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Synthesis and characterization of side chain derivatives of statins (antihyperlipidemic activity)

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Abstract: Statins are one of the largest selling drugs for the treatment of hypercholestromeia. They serve as potential competitive inhibitors of HMG-CoA reductase which catalyze the rate-limiting step of cholesterol biosynthesis. They can be broadly classified into fermentation-derived, semisynthetic, and synthetic statins. Rosuvastatin is one of the newer members of the statin family; this statins although very effective in lowering the cholesterol level, is even a very costly drug. The molecule is composed of the two parts i.e. heterocyclic moiety and side chain. The final step in the synthesis of these statin involves hydrolysis of ester part of the side chain to produce the carboxylic acid. The hydrolysis of methyl ester is slow and incomplete resulting in low yield of these synthetic statin. We synthesized t-butyl methyl ester side chain and even the hydrolysis of t-butyl ester group is expected to be significantly better compared to methyl ester. The aim of the proposed work is to synthesis side chain carrying a t-butyl ester group which can then be used to synthesize this statin in greater yield and thus reduce the overall cost of synthesis.

***Keywords*:** Statin, hyperlipidemia, cholesterol

Introduction

A cardiovascular disease (CVDs) hits approximately 17.9 million lives each year. This increase in number shows the concern related to CVDs. Hypercholesterolemia is unique hazard issue causing chronic heart related disease- a type of CVDs. This is a medical condition in which elevated level of saturated fatty materials i.e. lipids, large amount of cholesterol and triglycerides are present in the systemic circulation. Statins, also known as 3-hydroxy-3-methyl-glutaryl (HMG)-CoA reductase inhibitors, are a potent antihyperlipidemic group of drug which is widely used for the treatment of hyperlipidemia. The HMG-CoA reductase is the enzyme responsible for the rate-limiting step in the cholesterol synthesis of mevalonate pathway. HMG-CoA inhibition results in reduction of cholesterol synthesis and an increase in the synthesis of low-density lipoprotein receptors. This, results in increased clearance of LDL cholesterol from the blood

stream. Hyperlipidemia is a disease in which one or more plasma lipid profiles such as, cholesterol, cholesterol esters, triglycerides and phospholipids or plasma lipoproteins including very low-density lipoprotein (VLDL) and low-density lipoprotein (LDL) and reduced high-density lipoprotein (HDL) levels is enhanced. Hypertriglyceridemia and hypercholesterolemia are the chief reasons for atherosclerosis which are robustly related with ischemic heart disease. Atherosclerosis and atherosclerosis associated diseases such as cerebrovascular, coronary, and peripheral vascular diseases are accelerated by the presence of hyperlipidemia. The main causes of hyperlipidemia is the unusual rise in cholesterol levels which is a consequence of an unhealthy lifestyle that includes consumption of high-fat diet including other lifestyle factors like being overweight, smoking, heavy alcohol use, and lack of exercise. The main drug involved in the cure of hyperlipidemia is identified as statins which mainly includes rosuvastatin, atorvastatin, lovastatin, simvastatin, pravastatin etc.

2. Objectives

2.1 Hypertension

Hypertension (HT) also known as high blood pressure is a long-term medical state in which the blood pressure in the arteries is constantly raised. Long-term high blood pressure is a key risk factor for coronary artery disease, heart failure, stroke, vision loss, peripheral vascular disease. Hypertension is often called "the silent killer" because it generally has no symptoms until serious complications developed. Hypertension is classified into primary (essential) and secondary HT. Around 90–95% of cases are primary HT arising because of nonspecific lifestyle as well as genetic factors. Lifestyle factors that increase the risk include high salt intake, smoking, excess body weight, and intake of alcohol. The other 5-10% of cases is regarded as secondary HT, which happens due to an identifiable or known cause, for instance narrowing of the kidney arteries, chronic kidney disease, the use of birth control pills, or an endocrine disorder.

2.2 Statins: Hypercholesteemia and coronary heart disease (CHD), the most common form of heart disease, are consistently cited in this research as providing a clear and causative link. These are the major drugs for the treatment or management of Hyperlipidemia, also called as HMG-CoA reductase inhibitors e.g., Atorvastatin, Lovastatin, Fluvastatin, Pravastatin, Simvastatin and Rosuvastatin. Among the statins group of drugs, rosuvastatin for the purpose of a new drug delivery formulation because of the following reasons. This is a class III drug, also known as superstatin and its oral absorption is dissolution rate-limited. It is employed to alleviate primary dyslipidemia andhypercholesterolemia. Rosuvastatin is indeed an HMG-CoA reductase antagonist that is made up of a new chain containing methane sulphonamide pyrimidine and N-methanesulfonyl pyrrole-substituted 3,5-dihydroxy-6-heptenoates (heptanoic acid-derivative joint with a pyrimidine and sulphonamide group). [92-93] The inactivation of the enzyme is irreversible, compete with the substrate HMG-CoA but not with the co-substrate nicotinamide-adenine dinucleotide phosphate (NADPH). A persistent polar methane sulphonamide group as a hydrophilic component, in addition to the characteristic statin pharmacophore, confers its low membrane fluidity.

