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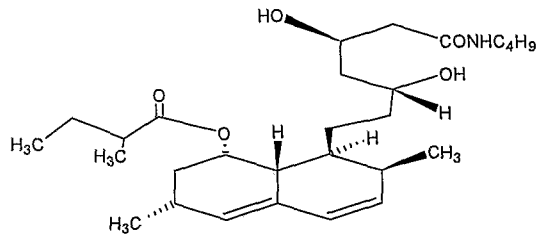
(54) Title: IMPROVED PROCESS FOR MANUFACTURING STATINS

(57) Abstract: The present invention provides an improved process for manufacturing statins comprising the following steps (i) reacting lovastatin with butyl amine to produce lovastatin amide (ii) isolating lovastatin butylamide in solid form by crystallization, from organic solvent (iii) optionally subjecting to hydroxyl protection to get diprotected lovastatin butylamide, (iv) subjecting proteceted or unprotected amide so obtained to C-Methylation employing lithium pyrrolidide prepared in situ by reacting butyl lithium and pyrrolidine, isolating the title product by conventional methods, and converting to its pharmacologically acceptable salt by known methods.

IMPROVED PROCESS FOR MANUFACTURING STATINS.

FIELD OF THE INVENTION

The present invention particularly relates to an improved process that involves isolation of intermediate product of formula.



in solid form and its C-methylation directly or after hydroxyl protection using in-situ generated lithium pyrrolidide, which is useful for making 3-hydroxy lactone-containing products such as HMG-CoA reductase inhibitors like Simvastatin etc. The process of this invention is thus high yielding leading to a title product with increased purity. Further, the process is cost effective as the reactants are not wasted and additional purification of the product is not required.

BACKGROUND OF THE INVENTION

Lovastatin, Simvastatin, Pravastatin, Atorvastatin, and Mevastatin are well known potent antihypercholesterolemic agents that function by limiting cholesterol biosynthesis by

inhibiting the enzyme, HMG-CoA reductase.This class of compounds, referred to generally as statins, are produced either by natural fermentation process or through semi-synthetic and totally synthetic means thereof. Two of the most popular compounds in this therapeutic category are Simvastatin and Atorvastatin. The former

is one of the most prescribed drugs in the treatment of primary hypercholesterolemia with minimum side effects and well established safety profile.

Several processes have so far been reported by different patents and publications. Broadly two types of approaches have been published. In one approach lactone ring of Lovastatin is not hydrolyzed, but the required side chain is directly attached to the main ring. This approach has been adopted by US patent US 4,444,784. Another approach is adopted and disclosed in US Patent Nos. US 4,582,915; US 4,820,850. US patent # US 4,582,915; US 4,820,850. According to the teaching of these patents, lactone ring of Lovastatin is first hydrolyzed using different bases followed by hydroxyl protection to give dihydroxy protected intermediate which is further C-methylated using methyl halide and lithium pyrrolidide prepared externally by reaction of butyl lithium and pyrrolidine. C-Methylated intermediate is further converted to Simvastatin through a sequence of reactions.

In our attempts to synthesize Simvastatin we have found that conversion of Lovastatin to Simvastatin becomes easier, safer and more qualitative as herein after explained if the hydrolyzed product of Step I in solid form by crystallization of reaction mass in appropriate solvent followed by filtration / centrifugation prior to C-Methylation and carrying out C-Methylation by employing lithium pyrrolidide in-situ by reaction of n-butyl lithium and pyrrolidine.

It has been observed that using externally prepared lithium pyrrolidide generally results in to incomplete C-Methylation leaving 10 to 20% unreacted dihydroxy intermediate there by resulting in lower yields. Additionally, the unreacted dihydroxy intermediate remains in the C-Methylated product as an impurity and gets carried over in the final product necessitating further purification steps. Thus, the process becomes cost extensive and results in the low quality title preduct.

