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Synthetic Methods for Simvastatin – an Overview

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Abstract: There are three basic methodologies for simvastatin production; biosynthesis or the fermentation technology method using fungal stains, biocatalytic method to convert lovastatin into simvastatin and synthetic methods for modification of lovastatin into simvastatin. Out of all three methodologies, synthetic modifications of lovastatin into simvastatin are commercialized and widely used methodologies. There are two possible synthetic routes for simvastatin; direct alkylation route and re-esterification route. Relatively high yield and fewer synthetic steps are the main advantages of adopting direct alkylation route while re-esterification route, wherein the 2-methyl butyrate side chain is completely removed and 2,2-dimethylbutyrate side chain is introduced, gives better quality of simvastatin, as the separation of the hydrolyzed product and the esterified product is much easier to achieve compared to the unreacted starting material and the methylated product.

Keywords: Simvastatin, Lovastatin, HMG Co-A reductase, Re-esterification, Direct methylation.

1 Introduction

Since high blood cholesterol levels is linked to cardio vascular disease, scientists around 1950s have started searching for drugs which can lower the level of cholesterol in blood. Many academic institutes and companies were involved in the search for molecules which can inhibit the synthesis of cholesterol. Cholesterol is either absorbed from the diet or if the diet is lacking sufficient cholesterol to meet the requirement of body, then it could be synthesized by body mainly in the liver and the intestine [1]. However, if the diet was rich in cholesterol then synthesis within the body virtually stopped this is controlled by a feedback mechanism in which cholesterol inhibit the enzyme β -hydroxy- β -methylglutaryl-CoA reductase (HMG Co-A reductase). By inhibiting enzyme HMG Co-A reductase, the conversion of HMG-CoA to mevalonic acid is stopped [2].

Mevastatin (Compactin) was the first HMG-CoA reductase inhibitor that belongs to the statins class and was isolated from the mold *Penicillium citrinum* by Akira Endo in the 1972. Clinical trials on mevastatin were performed in the late 1970s in Japan, but it was never marketed [3]. Lovastatin (Mevinolin), a statin similar to mevastatin in chemical structure was isolated in 1979 by scientists at Merck & Co. from the fungus *Aspergillus terreus* [4]. The first commercially available statin drug used for the treatment of high cholesterol was lovastatin.

After commercialization of lovastatin, 6 more statins have been introduced to the market, including 2 semi-synthetic statins (simvastatin and pravastatin) and 4 synthetic statins (fluvastatin, atorvastatin, rosuvastatin and pitavastatin). Merck and Co. developed simvastatin from lovastatin, Sankyo developed pravastatin from mevastatin and 4 synthetic statins were also subsequently developed [5]. Simvastatin is among most popular statin used for cardio vascular disease.

2 Synthetic Methodologies for Simvastatin

There are three basic methodologies for the synthesis of simvastatin; biosynthesis or the fermentation method, biocatalytic method to convert lovastatin into simvastatin and synthetic methods for modification of lovastatin into simvastatin. Out of all above described methodologies, synthetic modifications of lovastatin into simvastatin are commercialized and widely used.

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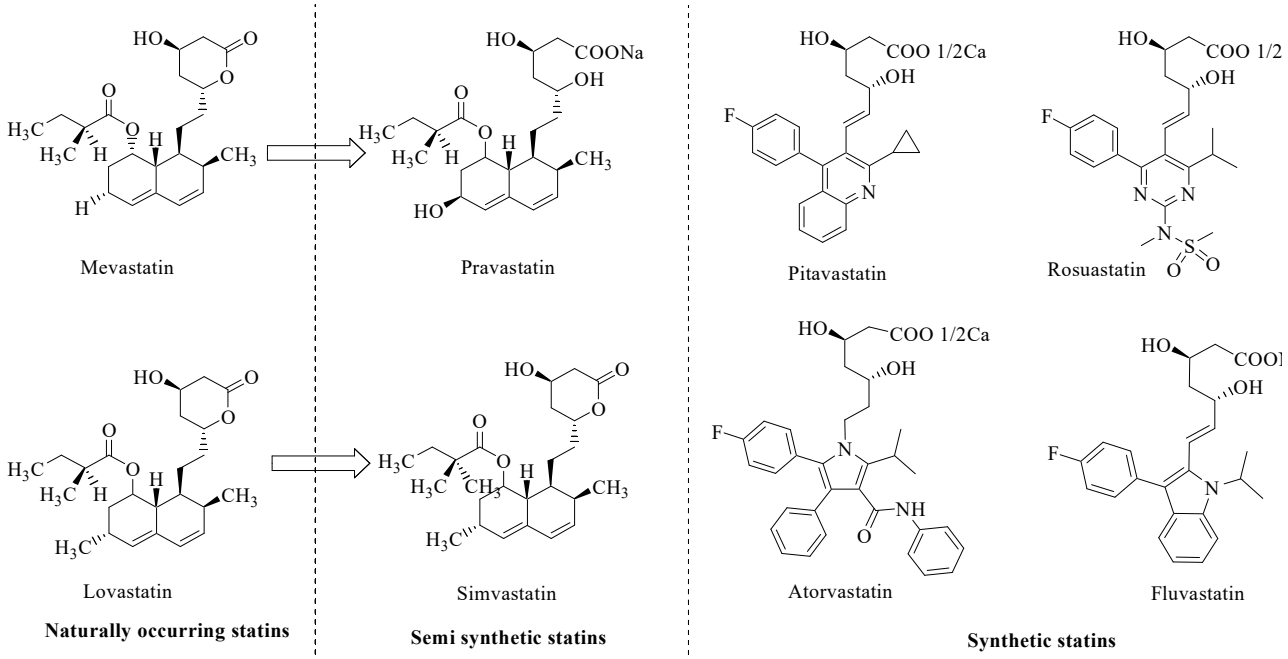

Fig. 1. Mevastatin, Lovastatin, their semi synthetic analogs and synthetic statins.

