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A Novel Process for Synthesis of Rosuvastatin

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A novel process for the preparation of antihypercholesterolemic drug rosuvastatin calcium using novel intermediates has been described. Novel intermediates have been characterized by using IR, NMR and Mass spectroscopy.

Keywords: Rosuvastatin calcium, Antihypercholesterolemic drug, N-methylmorpholine, Triphenylphosphine.

INTRODUCTION

Rosuvastatin calcium (monocalcium bis(+)-7-[4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulfonylamino-pyrimidin)-5-yl]-(3R,5S)-dihydroxy-(E)-6-heptenoate) is effective inhibitor [1] of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase (HMGR) and are the most powerful lipid-lowering agents in use as pharmaceutical agents for reducing cholesterol levels in human with or at risk of cardiovascular disease. Rosuvastatin [2] has been called a 'super-statin', because it can reduce LDL-cholesterol and triglycerides more effectively than first generation drugs without any adverse effects. Rosuvastatin is approved for the treatment of elevated LDL cholesterol (dyslipidemia) [3], total cholesterol (hypercholesterolemia) [4] and/or triglycerides (hypertriglyceridemia) [5]. The development of new and efficient strategies for their synthesis, capable of providing the drug in a low-cost and more convenient manner, is therefore extremely important and relevant.

Rosuvastatin was disclosed first time in US5260440 [6]. Rosuvastatin is being marketed under the proprietary name CRESTOR, as an oral tablet, for the treatment of hypercholesterolemia. In view of the importance of rosuvastatin as a lipid-lowering agent, several synthetic methods have been reported in the literature to prepare rosuvastatin, such as US 5,260,440 [6], US 6,844,437B1 [7], WO2011/104725A2 [8]. But, the final steps of aforementioned processes have several disadvantages. The processes reported in the prior are expensive, difficulty to handle on commercial scale, requires additional purification steps intermediately thus ending up with lower yields.

Therefore, there is an urgent need in the methodology to provide a process, which can overcome the aforesaid disadvantages and hence the present invention is simple, eco-friendly, inexpensive, reproducible and robust and is well suited on an industrial scale. Herein, report a novel process for the preparation of rosuvastatin calcium using novel intermediate diol-anilide (II).

EXPERIMENTAL

Preparation of bromo phosphonium salt (VI): To a solution of 4-(4-fluorophenyl)-6-isopropyl-2-[(N-methyl-N-methylsulfonyl)amino]-pyrimidine-5-yl-methanol (100 g) in dichloromethane (400 mL) was slowly added phosphorus tribromide (45.89 g) at 10-15 °C and stirred for 1 h at 10-15 °C. Reaction monitored by TLC, quench the reaction by adding water (200 mL) at 0-5 °C and stirred at 20-25 °C for 30 min, separated the organic layer. Wash the organic layer with sodium bicarbonate solution (30 mL) followed by water (100 mL). Distilled off solvent completely at 35-40 °C under reduced pressure to obtain the solid. To the above solid charged toluene (300 mL) and temperature rise to 85-95 °C to get clear solution and slowly added triphenylphosphine solution (74.22 g) dissolved in toluene (300 mL) at 85-95 °C. Rise the temperature to 100-105 °C and stirred for about 6-7 h. Reaction monitored by TLC, after completion of reaction cool the reaction mass to 25 to 30 °C. Filtered the solid and wash with toluene (100 mL) and dry to get compound-VI.

Preparation of rosuvastatin dioxaneter-butyl ester (V): To a stirred solution of [(4-(4-fluorophenyl)-6-(1-methylethyl)-

2-{methyl(methylsulfonyl)amino}-5-pyrimidinyl)methyl]triphenylphosphonium bromide (100 g) and *tert*-butyl (4*R*-*cis*)-6-formaldehyde-2,2-dimethyl-1,3-dioxane-4-acetate (45.66 g) in DMSO (350 mL) at 25-30 °C was added potassium carbonate (50 g) under N₂ atmosphere at 25-30 °C. Stir the reaction mass at 65-70 °C for 4 h. Reaction monitored by TLC, after completion of reaction add toluene (600 mL) at 50-55 °C and cool to 25-30 °C. Filter the reaction mass and washed with 200 mL toluene. Cooled the filtrate to 0-5 °C and slowly added 600 mL water, separated the organic layer and washed with water, distilled off solvent completely under vacuum at 65-70 °C to get the solid. Charged methanol (300 mL) stirred the separated solid for 1 h at 25-30 °C. Filtered the solid and washed with methanol (100 mL). Dried the material under vacuum at 50 °C to get compound-V.

