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(54) **Title:** PROCESS FOR PRODUCING 6(R)-[2-(8'(S)-2 ",2 "-DIMETHYLBUTYRYLOXY-2'(S),6'(R)-DIMETHYL-1,2,6,7', 8',8A'(R)- HEXAHYDRONAPHTHYL-L'(S))ETHYL]-4(R)-HYDROXY-3,4,5,6- TETRAHYDRO-2H-PYRAN-2-ONE

(57) **Abstract:** Disclosed herein is an improved process for producing HMG-CoA reductase inhibitor, 6(R)-[2-(8 '(S)-2 ",2 "-dimethylbutyryloxy-2'(S),6 '(R)-dimethyl- 1', 2', 6', 7', 8',8a'(R)-hexahydronaphthyl-r(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H- pyran-2-one, the process comprising hydrolyzing (lS,3R,7S,8S,8aR)-8-{2-[(2R,4R)-4-hydroxy-6-oxotetrahydro-2H-ρyran-2-yl]ethyl}-3,7-dimethyl-l,2,3,7,8,8a- hexahydronaphthalen-1-yl (2S)-2-methylbutanoate in presence of a base and antioxidant, lactonizing and selectively protecting the hydroxyl group of the resultant compound, followed by acylation with an acylating agent to obtain 6(R)-[2-(8'(S)- 2",2"-dimethylbutyryloxy-2 '(S),6 '(R)-dimethyl-1',2',6',7',8',8a'(R)- hexahydronaphthyl-r(S))ethyl]-4(R)-substituted)-3,4,5,6-tetrahydro-2H-pyran-2-one and further deprotection to obtain 6(R)-[2-(8'(S)-2",2"-dimethylbutyryloxy- 2'(S),6'(R)-dimethyl-1',2',6',7',8',8a'(R)-hexahydronaphthyl-1'(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one.

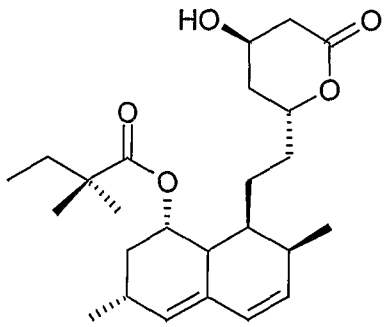
PROCESS FOR PRODUCING 6(R)-[2-(8′(S)-2′′,2′′-DIMETHYLBUTYRYLOXY-2′(S),6′(R)-DIMETHYL-1′,2′,6′,7′, 8′,8a′(R)-HEXAHYDRONAPHTHYL-1′(S))ETHYL]-4(R)-HYDROXY-3,4,5,6-TETRAHYDRO-2H-PYRAN-2-ONE

FIELD OF THE INVENTION

The present invention in general relates to an improved process for producing 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one (Simvastatin).

BACKGROUND OF THE INVENTION

Compactin, lovastatin and pravastatin are natural fermentation products, which possess a 2-methylbutyrate side chain at C-8 carbon of their hexahydronaphthalene nucleus. It is known that 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′, 8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one [Simvastatin [I]] inhibits cholesterol biosynthesis by inhibiting the enzyme HMG-CoA reductase. It possesses a 2,2-dialkylbutyrate C-8 side chain and is a better inhibitor of HMG-CoA reductase than its 2-alkylbutyrate counterpart.



[1]

There are two major approaches for the alkylation of 2-methylbutyrate side chain disclosed in the prior art.

The first major approach is direct alkylation of the 2-methylbutyrate chain. Several processes using direct alkylation approach for the methylation conversion are reported. In this route six chemical steps are involved; (a) Deactivation of α-methylene protons at C-5 position of pyranone moiety by ring opening and protecting,

thus generated carboxyl group, e.g. by making amide derivative; (b) protecting the two hydroxyl groups, e.g. via silyl protection; (c) alkylation of α-hydrogen atom of butyrate chain; (d) deprotection of hydroxyl groups in acidic media; (e) hydrolysis of carboxyl protecting group under basic condition to restore simvastatin dihydroxy acid derivative and isolating it; and (f) relactonization to give lactonized compound.

