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An improved industrial process for synthesis of HMG-CoA reductase inhibitor Pitavastatin

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ABSTRACT

An highly efficient cost effective, eco-friendly, commercially viable, convergent synthesis for the manufacturing of Pitavastatin, a HMG-CoA reductase inhibitor, has been developed.

Key words : Pitavastatin, HMG-CoA reductase inhibitor, E-alkene, *syn*-diol, Wittig-Horner-Emmons Coupling.

INTRODUCTION

Cardiovascular disease has been a major global problem[1]. The biosynthesis of cholesterol some times leads to persistence of high level cholesterol in our body. It has been well demonstrated that high cholesterol level is a risk factor, which may lead to cardiovascular diseases like atherosclerosis[2]. To avoid this, blocking of biosynthetic pathway of cholesterol by drug is found to be a better way. HMG-CoA reductase inhibitors are better antagonists for blocking the biosynthesis pathway of cholesterol. The **statins** (or **HMG-CoA reductase inhibitors**) form a class of hypolipidemic agents, used as pharmaceutical agents to lower cholesterol levels in people with or at risk for cardiovascular disease. They lower cholesterol by inhibiting the enzyme HMG-CoA reductase, which is the rate-limiting enzyme of the mevalonate pathway of cholesterol synthesis. Inhibition of this enzyme in the liver stimulates LDL receptors, resulting in an increased clearance of low-density lipoprotein (LDL) from the bloodstream and a decrease in blood cholesterol levels[3]. Several pharmaceutical companies has embarked to find a suitable inhibitor for the blocking of cholesterol biosynthesis and found that Pitavastatin is one of the potential HMG-CoA reductase inhibitor.

Pitavastatin calcium 1 which is chemically known as (3R, 5S)-7-[2-cyclopropyl-4-(4-fluorophenyl) quinolin-3-yl]-3, 5-dihydroxy-6(E)-heptenoic acid calcium salt having the following formula-1. Few methods for the synthesis of pitavastin have been reported[4] in literature But to meet the demand for Pitavastatin drug in the market, there is a need to develop a ideal commercial process, which is a safe, ecologically sound, economically viable and meets the quality specifications. As a part of our process R&D activity to develop more economic and cost effective process for important API's[5,6], we choose to develop a process for Pitavastatin calcium 1.

RESULTS AND DISCUSSION

The major challenges in developing process for Pitavastatin calcium 1 are, the synthesis of Quinoline ring, olefin with E-configuration and a 3,5-*syn*- diol. Based on the earlier synthesis[7] the retrosynthetic analysis is illustrated in Fig-1.

Accordingly our first priority was to develop process for Diphenyl-[4-(4-Fluorophenyl)-2-cyclopropyl-quinoline-2-yl]- phosphinylbromide intermediate (Scheme-1). Known processes for the preparation of intermediate 2 do not meet the demand of economic process. Our aim was to develop an ideal process, for this we have taken 2-