2.1 Biosynthesis or the Fermentative Method

In fermentative process simvastatin is formed along with lovastatin by *Aspergillus terreus* ATCC20542 fed with 2,2-dimethylbutyrate in a host cell. In this method simvastatin found present typically at 1/50th of the lovastatin level **[6]**.

2.2 Biocatalytic Method to Convert Lovastatin into Simvastatin

Scientists at University of California, Los Angeles have used whole cell biocatalyst and achieved more than 99% conversion of monacolin J to simvastatin without the use of any chemical protection group. In this process lovastatin is converted into monacolin J by hydrolysis and monacolin J is subjected to direct acylation with α-dimethylbytyryl-S-N-acetylcysteamine (DMB-S-NAC) using acyltransferage enzyme LovD to get converted into simvastatin. This direct acylation with α-dimethylbytyryl-S-N-acetylcysteamine (DMB-S-NAC) using acyltransferage enzyme LovD is highly regiospecific toward the C_8 alcohol only and is therefore a potential one step process to produce simvastatin from monacolin J without employing protective chemistry [7].

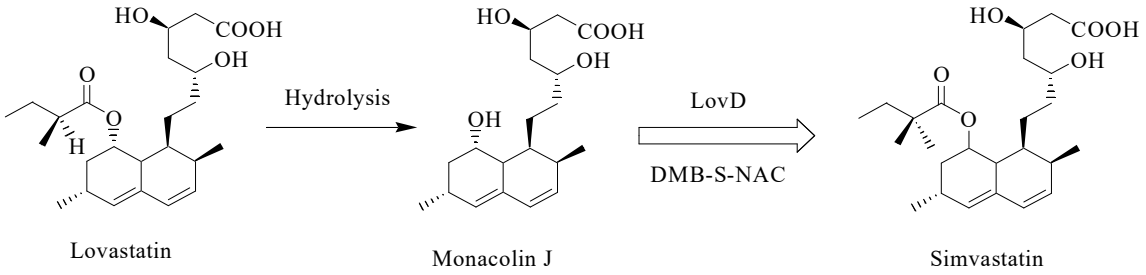

Fig. 2. Synthesis of Simvastatin by Use of Whole-Cell Biocatalyst LovD.

2.3 Synthetic Methods to Convert Lovastatin into Simvastatin

Synthetic methods to convert lovastatin into simvastatin are widely used and commercially successful routes of simvastatin production. There are two basic synthetic routes for the commercial production of simvastatin from lovastatin, one is hydrolysis followed by re-esterification route and other is direct methylation route.

2.3.1 Re- esterification Route for Simvastatin Production

Product simvastatin was first synthesized by Merck & Co. in 1980. Merck's five step synthetic process as described in United States Patent 4,444,784, starts with hydrolysis of lovastatin (III) with lithium hydroxide followed by lactonization to get diol lactone (IV). C13 hydroxyl group of diol lactone is then protected with t-butyldimethylsilyl by reacting diol lactone with t-butyldimethylsilyl chloride in presence of imidazole in the media of DMF at ambient temperature to get t-butyldimethylsilyl protected diol lactone (V). C8 hydroxyl group of t-butyldimethylsilyl protected diol lactone (V) is than esterified either by reaction with acid chloride side chain in presence of 4-dimethylamino pyridine in the media of pyridine or by reaction with acid side chain in presence of N,N'-dicyclohexylcarbodimiide and 4-pyridinopyridine in the media of dichloromethane to get t-butyldimethylsilyl protected simvastatin (VI). Deprotection of t-butyldimethylsilyl group from protected simvastatin (VI) is carried out in three equivalent tetrabutylammonium fluoride and four equivalent of acetic acid per equivalent of t-butyldimethylsilyl protected simvastatin in the media of tetrahydrofuran to get simvastatin (I) [8].

Merck & Co. described another process for the preparation of simvastatin, in United States Patent 5,159,104, which comprises the sequential acylation of a diol lactone (I) to form a bis acylated intermediate (III) followed by selective deacylation and lactone ring closure to form simvastatin (VI).

The diol lactone (I) is initially acylated at the lactone hydroxyl moiety employing an acid anhydride (R-CO)2O or an acyl halide R-COCl, wherein R is C-5 alkyl, to form a 4-acyl diol lactone compound of formula (II). Compound (II) is then acylated at the 8'-position of the polyhydronaphthyl ring with 2,2- dimethylbutyryl chloride or 2,2-dimethylbutyryl bromide to form a 4-acyl simvastatin compound of formula (III). The diacyl intermediate of formula (III) is deacylated at the 4-position of the lactone ring using an alcohol R1OH, wherein R1 is C14 alkyl, and an acid to form the simvastatin ester compound (IV) which is then treated with ammonium hydroxide to form the ammonium salt (V). The lactone ring is closed and simvastatin (VI) formed by treating the ammonium salt (V) with a dilute acid such as acetic acid, or hydrochloric acid or sulfuric acid [9].

