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One Pot Facile and Efficient Synthesis of Calcium bis-(E)-3, 5-dihydroxy-7-[4' (4''-flurophenyl)-2'-cyclopropyl-quinoline-3-yl]-hept-6-enoate a HMG-CoA Reductase Inhibitor in Aqueous Media

Kundan Singh Shekhawat and Digish Kumar Sharma*

Department of Chemistry, University of Rajasthan, Jaipur -302055, Rajasthan, India.

ABSTRACT

A process for the preparation of substantially pure calcium bis-(E)-3,5-dihydroxy-7-[4'-(4''-flurophenyl)-2'-cyclopropyl-quinoline-3-yl]-hept-6-enoate ***1,*** *pitavastatin calcium a HMG-CoA reductase inhibitor is described. The prior methods reported for the said conversion involves use of large amount of organic solvents. The new procedure reported here involves use of only water as solvent. The operational simplicity, high yield, eco-friendly conditions and easily scalable process are major benefits.*

Keywords. HMG-CoA reductase, Pitavastatin calcium, deprotection, hydrolysis, water.

INTRODUCTION

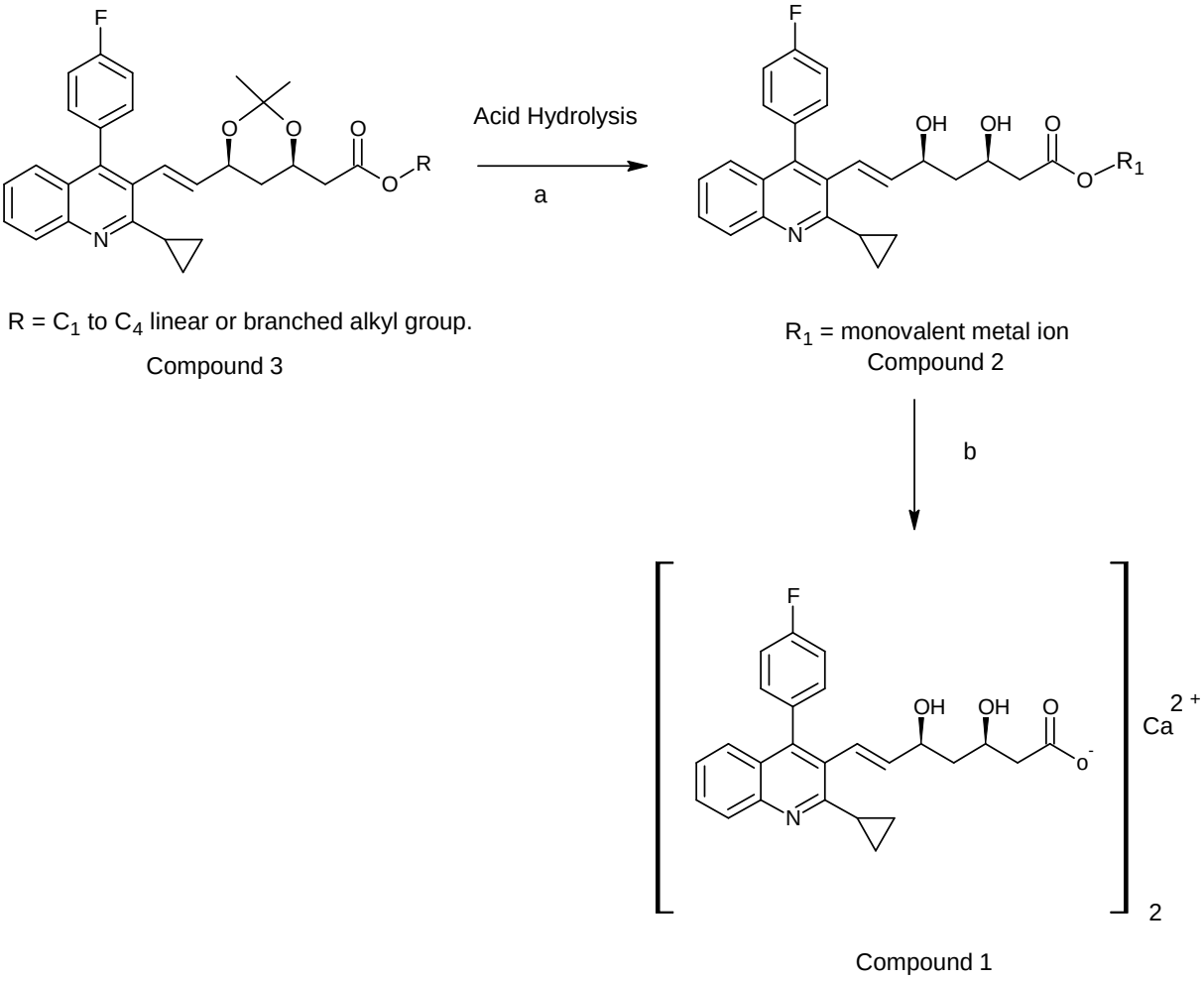
Statin drugs are currently the most therapeutically effective drugs available for reducing the level of Low density lipoprotein (LDL) in the blood stream of a patient at risk for cardiovascular disease. A high level of LDL in the bloodstream has been linked to the formation of coronary lesions which obstruct the flow of blood and can rupture and promote thrombosis. It is well known that inhibitors against HMG CoA reductase which is rate limiting enzyme for cholesterol biosynthesis [1] have been clinically proved to be potentially useful anti-hyperlipoproteinemic agents and they are considered very effective curative and preventive for coronary artery sclerosis or atherosclerosis [2].