3. Results and Discussion

3.1 Designing consideration

The title compounds SC-IX were prepared using the reaction sequence as described in below figure 1. This synthesis is carried out by taking diethyl 3-hydroxypentanedioate commercially and performed various reaction which explains below,

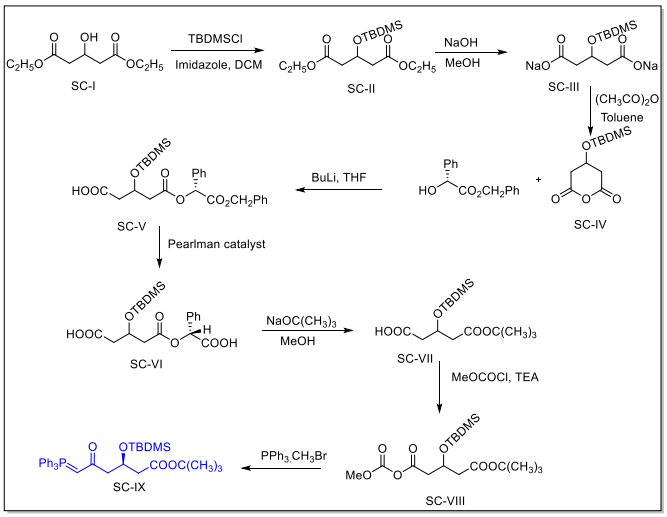

Figure 1. Synthetic scheme of key intermediate tert-butyl (R)-3-((tert-butyldimethylsilyl)oxy)-5-oxo-6-(triphenyl-l5-phosphanylidene)hexanoate (SC-IX)

3.1 Chemistry

The title compounds (**SC-II, SC-III, SC-IV, SC-V, SC-VI, SC-VII, SC-VIII, SC-IX**) were prepared using the reaction sequence described in figure 1. In the first scheme diethyl 3-hydroxypentanedioate **SC-1** is reacted with TBDMSCl in presence of imidazole and DCM at reflux temperature to give **(SC-II)**. While **SC-II** in the presence of sodium hydroxide and methanol at room temperature gives **SC-III**. **SC-III** reacts with acetic anhydride in the presence of toluene at reflux temperature result in formation of **SC-IV. SC-IV** reacts with benzyl (R)-2-hydroxy-2-phenylacetate in the presence of butyl lithium and tetrahydrofurane (THF) at cooling temperature to give **SC-V**. **SC-V** is treated with Pearlman catalyst to give **SC-VI**. **SC-VI** reacts with sodium acetate in the presence of methanol to give at room temperature to give **SC-VII**. **SC-VII** is treated with methyl chloroformate in the presence of triethylamine, DCM at reflux temperature to give **SC-VIII**. Then, intermediate **SC-VIII** react with triphenylphosphine methyl bromide in the DCM to afford the key intermediate **SC-IX**. The synthesis scheme of SC-IX is shown in figure 1.

4. Conclusion:

In conclusion, novel side chain derivatives were designed, synthesized, and characterized. The t-butyl methyl ester side chain and the hydrolysis of t-butyl ester group are expected to be significantly better compared to methyl ester. The result of this synthesis is expected to be beneficial for futuristic research.

5. Experimental

All solvents and chemicals used here were purchased from Sigma-Aldrich, TCI chemicals and Avra Synthesis Pvt Ltd., India and were used without further purification. Progress of each reaction was monitored by TLC. 1 H NMR (400 MHz) spectra were recorded (Bruker Avance FT-NMR spectrophotometer, USA) in deuterated solvent (DMSO-d_6) using tetramethylsilane (TMS) as an internal standard; the chemical shifts (δ, ppm) and coupling constants (J, Hz) are reported. FT-IR spectra were recorded on an Alpha ECO-ATR Spectrophotometer (Bruker, USA).

