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An Efficient Method for the Large-Scale Synthesis of Atorvastatin Calcium

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Abstract – Atorvastatin calcium salt (**1**) was obtained through the preparation of lactone compound (**8**) from 2-((4*R*,6*R*)-6-(2-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl)-ethyl)-2-phenyl-1,3,2-dioxaborinan-4-yl)acetic acid *tert*-butyl ester (**9**) by hydrolysis in basic condition. Efficient hydrolysis of boronate compound **9** aimed at the viable synthesis for commercial production and purification of Atorvastatin calcium is reported. Detail studies of evaluation procedure are also reported.

Keywords □ Atorvastatin, Large-scale synthesis, 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor, Hydrolysis

INTRODUCTION

Since Lovastatin was first introduced in the 1980s (Moore *et al.*, 1985), other statins have made their way to the market with improved efficacy. Statins (Atorvastatin, Pitavastatin, Rosuvastatin and Simvastatin *etc.*) inhibit 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase which catalyzes the rate-limiting step in cholesterol biosynthesis. They have been used as therapeutic agents for the treatment of hypercholesterolemia and also have become the standard of care in the management and prevention of coronary heart disease (CHD) (Graul *et al.*, 1997; Roth *et al.*, 1989; Kathawala, 1991; Brazil, 2002).

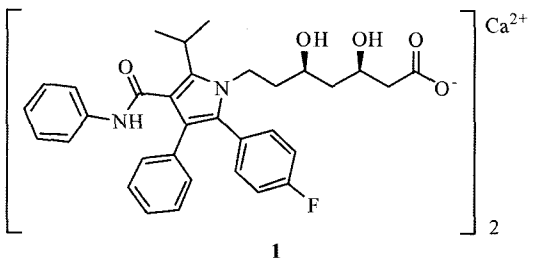

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Fig. 1. Structure of Atorvastatin calcium

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Atorvastatin (**1**) {[*R*-(*R**,*R**)]-2-(4-fluorophenyl)-*β*,*δ*-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrole-1-heptanoic acid calcium salt (2:1)}, launched by Pfizer in 1997, is widely marketed as low-density lipoprotein (LDL) cholesterol lowering drug. Numerous synthetic procedures which make the process less viable for commercial production have been reported over two decades (Roth *et al.*, 1987; 1991; 1993; Brower *et al.*, 1992; Baumann *et al.*, 1992; Wade *et al.*, 1997; Butler *et al.*, 2002; Moody *et al.*, 2005; Sattigeri *et al.*, 2005; Srinath *et al.*, 2002; 2005). An improved, economic, efficient and impurity-free suitable process for the GMP batch scale-up synthesis of **1** is described here by addressing various process development issues. The overall yield obtained from this developed synthetic method is around 67% (HPLC 99.5%) whereas the original process was 52% (HPLC 99.3%) in our hands.

MATERIALS AND METHODS

All solvents and reagents were obtained from commercial sources and were used without further purification. Melting points were determined on a Büchi 510 capillary apparatus and are uncorrected. The infrared spectra (IR) were recorded on a Bruker Vector 22 FT-IR spectrometer. NMR spectra were recorded on a Bruker DPX 400 MHz instrument operating at 400 MHz for proton and 100 MHz for carbon NMR and were performed in DMSO-d_6 solu-

tions using tetramethylsilane (TMS) as the internal reference, except where otherwise indicated. The coupling constants (*J*) are reported in Hz. Mass spectra were recorded on an LC/MSD SL 1100 series (Agilent Technologies), and the data system was an HP Chemstation. HPLC analyses were carried out with Agilant 1100 instrument using the following conditions: Waters Symmetry Shield RP-18 column (250 X 4.6 mm, 5 μ) at 40°C at 246 nm with flow rate of 1.0 mL/min and mobile phase consisting of mobile phase A (degassed mixture of MeCN: MeOH: H_2O = 154:10:36, v:v:v) and mobile phase B (Degassed buffer solution of 10 mmol potassium dihydrogen phosphate in water, 1 ml of triethylamine and dilute phosphoric acid to adjust pH of buffer solution to 2.5). Gradient program of mobile phase A: initial 50% to 10% for 45 min, and to 50% for 2 min, held 50% for 23 min (total 70 min of run time).

