

**PREPARATION OF ROSUVASTATIN INTERMEDIATES AND THEIR  
PHARMACEUTICALLY ACCEPTABLE SALT: A REVIEW**Premchand Patil<sup>1</sup>, Deepak V. Nagarale<sup>1</sup> and Dr. Bhata R. Chaudhari\*<sup>2</sup><sup>1</sup>Dept. of Chemistry, JET's Z.B. Patil College, Dhule (MS), India.<sup>2</sup>S.S.V.P.S's ACS College, Shindkheda.

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**ABSTRACT**

The present studies describe class by design-oriented progress and characterization of rosuvastatin calcium.<sup>[1]</sup> Rosuvastatin has several contraindications which include hypersensitivity to rosuvastatin. In this review, an attempt is made to present a current scenario of these compounds which is synthesized by various synthetic methods and various applications in cholesterol, cardiovascular disease.

**KEYWORDS:** The present studies describe class by design-oriented progress and characterization of rosuvastatin calcium.

**INTRODUCTION**

A link between cholesterol and cardiovascular disease, known as the lipid hypothesis, had already been suggested. Cholesterol is the main constituent of atheroma, the fatty lumps in the wall of arteries that occur in atherosclerosis and, when ruptured, cause the vast majority of heart attacks. Treatment consisted mainly of dietary measures such as a low-fat diet, and poorly tolerated medicines such as clofibrate, cholestyramine and nicotinic acid. Cholesterol researcher Daniel Steinberg writes that while the Coronary Primary Prevention Trial of 1984 demonstrated that cholesterol lowering could significantly reduce the risk of heart attacks and angina, physicians, including cardiologists, remained largely unconvinced.

To market statins effectively, Merck had to convince the public about the dangers of high cholesterol, and doctors that statins were safe and would extend lives. As a result of public campaigns, people became familiar with their cholesterol numbers and the difference between "good" and "bad" cholesterol, and rival pharmaceutical companies began producing their own statins, such as pravastatin (Pravachol), manufactured by Sankyo and Bristol-Myers Squibb. In April 1994, the results of a Merck-sponsored study, the Scandinavian Simvastatin Survival Study or "4S", were announced. Researchers tested simvastatin, later sold by Merck as Zocor, on 4,444 patients with high cholesterol and heart disease. After five years, the study concluded that patients saw a 35-percent reduction in their cholesterol, and their chances of dying of a heart attack were reduced by 42 percent. In 1995, Zocor and Mevacor both made Merck

over US\$1 billion. Endo was awarded the 2006 Japan Prize, and the Lasker-DeBaakey Clinical Medical Research Award in 2008.

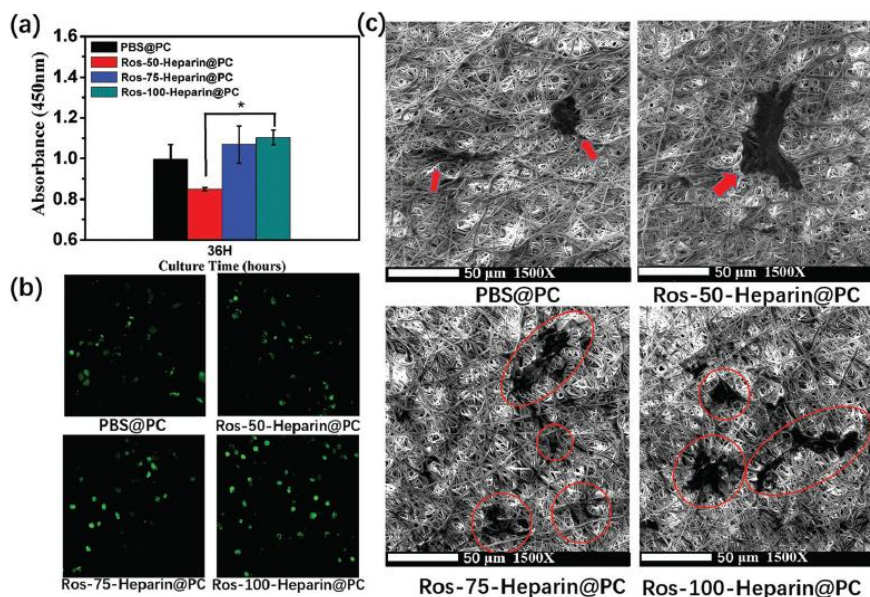
Fawaz N.S. Al-Heibshy et al gave the method in a Cs salts (acetate, lactate, aspartate and glutamate) have potentials for the preparation of rosuvastatin calcium a-loaded NPs by spray drying method. The physicochemical properties of all NPs were dependent on types of Cs salts. CA and CL salts provided enhanced drug release while CAs and CG salts showed slower drug releases with respect to the pure drug in phosphate buffer (pH 6.8) medium.<sup>[2]</sup>

Deacylation of chitin it is one of the method to obtained Cs which is natural polymer. Chitin is known to be the most abundant biopolymer in nature that occurs as the major organic skeletal substance of invertebrates and as a cell wall constituent of fungi and green algae.<sup>[3-4]</sup> Cs is regarded as biologically safe, non-toxic, biocompatible and biodegradable polysaccharide therefore Cs exhibits wide range of biological applications like hypobilirubinaemic and hypocholesterolemic effects, antacid and antiulcer activities, wound and burn healing properties<sup>[5]</sup> and widely regarded as an efficient intestinal absorption enhancer of therapeutic macromolecules, owing to its inherent mucoadhesive feature and ability to modulate the integrity of epithelial tight junctions reversibly.<sup>[6a-b]</sup>

Wenhao Feng et al studied the mechanical properties, water contact angle, release profile of rosuvastatin calcium, cell adhesion and proliferation, and

anticoagulation properties *in vitro* were investigated. The results showed that heparin and rosuvastatin calcium were successfully encapsulated in the nanofibrous matrix, and it would not rupture with the expansion of the stent-graft, relying on the excellent mechanical properties of the P(LLA-CL) coaxial nanofibers. The core-shell nanofibers exhibited a uniform and smooth

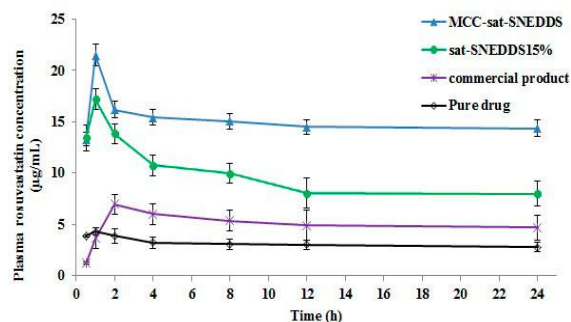
morphology. The rosuvastatin calcium loaded within the P(LLA-CL) coaxial nanofibers showed a sustained release profile. Because of the existence of rosuvastatin calcium, HUVECs can grow and proliferate well on these electrospun nanofibers, indicating that this material has good cytocompatibility.<sup>[7]</sup>



**Fig. Cell viability and cell morphology on the scaffolds. (a) CCK-8 assay of HUVEC viability ( $*p < 0.05$ ). (b) Live and dead assay of HUVECs. (c) SEM images of HUVECs on Ros-Heparin@PC and PBS@PC scaffolds (scale bar = 100  $\mu\text{m}$ ).**

In present study they also conclude that Ros-Heparin@PC nanofibers were fabricated and coated onto a stent successfully. The Ros-Heparin@PC nanofibers were continuous, smooth and bead-less, and possessed excellent mechanical properties. The release profile verified that Ros-Ca encapsulated in the nanofibers could be released continuously and stably. The Ros-Ca-loaded nanofibrous mats can promote HUVEC proliferation and adhesion on this scaffold and the morphology of the HUVECs is good.

Hadel A. Abo Enin et al illustrate the applicability of solid supersaturated selfnanoemulsifying drug delivery system (sat-SNEDDS) for the improvement of rosuvastatin calcium (RC) oral bioavailability. It result into the adsorption of the stable positively charged nanocarrier RC sat-SNEDDS onto solid carriers provided free flowing amorphous powder. The carrier could amend the morphological architecture and *in vitro* release of the RC solid sat-SNEDDS.<sup>[8]</sup>



**Fig 1: Plasma concentration of RC following oral administration of drug suspension, sat-SNEDDS15%, MCC-sat-SNEDDS and commercial tablet. Results are the mean of twelve determinations  $\pm$  SD.**

Develop simple, sensitive and precise HPLC method for the simultaneous determination of Aspirin and Rosuvastatin in pharmaceutical dosage form. The method was carried out using Greece C18 (4.6ID  $\times$  250mm; 5 $\mu\text{m}$ ) column and mobile phase comprised of methanol and PDP buffer adjusted to pH 2.8 with Ortho phosphoric acid in proportion of ratio 70:30 v/v and degassed under ultrasonication. The flow rate was 1 mL/min and detection was carried out at 243 nm. The Retention time of Aspirin and Rosuvastatin were found to be 2.84 and 3.46 respectively as given bellow tables.<sup>[9]</sup>

Sr.No.	Aspirin		Rosuvastatin	
	Concentration	Area	Concentration	Area
1	75	459670	10	144179
2	150	900960	20	603343
3	225	1407515	30	1127236
4	300	1889317	40	1702906
5	375	2238349	50	2221839
	Correlation coefficient( $r^2$ )	0.9966	Correlation coefficient( $r^2$ )	0.9987
	Slope(m)	454572	Slope(m)	525488
	Intercept(y)	15448	Intercept(y)	416564

Sr.No.	Parameter	Results		Limit
		Aspirin	Rosuvastatin	
1	Recovery in %	98.75-100.71	97.71-101.07	98-102
2	Method precision	0.585	0.564	Below 2
3	Limit of detection	0.0784	0.0107	
4	Limit of quantitation	0.23	0.0324	
5	Robustness in % change			
	i. % RSD in peak area response	0.05-0.266	0.513-0.944	Below 2
	ii. Theoretical plates	6875-6972	6412-6587	NLT 2000
	iii. Tailing factor	1.18-1.39	1.23-1.25	NMT 2
	iv. Retention time	2.97-3.51	3.24-4.28	
6	Formulation assay in %	99.37	99.74	98-102
7	Solution stability in %	24 hrs	24 hrs	98-102

Swapna Velivela et al studied Rosuvastatin calcium were it act as synthetic lipid lowering agent which inhibits the enzyme 3-hydroxy-3-methylglutaryl-coenzymeA to mevalonate, a precursor of sterols, including cholesterol. It comes under class II of Biopharmaceutical Classification System. The purpose of this study was to develop and evaluate Rosuvastatin calcium immediate release tablets by wet granulation method using different proportions of superdisintegrants and binder. Pre-formulation studies were done initially and the results were found to be within the limits.<sup>[10]</sup>

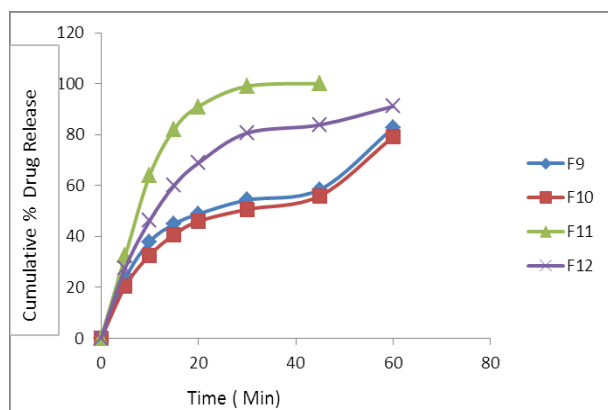


Fig: In vitro release profile F-9 to F-12 formulation.

From the above experimental results it can be concluded that immediate release tablets of Rosuvastatin calcium can be prepared by using different proportion & combination of superdisintegrants and binder and we selected F11 as best formulation based on dissolution profile and physical characteristics.

The oral bioavailability of rosuvastatin is 20 %, which is comparable to atorvastatin, pravastatin and fluvastatin, and qualitatively higher than simvastatin and lovastatin. After a single oral dose the peak plasma concentration is reached at 5 hours. This is longer than other HMG-CoA

inhibitors which achieve maximum plasma concentrations in less than 3 hours. In compiled data from pharmacokinetic trials, the peak plasma concentration and area under the concentration time curve show a largely linear relationship as the dose of rosuvastatin increases from 5 to 80 mg. Food intake decreases the rate of absorption of rosuvastatin by 20 % but not the extent of absorption. This does not reduce the cholesterol lowering potency; therefore rosuvastatin can be taken with or without food, and in the morning or evening.<sup>[11-16]</sup>

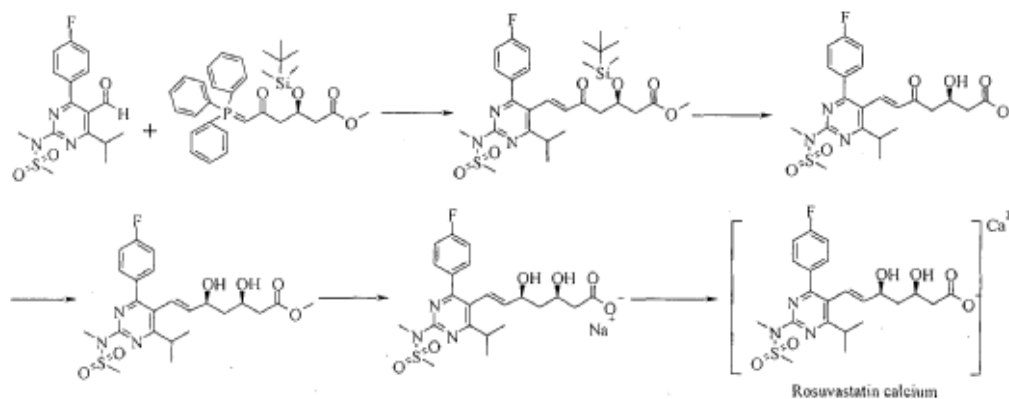
**How To Use Rosuvastatin:** Take this medication orally with or while not food as directed by your, typically once daily. The dose is predicated on your medical condition, response to treatment, age, and alternative medication you'll be taking take care to inform your doctor and health professional regarding all the merchandise you utilize. It's vital to still follow your doctor's recommendation regarding diet and exercise. It is going to take up to four weeks before you get the complete advantage of this drug.<sup>[17]</sup>

Swapnil Gaikwad and co-workers were done literature survey which revealed that several methods were reported for estimation of Rosuvastatin calcium and Fenofibrate individually or in combination with other drugs in pharmaceutical dosage forms. but, only single HPLC method has been reported up to date for successive estimation of Rosuvastatin calcium and Fenofibrate together. The authors developed a new, sensitive and suitable reversed-phase high performance liquid chromatography method and validated for the successive estimation both. The results of analysis in the method were validated in terms of accuracy, precision, specificity, linearity, limit of detection, limit of quantification and robustness.<sup>[18]</sup>

Rosuvastatin plays a significance role as a lipid control including some synthetic methods an patents that used by several researchers have revived here.