Preparation of 2-((4*R*,6*S*)-6-((*E*)-2-(4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methyl methyl sulfonamido)pyrimidin-5-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl) acetic acid (Compound IV): In a 2 L 4-necked round bottom flask was taken *tert*-butyl-6-[(1*E*)-2-[4-(4-fluorophenyl)-6-(1-methylethyl)-2-[methyl(methylsulfonyl)amino]-5-pyrimidinyl]ethenyl]-2,2-dimethyl-1,3-dioxane-4-acetate (compound-V, 100 g) and water (50 mL) to this methanolic sodium hydroxide solution (24.26 g in 1 L) was added at a temperature in the range of 25-30 °C under stirring. The reaction mixture was heated to 50-55 °C and stirred for 15 h. Reaction monitored by HPLC, after completion of the reaction distilled off solvent completely under reduced pressure. After distillation, 300 mL of dichloromethane and purified water (300 mL) were added and pH adjusted to 7.0-7.5 using 40 % acetic acid at 20 °C. The mixture was allowed to settle for about 10 min resulting in two layers, organic layer washed with 5 % aq. sodium chloride solution and dried over anhydrous sodium sulphate. To organic layer was added cyclohexane (1200 mL) precipitate forms which is heated to 40 °C for 30 min and cooled to 20 °C and stirred for 12 h. Filter the solid and wash with cyclohexane (200 mL) to obtain compound-IV in 80 % yield with HPLC purity 98.50 %. Compound was confirmed by analytical data such as IR (KBr, cm⁻¹) 3482, 2967, 1698, 1605, 1155. GC-MS (*m/z*): [M+1] 522.2 (m.w.: 521.6). ¹H NMR (400 MHz, CD₃OD) δ (ppm): 7.7-7.6 (2H, dd), 7.18-7.14 (2H, dd), 6.63-6.58 (1H, d), 5.5-5.4 (1H, dd), 4.55-4.50 (1H, m), 4.38-4.32 (1H, m), 3.4 (3H, s), 3.5 (3H, s), 3.2 (1H, m), 1.28 (6H, s), 1.26 (6H, s).

Preparation of N-(4-bromophenyl)-2-((4*R*,6*S*)-6-((*E*)-2-(4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methylmethylsulfonamido)pyrimidin-5-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetamide (compound III): In a 1 L 4-necked round bottom flask taken 2-((4*R*,6*S*)-6-((*E*)-2-(4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methylmethylsulfonamido)pyrimidin-5-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetic acid (compound-IV) (60 g) and dichloromethane (480 mL), added *N*-methyl morpholine and isobutyl chloroformate at 0-5 °C under nitrogen atmosphere and stirred for 2 h. The resulting reaction mixture was added to a mixture of 4-bromo aniline and dichloromethane (120 mL) at 25-30 °C and stirred for 2 h. Reaction monitored by TLC, after completion of the reaction purified water (180 mL) was added and stirred for 10 to 15 min and allowed to settle the layers, separated the organic layer

and twice washed with purified water (100 mL). Distilled the solvent completely under reduced pressure at 50 °C and co-distilled with toluene (120 mL) at 50 °C. Residue dissolved in toluene (480 mL) at 60 °C. Slowly cooled to 25 °C and left for 3 h. Filtered the solid and washed with toluene (120 mL) to yield N-(4-bromophenyl)-2-((4*R*,6*S*)-6-((*E*)-2-(4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methylmethylsulfonamido)pyrimidin-5-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetamide (compound-III). Yield 73 % and HPLC purity 97.6 %. Compound-III was confirmed by analytical data.