Synthesis of 5-(4-fluorophenyl)-1-(2-((2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl)ethyl)-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide (8)

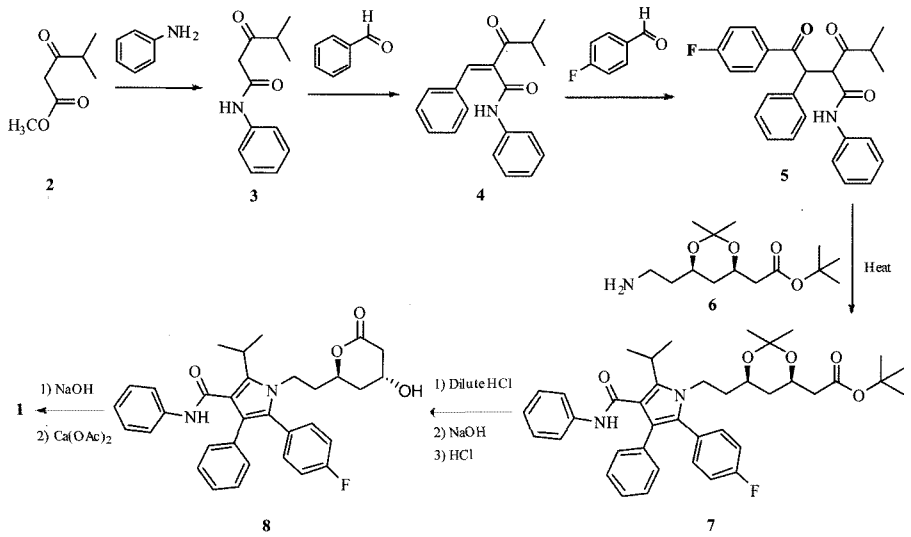
To a solution of 2-((4*R*,6*R*)-6-(2-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl)ethyl)-2-phenyl-1,3,2-dioxaborinan-4-yl)acetic acid *tert*-butyl ester **9** (200 g, 0.285 mol) in a mixture solution of THF/H_2O (4 L, 1/1, v/v) was added dropwise an aqueous solution of potassium hydroxide (48 g, 0.856 mol) in H_2O (1 L) for 1 h, and then the mixture was stirred for 2 h at 25°C. The reaction mixture was diluted with heptane (1.5 L) and agitated for 30 min. The combined aqueous layer was extracted with EtOAc (3 L) and washed with 2 L of brine. The combined organic layer was concentrated under reduced pressure to a half volume. To a solution were added heptane (1 L) and EtOAc (1.5 L), and washed with H_2O (2 L). The combined aqueous layer was extracted with EtOAc (3 L) and washed with 2 L of brine. The combined organic layer was dried over anhydrous $MgSO_4$, filtered, and then concentrated under reduced pressure. The resulting crude residue was reacted with 1 N aqueous solution of hydrochloric acid (30 g) in toluene (1 L) for 5 h at 60°C. The mixture was diluted with toluene (1 L) and washed with brine (2 X 1 L), dried over anhydrous $MgSO_4$, filtered, and then concentrated under reduced pressure to a half volume. The resulting crude residue was slurried with toluene for 4 h, filtered, dried in vacuum oven at 50°C to give 137.6 g (89%) of lactone compound (**8**) as a white solid (98.1% pure by HPLC); m.p. 160~162°C; ^{1}H-NMR (400 MHz, DMSO-d_6) 1.03 (d, J = 7.0 Hz, 6H), 1.06~1.62 (m, 2H), 1.74~1.76 (m, 2H), 2.30~2.35 (m, 1H), 2.56~2.61 (m, 1H), 3.20~3.36 (m, 1H), 3.89~4.05 (m, 3H), 4.47~4.50 (m, 1H), 5.18 (d, J = 3.2 Hz, 1H), 6.95~7.01 (m, 2H), 7.06~7.08 (m, 4H), 7.16~7.28 (m, 6H), 7.51 (d, J = 7.7 Hz, 2H), 9.84 (s, 1H) ppm; MS (ESI) *m/z* (M+1) = 541.2.