#### 1. U.S. Pat. No. 5,260,440<sup>[19]</sup>

Rosuvastatin for the first time disclosed in U.S. Pat. No. 5,260,440. Rosuvastatin is being marketed under the proprietary name CRESTOR, as an oral tablet, for the treatment of hypercholesterolemia. Disclose a process for preparing rosuvastatin in examples. The process is as shown below: The difficulties in the above process are that the intermediate (A) is not obtained in pure form readily. Further, its purification is tedious and overall yield is extremely low. Even when intermediate (A) is obtained in pure form, further condensation with intermediate (11) to form rosuvastatin, does not result in rosuvastatin of right quality as the product contains unacceptable quantity of impurity levels as shown in scheme 1.

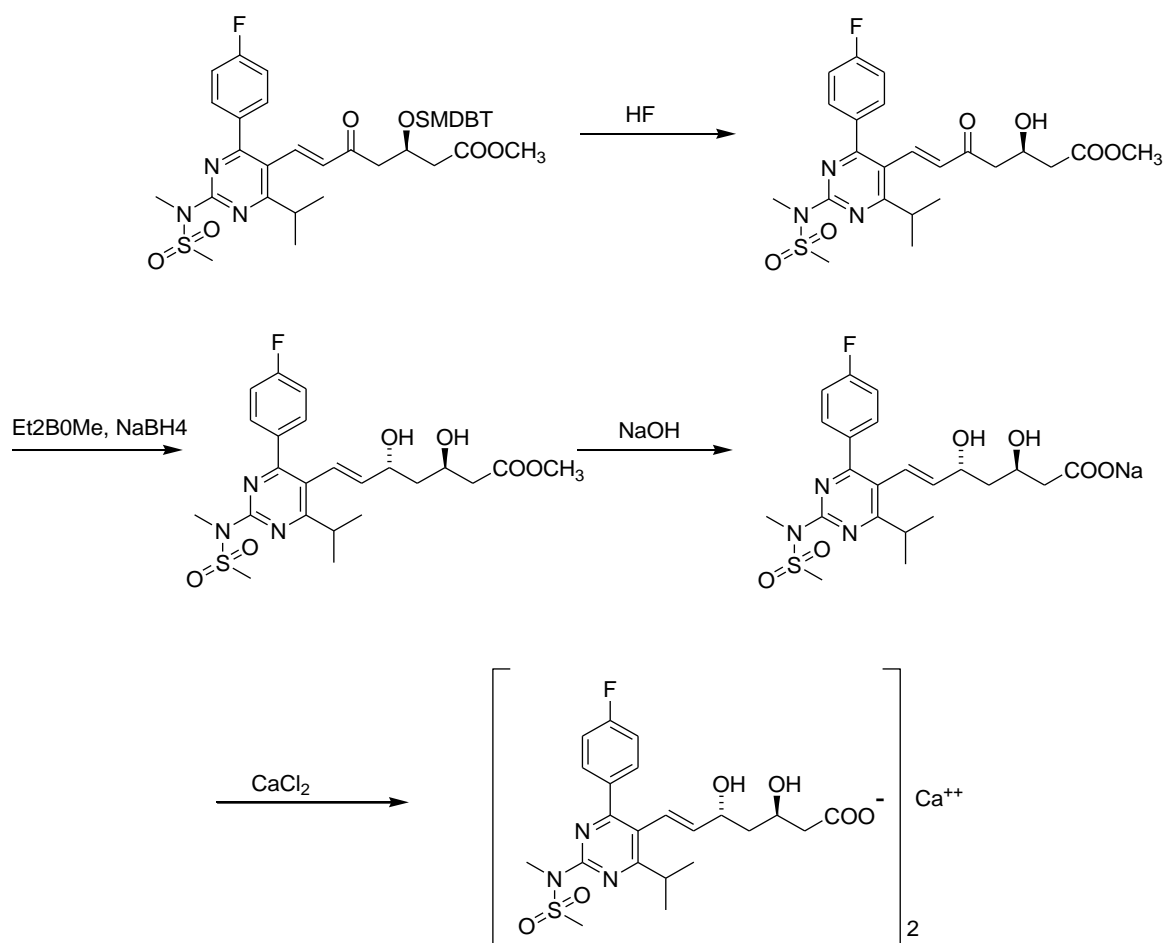


Scheme-1.

### 2. WO 03/097614 A2<sup>[20]</sup>

The procedure describes for the preparation of the starting material 4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-carboxaldehyde and its further conversion to rosuvastatin by condensing with methyl (3R)-3-[(tert-

butyldimethylsilyloxy]-5-oxo-6-triphenylphosphoranylidene hexanoate. The obtained product was deprotected using methanesulfonic acid and subsequently converted to rosuvastatin calcium salt as shown in scheme 2.

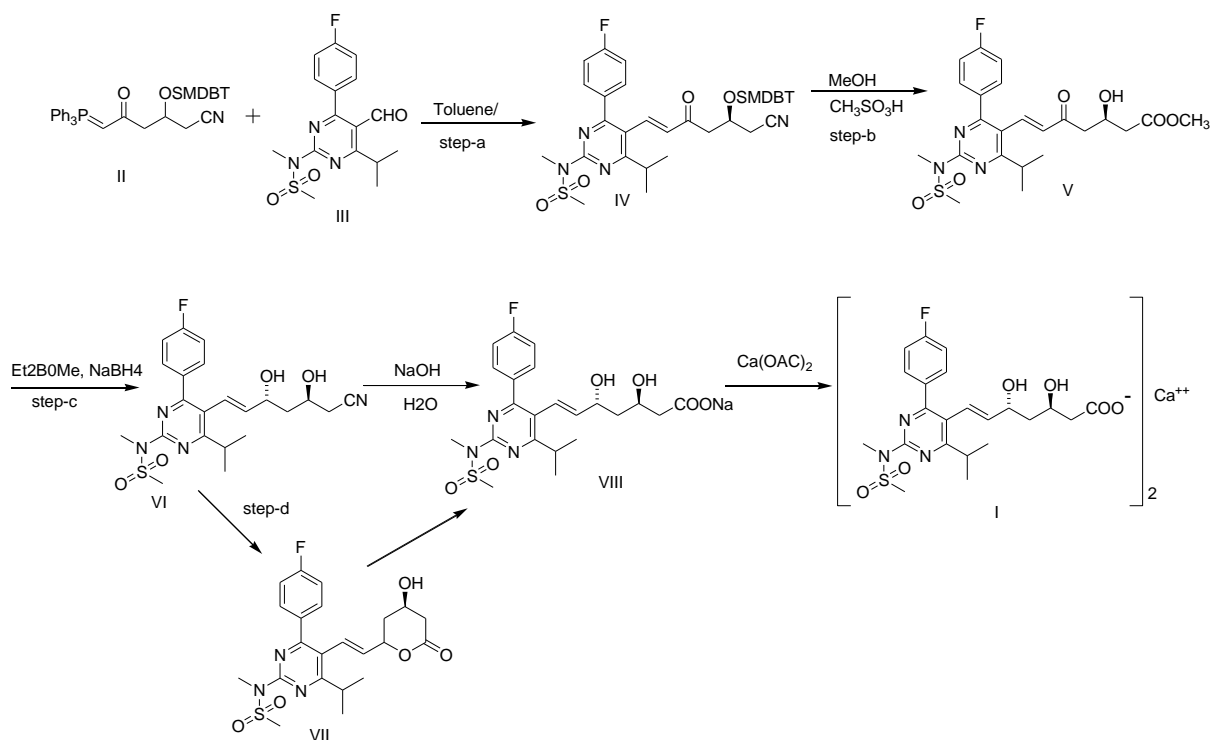


Scheme-2.

### 3. WO 2004/052867 A1<sup>[21]</sup>

The process describes to prepare rosuvastatin by condensing 1-cyano (2S)-2-[(tert-butyl dimethylsilyloxy)-4-oxo-5-triphenylphosphoranylidenepentane with 4-(4-

fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-carbaldehyde and subsequent deprotection of silyl group, followed by reduction and hydrolysis to get Rosuvastatin calcium as shown in scheme 3.

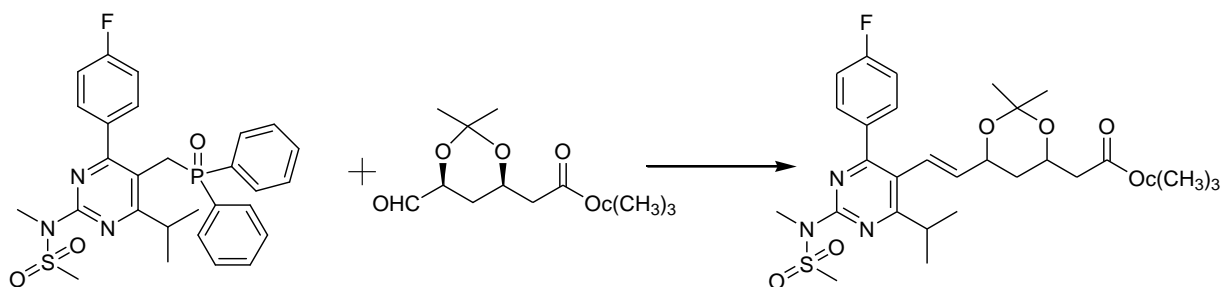


Scheme-3.

#### 4. WO 2000/049014 A1<sup>[22]</sup>

The chemical process describe for the using starting material diphenyl {4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl-

methyl}phosphineoxide condensing with tert-butyl 2-[(4R,6S)-6-formyl-2,2-dimethyl-1,3-dioxan-4-yl]acetate followed by deprotection, hydrolysis and purification to get Rosuvastatin calcium as shown in scheme 4.



Scheme-4.

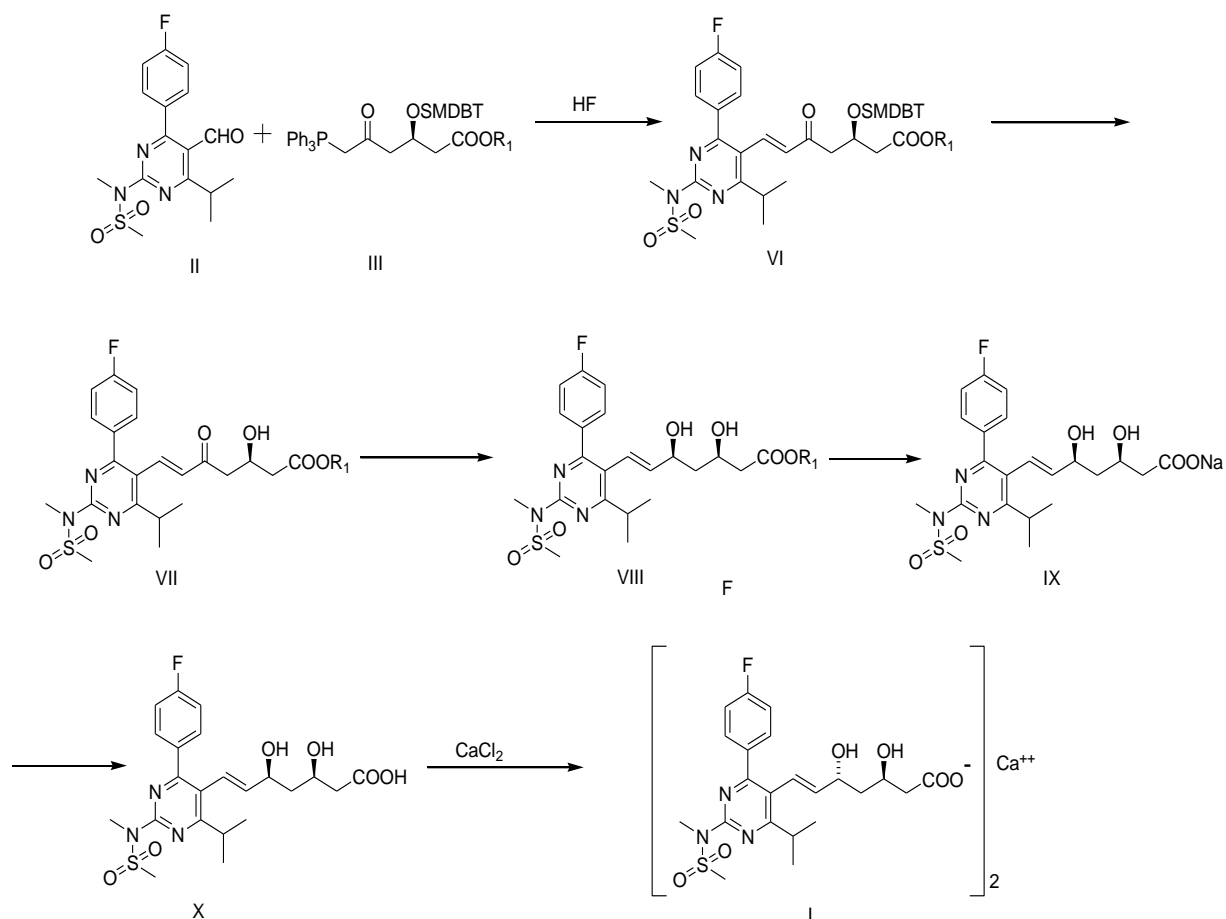
#### 5. WO 2004/014872 A1<sup>[23]</sup>

A process describes for the manufacture of rosuvastatin calcium (2:1) salt, which comprises mixing a solution of calcium chloride with a solution of water soluble salt of (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl](3R,5S)-3,5-dihydroxyhept-6-enoic acid. This process for the preparation of rosuvastatin using of phosphorane side chain, the preparation of side chain requires eight synthetic steps and involves expensive reagents. The process is both too expensive and time consuming, hence not appropriate for commercial scale operation.