Off-white crystalline solid; m.p.: 124-126 °C and DSC: 126.19 °C. GC-MS (*m/z*): 677 [M+1]; ¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.3 (1H, s), 7.6 (2H, m), 7.4 (4H, m), 7 (2H, t), 6.57 (1H, d), 5.4 (1H, dd), 4.4 (1H, bd), 4.3 (1H, m), 3.57 (3H, d), 3.51 (3H, s), 3.3 (1H, m), 2.5 (2H, d), 1.5 (6H, d), 1.3 (1H, s), 1.2 (6H, m); XRPD with specific peaks 2θ: 5.7, 9.3, 10.0, 11.4, 12.4, 13.4, 14.1, 14.4, 14.8, 16.6, 17.6, 19.3, 19.6, 20.2, 20.6, 21.0, 21.3, 22.0, 22.7, 23.7, 24.2, 24.6, 24.9, 25.5, 26.6, 27.1, 27.9, 28.6, 29.8, 31.3, 32.5, 33.5, 34.6 and 36.8. FT-IR (KBr, cm⁻¹): 3382, 2966, 1677, 1596, 1151, 504.

Few of the related compounds are prepared and confirmed by ¹H NMR and Mass data.

R: CH₃ (methyl): Mass value: 535.3 [M+1]; ¹H NMR (400 MHz, CDCl₃) δ (ppm): 7.7-7.6, (2H, dd), 7.18-7.14 (2H, dd), 6.5-6.4 (1H, d), 6 (1H, bd), 5.5-5.4 (1H, dd), 4.55-4.50 (1H, m), 4.38-4.32 (1H, m), 3.57 (3H, s), 3.51 (3H, s), 3.3 (1H, m), 2.8 (3H, d), 2.4 (2H, m), 1.6 (1H, s), 1.5 (3H, bs), 1.2 (3H, bs), 1.26 (6H, s), 1.19 (1H, m).

R: C₆H₅ (phenyl): Mass value: 597.3 [M+1]; ¹H NMR (400 MHz, CD₃OD) δ (ppm): 8.2 (1H, s), 7.7-7.6, (2H, dd), 7.5 (2H, d) 7.3 (2H, t), 7.1 (1H, t) 7.0 (2H, t), 6.5 (1H, dd), 5.5 (1H, dd), 4.4 (1H, m), 4.3 (1H, m), 3.5 (3H, s), 3.39 (3H, s), 3.35 (1H, m), 2.5 (2H, d), 1.6 (1H, m), 1.5 (6H, s), 1.3 (1H, s), 1.2 (6H, m).

R: C₆H₄-F (4-fluoro phenyl): Mass value: 615.2 [M+1]; ¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.2 (1H, s), 7.7-7.6 (2H, dd), 7.5 (2H, d), 7.3 (1H, m), 7.1 (4H, m) 6.80 (1H, t), 6.7 (1H, m), 6.5 (1H, dd), 5.4 (1H, dd), 4.4 (1H, m), 4.3 (1H, m), 4.3 (3H, t) 3.9 (4H, m), 3.5 (3H, s), 3.4 (3H, s), 3.3 (4H, m), 2.9 (3H, bt), 2.8 (5H, s), 2.5 (2H, d), 2 (1H, s), 1.5 (3H, s), 1.50 (3H, s) 1.27 (1H, s), 1.26 (6H, s), 0.9 (3H, s), 0.85 (1H, m).

Preparation of (3*R*,5*S*,*E*)-N-(4-bromophenyl)-7-(4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methyl methylsulfonylamido)pyrimidin-5-yl)-3,5-dihydroxyhept-6-enamide (compound II): N-(4-bromophenyl)-2-((4*R*,6*S*)-6-((*E*)-2-(4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methylmethylsulfonamido)pyrimidin-5-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetamide (1 mole eq, compound III) is treated with dilute hydrochloric acid (1 eq, 1.5 molar dilution in water) at 25-30 °C and stirred for 6 h. Reaction monitored by TLC. After completion of reaction diolanilide (compound II) is isolated by distillation of acetonitrile at 45 °C under vacuum.