The other approach involves deacylation of the C-8 side chain followed by reacylation through several chemical steps as disclosed in US Patent 4,444,784. The process comprises de-esterification of 2-methylbutyrate side chain of lovastatin with lithium hydroxide in water at reflux, protection of the 4-hydroxyl group of the pyranone ring with *t*-butyldimethylchlorosilane; re-esterification of the protected lactone compound with 2,2-dimethylbutyryl chloride and deprotection of the hydroxyl group of the pyranone ring using tetra-n-butylammonium fluoride. The process has several disadvantages that include high temperature and long reaction time (56 hours) in the hydrolysis steps, thereby leading to a number of undesirable side products resulting in low yield and purity of simvastatin. In addition, the tetra-n-butylammonium fluoride used in the process is corrosive and toxic in nature. Further, the use of such expensive reagent for the large scale production of simvastatin on industrial scale makes the process uneconomical. Additionally, the fluoride ions remain both in aqueous and organic phases, thereby making recycling of the solvents difficult. The use of fluoride ions is undesirable in view of ecology.

US Patent 4,845,237 discloses a process wherein acyl chloride is activated by an alkali metal bromide more specifically lithium bromide and 4-dialkylaminopyridine and used for acylation of silyl protected diol lactone. However the process has a number of disadvantages that includes an additional step involving preparation of acyl chloride from carboxylic acid and the lithium bromide used in activation of acyl chloride requires drying under vacuum condition at high temperature at 135°C for three days and subsequent storage under dry conditions due to its highly hygroscopic nature. Use of wet lithium bromide in the reaction results in increased formation of the by-products and thereby lower yield of the acylated product.

The processes disclosed above according to cited prior art involve longer reaction times, use of expensive reagents and low purity of the final product. In general the existing processes involve increased formation of by-products,

cumbersome steps and environmentally toxic reagents for the preparation of simvastatin, thereby making the processes uneconomical and undesirable for large scale production.

Therefore, it is desirable to develop an industrially feasible, high yielding and cost effective process for the preparation of simvastatin, which requires less reaction time with reduced formation of by-products.

OBJECTS AND SUMMARY OF THE INVENTION

It is a principal object of the present invention to provide an improved process for producing 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′, 8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one.

It is an another object of the present invention to provide a high yielding, industrially feasible and economical viable process for producing 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′, 8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one.

It is an another object of the present invention to provide an improved process for producing 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′, 8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one, wherein the process involves minimal steps and less time.

It is a yet another object of the present invention to provide an improved process for producing 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′, 8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one, wherein the process employs less expensive, ecologically desirable reagents.

It is still another object of the present invention to provide an improved process for producing highly pure 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′, 8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one, wherein the process produces minimal by-products.

The above and other objects of the present invention are further attained and supported by the following embodiments described herein. However, the scope of the invention is not restricted to the described embodiments herein after.

According to a preferred embodiment of the present invention, there is provided an improved process for producing 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-2H-pyran-2-one, wherein the process comprises of hydrolyzing (1S,3R,7S,8S,8aR)-8-{2-[(2R,4R)-4-hydroxy-6-oxotetrahydro-*2H*-pyran-2-yl]ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl (2S)-2-methylbutanoate (lovastatin) in presence of a base and an antioxidant to obtain 7-[1′,2,'6′,7′,8′,8a′(R)-hexahydro-2′(S),6′(R)-dimethyl-8′(S)-hydroxy-1′(S)-naphthyl]–3(R),5(R)-dihydroxy heptanoic acid, lactonizing the resultant 7-[1′,2,'6′,7′,8′,8a′(R)- hexahydro-2′(S),6′(R)- dimethyl -8′(S)-hydroxy-1′(S)-naphthyl]–3(R),5(R)-dihydroxy heptanoic acid by employing a lactonizing agent to obtain 6(R)-[2-(8′(S)-hydroxy -2′(S), 6′(R)-dimethyl -1′,2′,6′,7′,8′,8a′ (R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-*2H*-pyran-2-one followed by selective protection of hydroxyl group of the 6(R)-[2-(8′(S)-hydroxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-*2H*-pyran-2-one by employing a hydroxyl protecting group to obtain 6(R)-[2-(8′(S)-hydroxy-2′(S), 6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-substituted-3,4,5,6-tetrahydro-2H-pyran-2-one, acylating the resultant 6(R)-[2-(8′(S)-hydroxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-substituted-3,4,5,6-tetrahydro-*2H*-pyran-2-one with an acylating agent in presence of a base and an organic solvent to obtain 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-substituted)-3,4,5,6-tetrahydro-*2H*-pyran-2-one and subsequent deprotection of 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-substituted)-3,4,5,6-tetrahydro-*2H*-pyran-2-one in presence of a deprotecting agent and an antioxidant to obtain the final product 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-*2H*-pyran-2-one.