#### 6. US 8765947 B2<sup>[24]</sup>

A preparation method of a crystalline intermediate of a rosuvastatin compound 1, carry out a Wittig condensation of a compound (II) with a compound (III)

to get a compound (IV), deprotection the silane group of compound (IV) in the presence of HF acid to obtained a compound (V) carry out asymmetric reduction on the compound (V) in the presence of  $R^2_2BOME$  and sodium borohydrate to get a compound (VI), further alkaline hydration on the compound (VI) in the presence of sodium hydroxide to obtained a compound (VII), acidification of the compound (VII) in the presence of an acid to form a compound (VIII) and conducting esterification of the compound (VIII) and a halohydrocarbon  $R^3X$  in the presence of alkali to form a compound (IX), conducting alkaline hydration on the compound (IX) in the presence of alkali to form the compound (VII); and (h) Converting the compound (VII) in the presence of a soluble calcium salt to the compound (I) as shown in scheme 5.



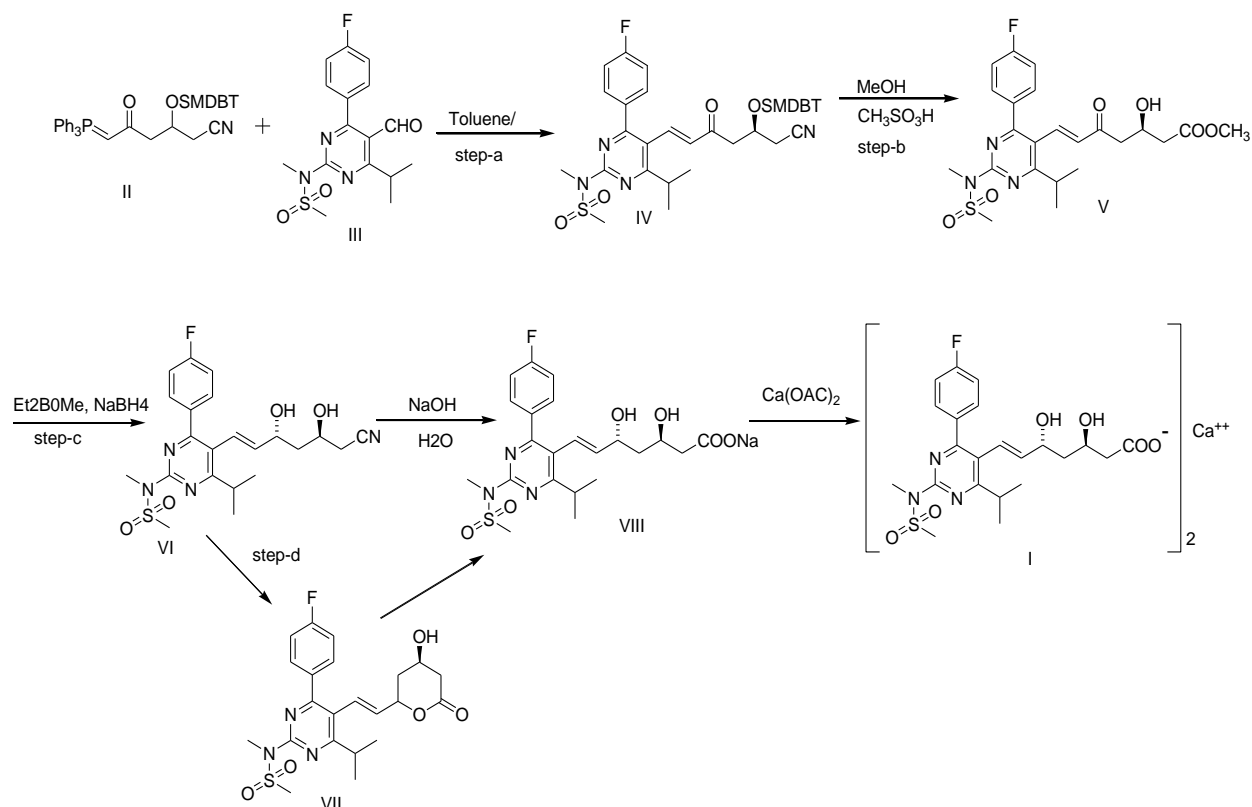
Scheme-5.

### 7. US 8049010 B2<sup>[25]</sup>

A method describe for preparation of an intermediate of rosvastatin calcium, using 4'-fluorophenyl-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidine-5-formaldehyde as a starting material,

- Reacting the raw material with a nitrilized reagent in an organic solvent to produce an intermediate I, 4'-fluorophenyl-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidine-5-acrylonitrile;
- Reacting the intermediate I with a reductant to produce an intermediate II, 4'-fluorophenyl-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidine-5-acraldehyde;
- Reacting the intermediate II with 1,3-bis(trimethyl siloxane)-1-ethoxy-1,3-butadiene to produce an

- intermediate III, 7-[4'-fluorophenyl-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidine-5-yl]-3-oxo-(5R)-5-hydroxy-(E)-6-ethyl heptenoate, wherein the reaction comprises: dissolving the intermediate II in tetrahydrofuran, protecting the intermediate II with an inert gas; adding dinaphthol, isopropyl titanate, and tetramethyl ethylene diamine as catalysts; adding 1,3-bis(trimethyl siloxane)-1-ethoxy-1,3-butadiene after agitating to uniformity, and reacting for 2-4 hours at 20-35° C.; and
- Reacting the intermediate III with an reductant to produce an intermediate IV, 7-[4'-fluorophenyl-6-isopropyl-2-(N-methyl-N-methylsulfonylamino)pyrimidine-5-yl]-(3R,5S)-dihydroxy-(E)-6-ethyl heptenoate as shown in scheme 6.

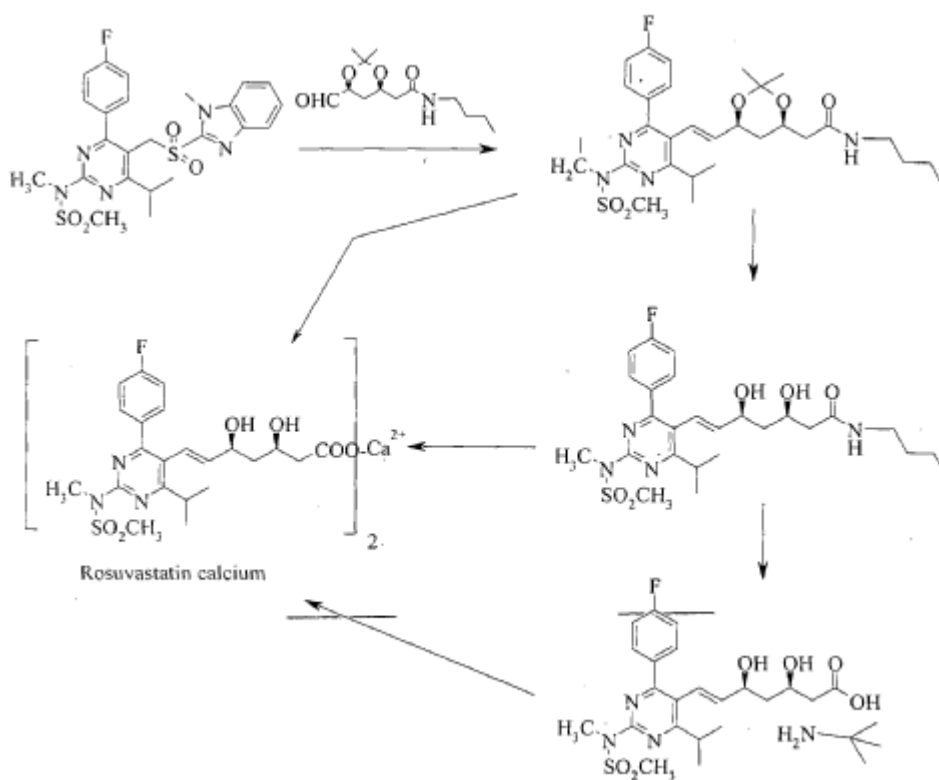


Scheme-6.

### 8. WO2008/044243A2<sup>[26]</sup>

Accordingly to the present invention is to describe a novel process for the preparation of rosuvastatin intermediates and their pharmaceutically acceptable salt

through novel intermediate compounds by employing Julia- modified olefination using novel sulfone, sulfide and sulfoxide compounds as shown in scheme 7.

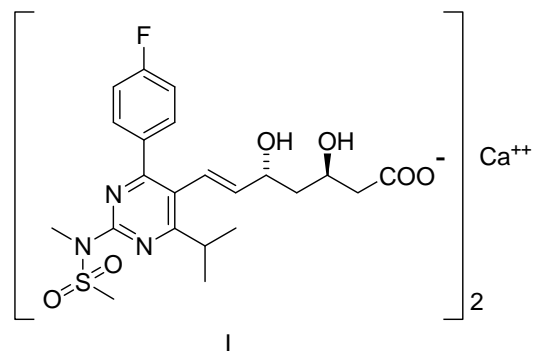


Scheme-7.

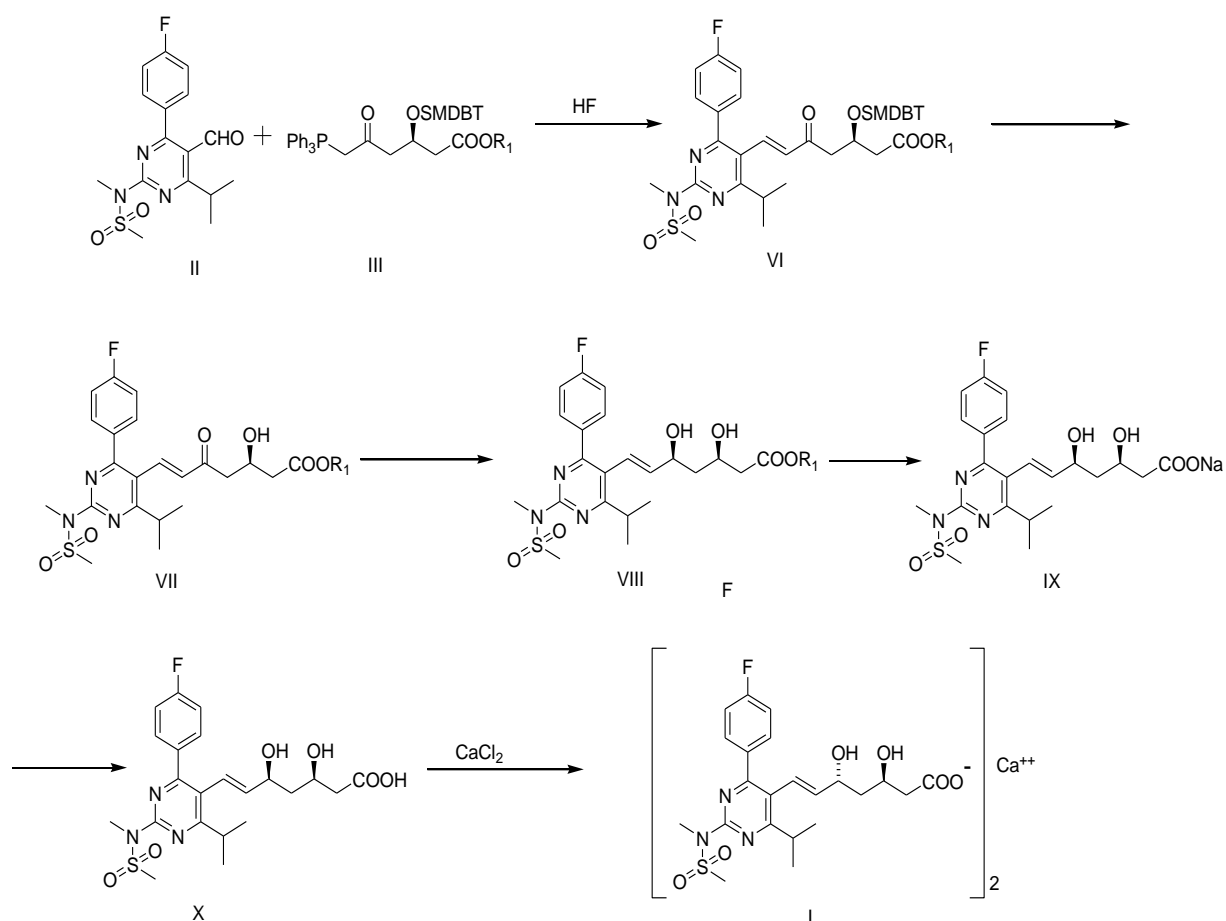
**9. US 20130197224 A1<sup>[27]</sup>**

A preparation method of a crystalline intermediate of a rosuvastatin compound of Formula I, conducting a Wittig condensation of a compound of Formula II with a compound of Formula III to form a compound of Formula IV, deprotecting the silane group of the compound of Formula IV in the presence of hydrofluoric acid to obtain a compound of Formula V conducting asymmetric reduction on the compound of Formula V in the presence of  $R^2_2BOMe$  and  $NaBH_4$  to form a compound of Formula VI, conducting alkaline hydration on the compound of Formula VI in the presence of sodium hydroxide to form a compound of Formula VII; conducting acidification of the compound of Formula VII in the presence of an acid to form a compound of Formula VIII; and conducting esterification of the compound of Formula VIII and a halohydrocarbon  $R^3X$  in the presence of alkali to form a compound of Formula IX, conducting alkaline hydration on the compound of Formula IX in the presence of alkali to form the

compound of Formula VII; and (h) Converting the compound of Formula VII in the presence of a soluble calcium salt to the compound of Formula I,