GC-MS: 636 [M+1]; DSC: 132.91 °C; XRPD with specific peaks 2θ: 3.2, 4.3, 9.1, 13.2, 13.7, 14.6, 16.9, 17.4, 18.4, 19.0, 19.7, 20.1, 20.8, 22.5, 23.7, 24.7, 25.8, 26.7 and 29.8. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.1 (1H, S), 7.6 (2H, m), 7.4 (3H, m), 7.3 (1H, s), 7.1 (2H, m), 6.6 (1H, d), 5.5 (1H, d), 4.5 (1H, m), 4.3 (1H, m), 3.6 (3H, s), 3.5 (3H, s), 3.3

(1H, m), 2.6 (2H, d), 1.8 (2H, m), 1.6 (2H, s), 1.3 (6H, s). FT-IR (KBr, cm^{-1}): 3521, 3362, 2972, 1669, 1603, 1139, 503.

Preparation of rosuvastatin calcium (compound-I): To a stirred solution of (3*R*,5*S*)-*N*-(4-bromophenyl)-7-(4-(4-fluorophenyl)-6-isopropyl-2-(*N*-methyl methyl sulfonylamido)-pyrimidin-5-yl)-3,5-dihydroxyhept-6-enamide (20 g) in methanol (160 mL) was added sodium hydroxide (1 M solution in water, 60 mL) at 25–30 °C. Stir the reaction mixture at 40–45 °C till to get the absence of diol-anilides (Compound II). Reaction monitored by TLC, adjusted pH to 8.5–9.0 with dil. HCl, distilled the methanol residue was dissolved in 140 mL purified water and washed with toluene and methyl *t*-butyl ether. Rosuvastatin calcium was isolated by filtration of the slurry, which was obtained by adding calcium chloride dihydrate (about 20 % solution in water) in to the above aqueous layer was treated with activated charcoal (1 g) for 1 h. Isolated rosuvastatin calcium was dried at 40–45 °C under vacuum till to get constant weight. The obtained rosuvastatin calcium has been characterized by ^1H NMR and mass.

GC-MS: 482 [M+1]; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ (ppm): 7.68 (2H, t), 7.26 (2H, t), 6.4 (1H, d), 5.4 (1H, dd), 5.0 (1H, m), 4.19 (1H, m), 3.76 (1H, s), 3.54 (3H, s), 3.44 (3H, s), 3.33 (1H, s), 1.96 (2H, dd), 1.27 (2H, m), 1.19 (6H, d).

RESULTS AND DISCUSSION

Initially, Py-alcohol reacted with PBr_3 in dichloromethane as a solvent gave bromo-variant compound-VII, which treated with triphenylphosphine in toluene as a solvent obtained Wittig reagent -VI. Then, compound-VI was reacted with *tert*-butyl 2-((4*R*,6*S*)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl)acetate (XII) in the presence of K_2CO_3 as base in DMSO solvent to from acetonide ester (V).

We optimized reaction conditions to synthesize acetonide acid (IV) from acetonide ester (V) using various organic and inorganic bases in various solvents. Organic bases such as triethylamine, tripropyl amine, pyridine, diisopropylamine, diisopropylethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), inorganic bases such as ammonium hydroxide, sodium hydroxide, potassium hydroxide, cesium hydroxide, sodium hydride, potassium hydride, sodium carbonate, potassium carbonate, cesium carbonate, sodium bicarbonate, potassium bicarbonate. Among them sodium hydroxide was found suitable base. Then, solvents used in this reaction are like water, methanol, ethanol, propanol, isopropanol, butanol, isobutanol, *tert*-butanol dichloromethane, tetrahydrofuran, ethylacetate, acetone, dimethylformamide, acetonitrile, dimethylsulfoxide, propylene carbonate, toluene, methyl *t*-butyl