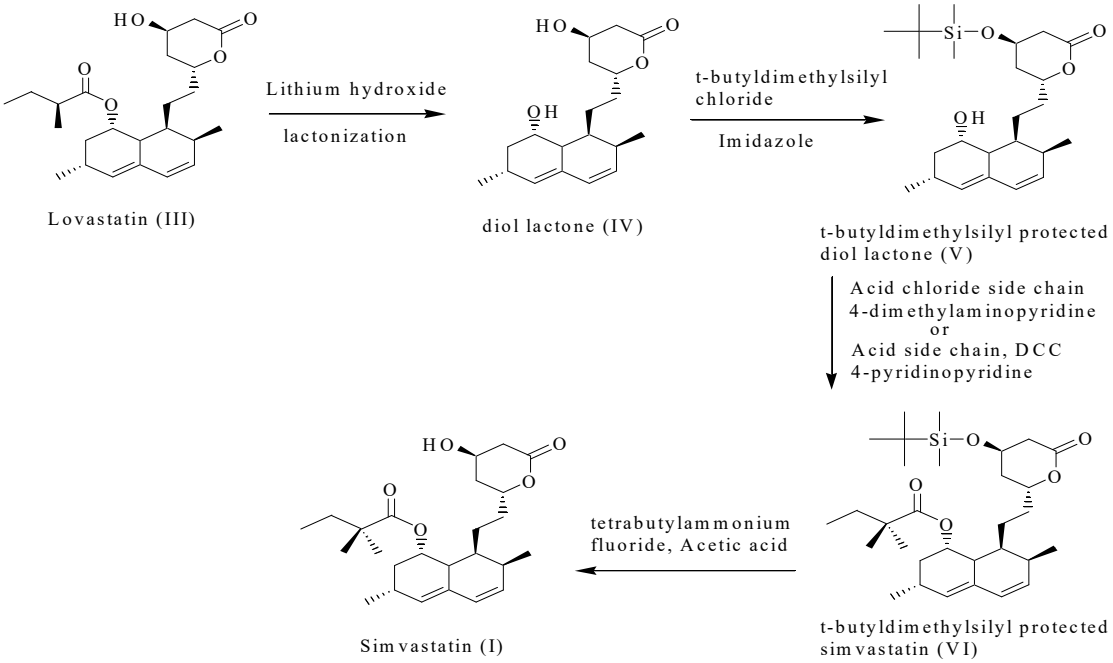

Fig. 3. Synthesis of simvastatin as described in U S Patent 4,444,784 A.

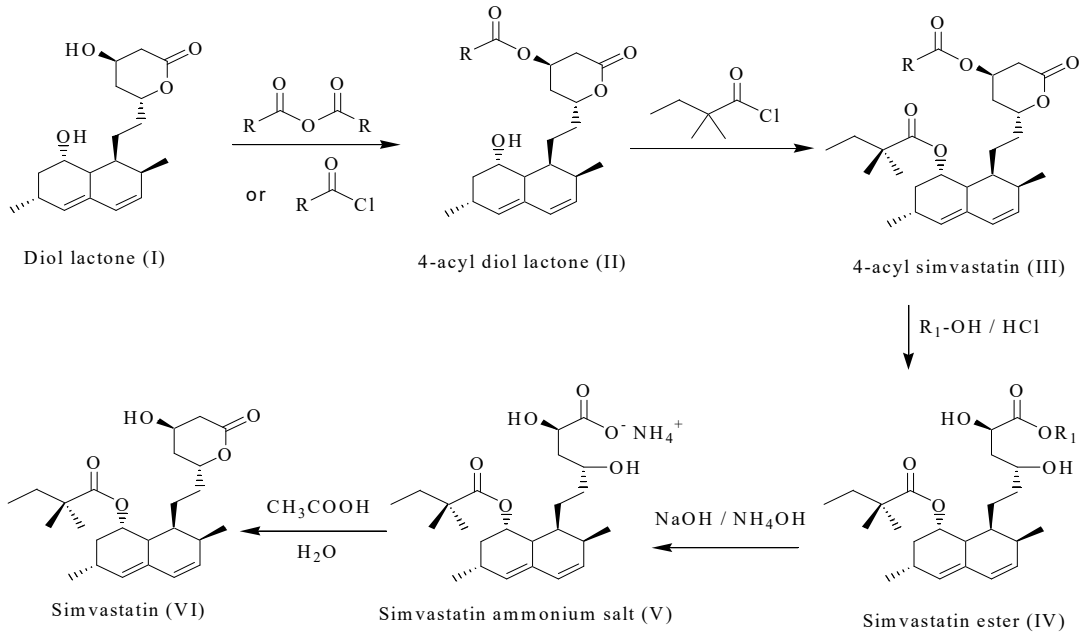

Fig. 4. Synthesis of simvastatin as described in U S Patent 5,159,104.

Kaneka Corporation described a process for producing Simvastatin, in United States Patent 6,331,641 B1, which comprises deacylation of lovastatin with an inorganic base and a secondary or tertiary alcohol and Subjecting the resulting diol lactone to Selective protection with a ketal or acetal protective group, acylation and deprotection-lactonization to give Simvastatin.

As per the process of Kaneka Corporation, lovastatin (1) is treated with an inorganic base and a secondary or tertiary alcohol to give a triol acid (2), the triol acid (2) is acidified and lactonized to give diol lactone (3). Diol lactone (3) is treated with an acid and a ketal or acetal in an organic solvent to give a triol acid derivative (4). This triol acid derivative (4) is further reacted with 2,2-dimethylbutyryl chloride in the presence of an organic base and a tertiary amine to give the simvastatin derivative (5). Finally, this simvastatin derivative (5) is treated with an acid catalyst and a protic solvent to get simvastatin (6) [10].

Krka Pharmaceuticals described a process in United States Patent 6,252,091 B1, for preparing simvastatin from diol lactone, According to Krka's process the major advantages of the process is higher yields of product (I)in comparison to the other processes, typically 90 to 95% (based on diol lactone (II) and the reduced amount of by-products. Process starts by converting the diol lactone of formula (II) to the protected diol lactone of formula (IIa) in the presence of N-methylimidazole, acylating the protected diol lactone (IIa) and finally removing t-BuMe2SiCl protecting group to give simvastatin (I) [11, 12].Lek Pharmaceutical and Chemical Company, in United States Patent 6,384,238 B1, described a novel method for the acylation of sterically hindered alcohols which is applicable in the process for the preparation of simvastatin. 2,2-dimethylbutyryl chloride is converted into reactive intermediate II by reacting with an alkyl halide of general formula KXn. The molecule KX is approached to the carbonyl group of acyl chloride and attached to the oxygen atom thus inducing shifts in the arrangement of electrons in the molecular orbitals in the carbonyl group affords easier elimination of the chloride atom from the acyl chloride molecule. This leads to acceleration of the acylation reaction.