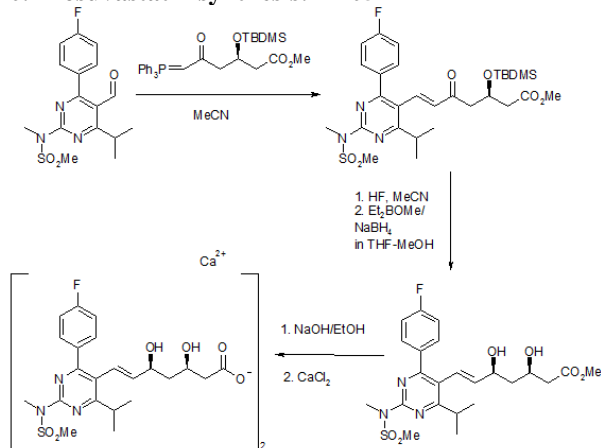


The crystalline intermediate obtained during the method comprising as shown in scheme 8:



**Scheme-8.**

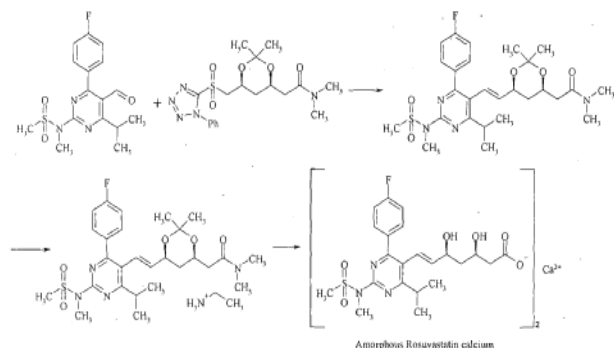


**10. Rosuvastatin synthesis: EP0521471B1<sup>[28]</sup>**

Scheme-9.

**11. EP0521471B1<sup>[29]</sup>**

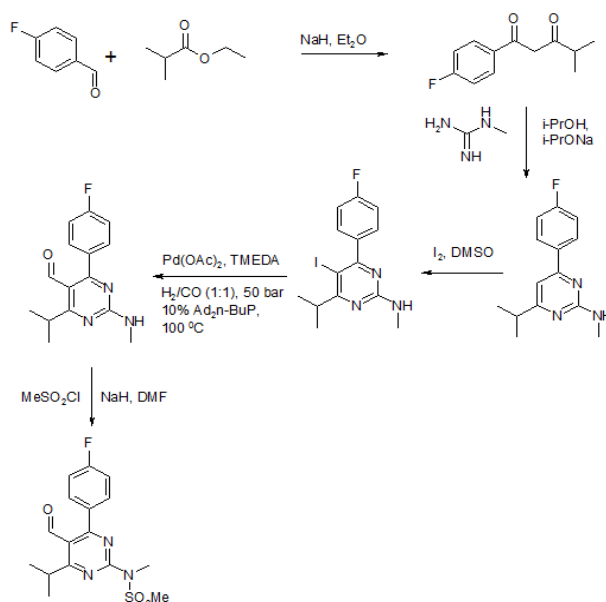
The invention relates to a novel compounds of Formula (1), process for the preparation of chiral diol sulfones of general Formula (1), and to the use of such compounds as intermediates for the preparation of HMG-CoA reductase inhibitors, like rosuvastatin as shown in scheme 10.



Scheme-10.

**12. Beilstein J Org Chem 2013, 9, 2265–2319<sup>[30]</sup>**

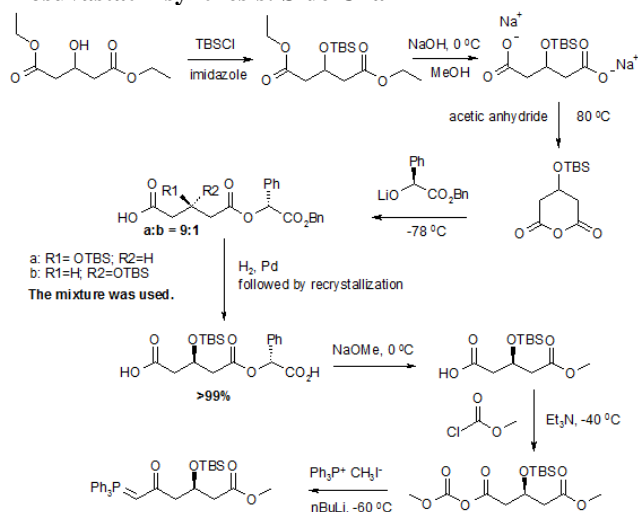
*Rosuvastatin synthesis: Starting material*



Scheme-11.

**13. J Org Chem 1994 59(25), 7849-7854<sup>[31]</sup>**

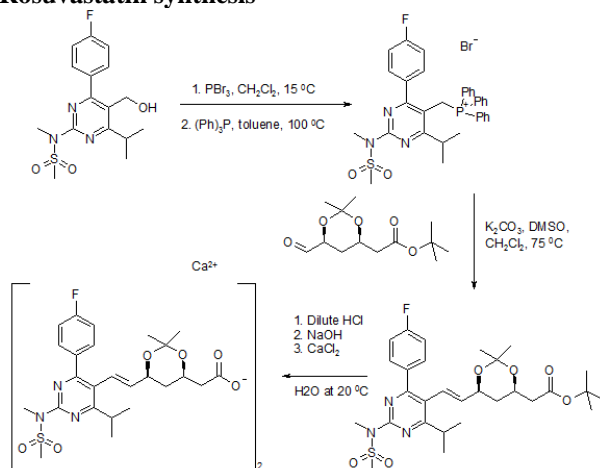
*Rosuvastatin synthesis: Side Chain*



Scheme-12.

**14. Int J Pharm Biomed Sci 2013, 4(4), 118-121<sup>[32]</sup>**

*Rosuvastatin synthesis*

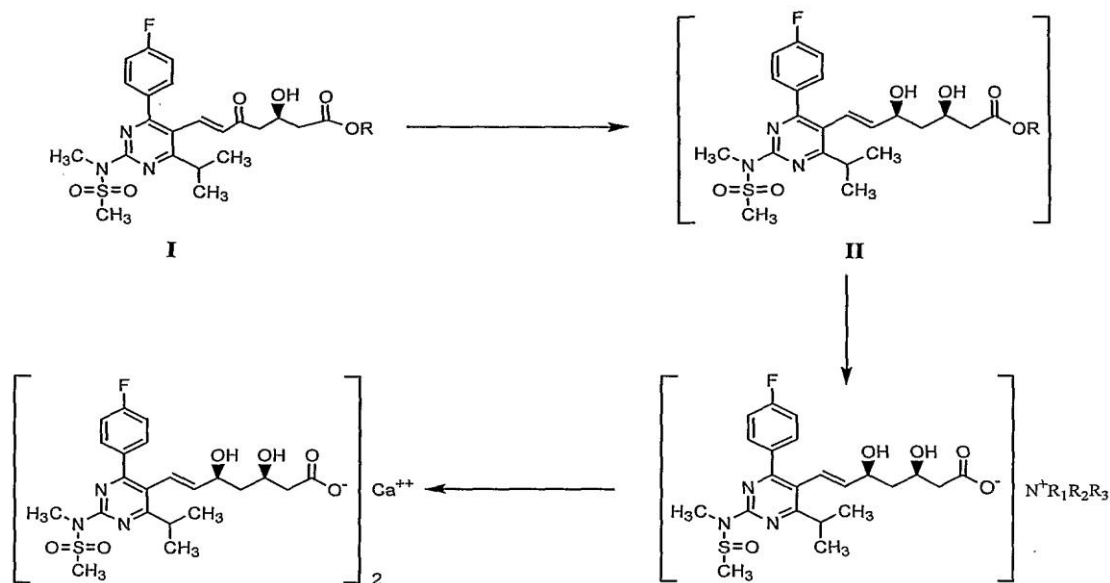


Scheme-13.

**15. US5260440.**<sup>[33]</sup>

The present invention describe to an improved process for preparation of rosuvastatin calcium from novel Rosuvastatin amine salts. The present invention also

describes a process for the preparation of Rosuvastatin amine salts. wherein the amine salt is (S)-2 -Amino-3 ,3 -dimethyl butane or (S)-(-)- $\alpha$ -methyl benzyl amine as shown in scheme 14.

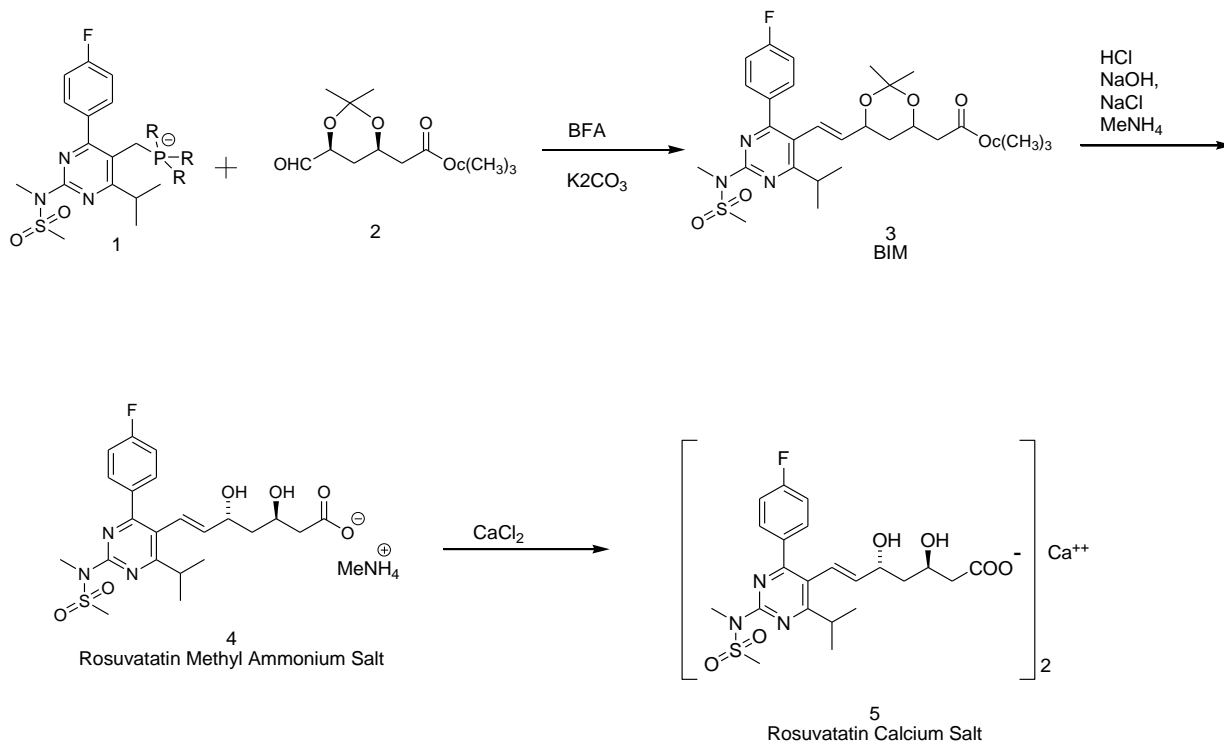


Scheme-14.

**16. WO2005/054207**<sup>[34]</sup>

A process for the preparation of an intermediate of rosuvastatin is provided. The intermediate tert-butyl[E]-6-{2-[4-(4-fluorophenyl)-6-isopropyl-2-

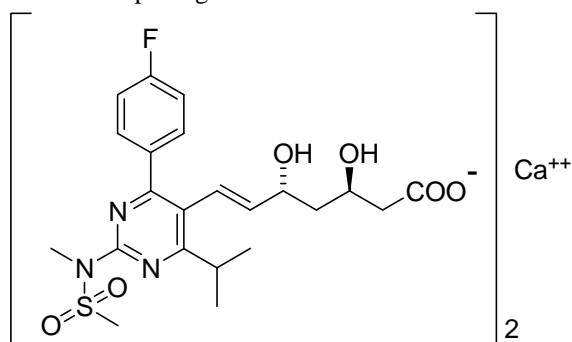
methyl(methylsulfonyl)amino]pyrimidin-5-yl]vinyl}-(4R,6S)-2,2-dimethyl[1,3]dioxan-4-yl)acetate (BEM) can be prepared by the process consist of reacting a Wittig reagent as shown in scheme 15.



Scheme-15.