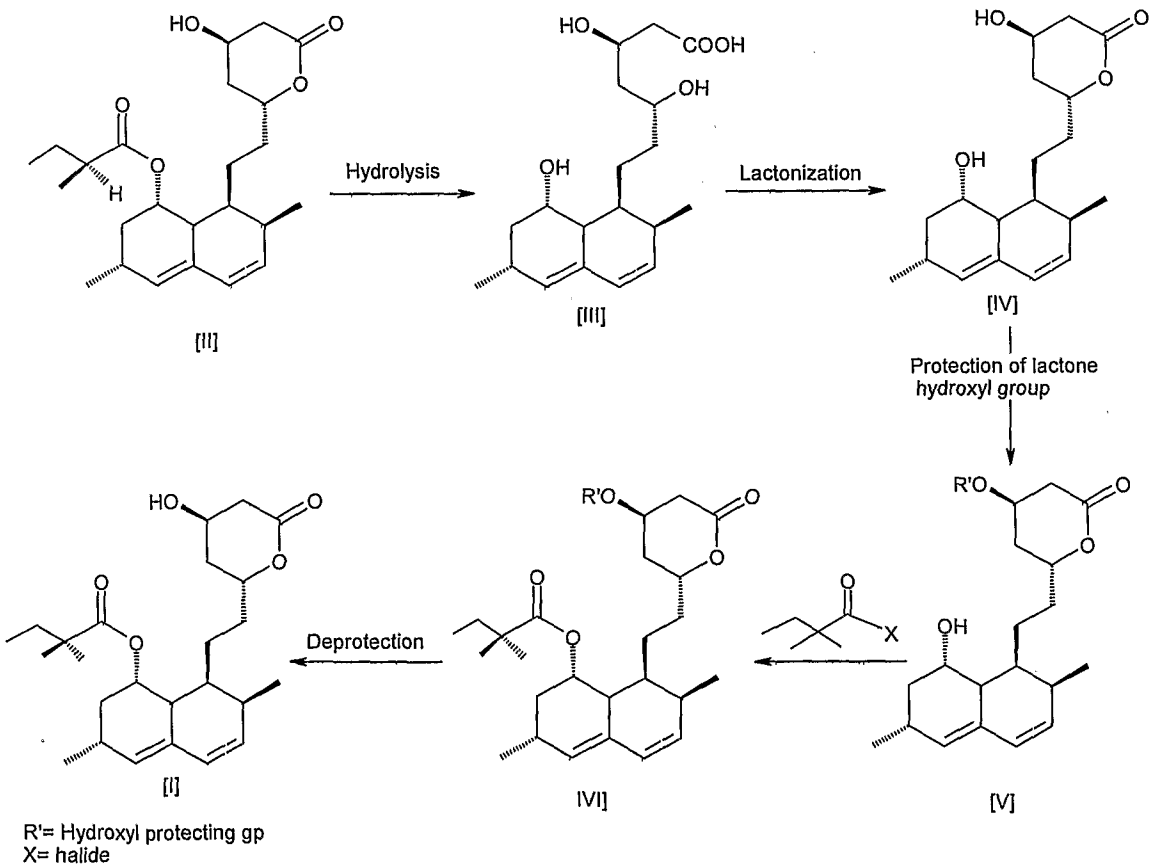
Additional features of the invention will be set forth in the description that follows, and in part will be obvious from the description, or may be learned by the practice of the invention.

DETAILED DESCRIPTION OF THE INVENTION

While this specification concludes with claims particularly pointing out and distinctly claiming that, which is regarded as the invention, it is anticipated that the invention can be more readily understood through reading the following detailed description of the invention and study of the included examples.

The present invention discloses an improved process for large scale and cost effective production of 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′, 8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-*2H*-pyran-2-one (Simvastatin) from (1S,3R,7S,8S,8aR)-8-{2-[(2R,4R)-4-hydroxy-6-oxotetrahydro-*2H*-pyran-2-yl]ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl (2S)-2-methylbutanoate (lovastatin) of formula [II] as shown in the Scheme A.

Scheme A



According to the present invention the process for producing 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy- 2′(S),6′(R)-dimethyl -1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-*2H*-pyran-2-one (Simvastatin) comprises ester hydrolysis of (1S,3R,7S,8S,8aR)-8-{2-[(2R,4R)-4-hydroxy-6-oxotetrahydro-*2H*-pyran-2-yl]ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl (2S)-2-methylbutanoate (lovastatin) of formula [II] in the presence of an antioxidant and a base under mild conditions to form compound 7-[1′,2,'6′,7′,8′,8a′(R)-hexahydro-2′(S),6′(R)-dimethyl-8′(S)-hydroxy-1′(S)-naphthyl]–3(R),5(R)-dihydroxy heptanoic acid of formula [III].