Pitavastatin calcium (compound **1**) discovered by Nissan Chemical Industries Limited [3] Japan and developed further by Kowa Pharmaceuticals Tokyo Japan is a novel member of the medication class of statins. Several methods for the preparation of pitavastatin calcium are known in literature [4-16]. However many of these method primarily suffer from different drawbacks such as use of excessive solvents, tedious workup, low yields of the product and need of purification of product. Secondly to maintain the desired stereochemistry in the final product and control the formation of side products in this case the lactone **4.**

Again because of global environmental legislation on chemical process industry, aqueous environment has been receiving considerable attention in organic chemistry because water is abundant in nature , has virtually no cost, and safest among all available solvents thus we herein report a new and highly efficient synthetic pathway to prepare calcium bis-(E)-3,5-dihydroxy-7-[4'-(4''-flurophenyl)-2'-cyclopropyl-quinoline-3-yl]-hept-6-enoate **1,** pitavastatin calcium exclusively in water and is thus environmentally benign.

MATERIALS AND METHODS

All materials were purchased from commercial suppliers and used without further purification. All NMR spectra were recorded on a Avance Bruker 500 MHz spectrophotometer. IR spectra were recorded in KBr on a SHIMADZU 400-50 infrared spectrophotometer. Mass were recorded on Waters Q-TOF (w) premier spectrometer. Elemental analysis of were determined by PERKIN ELMER elemental analysis. A Waters HPLC system equipped with Waters 2996 with Photodiode Array detector was used. The HPLC data were reported in area percent. Commercially available hydrochloric acid and sodium hydroxide were used as such.



Scheme 1. Reagents and conditions: (a) Hydrochloric acid (aq.), (b) Sodium hydroxide or potassium hydroxide, water, 40°-45° C, 5-6 hours, (c) Calcium chloride , Water, 0-5° C, 60.0 min