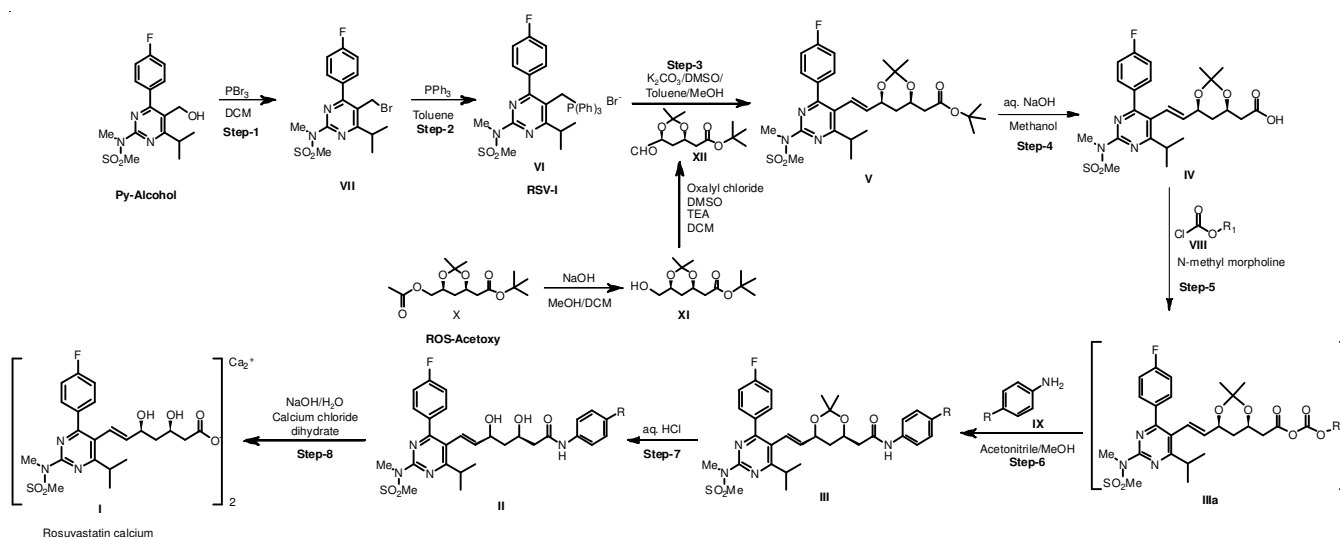
carbonate, cesium carbonate, sodium bicarbonate, potassium bicarbonate. Among them, NaOH was found suitable base and solvents screened such as water, methanol, ethanol, propanol, isopropanol, butanol, isobutanol, *tert*-butanol dichloromethane, tetrahydrofuran, ethylacetate, acetone, dimethylformamide, acetonitrile, dimethylsulfoxide, propylene carbonate, toluene, MTBE (methyl *t*-butyl ether), diisopropyl ether (DIPE). Among them methanol was found suitable solvent.

The acetonideanilide reaction with aq. HCl gave a diol-anilide (II). The diol-anilide(II) hydrolysis followed by reacting with CaCl_2 of reagent give rosuvastatin calcium (I) (**Scheme-I**).

Reaction of the compound-IV with the chloroformates-VIII such as isobutyl chloroformate, benzyl chloroformates in the presence of *N*-methylmorpholine as base to obtain an *in situ* of corresponding isobutyl carbonic compound (IIIa) which was reacted with anilines IX such as aniline, 4-fluoro-aniline, 4-bromo aniline, 4-nitro aniline to give the corresponding acetonideanilide compounds-III.

To cleave acetonide anilide compounds-III various acids were used in step-7 include organic acids (phosphonic acid, *para*-toluene sulfonic acid, pyridinium *para*-toluene sulfonic acid, methane sulfonic acid, benzene sulfonic acid), Inorganic acids (hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid). Among them hydrochloric acid was found suitable acid for these reaction to gave diolanilide-II.