The antioxidant employed herein is selected from butylated hydroxyanisole or butylated hydroxytoluene and the like. The base employed herein is selected from hydroxides or alkoxides of alkali metal or alkaline earth metal, the alkali or alkaline earth metal is selected from lithium, sodium, potassium, calcium and magnesium in an amount corresponding to 3-7 mole equivalent of (1S,3R,7S,8S,8aR)-8-{2-[(2R,4R)-4-hydroxy-6-oxotetrahydro-*2H*-pyran-2-yl]ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl (2S)-2-methylbutanoate of formula [II], preferably 4-6 mole equivalent of (1S,3R,7S,8S,8aR)-8-{2-[(2R,4R)-4-hydroxy-6-oxotetrahydro-*2H*-pyran-2-yl]ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl (2S)-2-methylbutanoate of formula [II].

The use of antioxidant during the ester hydrolysis of (1S,3R,7S,8S,8aR)-8-{2-[(2R,4R)-4-hydroxy-6-oxotetrahydro-*2H*-pyran-2-yl]ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl (2S)-2-methylbutanoate reduces the formation of impurities. Moreover the use of antioxidant improves the yield and purity of the compound 7-[1′,2',6′,7′,8 8a′(R)-hexahydro-2′(S),6′(R)-dimethyl-8′(S)-hydroxy-1′(S)-naphthyl]-3(R),5(R)-dihydroxy heptanoic acid which is further used as an intermediate in the preparation of 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-*2H*-pyran-2-one. The final product thus obtained is of high quality and purity.

The ester hydrolysis takes place in presence of an organic solvent selected from C_1-C_5 straight or branched chain alkyl alcohol under an inert atmosphere. In addition, the reaction is carried out in mild condition at a temperature between 50-135°C, preferably between 60-100°C, more preferably between 60-75°C for 5-48

hours preferably between 5-24 hours, more preferably between 8-12 hours. In accordance with an alternate embodiment of the invention, the ester hydrolysis takes place in presence of water under reduced pressure.

The 7-[1′,2′,6′,7′,8 8a′(R)-hexahydro-2′(S),6′(R)-dimethyl-8′(S)-hydroxy-1′(S)-naphthyl]-3(R),5(R)-dihydroxy heptanoic acid of formula [III] obtained after the ester hydrolysis is lactonized employing a suitable lactonizing agent to obtain 6(R)-[2-(8′(S)-hydroxy-2′(S), 6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-*2H*-pyran-2-one of formula [IV]. The lactonizing agent employed herein is selected from organic or inorganic compounds. The preferred organic compound is an organic acid selected from formic acid, acetic acid, methane sulphonic acid, *p*-toluene sulphonic acid, benzene sulphonic acid or trifluoroacetic acid. The preferred inorganic compound is an alkali metal hydrogen sulfate such as lithium, potassium and sodium hydrogen sulfate and the like.

The above lactonization reaction takes place in presence of a solvent selected from the group comprising aromatic hydrocarbon, chlorinated hydrocarbon, acetate, nitriles, ethers or mixture thereof. Preferably the solvent is selected from toluene, xylene, dichloromethane, chloroform, ethyl acetate, propyl acetate, butyl acetate, methyl propionate, acetonitrile, propionitrile, diethyl ether, diisopropyl ether, methyl tertiary butyl ether or mixtures thereof. The reaction is carried out at a temperature between -10°C to 30°C preferably between –5°C to 20°C for 0.5 hours to 4 hours preferably between 1-3 hours.

Further, the hydroxyl group of compound 6(R)-[2-(8′(S)-hydroxy-2′(S), 6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-*2H*-pyran-2-one of formula [IV] is selectively protected with hydroxyl protecting group in presence of a base e.g. imidazole to obtain protected intermediate 6(R)-[2-(8′(S)-hydroxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-substituted-3,4,5,6-tetrahydro-*2H*-pyran-2-one of Formula [V] which further participates in the process step for producing 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-*2H*-pyran-2-one of formula [I].