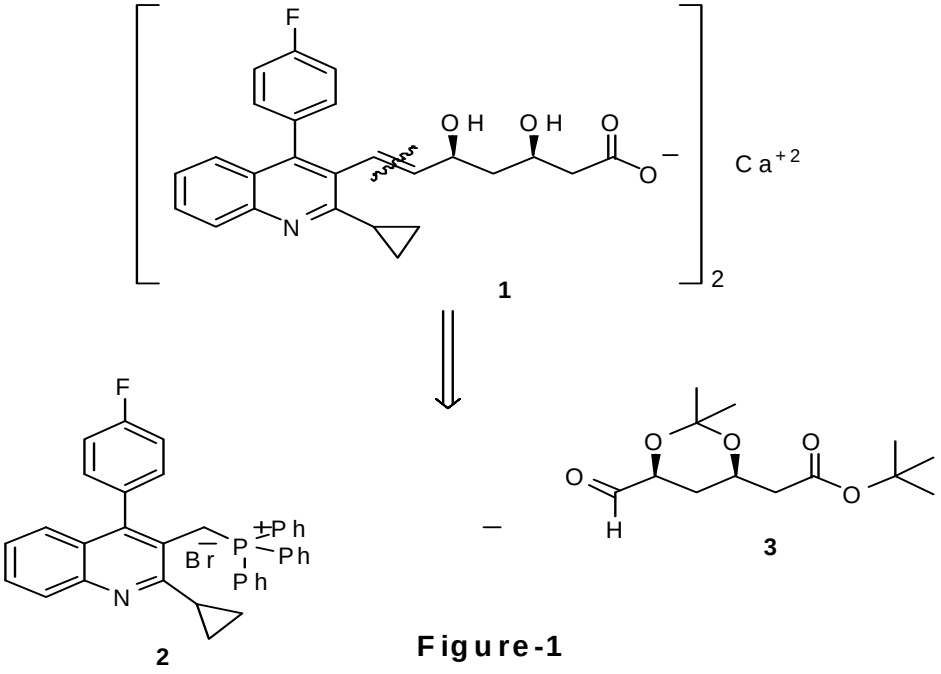
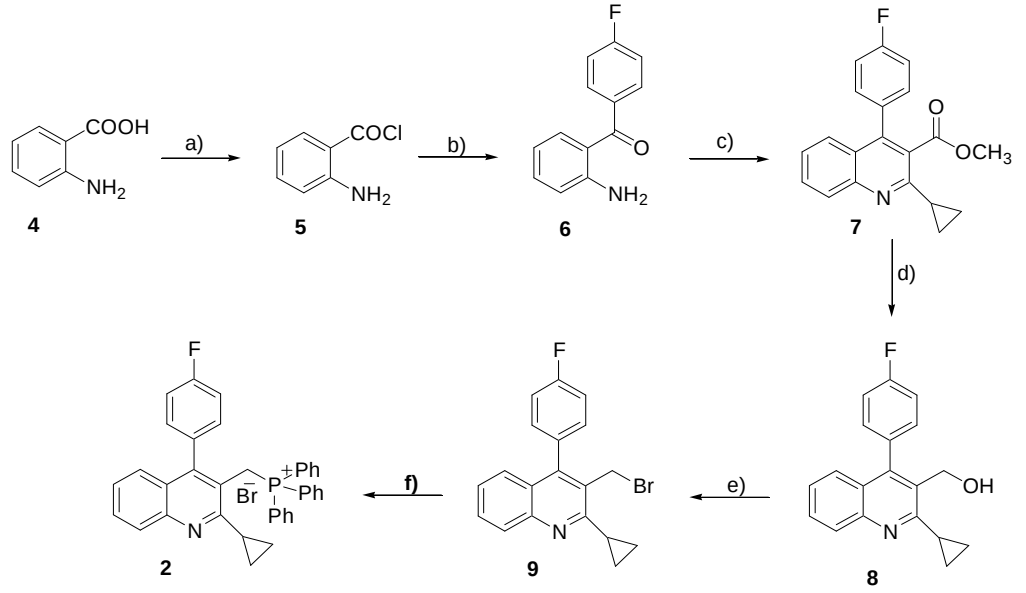


Figure-1

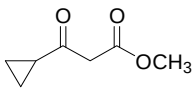
Aminobenzoic acid 4 as our starting material and converted it to acid chloride 5 with PCl_5. Compound 5 was utilized to benzoylate fluorobenzene to yield compound 6. This was condensed with methyl-3-cyclopropyl-3-oxopropanoate, followed by cyclisation in presence of sulphuric acid gave compound 7, which was reduced to compound 8 using DIBAL-H.

Compound 8 on treating with phosphorus tribromide gave compound 9. Compound 9 was converted to intermediate 2 by reacting with triphenylphosphine. We have developed this process by taking easily available, cost effective raw material with high yields.