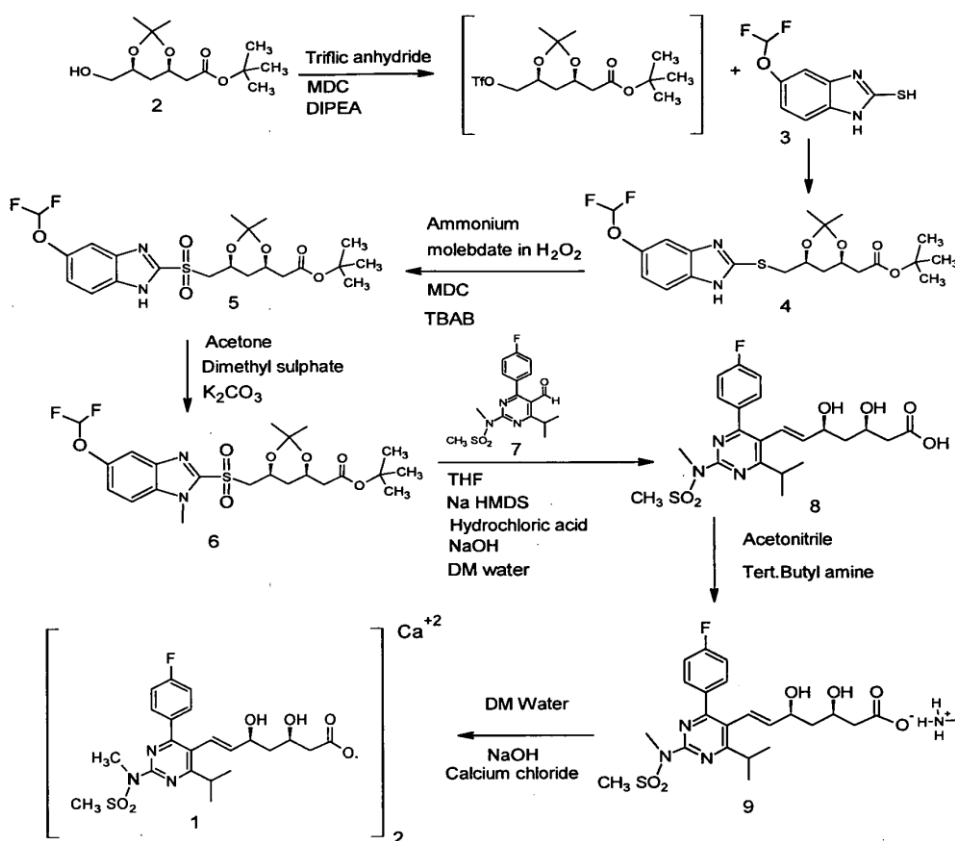
**17. WO 2011121595 A1<sup>[35]</sup>**

A process for the preparation of Rosuvastatin calcium of formula I comprising:



Rosuvastatin Calcium Salt

Rosuvastatin Calcium a) condensation of the compound 2 with compound 3 in the presence of an organic solvent, a base, and a reagent to give compound 4 further oxidation the compound 4 gives compound 5 in the presence of a solvent an oxidizing reagent, methylation of compound 5 to give compound 6 in the presence of a methylating agent; d) condensation of compound 6 with compound 7. To gives compound 8 in the presence of a solvent, base and a mineral acid, converting compound of formula 8 to its amine salt 9 in presence of a solvent and tertiary butylamine; and hydrolysis of compound 9 in the presence of a solvent, a base and a calcium source to give Rosuvastatin calcium as shown in scheme 16.

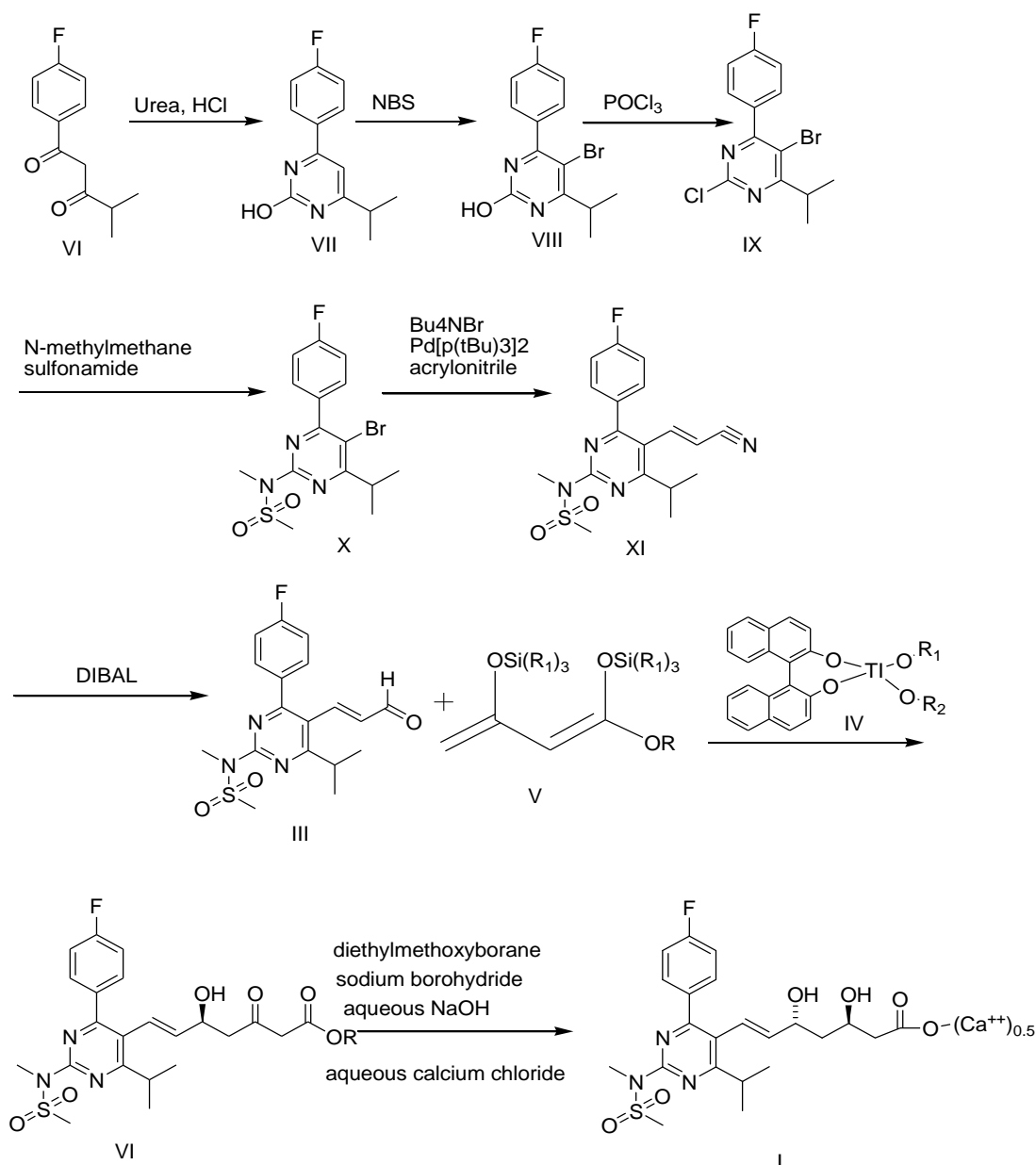


Scheme-16.

**18. WO2007007119A1<sup>[36]</sup>**

According to a first aspect of the invention, there is provided a process for the manufacture of a rosuvastatin calcium (I) thereof, consist of a) reaction of a compound (II) wherein each R<sup>1</sup> is independently selected from (1-6C)alkyl, and R is selected from (1-6C)alkyl, (3-6C)cycloalkyl or aryl(1-6C)alkyl; with a compound

(III) in the presence of a titanium (IV) catalyst, an alkali metal halide salt and an amine, in an inert solvent, to give a compound (V); (V) b) reduction of the keto-group in the compound (V) to give a compound (VI); (VI) and c) removal of the R group to give the compound (I) or a salt thereof; optionally followed by formation of a pharmaceutically-acceptable salt as shown in scheme 17.

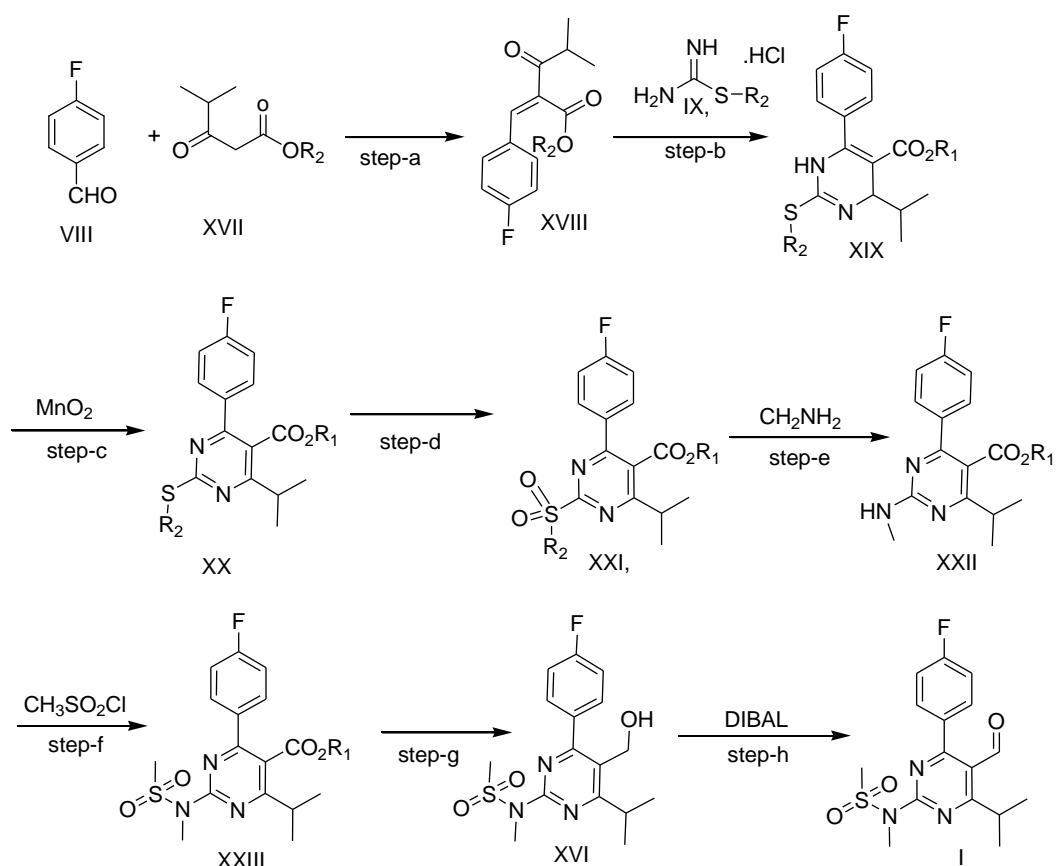


Scheme-17.

**19. US20050222415A1<sup>[37]</sup>**

A process for the preparation of 4-(4-fluorophenyl)-6-isopropyl-2-(N-methyl-N-methylsulphonylamino)pyrimidin-5-yl]carboxaldehyde of structural Formula I, condensing 4-fluorobenzaldehyde of Formula VIII with a compound of Formula XVII, wherein aralkyl, to give an olefin of structural Formula XVIII, reacting the olefin with isothiourea Formula IX, wherein aralkyl, to give a cyclized dihydropyrimidine derivative of Formula XIX, aromatizing the dihydropyrimidine derivative with  $\gamma$ -manganese dioxide to give a pyrimidine compound of

Formula XX, oxidizing the pyrimidine compound to give a sulphonyl derivative of Formula XXI, e. reacting the sulphonyl derivative with methylamine to give an N-methylpyrimidine derivative of Formula XXII, reacting the N-methylpyrimidine derivative with methanesulphonyl chloride to give an N-methylmethanesulphonamide derivative of Formula XXIII, g. reducing the N-methylmethanesulphonamide derivative with diisobutylaluminum hydride (DIBAL) in toluene to give an alcoholic compound of structural XVI, and oxidizing the alcoholic compound to give a pyrimidine aldehyde of Formula I as shown in scheme 18.

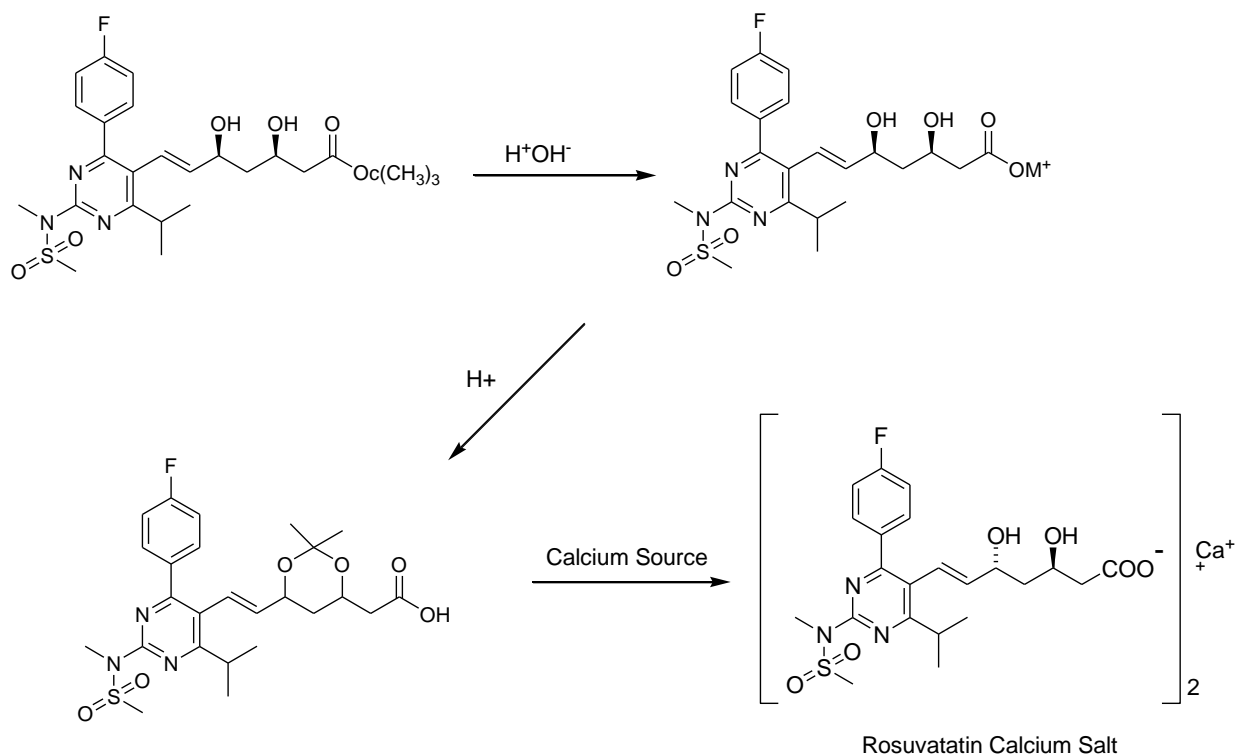


Scheme-18.