Finally in step-8, to synthesize compound-I from diolanilide-II in the presence of calcium chloride dihydrate. This reaction was optimized by changing the base and solvent. In this connection, various bases used organic bases such as triethylamine, tripropyl amine, pyridine, diisopropylamine, diisopropylethylamine, DBU, inorganic bases such as ammonia, sodium hydroxide, potassium hydroxide, cesium hydroxide, sodium hydride, potassium hydride, sodium carbonate, potassium carbonate, cesium carbonate, sodium bicarbonate, potassium bicarbonate. Among them sodium hydroxide was found suitable base. Then, solvents used in this reaction are like water, methanol, ethanol, propanol, isopropanol, butanol, isobutanol, *tert*-butanol dichloromethane, tetrahydrofuran, ethylacetate, acetone, dimethylformamide, acetonitrile, dimethylsulfoxide, propylene carbonate, toluene, methyl *t*-butyl

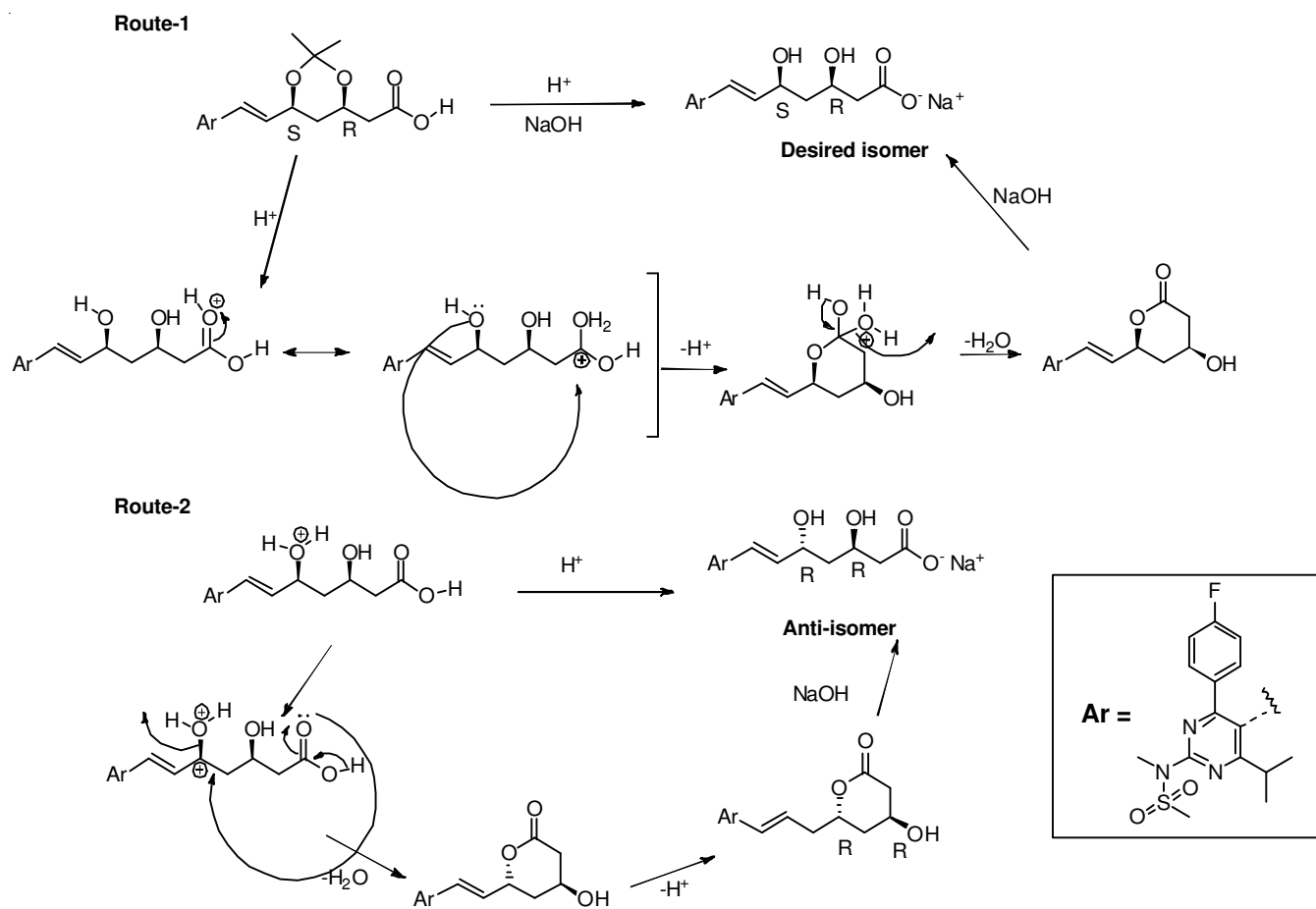


Scheme-I: Synthetic scheme of rosuvastatin calcium

ether, DIPE and so on. Among them water was found suitable solvent.

No other relevant references disclosed with purification of rosuvastatin calcium **I** with anti-isomer impurity **Ib** at a level of less than 0.15 % and all other unknown impurities at less than 0.10 %, which is an essential criterion of a bulk drug substance (**Scheme-II**). Hence, there is a call for development of an efficient, impurity-free, for the preparation of rosuvastatin calcium **I**. The optimization of various parameters involved in the de-protection of acetonid and hydrolysis of **III** resulted in a dramatic improvement in the purity and yield of **II** when using hydrochloric acid and sodium hydroxide. Various parameters such as normality of hydrochloric acid, temperature of the reaction, maintenance timings of the reaction and purification process were studied thoroughly. Great to optimize the normality of hydrochloric acid, temperature and maintenance timings. When we use 0.01, 0.015 and 0.03 N of HCl,