Reaction of intermediate II and an alcohol of the formula I in presence of pyridine under inert atmosphere give protected simvastatin, which can be converted into simvastatin by conventional deprotecting techniques [13, 14].

Industrial Technology Research Institute and Yung Shin Pharmaceutical Industry of Taiwan, in United States Patent 6,002,021, described an acylation process for manufacturing simvastatin using a sulfonic acid, a salt of the sulfonic acid, or a mixture thereof, as a catalyst. The 05 step process involves (i) Protecting the 4-hydroxyl group on the pyranone ring of the 8'-hydroxy compound (ii) acylation process uses a sulfonic acid, a salt of the sulfonic acid, or a mixture thereof, as a catalyst (iii) deprotection of protecting group with methane sulfonic acid (iv) formation of simvastatin ammonium salt and finally (v) cyclization of ammonium salt to simvastatin.

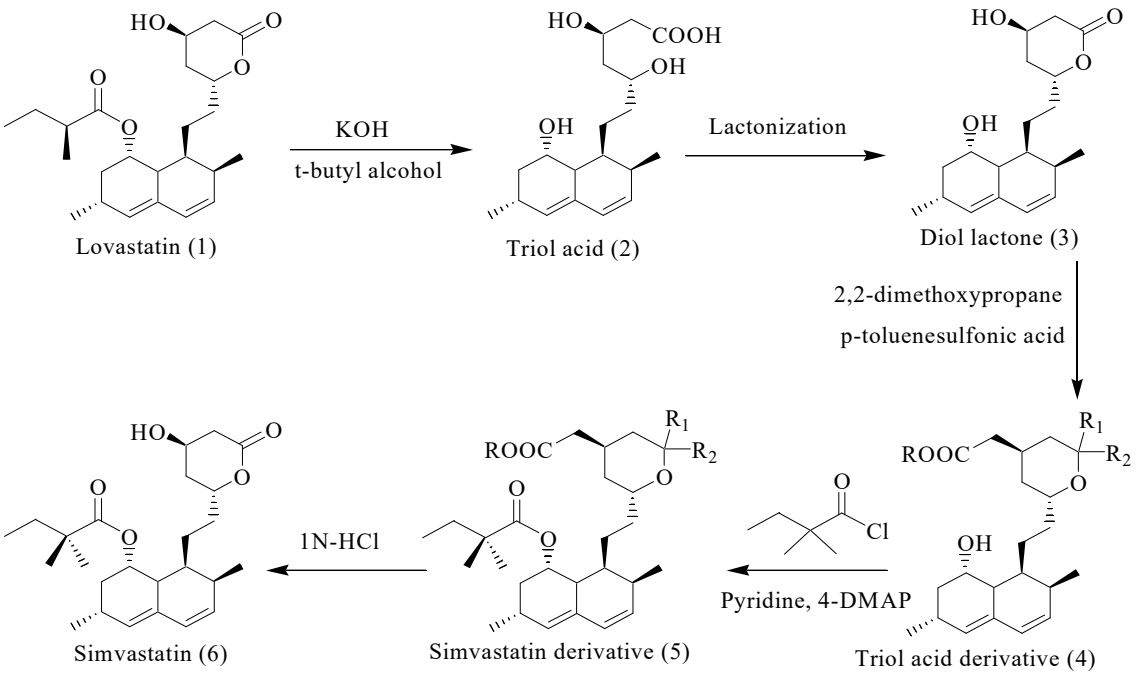

Fig. 5. Synthesis of simvastatin as described in U S Patent 6,331,641 B1.

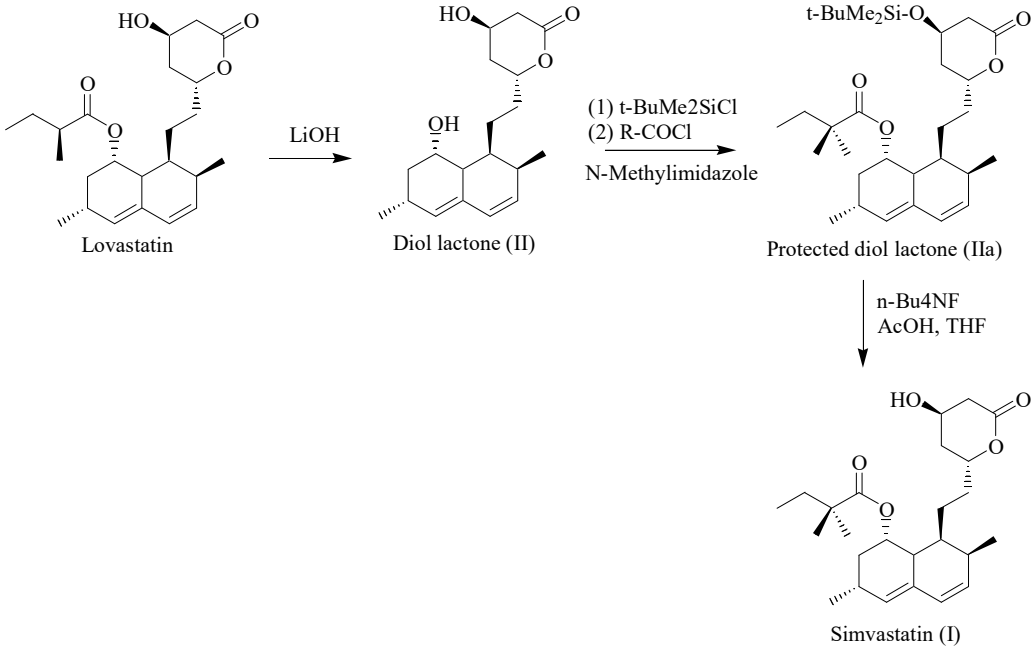

Fig. 6. Synthesis of simvastatin as described in U S Patent 6,252,091 B1.

