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A novel and efficient synthetic route for Pitavastatin calcium

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ABSTRACT

*A novel and efficient synthetic process developed for Pitavastatin calcium by preparation of key intermediate **2** with high yield and quality by condensing 2-cyclopropyl-4-(4-fluorophenyl)-3-((1-methyl-1H-benzo[d]imidazol-2-ylsulfonyl)methyl) quinoline **13** with (3R,5S)-tert-butyl 3,5-dimethoxy-6-oxohexanoate **10**. This synthetic approach efficiently provides highly pure Pitavastatin calcium with high yields.*

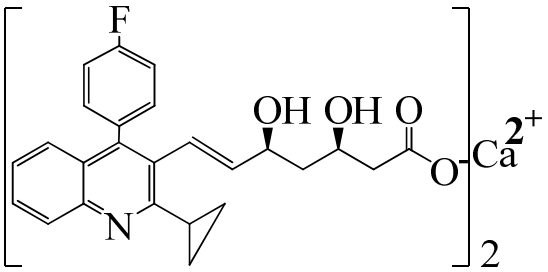
Key words: Pitavastatin, Pitavastatin coupled intermediate, minute level of Z-isomer, minute level of Methyl impurity, novel synthetic process, Wittig reaction, Julia olefination.

INTRODUCTION

Pitavastatin is a lipid lowering agent that belongs to the statin class of medications for treatment of dyslipidemia. It is also used for primary and secondary prevention of cardiovascular disease. Pitavastatin is mainly metabolized by liver. It undergoes glucuronidation by uridine 5-diphosphate glucuronosyl transferases (UGT 1A3 and UGT2B7) to form the major circulating metabolite, pitavastatin lactone. The cytochrome P450 system has little involvement with the metabolism of pitavastatin. There is some metabolism by CYP2C9 and to a lesser extent, CYP2C8. Studies suggest that concomitant therapy with drugs that are involved with the cytochrome P450 system will not affect the pharmacokinetics of pitavastatin [1].

Pitavastatin calcium is FDA approved drug. It contains 2 chiral centers with structural formula **1.** The reported synthetic method [3] for this drug involved 6 stages (scheme-1).

This process suffers with disadvantage of producing more Z-isomer and other process impurities in condensation reaction (i.e. Wittig reaction) and obtained lower yields due to formation of Z-isomer and other process impurities which are formed due to reaction conditions in higher temperature. We developed an alternate route for this drug especially for condensation reaction via Julia olefination with higher yield and quality. In this synthetic approach below 2% Z-isomer formed which is very low when compared with reported synthetic approach (i.e.20-30% Z-isomer). Other process impurities formation also very low in this approach due to reaction conditions in lower temperature. In this present paper we reported the results and improvements toward the synthesis of Pitavastatin calcium **1.**



Pitavastatin calcium

Formula-1

MATERIALS AND METHODS

The preparation of (2-cyclopropyl-4-(4-fluorophenyl) quinolin-3-yl)methanol **8** is described in ref [3]. PBr_3, Benzimidazole thiol, H_2O_2, Di methyl sulfate, NaOBt, Oxalic acid, Calcium chloride and sodium hydroxide were purchased from Aldrich Chemical Co. and used as received. Dichloro methane, acetone, THF and methanol were obtained from Spectrum Chemical and used as received.

3-((1H-benzo[d]imidazol-2-ylthio) methyl)-2-cyclopropyl-4-(4-fluorophenyl)quinolone 12:
The solution of PBr_3 (16.2 ml) and Dichloro methane (100 ml) was added drop wise to the solution of compound **8** (100 g) and Dichloro methane (400 ml) at ambient temperature. After stirring for 30 minutes reaction mass was quenched with aqueous sodium bicarbonate solution (30 g in 300 ml water) and then separated the organic layer from aqueous layer. Then washed the organic layer with hypo (10 g in 100 ml water). The resulted organic layer was distilled completely and charged acetone (200 ml) and water (200 ml) to the obtained crude. Then added Benzimidazole (52 g) thiol and aqueous NaOH (13.6 g in 50 ml) solution at 0-5°C. After 45 minutes maintenance at same temperature distilled the solvent completely and added water (500 ml) and stirred for 30 min. The resulting precipitate was collected, washed with water (100 ml) and dried in oven at 80-85°C for 10 hours to afford **12** (133.3 g, 92%); **m.p:**214-216°C.