The hydroxyl protecting group substituted at 4(R) position is selected from a silyl group, borate group, cyclic ether group, cyclic thioether group, an acetal, cyclic acetals, cyclic ketals and the like. More preferably the protecting groups are selected from the group comprising trimethylsilyl, triethylsilyl, dimethylhexylsilyl, diethylisopropylsilyl, tribenzylsilyl, tri-*p*-xylylsilyl, dimethylisopropylsilyl, *tert*-butyldimethylsilyl, *tert*-butylmethoxyphenylsilyl, *t*-butyldiphenylsilyl, diisopropylmethylsilyl, (triphenylmethyl)dimethylsilyl, diphenylmethylsilyl, triisopropylsilyl, triphenylsilyl, t-butylmethoxyphenylsilyl, t-butoxydiphenylsilyl, phenyl boronic acid, tetrahydropyran-2-yl, tetrahydrothiopyran-2-yl, 4-methoxytetrahydropyran-2-yl, 1,4-dioxane-2-yl, 1,3 dioxolanes, 4,6-dimethyl-1,3 dioxane, tetrahydrofuran-2-yl, acetonide and the like.

The selective protection reaction takes place optionally in presence of solvent selected from water immiscible solvents or mixture thereof. Preferably the solvent is selected from the group comprising aprotic solvents, chlorinated solvents and the like. Preferably the solvent is selected from dimethylsulphoxide, N,N-dimethylformamide, N,N-dimetylacetamide, N-methylpyrrolidone, dimethylimidazolidone, dichloromethane, chloroform, carbon tetra chloride or mixture thereof. The reaction is carried out at an elevated temperature, preferably at the reflux temperature of the reaction mixture depending upon the solvent used.

The resulting intermediate compound 6(R)-[2-(8′(S)-hydroxy-2′(S), 6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-substituted-3,4,5,6-tetrahydro-*2H*-pyran-2-one of formula [V] is acylated with an acylating agent preferably 2,2 dimethylbutyryl halide wherein the halide is selected from fluorine, chlorine and bromine, in presence of an organic solvent and base under mild conditions to produce protected 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-substituted)-3,4,5,6-tetrahydro-*2H*-pyran-2-one of formula [VI] in high yield (above 90%) with minimal byproducts.

The organic solvent used in the acylation reaction is selected from aromatic hydrocarbon, preferably toluene, xylene and the like. The base used in the acylation reaction is selected from triethylamine, N,N-dimethylaniline or heterocyclic amines such as pyridine, N-methyl morpholine, dimethyl amino pyridine preferably

triethylamine. The reaction is preferably carried out at a temperature of the boiling point of the solvent under anhydrous condition.

The resulting compound 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-substituted)-3,4,5,6-tetrahydro-*2H*-pyran-2-one of formula [VI] is subjected to deprotection in a single step to obtain 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-*2H*-pyran-2-one of formula [I] in high yield above 80% with the formation of minimal by products. The reaction is carried out in presence of an organic or inorganic acid as a deprotecting agent and an antioxidant. The reaction is carried out at a temperature between –5 to 30°C depending upon the type of deprotecting agent used, for 15-20 hours.

The deprotecting agent used herein is selected from organic or inorganic compounds. Preferred organic compound is an organic acid selected from formic acid, acetic acid, methane sulphonic acid, *p*-toluene sulphonic acid, benzene sulphonic acid or trifluoroacetic acid. Preferred inorganic compound is an alkali metal hydrogen sulfate such as lithium, potassium and sodium hydrogen sulfate. Alternately, the inorganic compound can be a lewis acid selected from $AlCl_3$, $ZnCl_2$, $CuCl_2$, $TiCl_4$, BF_3-Et_2O $SnCl_4$, metal triflates, alkyl and acyl triflates, I_2 and the like. Further, the inorganic compound can be mineral acids such as hydrochloric acid, sulfuric acid, nitric acid, perfluoric acid, perchloric acid, phosphoric acid and the like. The antioxidant employed in the deprotection reaction is preferably butylated hydroxyanisole or butylated hydroxytoluene.

The deprotection reaction takes place in presence of an aprotic solvent, nitriles, ethers and the like. Preferred solvent is selected from dimethylsulphoxide, N,N-dimethylformamide, N,N-dimetylacetamide, N-methylpyrrolidone, dimethylimidazolidone, acetonitrile, propionitrile, tetrahydrofuran, 1,3-dioxane, 1,4-dioxane, diethyl ether or a mixture thereof.

The 6(R)-[2- (8′(S) -2′′,2′′- dimethylbutyryloxy -2′(S) ,6′(R) - dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-*2H*-pyran-2-one of formula [I] is further purified according to the methods reported in the prior art.

In accordance with the present invention, the deprotection of the lactone hydroxy group and cyclization of lactone ring take place in single step.

The above described embodiments involve less no number of steps and smaller content of the colored side product generated in the deprotection step. Further, the process disclosed herein is economically and ecologically acceptable as it avoids the use of expensive and corrosive reagents like tetra-n-butylammonium fluoride.

