INTRODUCTION

Since early seventies, it has been observed that high levels of blood cholesterol and other fats in the blood are the major cause for the cardiovascular diseases such as atherosclerosis\textsuperscript{1,2}. Antihyperlipidemic agents and HMG-CoA reductase inhibitors are used to reduce the levels of blood cholesterol and other fats in the blood. Blocking of biosynthesis of cholesterol using HMG-CoA reductase inhibitors is considered to be a better way of reducing the levels of blood cholesterol. HMG-CoA reductase enzyme reduces 3-hydroxy-3-methylglutaric acid to mevalonic acid the main precursor in cholesterol biosynthesis. Most of the statin drugs resembles mevalonic acid and inhibit the biosynthesis of cholesterol by binding with the enzyme. Several pharmaceutical companies have embarked on a quest for a suitable inhibitor for blocking of cholesterol biosynthesis and found that fluvastatin is one of the potential HMG-CoA reductase inhibitor\textsuperscript{3}.

An efficient industrial process for the preparation of fluvastatin sodium

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ABSTRACT

A convergent synthesis of highly potent HMG-CoA reductase inhibitor Fluvastatin. This protocol is amenable to scale up and will be a valuable process for the commercial production of fluvastatin sodium.

Key words: Fluvastatin sodium, Industrial process.

INTRODUCTION

Fluvastatin is generally well tolerated by most of the patients. Its effect on liver has shown to be rare. Cases of muscle inflammation leading to muscle breakdown have been reported with other medicines in the same class. Muscle breakdown causes the release of muscle protein into the blood and kidney tubules and may result in kidney failure. To date significant muscle inflammation or breakdown has not been reported with Fluvastatin. This fact makes it a promising drug to be developed.

Fluvastatin sodium 17, chemically known as the sodium salt of (±)(E)-7-[3-(p-fluorophenyl)-1-isopropyl-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid, is an important indole derivative used in treatment of hyperlipoproteinaemia and arteriosclerosis. To meet the demand for fluvastatin drug in market, there is a need to develop a safe, ecologically sound, economically viable commercial process which meets the quality specifications. The contribution of Novartis in this regard has been valuable\textsuperscript{4,5} but there is still a need to develop a more economic process in respect of yield and cost. As a
part of our R&D programme to develop more economical and cost effective processes for important APIs,\textsuperscript{6,7} we choose to develop a new route for fluvastatin sodium 17.

The major challenges in the preparation of fluvastatin sodium 17 are the synthesis of indole ring, olefin with E-configuration and a 3,5-syn-diol. Based on the earlier synthesis,\textsuperscript{8,9} the retrosynthetic analysis is illustrated in Fig. 1.

Accordingly, our first priority was to develop process for diphenyl-[(4-Fluorophenyl)-1-isopropyl-1H-indol-2-yl]-phosphine oxide 6 intermediate (Scheme 1). Known processes for the preparation of indole moiety utilize procedures which cannot be used in a large scale process hence do not meet the demand of economic process. Our aim was to develop an ideal process which could be performed at a large scale. Fluorobenzene 1 was chosen as the starting material and it was acylated with 2-chloropropionyl chloride 2 in presence of aluminium chloride to give propiophenone 3. Propiophenone 3 was condensed with N-isopropylaniline followed by cyclisation with ZnCl\textsubscript{2} in ethanol to give N-isopropyl-2-methyl-3-(4-fluorophenyl)indole 4. Compound 4 was brominated using NBS in presence of radical initiator azobisisobutyronitrile (AIBN) to give indole 5 in good yield. Compound 5 was converted to desired intermediate 6 by reaction with ethyldiphenylphosphonite (EDPP).