The catalyst of the acylation is a Sulfonic acid, its Salts, or a mixture of the Sulfuric acid and the salts thereof. Examples of suitable sulfonic acids include trifluoromethanesulfonic acid and methanesulfonic acid. Examples of suitable salts of sulfonic acids include pyridinium trifluoromethanesulfonate and silver trifluoromethanesulfonate [15].

Cheil Jedang Corporation of Seoul Korea, in United States Patent 6,576,775 B1, described a 05 step process for manufacturing simvastatin wherein acylation is carried out using activation of carboxylic acid by trialkylphosphine and halogen compounds like hexachloroethane, carbon tetrachloride, carbon tetra bromide, or hexachloroacetone and is directly used without separation.

The process comprises the steps of acylating of tert butyldimethylsilyl protected compound 6(R)-2-(8(S)-hydroxy-2'(s), 6'(R)-dimethyl-1', 2', 6', 7, 8, 8'a(R)-hexahydronaphthyl-1'(S) ethyl-4(R)-t-butylmethylsilyloxy-3,4,5,6-tetrahydro-2H-pyran-2-on with activated carboxylic acid compound. Resulting compound 6(R)-2-(8'(S)-(4-butyl-2,2-dimethyloxy)-2'(S),6'(R)-dimethyl-1', 2', 6', 7", 8", 8"a (R)-hexahydronaphthyl-1'(S) ethyl-4(R)-t-butyl dimethylsilyloxy -3,4,5,6-tetrahydro -2H-pyran-2-on is treated with methanesulfonic acid followed by treatment with 2N NaOH and finally acidified to get simvastatin [16, 17].

Chong Kun Dang Pharmaceutical Corp of Seoul Korea, in United States Patent 6,833,461 B2, described a 04 step re-esterification process for the synthesis of simvastatin involving (i) hydrolysis of lovastatin as starting material with potassium t-butoxide in an organic solvent and small amount of water under a mild reaction condition, followed by lactonization of the obtained solid intermediate with preventing from formation of by-products; (ii) protection of an alcohol group with t-butyl dimethylsilyl group which can be easily removed with concentrated hydrochloric acid without the formation of by-products (iii) acylation of the obtained protected intermediate with acyloxytriphenyl phosphonium salt as an acylating agent under a mild reaction condition; and (iv) removal of the silyl protective group with a concentrated hydrochloric acid to get simvastatin. Acyloxytriphenylphosphonium salt of 2,2-dimethylbutyric acid used in the acylation is prepared by activating 2,2-dimethylbutyric acid with triphenylphophine and halogenation agent like N-bromosuccinimide (NBS) [18].

Hanmi Pharmaceutical, in United States Patent 7,528,265 B2, described a re-esterification process for the synthesis of simvastatin comprising the steps of treating lovastatin with potassium hydroxide dissolved in a mixture of water and methanol to obtain a triol acid, re-lactonizing the triol acid, and protecting the hydroxy group on the lactone ring and acylating the resulting compound with 2,2-dimethylbutyryl chloride or 2,2-dimethylbutyryl bromide in the presence of an acylation catalyst in an organic solvent, followed by removing the silyl protecting group on the lactone ring to obtain simvastatin. Acylation catalyst is prepared by reacting benzyl tri-n-butylammonium bromide and pyridine in the media of benzene. Acylation reaction is performed by refluxing substrate with 2,2-dimethylbutyryl halide in the presence of an acylation catalyst such as a quaternary ammonium halide or a quaternary phosphonium halide in benzene while azeotropically removing water using a Dean-stark trap [19].

UK Chemipharm Co., in WO2005058861A1, described a three step direct methylation process for preparing simvastatin from lovastatin. In first step lovastatin is added with an inorganic base such as potassium hydroxide and then heated with reflux to be deacylated and acidified, which results in the production of a triol acid. In second step the triol acid of is refluxed in toluene, successively removing water, to prepare a diol lactone. In third step two secondary alcohols in two diol lactone molecules are selectively protected with dialkyl (or diaryl or arylalkyl) silyl group in the presence of base to obtain a silyl-protected diol lactone dimer. Successively, the silyl-protected diol lactone is directly subjected to coupling reaction with 2,2-dimethylbutyryl chloride in the presence of 4,4-dimethylaminopyridine catalyst to prepare a silyl-protected simvastatin dimer. A silyl-protected simvastatin dimer of is easily deprotected in the presence of fluoride salt or acid catalyst to produce simvastatin [20].

Pficker Pharmaceuticals Ltd. China, in United States Patent Application 2009/0043115 A1, described a process for preparing simvastatin from lovastatin where lovastatin (2) is hydrolyzed by the catalysis of the inorganic base to form the compound of the formula (3) followed by cyclization and direct esterification of compound of formula (3) to afford compound of formula (4) (simvastatin derivative). This reaction does not require the protection and deprotection as described in prior art. The simvastatin derivative of formula (4) is converted to compound of formula (6) through a ring opening and an ester formation reaction. Finally open ring ester (6) is converted in to simvastatin by reaction with ammonia or aqueous solution of methylamine under a temperature from 0°C to 30°C, to remove 2,2-dimethylbutyryl group in C4-position without affecting the 2,2-dimethylbutyryl group in the C8-position, formed methyl ammonium salt is treated with strong acid to get simvastatin [21].