After successful completion of intermediate 2, we switched our focus to develop process for the side chain intermediate 3. The major difficulty in this moiety was obtaining stereospecific syn – diol at 3 and 5 positions. We achieved this synthesis (Scheme–2) starting from ethyl-4-chloroacetoacetate. Reduction of compound 10 using sodiumborohydride gave 11, which on condensation with tert-butylacetate gave 12. The aim in selecting bulky acetate was to inhibit lactone formation in further steps. Now the major hurdle is the stereoselective reduction[7] of β-hydroxyketone 12 to a *syn*-diol 13. This was solved by reducing with sodiumborohydride and methoxydiethylborane. Here methoxydiethylborane was first added to Compound 12 which displaces methoxy group in methoxydiethylborane by forming a covalent bond and allowing boron to chelate the ketone intramolecularly. Formation of chelate not only activates the ketone for reduction but also forms a

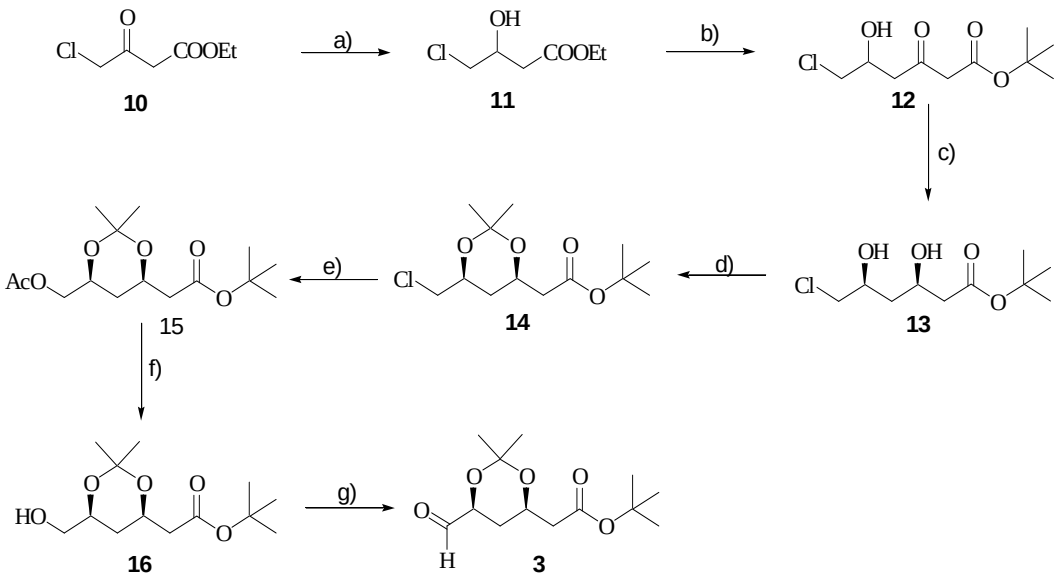


a) TsCl, Na_2CO_3, PCl_5, b) Fluoro benzene, $AlCl_3$, c) H_2SO_4,



d) DIBAL-H, e) PBr_3, f) PPh_3

Scheme 1



a) $NaBH_4$ /Acetic acid, b) Tertbutylacetate/L iH MDS, c) $NaBH_4$/Diethylmethoxyborance, d) 2,2-Dimethoxypropance/ Methanesulfonic acid, d) CH_3COONa/TBAB, f) K_2CO_3/Methanol g) Sodium pochlorite/TEMPO

Scheme 2

six membered ring with two faces, a more hindered and a less hindered face.

Due to this the reduction will occur from the less hindered side thus resulting in *syn*-diol, the chelate was broken by hydrolyzing with hydrogen peroxide in presence of base. *syn*-diol 13 was protected with 2,2-dimethoxypropane in presence of methane sulfonic acid to give compound 14, which was converted to 15 using sodium acetate. Compound 15 on further hydrolysis using mild base potassium carbonate to gave alcohol 16. This was converted to the desired intermediate 3 by mild oxidation with sodiumhypochlorite in presence of radical intiator TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy free radical).