Scheme 1: (a) AlCl\textsubscript{3} (b) N-Isopropylaniline/DMF (c) ZnCl\textsubscript{2}/ethanol (d) AIBN/NBS (e) EDPP/Toluene
After successful novel synthesis of an intermediate 6, a process for the preparation of a novel side chain intermediate 14 was developed. The major hurdle in the synthesis of this moiety was obtaining syn-diol at 3 and 5 positions. The synthesis (Scheme 2) was designed starting from ethyl 4-chloroacetoacetate. Reduction of 7 using sodium borohydride gave 8, which on condensation with tertiarybutyl acetate gave 9. The idea in selecting bulky acetate was to inhibit lactone formation in further steps. The next major hurdle was the stereoselective reduction of β-hydroxyketone 9 to a syn-diol 10 and it was solved by reduction with sodium borohydride and methoxydiethylborane. Methoxydiethylborane was first added to 9 which displaced methoxy group in methoxydiethylborane by forming a covalent bond and allowing boron to chelate with the ketone intramolecularly. Formation of chelate not only activated the ketone for reduction but also formed a six membered ring with a more hindered and a less hindered face. Due to this, the reduction occurred from the side which yielded the syn-diol. The chelate was broken by hydrolysis with hydrogen peroxide in presence of base. The syn-diol 10 was protected with 2,2-dimethoxypropane in presence of methanesulfonic acid to give compound 11, which was converted to 12 using sodium acetate. Compound 12 on further hydrolysis using potassium carbonate gave alcohol 13, which was converted to the desired intermediate 14 by mild oxidation with sodium hypochlorite in presence of radical initiator TEMPO.

The coupling of the two subunits appropriately functionalized to obtain the E-olefin was performed under Horner-Emmons conditions using NaHMDS as base to give coupled product 15 (Scheme 3). The acetonide (dihydroxy) protecting group of 15 was cleaved by treatment with hydrochloric acid and further saponification of ester group yielded fluvastatin 16 as free acid. Fluvastatin 16 was optionally converted into its organic amine salts (i.e., dicyclohexyl amine, tertiarybutyl amine). Conversion of 16 to the sodium salt of fluvastatin 17 was performed by treatment with 1N NaOH solution.

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

**EXPERIMENTAL**

Melting points were determined in open glass capillaries on a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were recorded on a Thermo Nicolet 380-model infrared spectrophotometer. $^1$H NMR (200 MHz) and $^{13}$C NMR (50 MHz) spectra were recorded on a Siemens spectrometer in CDCl$_3$ using TMS as internal standard. Mass spectra were acquired on a VG-micro mass 7070H instrument at 70eV. Elemental analysis were carried out on El Elemental Vario EL (Germany) apparatus.

**Preparation of 4-(2-Methyl-2-chloroacetyl)-1-fluorobenzene (3)**

2-Chloropropionyl chloride (2.6g, 0.02 mole) was added over a 50 minutes period to a mixture of 4.1 g. (0.04 mole) of fluorobenzene and 3.0 g. (0.0225 mole) of anhydrous aluminium chloride stirred at 75°C under nitrogen. The reaction mixture was stirred at 80°C under nitrogen for 1 hour, cooled to 50°C and 500 ml of fluorobenzene was added to it. The reaction mixture was cooled to 0°C and 4 ml of 6N hydrochloric acid was gradually added (over a 30 minutes period) and stirred at 0°C (The temperature of the aqueous hydrochloric acid was maintained at or below 25°C throughout the addition). The quenched, acidified reaction mixture was stirred for 15 minutes, and the aqueous phase was separated and extracted with 35 ml of fluorobenzene. The two organic phases were combined and washed twice with 50 ml portions of 3N hydrochloric acid and once with 50 ml of water. The fluorobenzene was distilled off under reduced pressure at 60°C to obtain oily residue which upon cooling solidified to give title compound as a light yellow colored oil (1.85 g.).

$^1$H NMR(CDCl$_3$): $\delta$ 7.87 (m, 2H), 7.05 (m, 2H), 5.15 (s, 1H), 1.81 (s, 3H); MS: m/e 187 M$^+$.  