2.3.2 Direct Methylation Route for Simvastatin Production

Direct methylation route for the production of simvastatin is relatively shorter route in comparison to hydrolysis followed by esterification route and due to the fewer

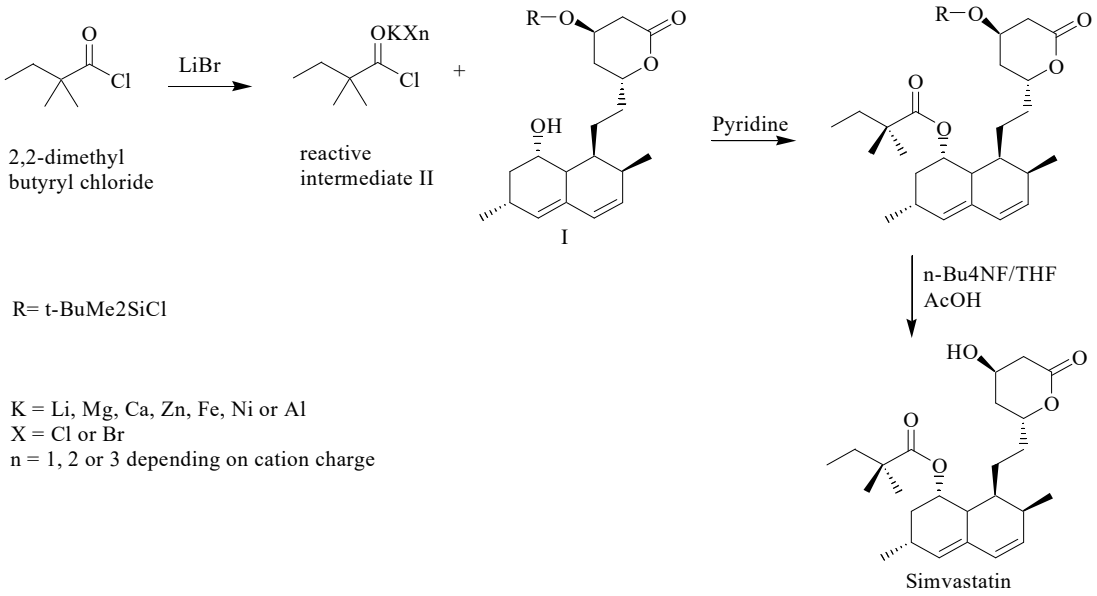

Fig. 7. Synthesis of simvastatin as described in U S Patent 6,384,238 B1.

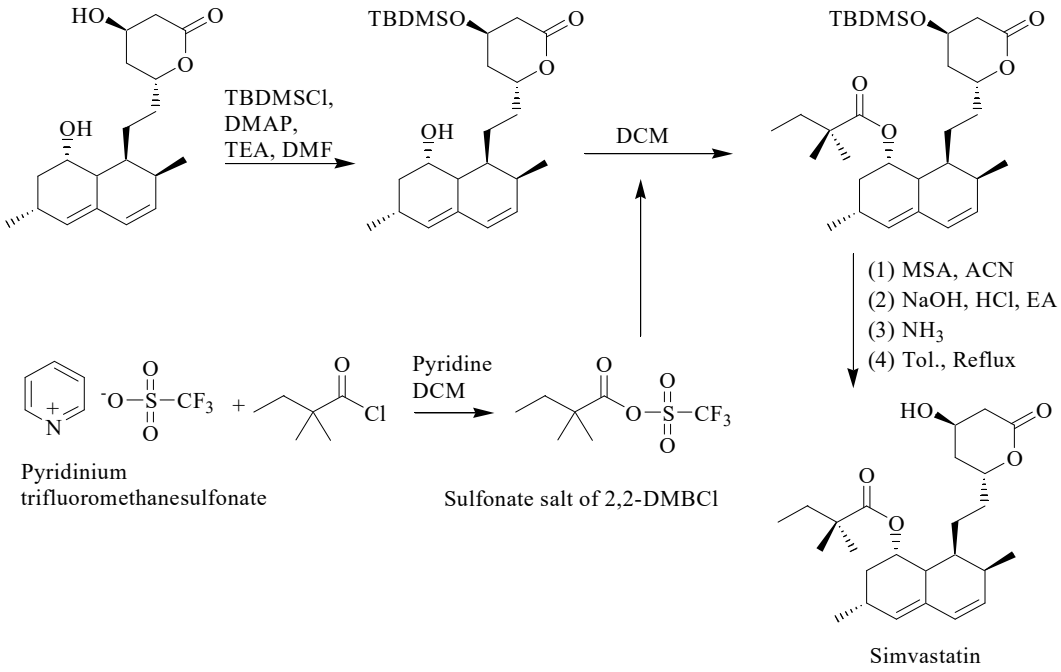

Fig. 8. Synthesis of simvastatin as described in U S Patent 6,002,021 A.