1H-NMR (300MHz, $CDCl_3$): δ 1.019-1.064(2H,m), 1.321-1.359(2H,m), 2.501-.541(1H,m), 4.700(2H,s), 7.027-7.070(2H,t), 7.173-7.316(5H,m), 7.330-7.354(2H,m), 7.608-7.649(2H,m), 7.965-7.986(1H,d)

2-cyclopropyl-4-(4-fluorophenyl)-3-((1-methyl-1H-benzo[d]imidazol-2-ylsulfonyl) methyl) quinolone 13:
To the stirred solution of Dichloro methane (300 ml) and 3-((1H-benzo[d]imidazol-2-ylthio)methyl)-2-cyclopropyl-4-(4-fluorophenyl)quinolone **12** (100 g) added Tetra butyl ammonium bromide (1 g) and Hydrogen peroxide solution which is prepared by dissolving ammonium hepta molibdate tetra hydrate(1 g) in 50% H_2O_2(80ml) at 10-20°C. After stirring for 5-6 hours at same temperature observed the conversion of **12** to an insitu intermediate sulfone by TLC then quenched with aqueous sodium sulfite (15 g in 100 ml). Added aqueous sodium hydroxide solution (16.5 g in 38 ml water) and Di methyl sulfate (26.7 ml) to above mass at 20-30°C. After stirring for 60 minutes at same temperature observed the conversion of sulfone to **13** by TLC then separated the organic layer and washed with aqueous sodium bicarbonate solution (5 g in 100 ml) and water (100 ml). Distilled the solvent completely and added methanol (500 ml) and stirred for 60 min at 0-5°C. The resulting precipitate was collected, washed with methanol (100 ml) and dried in oven at 60-65°C for 5 hours to afford **13**(95.0g,86.3%);**m.p:**186-190°C.

1H-NMR (300MHz, $CDCl_3$): δ 0.910-0.937(2H,m), 1.665(2H,s), 2.461(1H,m), 3.753(3H,s), 5.314(2H,s), 7.035(2H,t), 7.168-7.207(3H,t),7.309-7.497(4H,m), 7.644-7.686(1H,m), 7.815-7.837(1H,d), 7.976-7.997(1H,d)

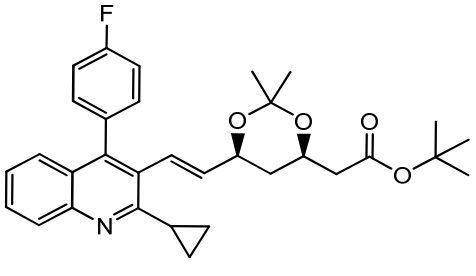
(3R,5S,E)-tert-butyl-7-(2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl)-3,5-dimethoxy hept-6-enoate 2:
To the stirred solution of 2-cyclopropyl-4-(4-fluorophenyl)-3-((1-methyl-1H-benzo[d]imidazol-2-ylsulfonyl) methyl) quinolone **13**(41.6 g) and THF (100 ml) added sodium tertiary butoxide (10 g) at -25°C to -20°C. Then added (3R,5S)-tert-butyl 3,5-dimethoxy-6-oxohexanoate 10 by dissolving in THF (50 ml). After stirring for 60 minutes at same temperature quenched with aqueous sodium bicarbonate solution (22 g in 100 ml water) at below 5°C and stirred for 3 hours at 25-30°C. The resulting precipitate was collected, washed with water (100 ml) to afford 80 g of wet material. Then the wet material was purified in methanol (250 ml) and dried in oven at 60-65°C for 5 hours to afford pure material **2** (41 g, 89.9%)

1H-NMR (300MHz, $CDCl_3$): δ 0.9-1.1(3H, m), 1.3-1.5(18H,m), 1.6(1H,s), 2.2-2.5(3H,m), 4.2-4.4(2H,m), 5.6(1H,dd), 6.6(1H,d), 7.1-7.4(6H,m), 7.6(1H,m), 7.9(1H,d)