Preparation of 3-(4'-Fluorophenyl) -2-methyl-1-(1'-methylmethyl) indole (4)

N-isopropylaniline (5.62 g, 0.04 mole) was rapidly added to a solution of the crude product of 4-(2-methyl-2-chloroacetyl)-1-fluorobenzene (3g, 0.0161 mole) in 50 ml of dimethyl formamide stirred at 50°C under nitrogen atmosphere for 10 hours and allowed to cool to room temperature overnight. The reaction mixture was heated to 60°C, 200 ml of water was added, extracted with methylene chloride and combined organic phase washed with water and distilled the solvent completely. 12.5 g. (0.9 mole) of anhydrous Zinc chloride was added portion wise to 190 ml of absolute methanol and stirred at 25-35°C under nitrogen. The addition was exotherimc. Then the above obtained residue in methanol solution was added to the resulting hot (70°C) zinc chloride solution, and the reaction mixture was stirred at 100-103°C under nitrogen for 3 hours and cooled to 25°C, 150 ml of 1N. hydrochloric acid was added, followed by 100 ml of methylene chloride. The resulting two phase system was stirred for 5 minutes, the organic phase was separated, and the aqeous phase was washed twice with 100 ml portions of methylene chloride. The three methylene chloride phases were combined, the volume was reduced by about 50% by partial concentration of the methylene chloride at 40°C under reduced pressure, and hexane was added to afford the title compound (5.1 g., 50.68%).

1H NMR (CDCl3) : δ 7.42 (m, 1H), 7.26 (m, 1H), 6.62 (m, 1H), 6.32 (m, 1H), 4.04(m, 1H) , 1.56(s, 6H), 2.60(s, 2H), 7.46(m, 2H), 7.03(m, 2H) ;MS : m/e 268 M⁺.


Preparation of 3-(4'-Fluorophenyl) –2-bromomethyl-1-(1'-methylmethyl) indole (5)

N-bromo succinimide (6.19 g., 0.0348 mole) was added to a solution of 8 g. of 3-(4'-fluorophenyl) –2-methyl-1-(1'-methylethyl) indole and 50 ml of dichloromethane and 1.0 g. (0.005 mole) of azobisisobutyronitrile. The reaction mixture was stirred at 65-75°C for 2 hrs, then heated to 105-110°C and stirred for another 2 hrs. Distilled the solvent completely under reduced pressure and hexane was added to afford the title compound (8.0 g., 74.12%). M.R : 156-163°C.

1H NMR (CDCl3) : δ 7.42 (m, 1H), 7.26 (m, 1H), 6.62 (m, 1H), 6.32 (m, 1H), 4.04(m, 1H) , 1.56(s, 6H), 2.60(s, 2H), 7.46(m, 2H), 7.30 (m, 10H), 7.03(m, 2H) ;MS: m/e 468 M⁺

Anal. Calcd for C30H27FNOP : C, 77.07; H, 5.82; N, 3.00. Found : C, 77.16; H, 5.68; N, 2.89.

Preparation of (+) ethyl –4- chloro-3-hydroxy butanoate.(8)

A solution of ethyl–4-chloro acetoacetate (500 g.), methylene chloride (1000 ml) and tetrahydrofuran (500 ml) was cooled to –10°C and added sodium borohydride (86.5 g.) lot wise at –
10°C. Stirred for 2 hrs at –15 to –10°C. Quenched
the reaction mixture with chilled water. Separated
the organic layer and aqueous layer and extracted
the aqueous layer twice with methylenechloride
(2x500 ml). Combined organic layer and washed
with 10% sodium bicarbonate solution followed by
water. Distilled the solvent completely under reduced
pressure to afford title compound (400 g.) as a
residue.

Preparation of (±)6-chloro –5-hydroxy-3-oxo
hexanoic acid 1,1-dimethyl ethyl ester (9)
A solution of lithium hexamethyl disilazane
(3511 ml of 1 molar solution) and tetrahydrofuran
(666 ml) was cooled to –75°C and tert-butyl acetate
(70 ml) was added slowly in 45 minutes and
maintained for 25 minutes at –72°C. (±) Ethyl –4-
chloro-3-hydroxy butanoate (185 g.) solution in
tetrahydrofuran (185 ml ) was added in 40 minutes
at –73°C and stirred for 1 hr 45 minutes at –75°C.
Raised the temperature to –45°C and stirred for 1
hr at –45°C. Quenched the reaction mixture with
chilled 20% aqueous hydrochloric acid (4400 ml)
solution. Separated the organic layer and washed
with 10% sodium bicarbonate solution (100 ml).
Finally dried the organic layer using sodium sulfate
and distilled the solvent completely under reduced
pressure. Residue was purified using hexane at –
10 to –5° to afford title compound (240 g.) as a pale
yellow solid.