**20. WO2006136408A2<sup>[38]</sup>**

Process describes for preparing pure rosuvastatin calcium, substantially free of impurities using Rosuvastatin methyl ester or tert-butyl ester, is disclosed. A process consist of hydrolysing a C1 to C5 alkyl ester of rosuvastatin, preferably methyl rosuvastatin or tert-butyl rosuvastatin, with a base, e.g. sodium hydroxide, in the presence of an aprotic solvent, preferably tetrahydrofuran and N,N-dimethyl acetamide, or in the presence of a mixture of an aprotic solvent and water, to

obtain a solution of rosuvastatin sodium salt, which may be converted to another rosuvastatin salt using another cation, e.g. with calcium cation to obtain rosuvastatin calcium. Rosuvastatin amine salts may be obtained as well. In another preferred feature of the invention rosuvastatin free acid may be converted to various rosuvastatin salts, e.g. to rosuvastatin calcium, rosuvastatin sodium or different rosuvastatin amine salts, including rosuvastatin solvates, e.g. rosuvastatin calcium hydrate as shown in scheme 19.

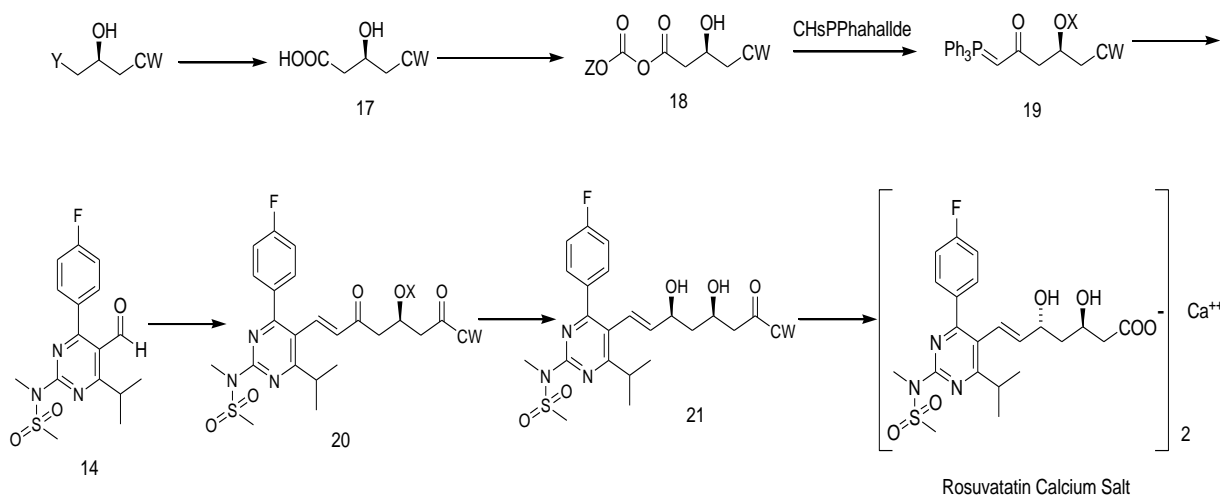


Scheme-19.

**21. WO2007041666A1<sup>[39]</sup>**

The development describe for preparation of rosuvastatin calcium salt, provides processes for the preparation of rosuvastatin intermediates thereof in high yield using cost effective reagents. The processes of the invention

provide for the quantitative conversion of reagents and decreased formation of side reaction and byproducts, resulting in a process for preparing rosuvastatin requiring fewer purification steps as shown in scheme 20.

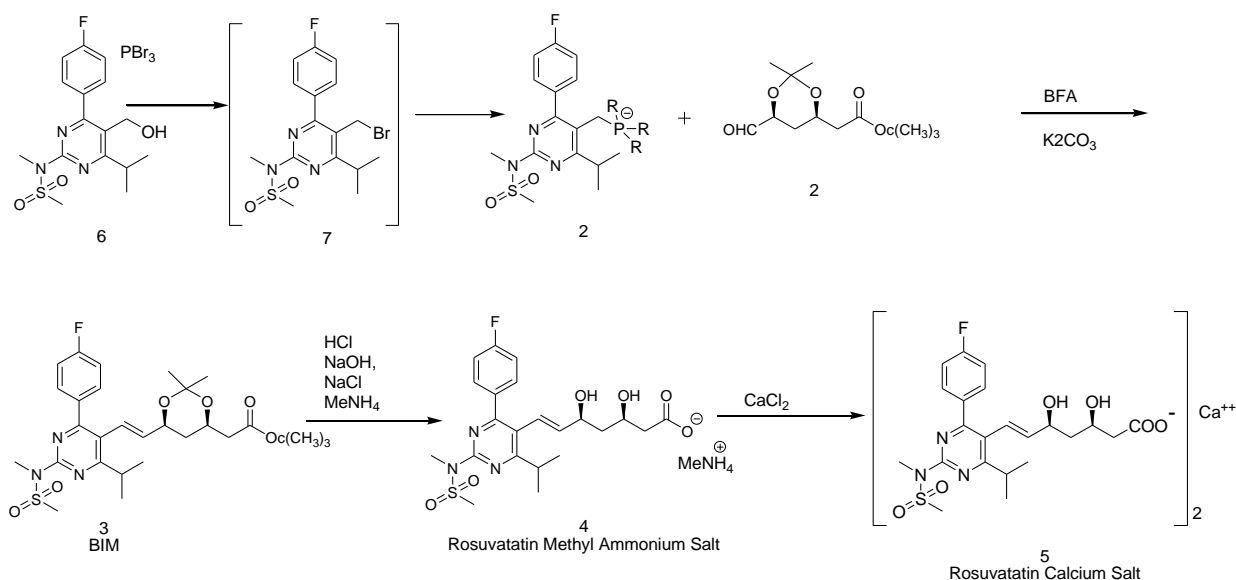


Scheme-20.

**22. US20050124639A1<sup>[40]</sup>**

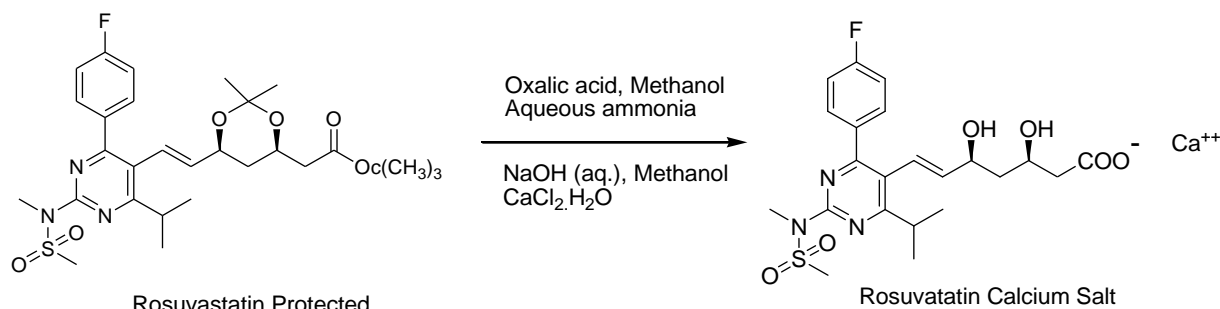
The present invention describe, an improved process for the preparation of rosuvastatin is provided including the steps steps of (a) reacting an alcohol of compound 6 with  $\text{PBr}_3$  to get a bromide intermediate (7); in the step (b) reacting the bromide intermediate (7) with  $\text{P}(\text{Ph})_3$  to get the Wittig reagent TPPBr (1a); in the step (c) reacting TPPBr (1a) with BFA (2) to form BEM (3); in the step

(d) deprotection and hydrolysis of the BEM (3) with hydrochloric acid, sodium hydroxide, sodium chloride and followed by treating with methylamine to form the methylammonium salt of rosuvastatin (4); and (e) reacting the methylammonium salt of rosuvastatin (4) with calcium chloride or calcium acetate to form the calcium salt of rosuvastatin (5 as shown in scheme 21.

**23. WO2007099561A1<sup>[41]</sup>**

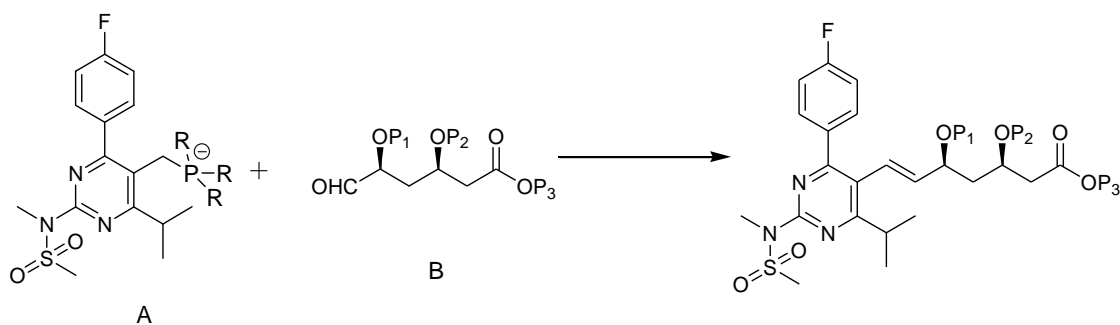
As per the present invention, there is describe a process for the preparation of Rosuvastatin calcium using starting material as a Rosuvastatin diol ester of formula (Ia), which is reacting tert-butyl (E)- (6- {2- [4- (4-fluorophenyl)-6-isopropyl-2- [methyl (methylsulfonyl) amino]pyrimidin-5-yl] vinyl}- (4R, 6S)-2,2-dimethyl[1,3] dioxan- 4yl) acetate of formula (II) treating the

rosuvastatin diol ester of formula (Ia) with a base in alcohol solvent to obtain the solution; cooling the solution and addition of acid to adjust the pH; after that removing the traces of organic solvent; then addition of source of calcium chloride solution to precipitate rosuvastatin calcium; and isolating amorphous rosuvastatin calcium substantially free from impurities as shown in scheme 22.

**24. CN1340052A<sup>[42]</sup>**

At the presence of a strong base, let an oxidized diphenyl [4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonylamino)amino]pyridine-5-ylmethyl]phosphine react with 2-[(4R,6S)-6-formyl group-2,2-dimethyl-1,3-dioxo-4-yl]tert-butyl acetate, then disconnect the protecting group of dihydroxy in the product, alkalinely hydrolyze the tert-butyl ester group, and finally produce rosuvastatin calcium as a calcium salt. In the first route, it takes a long reaction time to synthesize a phosphine (A), with a low yield and at the same time a usage of highly toxic and severely

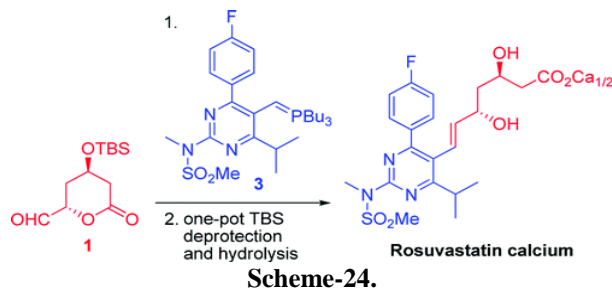
pollutive  $PBr_3$ . There are many synthetic methods of its side chain (B) (U.S. Pat. No. 5,278,313, EP0319847, U.S. Pat. No. 5,399,722, U.S. Pat. No. 5,481,009, U.S. Pat. No. 5,998,633, U.S. Pat. No. 6,140,527, EP0104750, and WO0307733), but most of them have such problems as a long synthetic route (7-9 steps), most of intermediates being viscous, multiple steps of high vacuum (around 0.1 mmHg) distillation and silica gel column purification, a usage of hypertoxic potassium cyanide or sodium cyanide, a poor purity of products, unsteadiness, and difficulty in production industrialization as shown in scheme 23.



Scheme-23.