Preparation of Calcium bis-(E)-3R,5S-dihydroxy-7-[4'-(4''-flurophenyl)-2'-cyclopropyl-quinolin--e-3-yl]-hept-6-enoate (Pitavastatin calcium, Compound 1) : 25.0g (0.048 mol) of 1,3-Dioxane-4-aceticacid,6-[2-[2cyclopropyl-4-(4-fluorophenyl)-3-quinolinyl]-ethenyl]-2,2-dimethyl-,1,1dimethyl ethyl ester, [4R[4,6(E)]] **(3)** was suspended in 500ml water. To it 150ml (0.025 mol) of 5% hydrochloric acid solution in water was added dropwise at 23°-25° C. The reaction mixture was then stirred for 24hrs at 23°-25° C. The reaction was monitored by TLC (hexane: ethyl acetate, 7:3). After reaction completion, 200ml (0.5 mol) of 10% aqueous sodium hydroxide solution was added dropwise into it and stirred for 3.0hrs. Then 7.5g (0.051 mol) of calcium chloride dihydrate dissolved in 75.0ml of purified water was added dropwise and stirred for 1hour at ambient temperature. The precipitated solid was then filtered, washed with excess of water and finally dried under high vacuum at 50° C for 12 hrs which afforded 19.0g of the compound **1** as a white powder.

Melting Point: 207° C; yield 44.6%; **IR υ_{max} (KBr) cm^{-1}**: 3366 (OH), 2911, 1603 (C=O), 1567 (C=N), 1513 (C=C), 1488 (C-H), 1416 (C-H), 1313, 1275, 1221 (C-O-C), 1158, 1065 (C-H), 972, 843, 763.

^{1}H-NMR (500MHz, DMSO-d6): δ 1.01 (m, 2H), 1.09 (m, 1H), 1.19 (m, 2H), 1.41 (m, 1H), 1.98 (dd, 1H, J_1 =8.5, J_2 =15.5Hz), 2.11(d, 1H, J_1 =3.0, J_2 =15.5Hz), 2.50 (m, 2H), 3.66 (m, 1H), 4.13 (m, 1H), 4.95 (s, 1H), 5.58 (dd, 1H, J_1 =5.5, J_2 =10.5Hz), 6.49 (d, 1H, J = 16.0Hz), 7.35 (m, 6H), 7.59 (m, 1H, J = 7.0Hz), 7.83 (d, 1H, J =8.5Hz). **^{13}C-NMR & DEPT (125.76MHz, DMSO-d6)**: δ 11.12(CH2, C-17), 11.23(CH2,C-18), 15.80(CH2, C-16), 44.29(CH2, C-22), 44.61(CH2, C-24), 66.61(C-O, C-23), 69.34(C-O,C-21),115.53(C=C, C-20), 15.62(CH), 115.79(CH), 123.59(CH), 126.07(C=C, C-19), 128.79(CH),129.20(CH),130.07(CH), 32.30(CH), 132.56(CH), 133.51(C), 142.60(C), 144.09(C), 146.37(C), 161.02(C), 163.00(C), 179.13(C=O, C-25).

ESI-MS: m/z (%) 318 (100), 274 (23), 423 (13), 422 (M+, 70); EI calcd for $C_{25}H_{24}FNO_4$, 421.461; found, 422.220 (M+). HPLC Purity: 99.79%, (Lactone impurity: 0.21%).

RESULTS AND DISCUSSION

The synthesis of the compound **1** as depicted in scheme 1 was initiated by preparing the key starting material compound **3** by known literature methods [17]. The starting material **3** as its methyl ester was first subjected to acid treatment for deprotection of the acetonide group to free hydroxyl acid group using inorganic acid like hydrochloric acid, phosphoric acid or sulphuric acid, most preferable was 5% aqueous solution of hydrochloric acid which was then hydrolyzed with the desired monovalent metal hydroxide (like sodium hydroxide or potassium hydroxide) in water as a solvent. The prepared sodium and potassium salt of pitavastatin was then treated insitu with calcium source like calcium chloride, calcium acetate or calcium hydroxide most preferably calcium chloride dehydrate to afforded the compound **1** in 44.6% yield as in scheme1**.** The reaction was highly pH dependent, during deprotection pH of reaction mass was carefully adjusted to less than 1.0 while it was above 13.5 during hydrolysis as it avoids formation of undesired impurities. The compound **1** obtained from the procedure was free from desfluoro impurity, pitavastatin lactone, methyl ester of pitavastatin, pitavastatin tertiary butyl diol impurities [18]. The obtained compound **1** having purity 99.79% by area percent of HPLC. In particular, containing less than 0.5% of single lactone impurity.

