), 4.40 (1H, dd), 3.81 (1H,dd), 3.72 (1H, dd), 3.55 (3H, s), 3.48 (3H, s), 3.40 (1H, hept), 2.40 (2H, dd), 1.50 (9H, s), 1.30 (6H d). The Mass shows m/z 578 (base peak).

Step-4: Preparation Rosuvastatin ammonium salt (6)

Rosuvastatin tert butyl ester was dissolved in methanol at ambient temperature. Slowly added diluted aqueous hydrochloride solution (2.16ml HCl in 10ml water) at 0-5°C. Reaction was stirred to 12hrs at ambient temperature. After completion of reaction was cool to 0-5°C, and then slowly added aqueous sodium hydroxide solution. Reaction was stirred for 6hrs at 25-30°C. After completion of reaction were methanol distilled out completely under reduced pressure below 40°C. Water added to residue. Wash the aqueous layer with toluene. Settle and separate the toluene layer. DCM added to aqueous layer. Adjust the pH 3.5 – 4.0 by dilute hydrochloric acid at 0-5°C. Settle and separate out organic layer. Transfer organic layer in another clean and dry RBF. Were mono methyl amine slowly added in organic layer at 0 to

5°C. Then raise temperature at 25-30 °C. DCM completely distilled out under reduced pressure below 40°C. Then Acetone added to residue and stirred for 60min at 20-25°C. Filtered, washed with chilled acetone and dried to get pure Rosuvastatin ammonium salt (6). Yield: 75% w/w. The ¹H-NMR (CDCl₃) shows the following signal δ 7.7- 6.5 (5H,m), 5.5 (1H,dd), 4.2 (1H,m), 3.8(1H,m), 3.5-3.2 (9H,s), 1.9-2.0 (2H,dd), 1.3-1.5 (2H,m), 1.2 (6H,d). Mass shows m/z 482 (base peak).

Step-5: Preparation of Rosuvastatin Calcium (1)

Rosuvastatin ammonium salt (6) was subsequently hydrolyzed by using base in water at 25-30°C to get Rosuvastatin sodium salt. Then water was distilled out completely under reduced pressure below 40°C Rosuvastatin sodium salts get suspended in water, then were added aqueous calcium chloride solution to precipitate Rosuvastatin calcium salt, filtered, washed with water and after drying under reduced pressure at 40-45°C to get pure Rosuvastatin calcium salt (1). Yield: 90% w/w. HPLC: >99%. IR (KBR) ν cm⁻¹: 3411, 2968, 2933, 1604, 1549, 1381, 1155, 965. Cm⁻¹. The ¹H-NMR (DMSO-d₆) shows the following signal δ7.45-7.80 (4H, m), 6.70 (1H, d), 6.40 (1H, t), 3.95 (1H, t), 3.80 (1H, m), 3.55 (3H, s), 3.50 (1H, t), 3.50 (3H, s), 2.20 (1H, d), 2.10 (1H, d), 2.00 (2H, s), 1.80 (2H, t), 1.20 (6H, d). The Mass shows m/z 480 (base peak).

CONCLUSION

The present invention provides a process which is eco-friendly, easy to scale-up via Julia-modified olefination and commercially viable for the preparation of statins and its pharmaceutically acceptable salts thereof.

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