Preparation of (±)6-chloro-3, 5-dihydroxy
hexanoic acid 1,1-dimethyl ethyl ester. (10)
A solution of (±) 6-chloro –5-hydroxy-3-oxo
hexanoic acid 1,1-dimethyl ethyl ester (500 g.),
3.5 lit of tetrahydrofuran and methanol (1 lit) was
cooled to –70°C. Diethyl methoxy borane (433 ml)
was added slowly in 25 minutes to the reaction
mixture. Stirred the reaction mixture at –70°C for
another 25 minutes and sodium borohydride (86.5
g.) was added in 9 lots. Stirred the reaction mixture
for 2 hrs at –75°C. Quenched the reaction mixture
with hydrogen peroxide solution, separated the
organic layer and washed with 10% sodium
bicarbonate solution followed by water and brine
solution. Finally organic layer was dried over sodium
sulfate and distilled the solvent completely under reduced
pressure to afford the title compound (446 g.) as a residue.

Preparation of (±) 6-(chloromethyl)-2,2-dimethyl-
1,3-dioxane-4-acetic acid-1,1dimethyl ethyl ester. (11)
A solution of (±) 6-chloro-3,5-dihydroxy
hexanoic acid 1,1-dimethyl ethyl ester (280 g.) and
acetone (1560 ml) was cooled to 25-30°C. 2,2-
dimethoxy propane (1039 ml) and methanesulfonic
acid (2.6 ml) solution was added to the reaction
mixture and stirred at 25-35°C for 9 hrs. Quenched
the reaction mixture with sodium bicarbonate
solution and separated the organic layer. Extracted
the aqueous layer with hexanes and washed the
organic layer with hexanes and distilled the
solvent completely under reduced pressure to afford
the title compound (254 g.) as a residue.

Preparation of (±)6-(Acetlyoxy) methyl]-2,2-
dimethyl-1,3-dioxane-4-acetic acid,1,1-
dimethylethyl ester. (12)
(±) 6-(chloromethyl)-2,2-dimethyl-1,3-
dioxane-4-acetic acid-1,1dimethyl ethyl ester (250 
g.), sodium acetate (225 g.) and tetrabutyl
ammonium bromide (290 g.) were heated to 110-
115°C and stirred for 12 hrs. Reaction mixture was
diluted with hexanes and filtered the by-product.
Organic layer washed with water. Distilled the
solvent completely under reduced pressure and
hexane was added to afford the title compound (100 
g, 36%). M.R: 62-65°C.

Preparation of (±) 6-(Hydroxymethyl)-2,2-
dimethyl-1,3-dioxane-4-acetic acid,1,1-
dimethylethyl ester (13).
(±) 6-(Acetlyoxy) methyl]-2,2-dimethyl-1,3-
dioxane-4-acetic acid-1,1dimethyl ethyl ester (50 g.)
was dissolved in methanol (250 ml), added
potassium carbonate and cooled to 0-5°C. Stirred
the reaction mixture at 0-5°C for 2 hrs. Quenched
the reaction mixture with chilled water and stirred
for 20 minutes. Extracted the reaction mixture thrice
with dichloromethane (3x100 ml). Combined organic
layer washed with brine solution and water (50 ml).
The total organic layer dried over sodium sulfate and
distilled the solvent under reduced pressure to afford
the title compound (35 g, 81.39%).

Preparation of (±) tert-butyl 2-[6-formyl –2,2-
dimethyl-1, 3-dioxane-4-y] acetate (14).
A solution of (±) 6-(hydroxymethyl)-2,2-
dimethyl-1,3-dioxane-4-acetic acid, 1,1-dimethylethyl ester (25 g.) and methylene chloride was cooled to 0-5°C. KBr (1 g.), TEMPO (0.1 g.) (2,2,6,6-tetramethyl piperidinylxylo free radical) were added to the above reaction mixture. Sodium hypochlorite was added to the reaction mixture at 0-5°C in 60 minutes and stirred for another 30 minutes at 0-5°C. Quenched the reaction mixture with sodium thiosulphate solution (10%) (50 ml), separated the organic layer and washed the organic layer with water (50 ml). Organic layer dried over sodium sulfate and distilled completely under reduced pressure to afford title compound (10 g.).