5.1 Synthesis of diethyl-3-(*tert*-Butyldimethylsilyloxy)pentanedioic acid (SC-II)

Under an oven dried 500 mL round bottomed flask were placed 55.42g (0.367 mol) of *tert*-butyldimethylsilylchloride and 33.34 g (0.49 mol) imidazole as well as 200 mL DCM, at 25-30°C. Cooled the reaction up to 5-10°C and added the mixture (3-hydroxyglutarate (50g) in 50 mL DCM) in 1 h, heated the reaction mixture up to 4 h, after that reaction monitored by TLC, now cooled the reaction at room temperature. Washed the reaction mixture with DM water and stirred for 20 min. separated the layer and distilled the organic layer under vacuum at 40-45°C to afford 90 g of crude mass (117%). This was taken as such for next step preparation.

MS (E1) m/z value $[M+H]^+$ 319.2; **^{1}H NMR (400MHz, $CDCl_3$-d_6) δ** 4.5 (m, 1H), 4.06 (m, 4H), 2.47 (d, J=6.4 Hz, 4H), 1.19 (s, 6H), 0.83 (s, 9H). **IR (v, cm-1):** 2983.1 (C-H), 1732.32 (C=O), 1446.5 (-CH_2), 1272.4 (C-O).

5.2 Syntehsis of sodium salt of 3-(*tert*-Butyldimethylsilyloxy)pentanedioic acid (SC-III)

Under an oven dried 1000 mL (RBF) were placed 450 mL methanol and added the diethyl-3-(*tert*-Butyldimethylsilyloxy)pentanedioic acid 90 g (0.29 mol), maintained the reaction up to 5-10°C and charged the sodium hydroxide 29.3 g (0.73 mol) stirred the reaction mixture up to 15-16 h. Reaction monitored by TLC, if reaction completed than distilled the reaction mixture under vacuum (u\v) at 50-55°C to afford 102 g off white solid mass (97%). On the basis of TLC proceed for next step.

MS (E1) m/z alue $[M+H]^+$ 307.2

5.3 Synthesis of 3-[(*tert*-butyldimethylsilyloxy)pentanedioate anhydride (SC-IV)

Under an oven dried 3L RBF were placed 1020 mL toluene and added sodium salt of 3-(*tert*-Butyldimethylsilyloxy)pentanedioic acid 102g (0.33 mol), as well as added acetic anhydride 306 mL. Condensed the reaction up to 3 hr at 110°C and after that reaction monitored by TLC. Quenched reaction mixture with water and extracted with toluene, stirred the reaction 15 minute. Separated the layer and separated organic layer again washed with water. Separated organic layer and concentrated u\v at 50-55°C to afford 44g off white solid mass (54%).

MS (E1) m/z value $[M+H]^+$ 510.77; **^{1}H NMR (400MHz, $CDCl_3$-d_6) δ** 4.5 (m, 1H), 2.88 (, 2H), 2.75 (m, 2H), 2.6 (d, J=8 Hz, 1H), 0.83 (s, 9H), 0.02 (s, 6H).

5.4 Synthesis of 3-[(*tert*-butyldimethylsilyloxy)pentanedioic acid 1-benzyl (*R*)- mandelate]ester (SC-V)

Under an oven dried 1000 mL RBF were placed a solution of benzyl *(R*) mandelate (19.9g) in THF (400 mL) was cooled to -78°C, and a solution of 1.6M BuLi in hexane (53.9 mL) was added dropwise, and the mixture was stirred for 30 minute. To the reaction mixture was added a solution of 3-(*tert*-butyldimethylsilyloxy) pentanedioate anhydride (20.0 g) in THF (40mL), and the resulting mixture was stirred for 2.0 h. After that reaction monitored by TLC and acidified the reaction mixture with 2N hydrochloric acid solution, added ethyl acetate and DM water, stirred the reaction mixture for 20 minute. Now separated the layers, separated organic layer was distilled u\v at 40-45°C and obtained (34.86 g) light yellow liquid.

^{1}H-NMR ($CDCl_3$, δ): 7.32 (s, 10H), 5.99 (s, 1H), 5.19 (m, 2H), 4.56 (s, 1H), 4.24 (m, 1H), 2.75 (m, 2H), 2.1 (s, 2H), 1.22 (m, 2H), 0.8 (s, 9H), 0.06 (s, 6H).