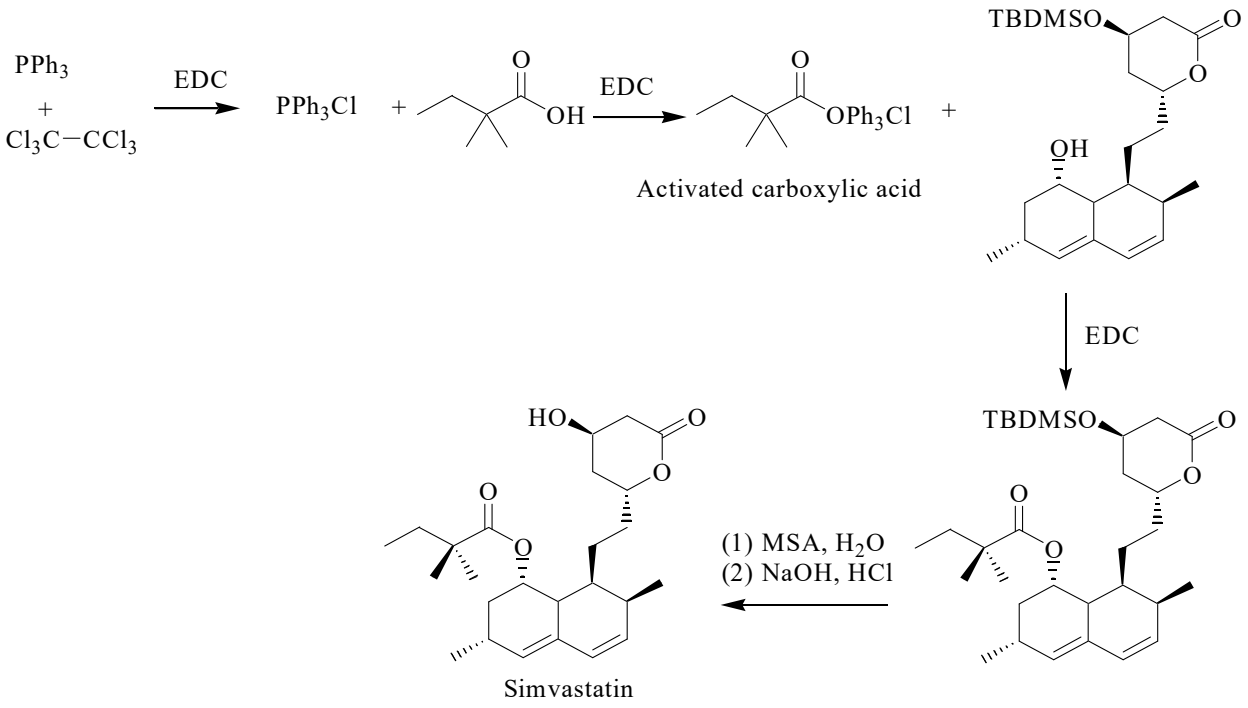

Fig. 9. Synthesis of simvastatin as described in U S Patent 6,576,775 B1.

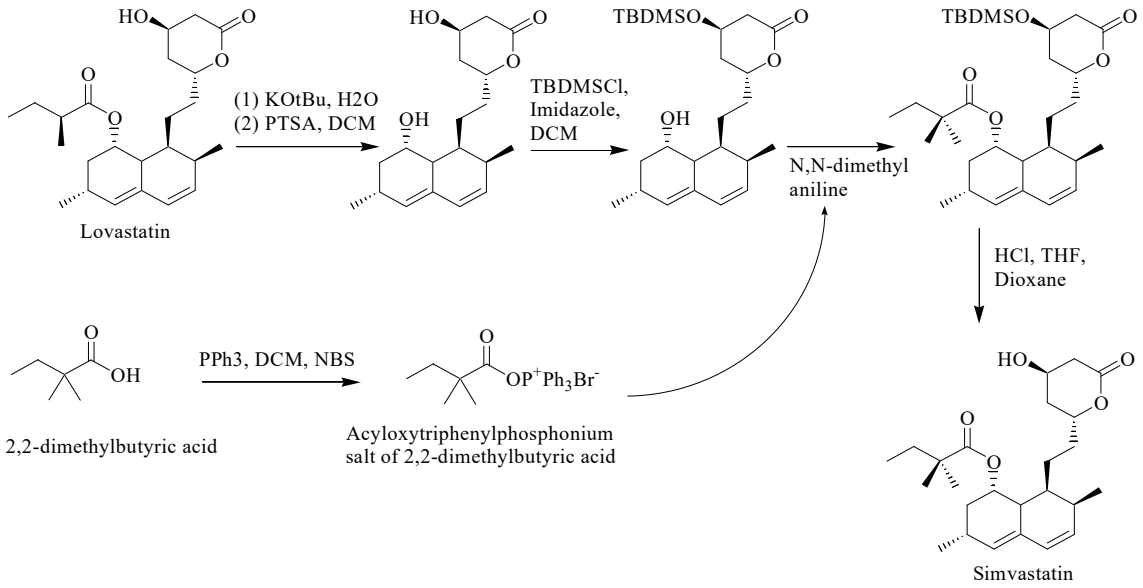

Fig. 10. Synthesis of simvastatin as described in U S Patent 6,833,461 B2.

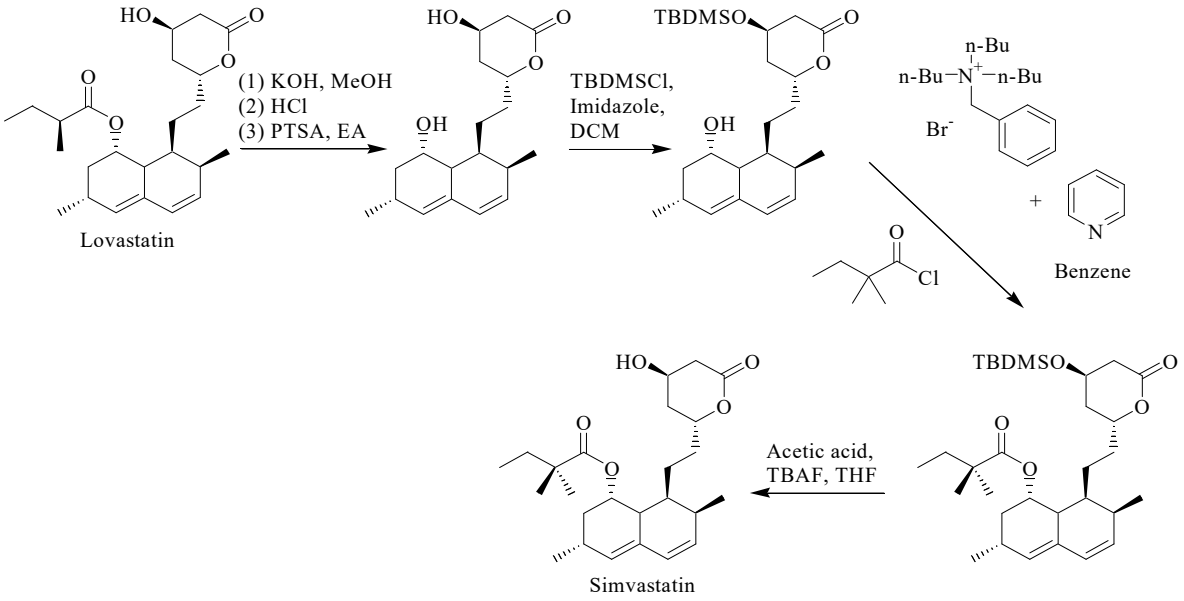

Fig. 11. Synthesis of simvastatin as described in U S Patent 7,528,265 B2.