The process of the present invention employs lithium pyrrolidide preparated in-situ by reacting n-butyl lithium and pyrrolidine. Due to this technological advancement, reaction of C-Methylation goes to completion leaving no unreacted dihydroxy intermediate after reaction thereby resulting into higher yields and better quality of final product.

SUMMARY OF THE INVENTION

The main objective of the present invention is to provide an improved process for manufacturing statins obviating most of the drawbacks of the existing prior art.

Other object is to provide a process that provides isolation of substantially pure intermediate product in solid form thereby leaving most of the impurities in mother liquor.

Another object is to provide a process that involves C-Methylation of the said intermediate directly or after hydroxyl protection using in-situ generated lithium pyrrolidide, which is useful for making 3-hydroxy lactone containing products.

Yet other object is to provide a process that is economical and high yielding.

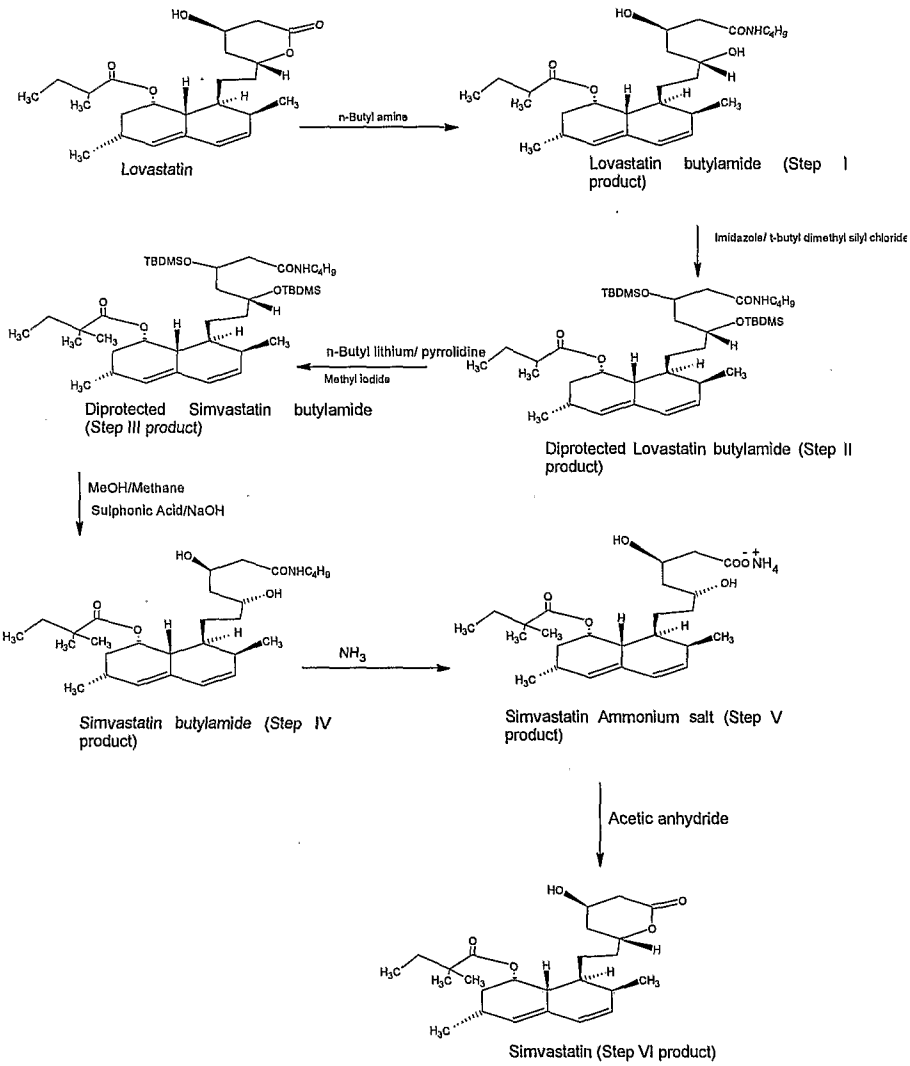
Yet another object is to provide a process resulting in to a little product with substantially reduced impurities.