The present invention is further described in greater detail as illustrated in non-limiting examples. It should be understood that variation and modification of the process are possible within the ambit of the invention broadly disclosed herein.

Example-1

Preparation of 7-[1′,2,'6′,7′,8′,8a′(R)-hexahydro-2′(S),6′(R)-dimethyl-8′(S)-hydroxy-1′(S)-naphthyl]–3(R),5(R)-dihydroxy heptanoic acid [III]

Potassium hydroxide (80 g) and isopropyl alcohol (500 ml) was taken and the resulting mixture was heated to 65-70°C. To the resulting mixture, butylated hydroxyanisole (2.0 g) and butylated hydroxytoluene (2.0 g) and (1S,3R,7S,8S,8aR)-8-{2-[(2R,4R)-4-hydroxy-6-oxotetrahydro-*2H*-pyran-2-yl]ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl (2S)-2-methylbutanoate (100 g) was added. The reaction mixture was stirred for 9-12 hours at 70-75°C. The resulting mixture was cooled to 50°C and solvent was distilled off under reduced pressure. Water was added and the resulting mixture was cooled to 0-5°C. The reaction mixture was acidified to pH 1.5-2.0 with concentrated hydrochloric acid and stirred for 2 hours at 0-10°C. The resulting solid was filtered, washed with water and then dried to obtain title compound. Yield (90-95%). HPLC Purity: 97-98%.

Example-2

Preparation of 6(R)-[2-(8′(S)-hydroxy-2′(S), 6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-*2H*-pyran-2-one [IV]

7-[1′,2′,6′,7′,8′,8a′(R)-hexahydro-2′(S),6′(R)-dimethyl-8′(S)-hydroxy-1′(S)-naphthyl-3(R), 5(R)-dihydroxy heptanoic acid (100 g) was suspended in dichloromethane (800 ml) and the reaction mixture was cooled to 0-5°C. *p*-toluene sulfonic acid (4 g) was added at the above temperature. The reaction mixture was stirred at 0-15°C for 2 hours. To the resulting mixture, saturated sodium bicarbonate solution was added and the mixture was stirred for 30 minutes. Solvent was distilled

off and water was added. The precipitated solid was filtered off, wash with water and dried at 45-50°C for 18 hours to obtain title compound. Yield (88-90%). HPLC Purity: 96-98%.

Example-3

Preparation of 6(R)-[2-(8′(S)-hydroxy-2′(S),6′(R)-dimethyl-1′,2′,6',7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-(dimethyltertbutylsilyloxy)-3,4,5,6-tetrahydro-*2H*-pyran-2-one [V]

6(R)-[2-(8′(S)-hydroxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S) ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-*2H*-pyran-2-one (100 g) was dissolved in dichloromethane (400 ml). Imidazole (36 g) and *t*-butyldimethylchlorosilane (65 g) were added. The reaction mixture was heated at 35-40°C for 4-6 hours under stirring. The mixture was cooled to room temperature and filtered. The resulting filtrate was first wash with aqueous hydrochloric acid solution and then with water. The organic layer was separated and solvent was distilled off under vacuum to obtain the title compound.

Yield (85-90%). HPLC Purity: 98-99%.

Example-4

Preparation of 6(R)-[2-(8′(S)-2", 2"-dimethylbutyryloxy -2′(S),6′(R)-dimethyl-1′,2′,6',7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-(dimethyltertbutylsilyloxy)-3,4,5,6-tetrahydro-*2H*-pyran-2-one [VI]

6(R)-[2-(8′(S)-hydroxy-2′(S),6′(R)-dimethyl-1′,2′,6',7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-(dimethyltertbutylsilyloxy)-3,4,5,6-tetrahydro-2H-pyran-2-one (100 g) was taken in toluene (1000 ml) and 2,2,dimethyl butyryl chloride (62.3g) and triethylamine (81.4ml) was added. The reaction mixture was heated to 106-110°C for 19-24 hours. The resulting mixture was cooled to 30°C, within one hour, filtered, wash the filtrate first with saturated sodium bicarbonate solution and then with water. The organic layer was separated and solvent was distilled off. To the resulting mass, methanol (560 ml) was added and was cooled to 10-15°C. Water was added and the reaction mixture was seeded with pure 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-