Synthesis of Atorvastatin {[*R*-(*R**,*R**)]-2-(4-fluorophenyl)-β,δ-dihydroxy-5-(1-methylethyl)-3-phenyl-4-[(phenylamino)carbonyl]-1*H*-pyrrole-1-heptanoic acid calcium salt (2:1)} (1)

To a suspension of lactone **8** (137 g, 0.253 mol) in a mixture solution of THF/H_2O (4 L, 1/1, v/v) was added dropwise an aqueous solution of sodium hydroxide (11 g, 0.275 mol) in H_2O (1 L) for 1 h and the mixture was stirred for 4 h at room temperature (monitoring reaction ending point by HPLC). The reaction mixture was diluted with heptane (1.5 L) and agitated for 30 min. The combined aqueous layer was extracted with EtOAc (3 L) and washed with 2 L of brine. The combined organic layer was dried over anhydrous Na_2SO_4, filtered, and then concentrated under reduced pressure. The resulting crude white solid (144 g) was dissolved in a mixture solution of MeOH/H_2O (4.2 L, 1/2, v/v) and stirred for 30 min at 50°C. To a mixture was added an aqueous solution of calcium chloride dihydrate (36.5 g, 0.248 mol) in H_2O (2.8 L) for 2 h and stirred for 30 min at 50°C, cooled to 0°C for 2 h, filtered, rinsed with H_2O (1 L). The obtained white precipitate was slurried in diisopropyl ether (IPE) for 12 h, filtered, washed with IPE (0.5 L) and dried in vacuum oven at 50°C for 24 h to give Atorvastatin (**1**, 108 g, 75%) as a white solid (99.5% pure by HPLC); IR (KBr) 3406 (OH, NH, s), 2964, 1651(CO, s), 1600, 1565, 1510, 1441, 1316, 1222 (CF, s), 1154 (CN, s), 1113, 752 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6) 1.23 (m, 1H), 1.36 (d, J = 6.5 Hz, 6H), 1.38~1.63 (m, 3H), 1.99 (m, 1H), 2.12 (m, 1H), 3.17~4.05 (m, 7H), 6.96~7.27 (m, 12H), 7.51 (d, J = 7.8 Hz, 2H), 9.85 (s, 1H) ppm; MS (ESI) *m/z* (M+1) 559.2.

RESULTS AND DISCUSSION

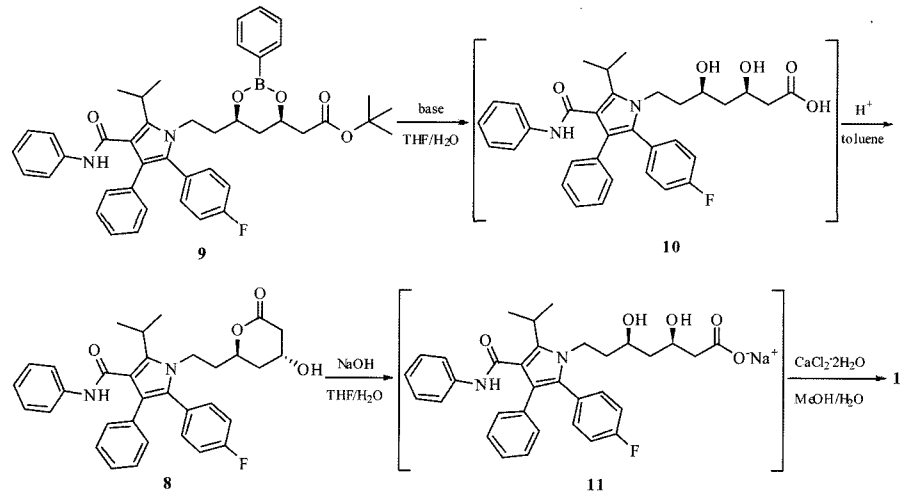
First reported synthetic method for the Atorvastatin (**1**) consists of 6 steps (Scheme 1) (Butler *et al.*, 1989). 4-Methyl-3-oxo-*N*-phenylpentanamide (**3**) is obtained by heating a mixture of 4-methyl-3-oxopentanoic acid methyl ester (**2**) with aniline and ethylene diamine in toluene. Knoevenagel condensation of **3** with benzaldehyde in hexane