Thus, the novelty of this invention resides in:

1) Isolating step I intermediate in solid form by crystallization in a suitable solvent followed by centrifugation or filtration for removal of impurities and traces of base (used in step (I) in mother liquor) and

2) C-methylation of step I or step II product generating lithium pyrrolidide in-situ to get smooth reaction completion.

The invention is further illustrated by Synthetic scheme given below:



STATEMENT OF INVENTION

Accordingly the present invention provides an improved process for manufacturing statins comprising the following steps:

i) crystallizing in a known manner such as herein described lovastatin butylamide from the reaction mass resulting from the reaction between lovastatin and butyl amine

ii) optionally subjecting to hydroxyl protection the said lovastatin butylamide obtained in step (i) to get a diprotected lovastatin butylamide,

iii) C-Methylating lovastatin butylamide/ diprotected lovastatin butylamide employing lithium pyrrolidide prepared in situ by reacting butyl lithium and pyrrolidine, followed by

iv) isolating the title product by conventional methods, and converting to its pharmacologically acceptable salt by known methods.

The crystallization in step (i) may be effected in organic solvent. The organic solvent used for crystallization in step (i) may be any low polar hydrocarbon solvent like hexane, heptane, xylenes, benzene, toluene etc.; any ethereal solvent like isopropyl ether methyl ter butyl ether, diethyl ether etc. But more preferable is hexane and cyclohexane and most preferable is hexane. Step (i) product may further optionally be hydroxyl protected before C-methylation.

C-methylation is carried out using in-situ generated lithium pyrrolidide by reaction of butyl lithium and pyrrolidine in a suitable organic solvent at low temperature. The suitable organic solvent used for C-methylation may be aliphatic ether that includes without limitation to tetrahydrofuran, methyl-t-butyl ether, hydrocarbons like hexane, cyclohexane or a mixture thereof. More preferred solvent being tetrahydrofuran, hexane and cyclohexane or a mixture of two or more of these solvents.

C-Methylation may preferably be carried out at low temperature of -80 to 0°C. The more preferred temperature being -60 to -20°C. The most preferred temperature being

-40 to -30°C.

The invention may further be described by taking following examples which are only illustrative and are not to be construed as any limitation thereof.

The steps indicated in all the examples are indicative of the one shown in the schematic representation and not to the statement of invention or claims.

EXAMPLE 1

Preparation of Lovastatin butyl amide-step I product

100 g Lovastatin (HPLC purity 85%) was reacted with 90 g n-butyl amine under refluxing. Un-reacted amine was distilled off. 800 ml of Hexane was added to the residue and the resultant mass was stirred to get complete crystallization. Crystallized mass was filtered and washed with hexane. 100 gram of the title compound was obtained after drying having HPLC purity 99.65%.

EXAMPLE 2

Preparation of diprotected Lovastatin butyl amide-step II product

100 g of step I product was added to 180 ml of dimethylformamide. Mass was stirred at 60-65°C after adding 45 g of imidazole and 105 g of tertiary butyl dimethylsilyl chloride. Reaction mass was extracted with cyclohexane after dilution with water. Organic layer was washed further with sodium bicarbonate solution. Oily residue, 140 g, was obtained after recovery of cyclohexane.

EXAMPLE 3

Preparation of diprotected Simvastatin butyl amide-step III product

100 g of step II product was added to 1.5 ltr of tetrahydrofuran. Mass was cooled to -35 to -40°C. 50 g of pyrrolidine was added followed by addition of 600 ml of n-butyl

lithium (~10% solution in hexane). Stirring was continued for 1 hr. 100 g of methyl iodide was slowly added to the mass. Stirring was further continued for reaction completion. Reaction mass was quenched by adding 1 ltr of water. Organic layer was separated. Aqueous layer was extracted with cyclohexane. Combined organic layer was washed with 1N Hydrochloric acid followed by washing with 10% sodium bisulfite solution followed by water washing. Washed organic layer was concentrated to get 107 g viscous oily residue having step II product < 1.0%.