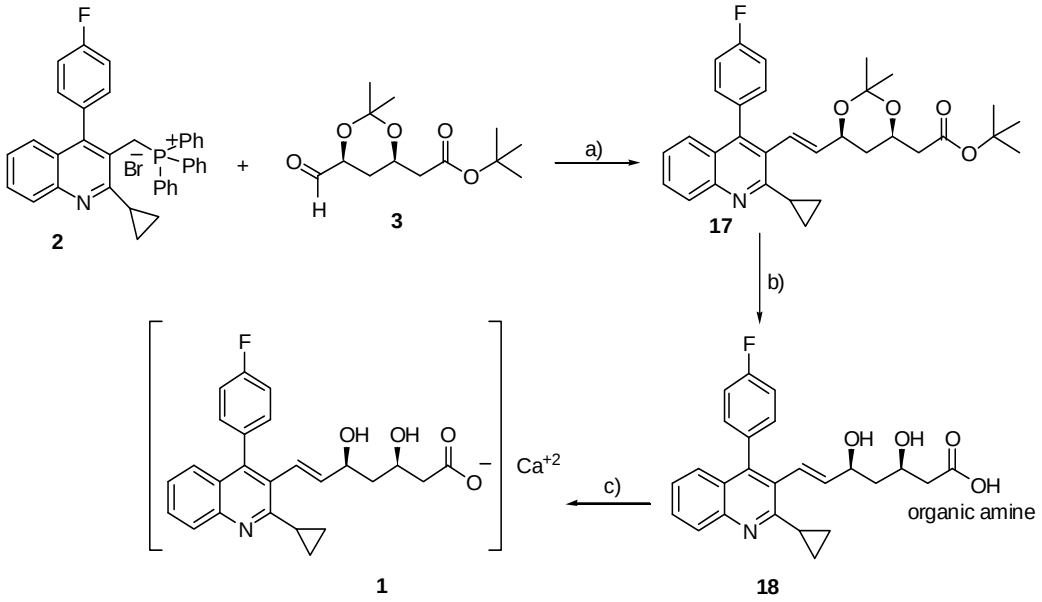
With the two subunits in hand we focused on their coupling (Scheme-3). This has to be functionalized appropriately as there is need to get E-olefin. This was solved by coupling both the intermediates under wittig conditions using K_2CO_3 as base to give coupled product 17. The acetonide (dihydroxy) protecting group of compound 17 was cleaved by treating with hydrochloric acid and further saponification of ester group and tert.butylamine gave compound 18 as amine salt. Calcium salt of pitavastatin 1 obtained by treating 18 with calcium chloride.

In summary, we have achieved a convergent synthesis of highly potent HMG-CoA reductase inhibitor. This protocol is amenable to scale up and will be a valuable process for the commercial production of Pitavastatin calcium.

Experimental section

General Procedures

Melting points were determined in open glass capillaries on a Fisher Johnes melting point apparatus and are uncorrected. IR spectra were recorded on Thermo nicolet 380-model infrared spectrophotometer. 1HNMR (200 MHz) and 13C NMR(50 MHz) spectra were recorded on Seimens spectrometer in $CDCl_3$ solvent using TMS as internal standard. Mass spectra were recorded on a VG-micro mass 7070H instrument at 70eV.Elemental analyses were carried out on EI Elemental Vario EL (Germany) apparatus Preparation of Triphenyl [2-cyclopropyl-4-(4-fluorophenyl)-quinoline-3-ylmethyl)-phosphonium] bromide compound of formula-2