hexahydronaphthyl-1′(S))ethyl]-4(R)-dimethyltertbutylsilyloxy)-3,4,5,6-tetrahydro-*2H*-pyran-2-one compound. The reaction mixture was stirred for one hour, for 8-12°C, water was added within 40-45 minutes and stirred for 2 more hours. The precipitated solid was filtered, wash first with methanol:water (3:1) mixture and then with water. The solid was dried for 12 hours at 50°C. The resulting solid was taken in methanol and was cooled to 10-15°C. Water was added within 30 minutes. The resulting mass was stirred for 30 minutes at 15-20°C. The resulting mixture was seeded with pure 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-dimethyltertbutylsilyloxy)-3,4,5,6-tetrahydro-*2H*-pyran-2-one compound, and add water within 30 minutes. The reaction mixture was stirred for 2 hours as a result solid precipitate off. The resulting solid was filtered, wash first with methanol: water (3:1) mixture and then with water, dried for 24 hours at 45°C to obtain title compound. Yield (90-92%). HPLC Purity: 98%.

Example-5

Preparation of 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-*2H*-pyran-2-one [1]

6(R)-[2-(8′(S)-2",2"-dimethylbutyrylloxy-2′(S),6′(R)-dimethyl-1′,2′,6',7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-(dimethyltertbutylsilyloxy)-3,4,5,6-tetrahydro-*2H*-pyran-2-on (100 g), butylated hydroxyanisole (0.1 g), *p*-toloune sulphonic acid (35.8 g) was taken in dimethylformamide (700 ml) and was cooled to 10-15°C under stirring. The resulting mixture was further stirred at 15-20°C for 14-20 hours. The resulting mass was cooled to 0-5°C, and sodium bicarbonate solution was added, and seeded with pure 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-*2H*-pyran-2-one seed. Water (300 ml) was added and the mixture was stirred for 2-3 hours at. 0-10°C to obtain title compound. Yield (94-96%). HPLC Purity: 95-98%.

Example 6

Preparation of pure 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′, 8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-*2H*-pyran-2-one [I]

Crude 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-*2H*-pyran-2-on (100 g) was taken in cyclohexane (2500 ml) and toluene (20 ml) and was heated to 80-85°C under stirring for one hour. The resulting solution was cooled to 25-30°C within 2- 6 hours and seeded with pure 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-*2H*-pyran-2-one seed. The resulting mixture was stirred for 2-4 hours at 15-20°C. The resulting solid was filtered off, wash with cyclohexane and dried under vacuum for 6 hours at 45-50°C. The resulting solid was further dissolved in methanol (1200 ml) and small amount of activated carbon was added. The resulting mixture was stirred for one hour at 20-25°C. The activated carbon was removed by filtration and methanol (200 ml) was added to the filtrate. The resulting mass was cooled to 15-20°C, water (600 ml) was added and the resulting mixture was seeded with pure 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-*2H*-pyran-2-one seed. The resulting mixture was stirred for 1 hour. The precipitated solid was filtered, wash with water and dried under vacuum to obtain pure simvastatin. Yield (85-87%). HPLC Purity: 99.5%.

Certain modifications and improvements of the disclosed invention will occur to those skilled in the art without departing from the scope of invention, which is limited only by the appended claims.

We Claim:

1. An improved process for producing 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-*2H*-pyran-2-one , the process comprising:

(a) hydrolyzing (1S,3R,7S,8S,8aR)-8-{2-[(2R,4R)-4-hydroxy-6-oxotetrahydro-*2H*-pyran-2-yl]ethyl}-3,7-dimethyl-1,2,3,7,8,8a-hexahydronaphthalen-1-yl (2S)-2-methylbutanoate in presence of a base and an antioxidant to obtain 7-[1′,2,'6′,7′,8′,8a′(R)-hexahydro-2′(S),6′(R)-dimethyl-8′(S)-hydroxy-1′(S)-naphthyl]–3(R),5(R)-dihydroxy heptanoic acid;

(b) lactonizing the 7-[1′,2,'6′,7′,8′,8a′(R)-hexahydro-2′(S),6′(R)-dimethyl-8′(S)-hydroxy-1′(S)-naphthyl]–3(R),5(R)-dihydroxy heptanoic acid by employing a lactonizing agent to obtain 6(R)-[2-(8′(S)-hydroxy-2′(S), 6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-*2H*-pyran-2-one ;

(c) selectively protecting the hydroxyl group of the 6(R)-[2-(8′(S)-hydroxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-*2H*-pyran-2-one by employing a hydroxyl protecting group to obtain 6(R)-[2-(8′(S)-hydroxy-2′(S), 6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-substituted-3,4,5,6-tetrahydro-*2H*-pyran-2-one,;