Scheme 1. Atorvastatin total synthesis scheme by Pfizer

is followed with the use of Dean-Stark apparatus at elevated temperature. Catalytic amount of *β*-alanine and glacial acetic acid are used in this condensation step and 20 hours of reaction yielded 4-methyl-3-oxo-*N*-phenyl-2-(phenylmethylene)pentanamide (**4**). Stetter reaction of **4** with 4-fluorobenzaldehyde is carried out in the ethanol solution containing catalytic amount of 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide and triethylamine at 80°C for about 24 h to afford diketone compound (**5**). Paal-Knorr pyrrole formation of **5** with (4*R-cis*)-1,1-dimethyl-6-(2-aminoethyl)-2,2-dimethyl-1,3-dioxane-4-acetate (**6**) depicted in Scheme 1 yielded compound **7**. Pivalic acid catalyst in toluene-heptane co-solvent system and continuous water separation with Dean-Stark trap *via* azeotropic distillation are detail reaction conditions. Treatment of **7** with dilute hydrochloric acid afforded de-protected diol intermediate, and additional *in situ* treatment of NaOH to removed *tert*-butyl ester group followed by acidification under hydrochloric acid upon mild heating yielded lactone compound **8**. Finally, treatment of NaOH on compound **8** to break the lactone ring and additional treatment with 0.5 equivalent of $Ca(OAc)_2$ on corresponding sodium salt intermediate produced Atorvastatin calcium salt (**1**).

Our efficient and impurity-free synthesis of **1** having regulatory quality with an overall yield of 67% has accomplished by modifying the original process. Our investiga-



Scheme 2. Optimized process for scale-up manufaturing of Atorvastatin

tion starting point was set to commercial available starting material **9** which is readily available from Biocon Ltd., in India (Srinath *et al.*, 2002; 2005). Our synthetic strategy, as depicted in Scheme 2, for Atorvastatin (**1**) involves hydrolysis of boronate compound (**9**) under basic condition as a key step and lactonization of Atorvastatin free acid, calcium salt formation with calcium chloride dihydrate are following sequentially.

Compound **10** was prepared from **9** either by alkaline or alkaline earth base hydrolysis of boronate protection group. This reaction turned out to be very successful for the reason that the reaction time was remarkably shorten. Originally reported procedure for the same reaction, but from **7** with different acetonide protection group, took about 30 hours which, in turn, is very long reaction time compared to our method of within 3 hours. This shorten reaction time clearly was reasoned due to the intrinsic bond strength difference between B-O and C-O bonding (Butler *et al.*, 1989).

The hydrolysis of **9** was first tested under various base conditions within the time and temperature window of 2~19 h and 0~50°C. The test results are summarized in Table I. Because **9**→**8** transformation is an *in-situ* process, efficiency of **9**→**10** hydrolysis was determined indirectly by measuring the yield and impurity profile of Atorvastatin lactone (**8**).

Typical yield range of **9**→**8** transformation was 75~98%. As for the impurity profile, when hydrolysis reactions were carried out in the presence of K_2CO_3, $NaHCO_3$, Na_2CO_3, or $CaCO_3$, impurities such as *tert*-butyl ester **12** (HPLC > 10%), desfluoro **13** (HPLC < 3.1%), amide **14** (HPLC < 0.18%) and diastereoisomer **15** (HPLC < 0.24%) in compound **8** were higher than other conditions tested in Table I.

Table I. Optimal Hydrolysis of **9** under various base conditions[a]

Entry	Base	eq	Time(h)	Yield **8**(%)[b]
1	LiOH	3	4	89.5
2	NaOH	3	3	97.2
3	$NaHCO_3$	3	18	82.1
4	Na_2CO_3	3	7	76.9
5	KOH	3	2	98.1
6	K_2CO_3	3	7	89.8
7	$Ca(OH)_2$	3	13	87.6
8	$CaCl_2$	3	8	89.4
9	$CaCO_3$	3	19	75.4

[a]Reactions were carried out at rt.
[b]Determined by HPLC.