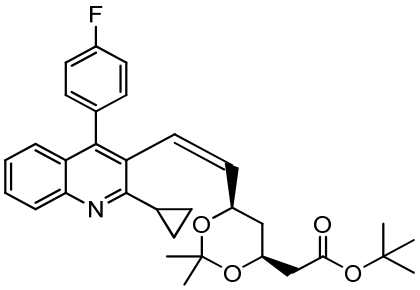
RESULTS AND DISCUSSION

The reported synthetic approach[3] [scheme-1] for the preparation of Pitavastatin calcium describes the coupling of Triphenyl-2-cyclopropyl-4-(4-Fluoro phenyl)-quinoline-2-yl]-phosphonium bromide **9** with (3R,5S)-tert-butyl-5-formyl-3,5-dimethoxypentanoate **10** in presence of a base to give condensed intermediate i.e. tert-butyl 2-((4R,6S)-6-((E)-2-(2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl)vinyl)-2,2-dimethyl-1,3-dioxan-4-yl)acetate **2**. The disadvantages of this process are formation of 20-30% Z-isomer impurity **3** and formation of ~10% Methyl impurity **4,** significant amount of yield loss is observed due to washout of these impurities during isolation and purification process.

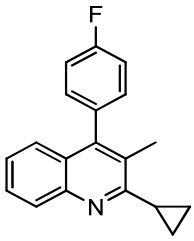
We extensively worked to develop new synthetic methods for Pitavastatin calcium to minimize the formation of Z-isomer impurity **3** and Methyl impurity **4** in condensation step.



Condensed intermediate 2

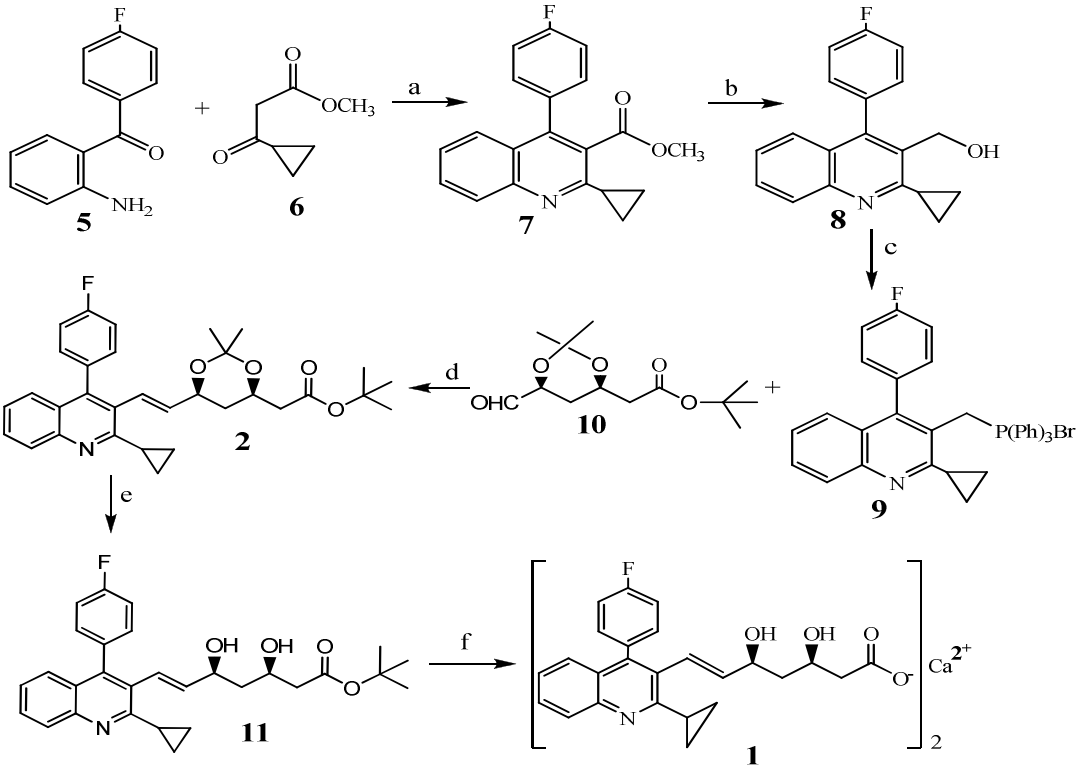


Z-isomer of condensed intermediate 3



Methyl impurity 4

Scheme-1:

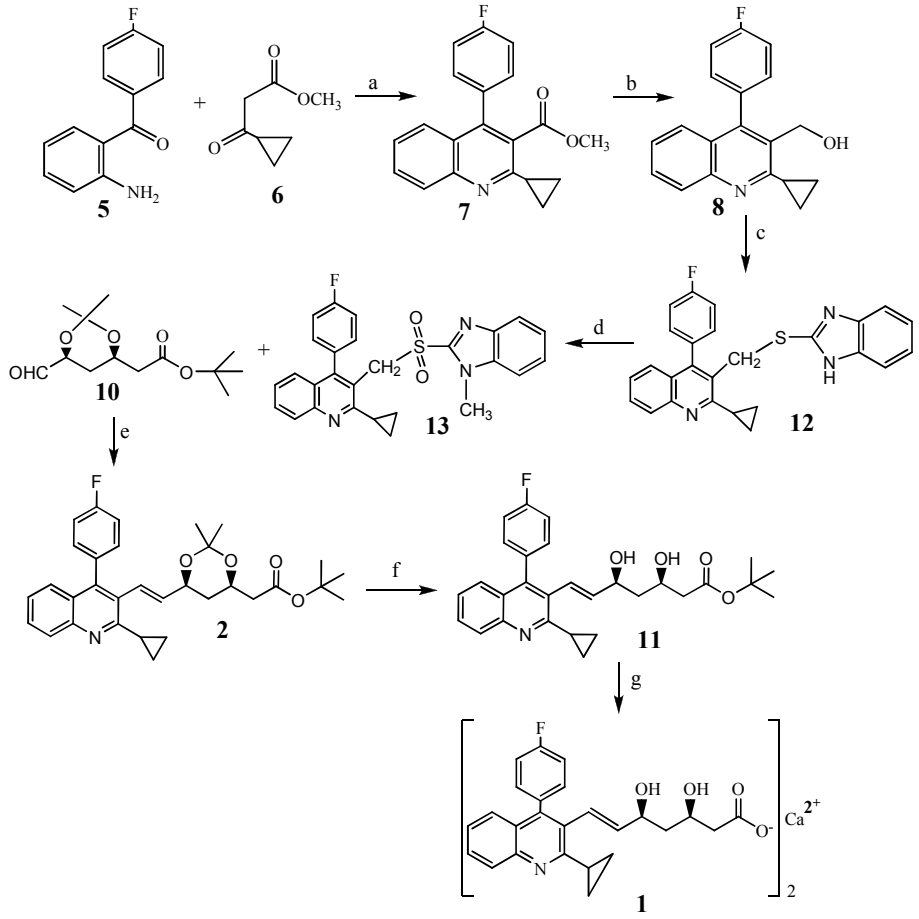


***Scheme 1: a)** Methanol, sulphuric acid **b)** Toluene, DIBAL-H **c)** Di chloro methane, PBr3, Tri phenyl phosphine **d)** Potassium carbonate, DMSO **e)** Oxalic acid, Methanol **f)** NaOH, Calcium chloride, Purified water.*

We here in report a new synthetic route (scheme-2) for synthesis of Pitavastatin calcium **1**. (2-cyclopropyl-4-(4-fluorophenyl) quinolin-3-yl) methanol **8** is prepared as per previous literature [3]. 3-((1H-benzo[d]imidazol-2-ylthio) methyl)-2-cyclopropyl-4-(4-fluorophenyl) quinolone **12** is prepared from **8** by doing bromination followed by condensation with benzimidazole thiol. Further 2-cyclopropyl-4-(4-fluorophenyl)-3-((1-methyl-1H-benzo[d]imidazol-2-ylsulfonyl) methyl) quinoline **13** is prepared from **12** by doing oxidation followed by N-

methylation. The key intermediate **2** is prepared from **13** by doing condensation with **10** in presence of a strong base in ether solvent. The quality of coupled product depends on the temperature and base used in this reaction. So we have investigated the reaction conditions by varying different bases and temperatures. Among all attempts we identified sodium tertiary butoxide (NaOBt) as suitable base and ~ -20°C is the optimum temperature. The coupling with NaOBt yielded the respective coupled product predominantly along with minute level of Z-isomer and methyl impurity.

Scheme-2



Scheme 2: a) *Methanol, sulphuric acid* ***b)*** *Toluene, DIBAL-H* ***c)*** *Di chloro methane, PBr_3, acetone, Benzimidazole thiol, Sodium hydroxide* ***d)*** *H_2O_2, Di chloro methane, Dimethyl sulfate, sodium hydroxide* ***e)*** *THF, NaOBt, Methanol* ***f)****Oxalic acid, Methanol* ***g)*** *NaOH, Calcium chloride, Purified water.*

CONCLUSION

In conclusion, we developed novel and efficient synthetic route for the synthesis of Pitavastatin coupled intermediate with 85-90% of yield with controlling the formation of Z-isomer and methyl impurity.

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