EXAMPLE 4

Preparation of Simvastatin butyl amide-step IV product

150 g of viscous oily residue from example 3 is charged to 1.0 ltr of methanol followed by addition of 4.5 g of methane sulfonic acid and 100 mf water. Stirring is continued for reaction completion at 25-30°C. Obtained reaction mass is proceeded as such for next step.

EXAMPLE 5

Preparation of Simvastatin ammonium salt-step V product

Reaction mass from example 4 was refluxed for 1-3 hr after adding 10%, 600 ml sodium hydroxide solution to get reaction completion. Solvent was removed under reduced pressure to get hazy reaction mass. 500 ml of water was added followed by cooling to 10-15°C. pH was adjusted to 4.8-5.0 by dilute hydrochloric acid. Reaction mass was extracted with 1.8 ltr ethyl acetate. Organic layer was diluted with methanol. pH was adjusted to 9.0-9.5 with dilute ammonia solution. Mass was cooled to get crystallization. 75 g product was isolated after filtration and drying.

EXAMPLE 6

Preparation of Simvastatin-step VI product

Simvastatin ammonium salt from example 5 (50 g) is reacted with acetic anhydride (125 g) in acetonitrile (750 ml) at 20-25°C for 10-15 hours. Reaction mass is cooled and water is added slowly to bring about crystallization of the product. Slurry is filtered and washed with water followed by purification in ethyl acetate-hexane and recrystallization in methanol-water to give the final Simvastatin 40 g having Lovastatin impurity < 0.7%, dimmer impurity < 0.05% and product purity > 98.5%.

ADVANTAGES:

i) Lovastatin butylamide produced after crystallization is highly pure (>98%) even after taking impure Lovastatin as the impurities pass into mother liquor of crystallized mass.

ii) C-Methylation reaction becomes smoother and proceeds to its completion without much involvement of specialized machinery at large scale. This results into highly pure final product (Simvastatin) having Lovastatin impurity well below 1%.

WE CLAIM:

1. Improved Process for Manufacturing Statins comprising following steps:

(i) crystallizing in a known manner such as herein described lovastatin butylamide from the reaction mass resulting from the reaction between lovastatin and butyl amine,

(ii) optionally subjecting to hydroxyl protection the said lovastatin butylamide obtained in step (i) to get a diprotected lovastatin butylamide,

(iii) C-Methylating lovastatin butylamide/ diprotected lovastatin butylamide

employing lithium pyrrolidide prepared in situ by reacting butyl lithium and pyrrolidine, followed by

(iv) isolating the title product by conventional methods, and converting to its pharmacologically acceptable salt by known methods.

2. A process as claimed in claim 1 wherein the crystallization in step (i) is effected in organic solvent selected from any low polar hydrocarbon solvent preferably hexane, heptanes, benzene, xylenes, toluene; any ethereal solvent preferably isopropyl ether, methyl ter butyl ether, diethyl ether or a mixture thereof, more preferably hexane and cyclohexane and most preferably hexane followed by isolating the crystallized amide by filtration or decantation or solvent evaporation.

3. A process as claimed in claim 1 wherein methylation is carried out using in-situ generated lithium pyrrolidide by reaction of butyl lithium and pyrrolidine in a organic solvent such as herein described, at sub zero temperatures.

4. A process as claimed in claim 3 wherein the organic solvent used is aliphatic ether that includes without limitation to tetrahydrofuran, methyl-t-butyl ether, hydrocarbons like hexane, cyclohexane preferably tetrahydrofuran, hexane and cyclohexane or a mixture of.

5. A process as claimed in claim 3 wherein the reaction is performed at a temperature of -80 to 0°C. The more preferred temperature being -60 to -20°C. The most preferred temperature being -40 to -30°C.