Table II. Optimal Hydrolysis of **9** in the presence of KOH in solvents

Entry	Solvent	eq (KOH)	Temp (°C)	Time (h)	Yield **8**(%)[a]
1	THF/H_2O	3	25	4	89.5
2	THF/H_2O	3	25	3	97.2
3	THF/H_2O	3	25	18	82.1
4	THF/H_2O	3	25	7	76.9
5	THF/H_2O	3	25	2	98.1
6	$MeOH/H_2O$	3	25	7	89.8
7	$THF/MeOH/H_2O$	3	25	13	87.6

[a]Determined by HPLC

In general, alkaline hydroxide gave acceptable yields and impurity profiles. Finally, when compound **9** was treated with KOH at room temperature, compound **10** was formed within 2 hour and impurity profile of compound **8**

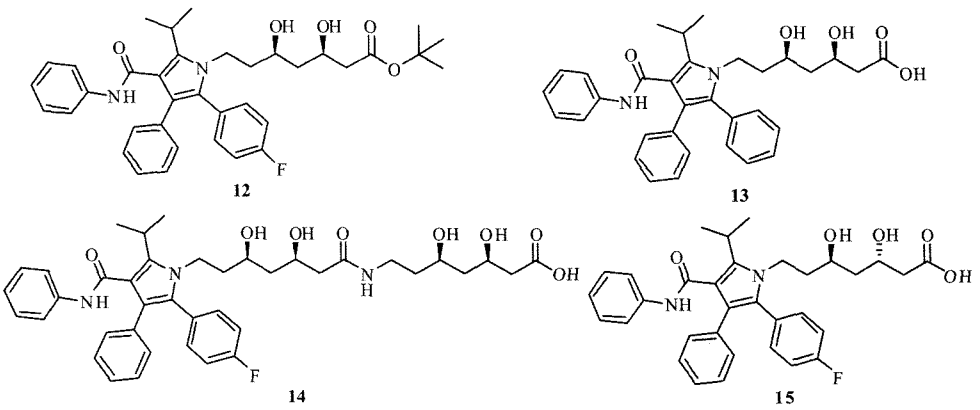


Fig. 2. Observed by-products in the synthetic process of Atorvastatin

Table III. Calcium salt formations

Entry	Base	Temp (°C)	Time (h)	Yield **1** (%)[a]
1	$Ca(OH)_2$	50	1	81
2	$CaCl_2 \cdot 2H_2O$	50	0.5	86
3	$CaCO_3$	50	1	72
4	$CaSO_4$	50	1	71
5	$Ca(OAC)_2 \cdot 2H_2O$	50	1	78

[a]Isolated yield

from this KOH hydrolysis was satisfactory. Detail purification procedure of **10** comprises aqueous hydrochloric acid (pH = 3) treatment followed by potassium salt formation in ethyl acetate (EtOAc). This process efficiently removed the crucial impurities-desfluoro, amide and diastereoisomer compound-which are usually difficult to remove by crystallization or slurry at the final stage. This hydrolysis condition has optimized by varying conditions and the results were summarized in Table II. Among the conditions we tested in Table II, entry 4 was the best condition.

In the next step, **8** was converted to a corresponding pharmaceutically acceptable calcium salt *via* a sodium salt formation using 1.1 equivalent of sodium hydroxide as a base in methanol and H_2O. This sodium salt formation with sodium hydroxide opens the lactone ring to afford its sodium salt and calcium salt was formed with the use of $CaCl_2$ dihydrate in a mixture of methanol and H_2O (1/4, v/v). The precipitated Atorvastatin calcium salt was directly collected by filtration and washed with diisopropyl ether (IPE).

Various options explored to remove the impurities during optimization lead to the above final process. The overall yield and quality of the atorvastatin obtained from this process at scale-up were tabulated below in Table VI.

In conclusion, we provided an improved and industrially feasible manufacturing process for atorvastatin that is substantially free from impurities and meets the requirements of specification with an overall yield of around 67%.

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Table IV. Content of impurities in the Atrovastatin (1)

Entry	Purity[a] of **1**(%)	Impurities (%)					Overall yield[b] (%)
		12	**13**	**14**	**15**	any other	
1	99.52	0.12	0.06	0.08	0.07	0.15	65.6
2	99.56	0.07	0.05	0.06	0.05	0.21	66.6
3	99.49	0.09	0.08	0.08	0.08	0.18	68.5

[a]Determined by HPLC
[b]Isolated yield

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