Preparation of (E)-(±)-6-{2-(1-wasopropyl-3-(4-fluoro phenyl)-1H-indol-2-yl)-vinyl}2,2-dimethyl-[1,3]-dioxane–4-yl}-acetic acid tert-butyl ester (15)

A mixture of 12 g. of compound 6 and THF (120 ml) were warmed briefly to 40°C until a clear solution observed, then inserted by the sequential application of reduced pressure and nitrogen. The mixture was cooled to –75°C. Sodium bis (trimethyl silyl) amide (30 ml) was added to the reaction mixture over 30 minutes through dropping funnel maintaining the temperature below –75°C. The mixture stirred for further 1 hr at –76°C. Compound 14 (6 g. in 50 ml of toluene) was added in portions to the suspension over 30 minutes through dropping funnel maintaining the temperature below –73°C.

The mixture stirred for further 15 minutes at –76°C. The suspension allowed to warm to 10°C over 1.0 hr. Glacial acetic acid (10%, 30 ml) was added in one portion raising the temperature to 18°C and dissolving all solids and the mixture was stirred for further 5 minutes. Further reaction mixture diluted with water and organic layer separated. Organic layer washed with sodium bicarbonate solution (10%) (60 ml) followed by washing with saturated sodium chloride solution (50 ml). Organic layer distilled under reduced pressure and crude product isolated using n-hexane. The crude product taken into diisopropyl ether and filtered the unwanted, Filtrate was concentrated by distillation under reduced pressure and acetonitrile was added to afford title compound (5 g.) M.R : 133-137°C.

Preparation of (±) (E)-7-[3-(p-fluorophenyl)-1-isopropylindol-2-yl]-3,5-dihydroxy-6-heptenoic acid. (16)

A solution of (E)-(±)-6-{2-(1-isopropyl-3-(4-fluoro phenyl)-1H-indol-2-yl)-vinyl}2,2-dimethyl-[1,3]-dioxane–4-yl}-acetic acid tert-butyl ester (10 g.) and acetonitrile (400 ml) was cooled to 20-25°C. Aqueous hydrochloric acid solution (0.75 ml in 58 ml water) was added slowly in 30 minutes. Stirred for 1.5 hrs. Sodium hydroxide (1.5 gm) in water (75 ml) solution was added slowly in 20 minutes and stirred the reaction mixture for 3 hrs at 30-35°C. Reaction mixture was cooled to 0-10°C and pH was adjusted to 4 with 10% hydrochloric acid and organic layer washed with brine solution. Dicyclohexyl amine (3 g.) was added to the reaction mixture at 0-10°C and reaction mixture was further diluted with 100 ml of acetonitrile and raised the temperature to 25-35°C, further stirred for 2 hrs at 25-35°C, filtered the cake and washed with acetonitrile (50 ml). It was recrystallized in a mixture of acetonitrile and isopropyl alcohol followed by treatment with acetic acid afforded the title compound (7.5 g, 92.5%). HPLC Purity: 99.84%.

Preparation of sodium salt of (±) (E)-7-[3-(p-fluorophenyl)-1-isopropylindol-2-yl]-3,5-dihydroxy-6-heptenoic acid (17)

A solution of 4.5 ml of 1N sodium hydroxide, 2.0 g. of 16 and 150 ml of methanol was stirred at 25-35°C for 2 hours. The solvent was evaporated under reduced pressure and acetone was added to afford the title compound (1.5 g, 70.8%).

1H NMR (CDCl3) : δ 7.36 (m, 2H), 7.25 (m, 2H), 7.01 (2H), 6.78 (m, 2H), 6.58 (d, 1H), 6.18 (m, 1H), 4.0 (m, 1H), 3.8 (m, 2H), 2.45 (m, 1H), 2.18 (m, 1H), 1.98 (s, 2H), 1.58 (m, 2H), 1.51 (d, 6H); MS : m/e 412 M+.

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