### 25. Č. Zdenko gave method statins via lactonized side chain<sup>[43]</sup>

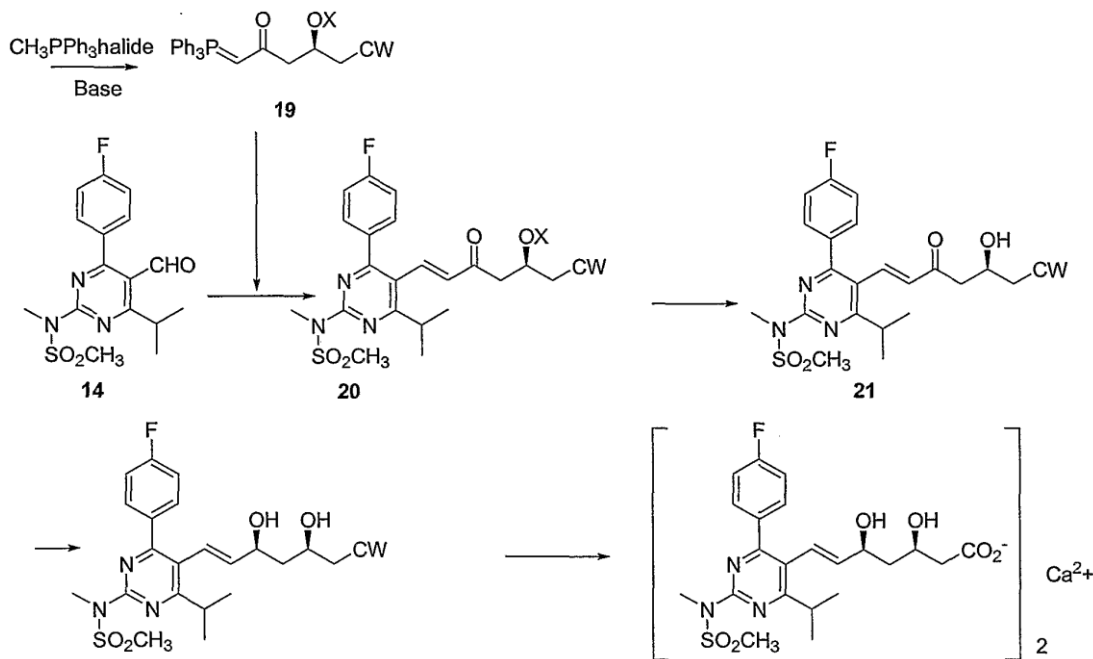
The first way in to statins via lactonized side chain is reported, exemplified by the synthesis of rosuvastatin. The key step is Wittig coupling of (2*S*,4*R*)-4-(tert-butylidimethylsilyloxy)-6-oxotetrahydro-2*H*-pyran-2-carbaldehyde and phosphonium salt of an suitably functionalized pyrimidine heterocycle. One-pot deprotection and hydrolysis of the resulting 4-*O*-TBS rosuvastatin lactone to get rosuvastatin calcium as shown in scheme 24.



Scheme-24.

### 26. W02004/052867<sup>[44]</sup>

The invention describes improved processes for the preparation of rosuvastatin and intermediates thereof in high yield using cost effective reagents. The processes of the invention describe for the quantitative conversion of reagents and decreased formation of by-products, resulting in a process for preparing rosuvastatin requiring fewer purification steps as shown in scheme 25.



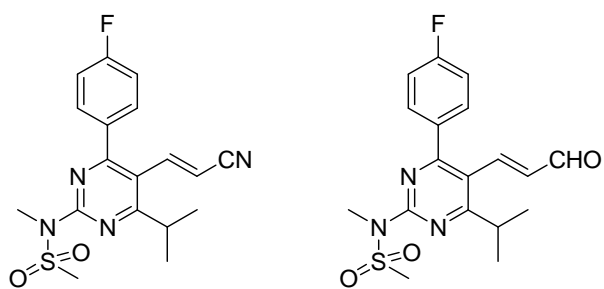
Scheme-25.

### 27. US20080091014A1<sup>[45]</sup>

A method for synthesizing rosuvastatin calcium, using 4'-4'-fluorophenyl-6-isopropyl-2-(*N*-methyl-*N*-methylsulfonylamino)pyridine-5-formaldehyde as the raw material, and including such unit processes as

nitrilized reaction, aldehydized reaction, side-chain extension, ketone-group reduction, ethyl-group hydrolysis and neutralization reaction or decomposition reaction, with the processing steps as shown in scheme 26.

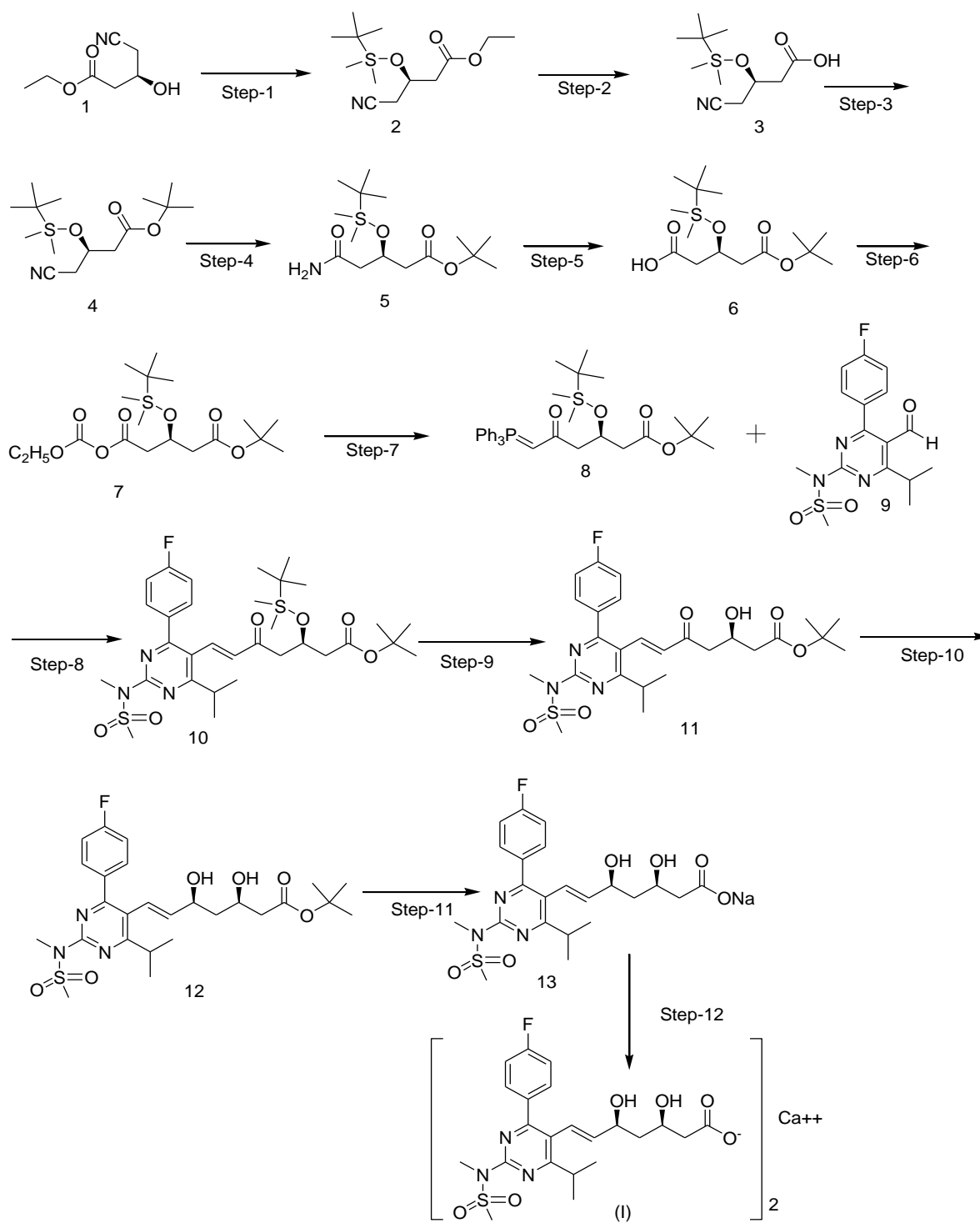




Scheme-26.

**28. US20160304468A1<sup>[46]</sup>**

In one aspect, the present invention describe to the novel intermediates of the formula (4) and formula (5), which are useful in the preparation of Rosuvastatin Calcium as shown in scheme 27.

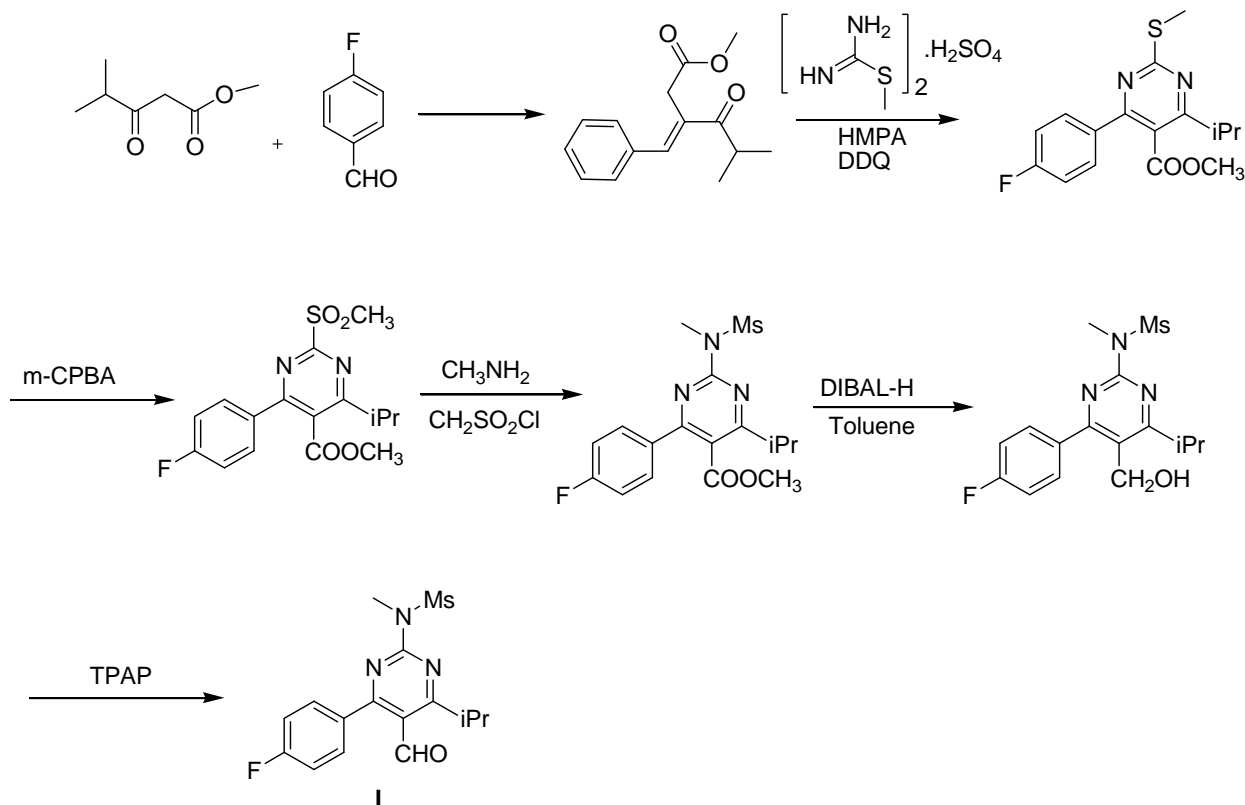


Scheme-27.

**29. US 20130143908<sup>[47]</sup>**

This invention described to a method for preparing a rosuvastatin calcium intermediate, and more particularly

to a method for preparing a compound as shown in scheme 28.



**Scheme-28.**

However, the method is drawbacks in the following aspects:

1. DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) is compulsory in the process, but DDQ is extremely toxic;
2. Raw materials, such as 4-methylmorpholine-N-oxide, TPAP (tetrapropylammonium perruthenate), and DIBAL-H, are costly;
3. DIBAL-H reacts at a low temperature about  $-70^\circ\text{C}$  to  $-40^\circ\text{C}$ , thus resulting in a high energy utilization and manufacture costs, which is not suitable for large-scale industrial manufacture; and
4. The yield in the reaction is low.

**30. US 8404841 B2<sup>[48]</sup>**

Accordingly the first phase of the present invention is described a novel process for the preparation of statins and their pharmaceutically acceptable salt compounds through novel intermediate compounds by employing Julia-modified olefination.

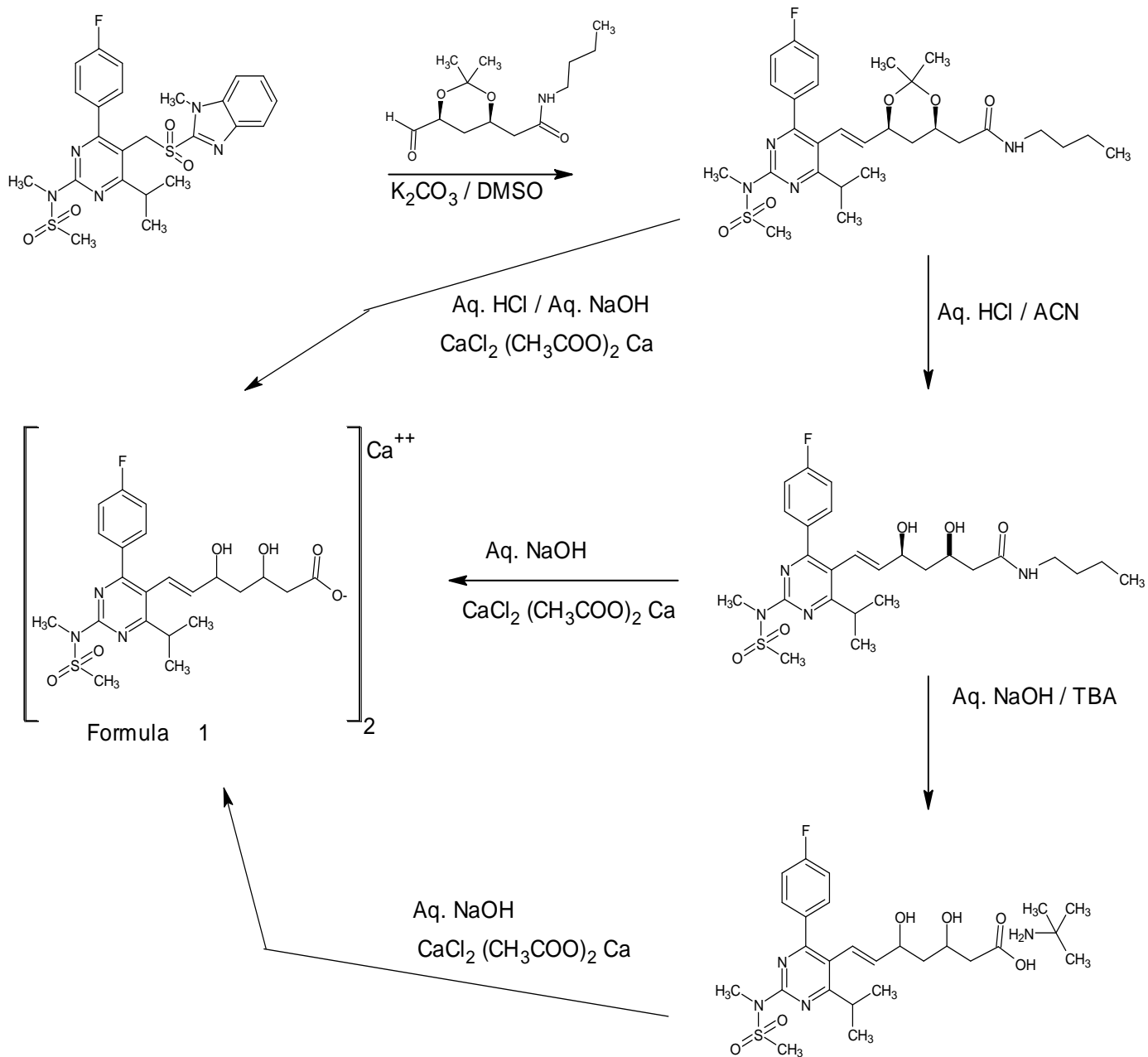
The second phase of the present invention is described a novel process for the preparation of statins and their

pharmaceutically acceptable salt compounds through novel intermediate compounds by employing Wittig-horner reaction.