40-45 °C temperature maintenance reaction did not results well (Table-1); and 0.2 equiv of the hydrochloric acid, temperature and maintenance at 40-45 °C was found to be the most ideal for getting the required compound **Ia** with high purity and good yield (Table-1). After the optimization of normality of hydrochloric acid, the next task was to study the effect of temperature on the reaction. It was found that the temperature at which the reaction was carried out also proved to be a very important factor in controlling the levels of anti-isomer **Ib**. The percentage of anti-isomer was found to be increasing with reaction temperature 45-50 °C (Table-2). The reaction proceeded slowly at lower temperature 25-30 °C (24 h), due to the reason, increased the maintenance time as well as anti-isomer formation also (Table-2). This minimized the formation of anti-isomer by the de-protection carried out at temperatures of 40-45 °C produced a compound with minimal levels of anti-isomer (entry 3, Table-2).



Scheme-II: Mechanisms for formation of Rosuvastatin calcium isomer **Ia** and anti-isomer **Ib**

TABLE-1
EFFECT OF THE NORMALITY OF HYDROCHLORIC ACID ON QUALITY

Entry	HCl (normality)	NaOH (equiv)	T (°C) ^a	Time (h)	Yield (%)	Purity by HPLC	
						Purity (Ia) ^b (%)	Anti-isomer
1	0.010	1.1	40-45	2.0	87	99.65	0.14
2	0.015	1.1	40-45	2.0	90	99.65	0.19
3	0.020	1.1	40-45	2.0	90	99.54	0.13
4	0.030	1.1	40-45	2.0	64	99.59	0.16

^aTemperature of reaction mass; ^bRosuvastatin

TABLE-2
EFFECT OF THE TEMPERATURE AND TIME ON QUALITY

Entry	HCl (normality)	NaOH (equiv)	T (°C) ^a	Time (h)	Purity by HPLC	
					Purity (1a) ^b (%)	Anti-isomer
1	0.02	1.1	25-30	24.0	98.40	0.34
2	0.02	1.1	35-40	4.0	99.06	0.36
3	0.02	1.1	40-45	2.0	99.54	0.13
4	0.02	1.1	40-45	4.0	98.56	0.37
5	0.02	1.1	45-50	4.0	99.42	0.47

^aTemperature of reaction mass; ^bRosuvastatin

Conclusion

In this article, a novel process is developed for the preparation of anti-hypercholesterolemic drug rosuvastatin calcium using novel intermediates.

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