The main highlight of this process is to maintain the desired stereochemistry in the final product and control the formation of side products in this case the lactone **4** which was formed in small quantity during deprotection of ketal group using aqueous hydrochloric acid**.** Lactone impurity was substantially controlled in aqueous media and it was observed that the prepared compound **1** was not contaminated with the undesired isomer and other impurities.

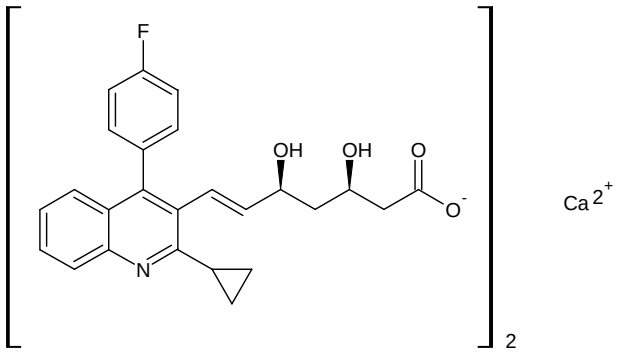


Figure 1. Calcium bis-(E)-3R,5S-dihydroxy-7-[4'-(4''-flurophenyl)-2'-cyclopropyl-quinoline-3-yl]-hept-6-enoate (Pitavastatin calcium).

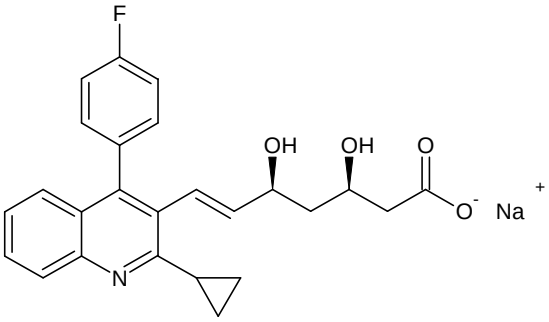
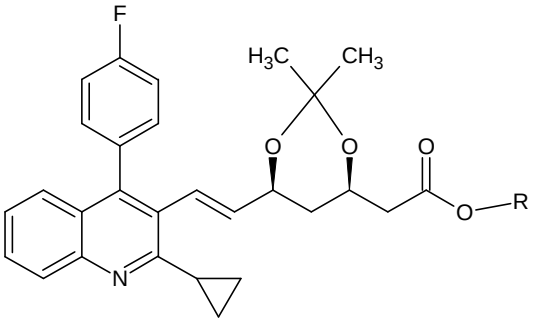


Figure 2. (E)-3R,5S-dihydroxy-7-[4'-(4''-flurophenyl)-2'-cyclopropyl-quinoline-3-yl]-hept-6-enoate sodium salt.



R = C 1 to C 4 linear or branched alkyl group.

Figure 3. 1,3-Dioxane-4-acetic acid,6-[2-[2cyclopropyl-4-(4-fluorophenyl)-3-quinolinyl] ethenyl] -2,2-dimethyl-,1,1dimethyl alkyl ester, [4R[4,6(E)]]. (Compound 3)

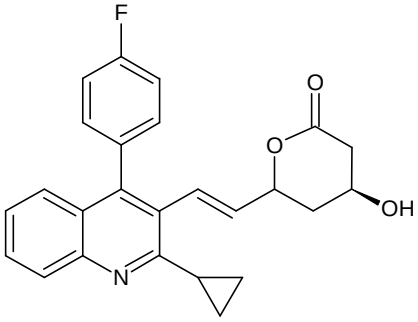


Figure 4. (R,6S,E)-6-[2-[2-Cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl] vinyl] tetrahydro-4-hyd-roxypyran-2-one (Lactone impurity).

CONCLUSION

In conclusion, we have developed a new and highly efficient neat reaction protocol for compound **1**. The primarily advantage of the present protocol need not require any solvent, excellent yield and eco-friendly. Secondly on the basis of the result obtained, the prepared compound **1** was not contaminated with the undesired isomer and other impurities.

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