(d) acylating 6(R)-[2-(8′(S)-hydroxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-substituted-3,4,5,6-tetrahydro-*2H*-pyran-2-one with an acylating agent in presence of a base and an organic solvent to obtain 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-substituted)-3,4,5,6-tetrahydro-*2H*-pyran-2-one ;

(e) deprotecting 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-hexahydronaphthyl-1′(S))ethyl]-4(R)-substituted)-3,4,5,6-tetrahydro-*2H*-pyran-2-one in a single step in presence of a deprotecting agent and an antioxidant to obtain 6(R)-[2-(8′(S)-2′′,2′′-dimethylbutyryloxy-2′(S),6′(R)-dimethyl-1′,2′,6′,7′,8′,8a′(R)-

hexahydronaphthyl-1′(S))ethyl]-4(R)-hydroxy-3,4,5,6-tetrahydro-*2H*-pyran-2-one.

2 The process according to claim 1, wherein the base employed in step (a) is selected from hydroxides or alkoxides of alkali metal or alkaline earth metal.

3. The process according to claim 2, wherein said alkali or alkaline earth metal is selected from lithium, sodium, potassium, calcium or magnesium.

4 The process according to claim 1, wherein the antioxidant employed in step (a) is selected from butylated hydroxyanisole or butylated hydroxytoluene.

5. The process according to claim 1, wherein the lactonizing agent employed in step (b) is selected from an organic or an inorganic compound.

6. The process according to claim 5, wherein the organic compound is preferably an organic acid selected from a group consisting of formic acid, acetic acid, trifluoroacetic acid, methane sulphonic acid, *p*-toluene sulphonic acid and benzene sulphonic acid.

7. The process according to claim 5, wherein the inorganic compound is preferably alkali metal hydrogen sulfate.

8. The process according to claim 7, wherein the alkali metal hydrogen sulfate is selected from lithium, potassium and sodium hydrogen sulfate.

9. The process according to claim 1, wherein the hydroxyl protecting group employed in step (c) is selected from a group consisting of silyl, borate, cyclic ether, cyclic thioether, acetal, cyclic acetal, and cyclic ketal.

10. The process according to claim 9, wherein the hydroxyl protecting group is selected from trimethylsilyl, triethylsilyl, dimethylhexylsilyl, diethylisopropylsilyl, tribenzylsilyl, tri-*p*-xylylsilyl, dimethylisopropylsilyl, *tert*-butyldimethylsilyl, *tert*-butylmethoxyphenylsilyl, *t*-butyldiphenylsilyl, diisopropylmethylsilyl, (triphenylmethyl)dimethylsilyl, diphenylmethylsilyl, triisopropylsilyl, triphenylsilyl, *t*-butylmethoxyphenylsilyl, *t*-butoxydiphenylsilyl, phenyl boronic acid, tetrahydropyran-2-yl, tetrahydrothiopyran-2-yl, 4-methoxytetrahydropyran-2-yl, 1,4-dioxane-2-yl, 1,3 dioxolanes, 4,6-dimethyl-1,3 dioxane and tetrahydrofuran-2-yl, or acetonide.

11. The process according to claim 1, wherein the acylating agent employed in step (d) is 2, 2-dimethylbutyrylhalide.

12. The process according to claim 1, wherein the base employed in step (d) is selected from triethylamine, N, N- dimethylaniline, pyridine, N-methyl morpholine, dimethyl amino pyridine or a mixture thereof.

13. The process according to claim 1, wherein the organic solvent employed in step (d) is an aromatic hydrocarbon.

14. The process according to claim 1, wherein the deprotecting agent employed in step (e) is selected from an organic or an inorganic compound.

15. The process according to claim 14, wherein the organic compound is selected from formic acid, acetic acid, trifluoroacetic acid, methane sulphonic acid, *p*-toluene sulphonic acid and benzene sulphonic acid.

16. The process according to claim 14, wherein the inorganic compound is a lewis acid selected from $AlCl_3$, $ZnCl_2$, $TiCl_4$, BF_3-Et_2O and $SnCl_4$., metal triflates, alkyl and acyl triflates and I_2.

17. The process according to claim 14, wherein the inorganic compound is selected from hydrochloric acid, sulfuric acid, nitric acid, perfluoric acid, perchloric acid, phosphoric acid.

18. The process according to claim 14, wherein the inorganic compound is an alkali metal hydrogen sulfate.

19. The process according to claim 18, wherein the alkali metal hydrogen sulfate is selected from lithium, potassium or sodium hydrogen sulfate.

20. The process according to claim 1, wherein the antioxidant employed in step (e) is butylated hydroxyanisole or butylated hydroxytoluene.