Scheme - 3

a) K_2CO_3, DMSO, b) aqHCl, aqNaOH, ter, butylamine c) NaOH, $CaCl_2$

Added a solution of 16.1 grams of triphenyl phosphine in 50 ml of toluene to 15grams of 3-(bromomethyl)-2-(1-cylclopropyl)-4-(4'-fluorophenyl)quinoline compound of formula-9a. Heated the reaction mixture to 110°C. Stirred the reaction mixture for 60 minutes at 110°C. Cooled the reaction mixture to 25-35°C. Filtered the solid and washed with hexanes to get the title compound.
Yield: 20 gramsM.R: 218 - 225°C (decomposed)

Preparation of (4R, 6S)-(E)-6-[2-(2-cyclopropyl-4-(4-fluorophenyl) quinoline-3-yl)-vinyl]-2, 2-dimethyl-1, 3-dioxane-4-yl] acetic acid tertiary butyl ester compound of formula-17

Added a solution of 2.7 grams tert-butyl-2-((4R,6S)-6-formul-2,2-dimethyl-1,3-dioxan-4-yl)acetate compound of formula-3 in 46 ml of dimethylsulfoxide to a mixture of 5 grams of triphenyl[2-cyclopropyl-4-(4-fluorophenyl)-quinoline-3-ylmethyl)-phosphonium]bromide compound of formula-2 and 2.88 grams of potassium carbonate. Heated the reaction mixture to 70°C. Stirred the reaction mixture for 3 hours at 70°C. Quenched the reaction mixture with water. Extracted the reaction mixture with toluene. Concentrated the organic phase and isolated the title compound using hexanes.
Yield: 13 gram
M.R: 105 – 116°C

Preparation of pitavastatin tertiary butyl amine compound of formula-18

A mixture of 7.2 grams of (4R,6S)-(E)-6-[2-(2-cyclopropyl-4-(fluorophenyl)quinoline-3-yl)-vinyl]-2,2-dimethyl-1,3-dioxane-4-yl]acetic acid tertiary butyl ester compound of formula-5 and 216 ml of acetonitrile was cooled to 23-28°C. Added 45.36 ml of 4.75% aqueous hydrochloric acid to the reaction mixture. Stirred the reaction mixture for 2 hours at 23-28°C. Added 21.6 ml of 10% sodium hydroxide solution to the reaction mixture. Stirred the reaction mixture for 2 hours 30 minutes at 25-35°C. Distilled the solvent completely. Quenched the reaction mixture with water and filtered through hyflow. Washed the reaction mixture tertiary butyl acetate and expelled the aqueous phase. Added sodium chloride solution followed by acetonitrile. Cooled the reaction mixture to 0-10°C. Adjusted the pH of the reaction mixture to 4.5 with 10% hydrochloric acid. Stirred the reaction mixture for 1 hour. Separated the organic and aqueous phases. Cooled the organic phase to 0-10°C. Added 2.38 ml of tertiary butyl amine to the reaction mixture. Stirred the reaction mixture for 30 minutes at 25-35°C. Distilled the solvent completely under reduced pressure and isolated the title compound using acetonitrile as a solvent.
Yield: 2.4 grams

Preparation of pitavastatin calcium compound of formula-1

A solution of 2 grams of pitavastatin tertiarybutyl amine compound of formula-18b in 12 ml of water was cooled to 25-30°C. Added 2 ml of 8% aqueous sodium hydroxide solution at 25-30°C. Stirred the reaction mixture for 1 hour at 25-30°C. Washed the reaction mixture with tertiary butyl acetate and expelled the solvent completely under nitrogen atmosphere. Filtered the reaction mixture through filter paper. The aqueous phase of the reaction mixture was added to a solution of 0.4 grams of calcium chloride dihydrate in 2 ml of water in 15 minutes at 45°C. Stirred the reaction mixture for 30 minutes. Filtered the solid and washed with water to get the title compound.
Yield: 2.45gram; HPLC : 99.70%, 0.1%.

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