5.5 Synthesis of (3*R*)-3-(*tert*-butyldimethylsilyloxy)pentanedioic acid, 1-(*R*) - mandelic acid] ester (SC-VI)

Under an oven dried RBF were placed 3-(*tert*-butyldimethylsilyloxy)pentanedioic acid, 1-benzyl (*R*)-mandelate (16.6 g) in ethyl acetate (115.6 mL), was added Pearlman catalyst (0.5 g), and the mixture was stirred for 6.0 h at RT in a hydrogen atmosphere under ordinary pressure until 3.36 L of hydrogen was absorbed. After that reaction monitored by TLC and the reaction mixture was filtered to remove the catalyst, and the added DM water and stirred the reaction for15 min. Separated the layers and separated organic layer washed two times with DM water, separated layers are was distilled u\v at 45-50°C to afford (15.11g) semi liquid material.

MS (E1) m/z value $[M+H]^+$ 395.05; **^{1}H NMR (400MHz, $CDCl_3$-d_6) δ** 7.32 (s, 10H), 5.99 (s, 1H), 5.19 (m, 2H), 4.56 (s, 1H), 4.24 (m, 1H), 2.75 (m, 2H), 2.1 (s, 2H), 1.22 (m, 2H), 0.8 (s, 9H), 0.06 (s, 6H).

5.7 Synthesis of (3*R*)-1-t-Butyl-3-(*tert*-butyldimethylsilyloxy) pentanedioate (SC-VII)

Under an oven dried 250 mL RBF were placed an ice cold solution of sodium *tert*iarybutoxide (23.7 g) in methanol (60 mL) was added dropwise a solution of (3*R*)-3-(*tert*-butyldimethylsilyloxy)pentanedioic acid, 1-[(*R*) - mandelic acid] ester (10.0 g) in methanol (10.0 mL) over 45 min. Keeping the reaction temperature below 5°C. Stirring was continued for 4.3 h after that reaction monitored by TLC and the mixture was poured into the of DM water. Acidified with 1N HCl around 3-4 pH and extracted with DCM three times. Separated the organic layer and washed with water three times. Separated organic layer and distilled u\v at 40-42°C to afford (7.3 g) oily mass. On the basis of TLC

IR (cm-1): 3441.76 (O-H), 2956.91 (C-H), 1720.25 (C=O), 1254.75 (C-O).

5.8 Synthesis of 3-(*tert*-butyldimethylsilyloxy)-5-methoxycarbonyloxy-5-oxo-pentanoic acid *tert*-butyl ester (SC-VIII).

Under an oven dried 250 mL RBF were placed a solution of (3*R*)-1-methyl 3-(*tert*-butyldimethylsilyloxy)pentanedioate (8.0 g) and TEA (3.04 g) in toluene (100.0 mL) was cooled to -40°C, and methyl chlorocarbonate (2.3 g) was added dropwise. The reaction mixture was allowed to warm to 0°C and was stirred for 1.0 h, after that reaction monitored by TLC and then poured into the water and washed with saturated sodium bicarbonate ($NaHCO_3$). Separated organic layer was distilled u\v at 45-50°C to afford (8.9 g) as an oily mass. On the basis of TLC this can be proceed in the next step.

IR (cm-1): 3441.76 (O-H), 2956.91 (C-H), 1720.25 (C=O), 1254.75 (C-O).

5.9 Synthesis of t-Butyl-(3*R*)-3-(*tert*-butyldimethylsilyloxy)-5-oxo-6-triphenylPhospho

ranylidene hexanoate (SC-IX)

Under an oven dried 250 mL RBF were placed a suspension of methyltriphenylphosphonium bromide (8.0 g) in THF (80.0 mL) was cooled to -60°C, and 1.6M BuLi in hexane (7.0 mL) was added dropwise over 20 min. The reaction mixture was allowed to warm to 0°C. The reaction mixture was cooled to -60°C, and the toluene solution of the (3R)-1-methyl 3-[(*tert*-butyldimethylsilyloxy)pentanedioate (mixed anhydride) [8.45 g] was added through a cannula over 1.0 h. The resulting mixture was allowed to warm to room temperature and stirred for 1.0 h, after that reaction monitored by TLC. The mixture was poured into water, the aqueous washing was extracted with ethyl acetate and the combined organic fractions were distilled u/v at 45-50°C to afford (5.0 g) as a solid mass.

MS (E1) m/z value $[M-H]^-$ 578.86; **^{1}H NMR (400MHz, $CDCl_3$-d_6) δ** 7.3-7.4 (s, 15H), 4.56 (m, 1H), 2.4-2.9(m, 4H), 1.4 (s, 9H), 0.82 (s, 9H), 0.04 (s, 6H); **IR (cm-1):** 3056.07 (=C-H), 2951.92 (C-H), 1741.19 (C=O).

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