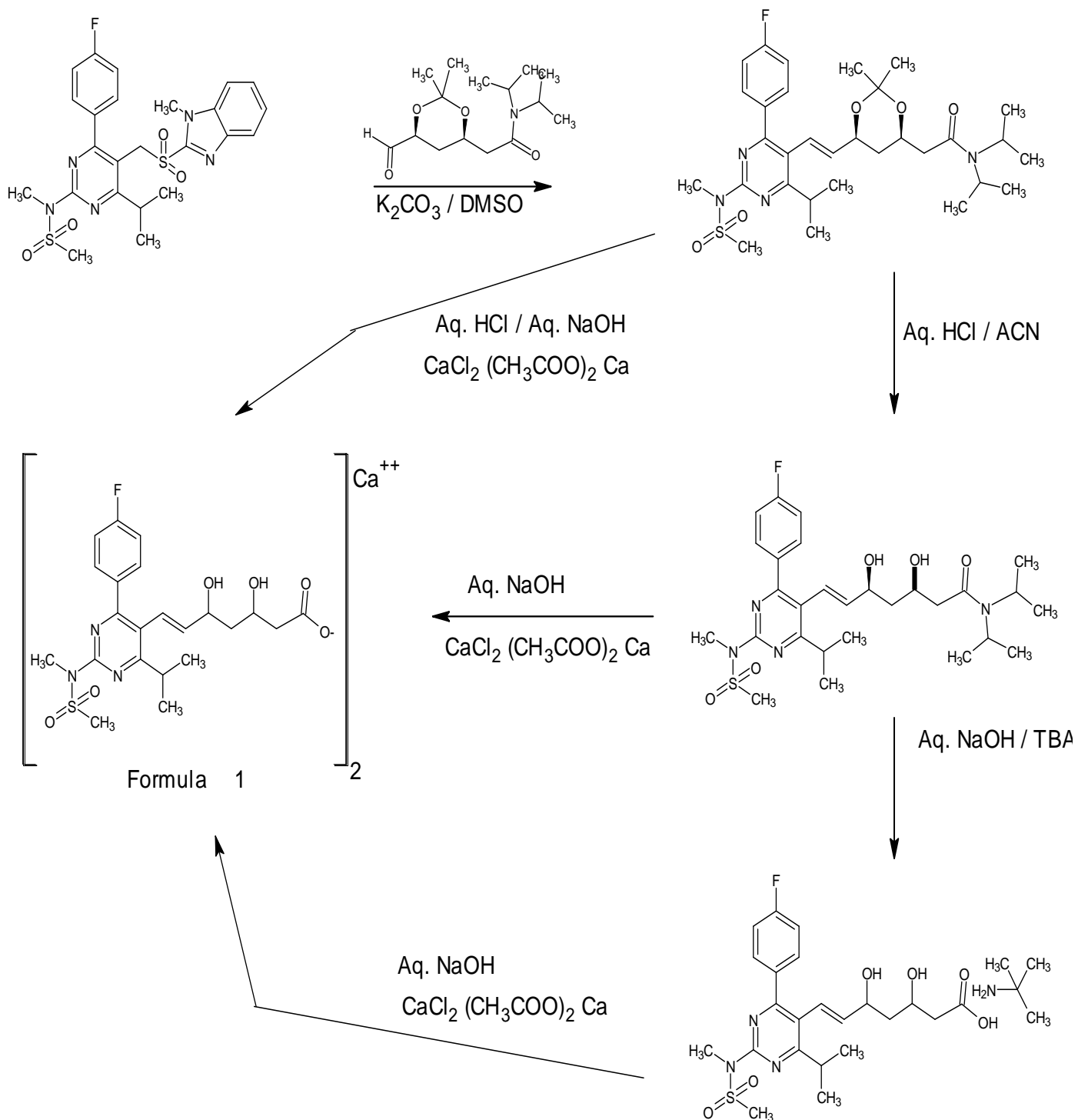
The third phase of the present invention is described a novel process for the preparation of statins and their pharmaceutically acceptable salt compounds of general formula-1 through novel intermediate compounds by employing Wittig reaction and Vilmeier-Haack reaction.<sup>[49-52]</sup>

The fourth phase of the present invention is described a novel amide compounds and process for their preparation. The fifth phase of the present invention is to described a novel sulfone, sulfide and sulfoxide compounds and process for their preparation.

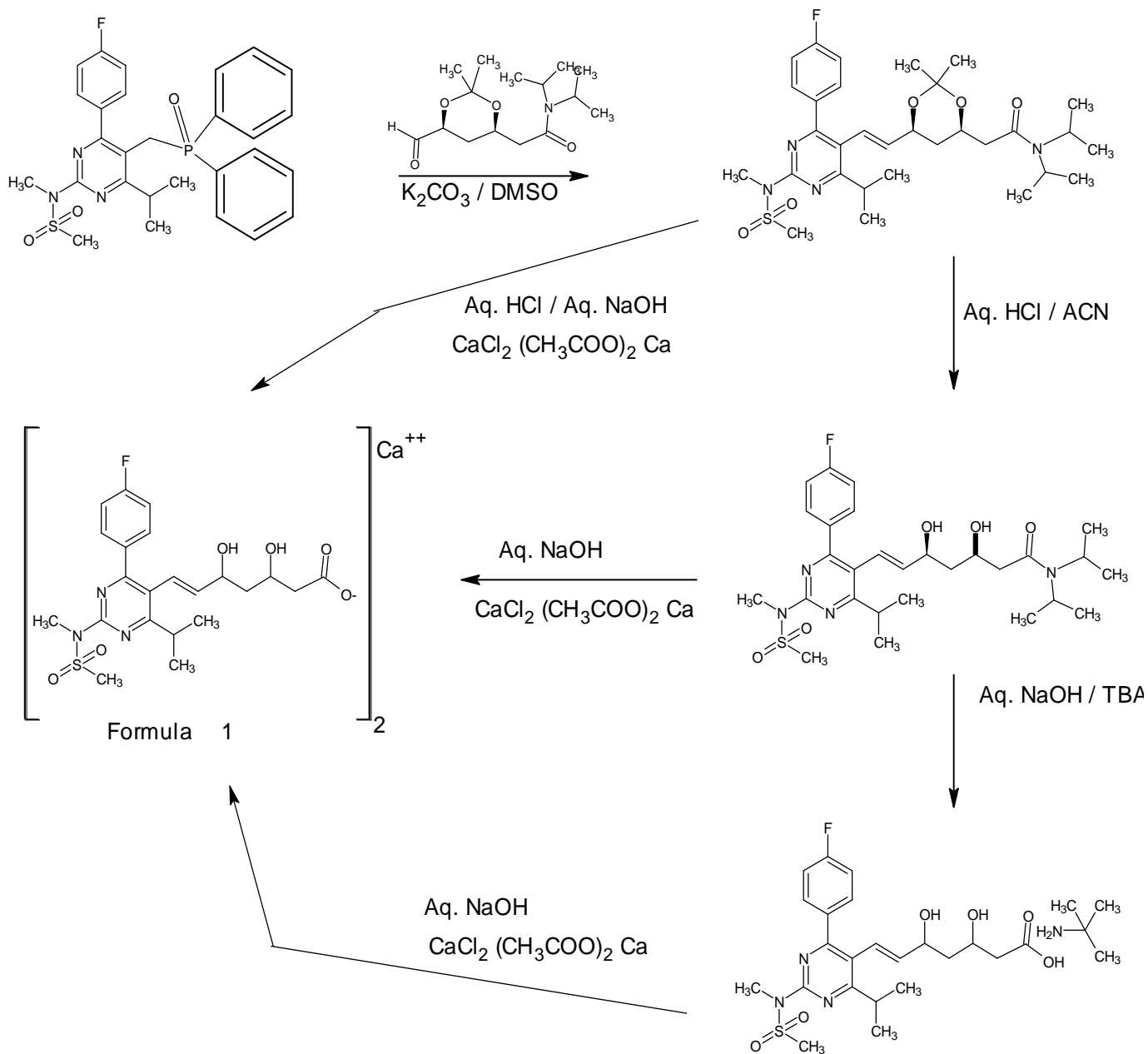
The present invention schematically represented as the following sets of schemes 1- 4.



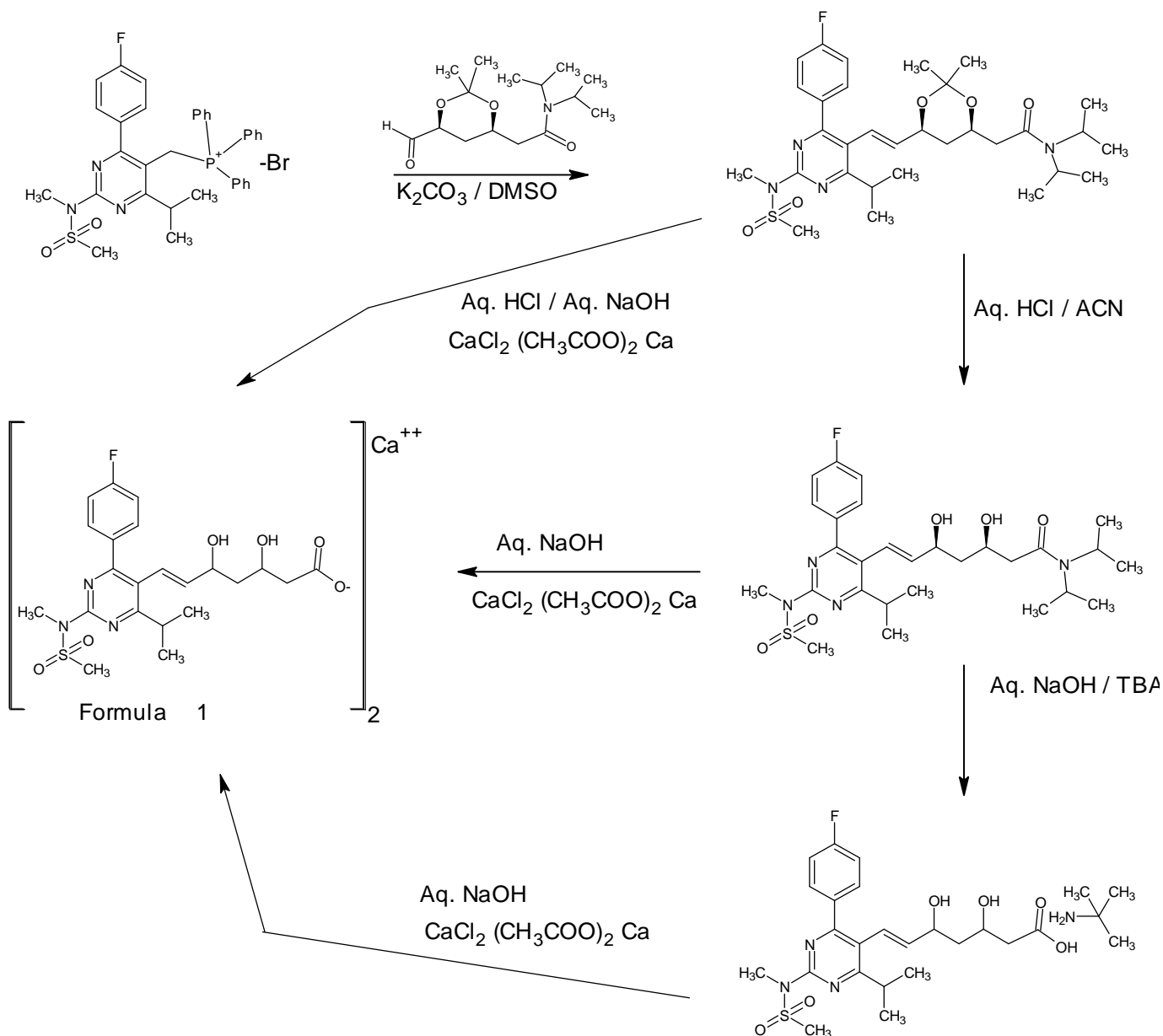
Scheme-1: Employing Julia-modified olefination.



Scheme-2: Employing Julia-modified olefination.



Scheme-3: Employing Wittig-horner reaction.



Scheme-4: Employing Wittig reaction.

**CONCLUSION**

The syntheses of Rosuvastatin were given by various methods as literature survey of papers and through patents. The current review gives overall idea of current and previous development done by chemists and pharmacists.

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