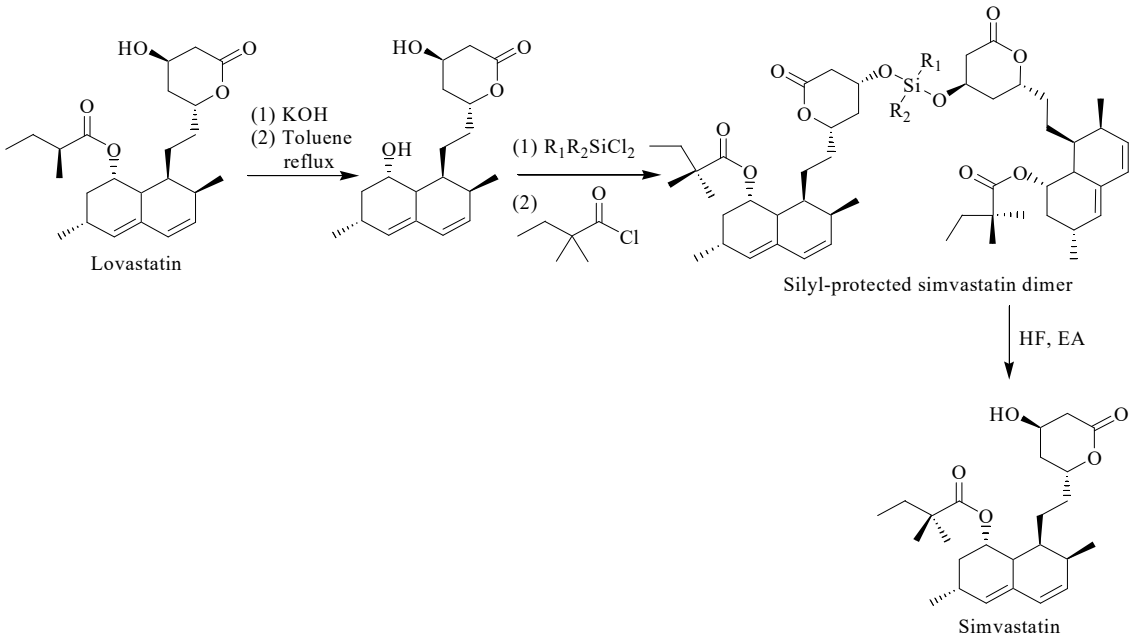

Fig. 12. Synthesis of simvastatin as described in WO2005058861A1.

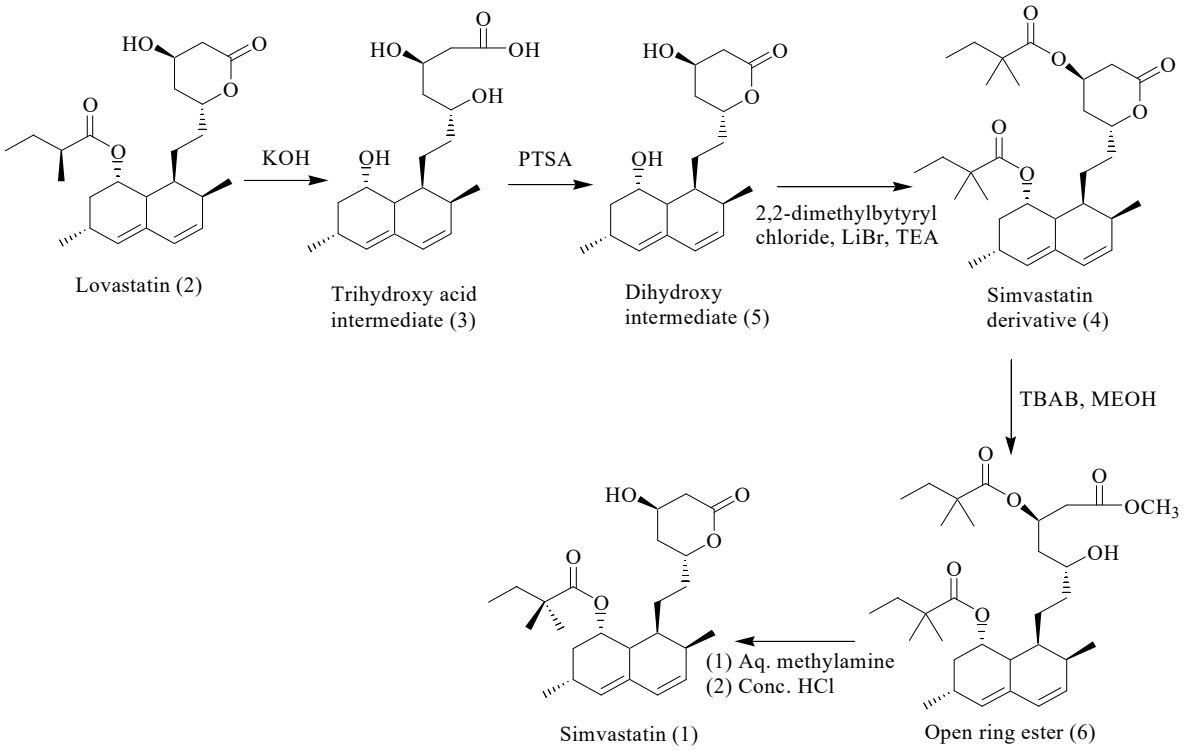

Fig. 13. Synthesis of simvastatin as described in U S Patent Application 2009/0043115 A1.

conversion steps, lovastatin to simvastatin conversion ratio is also better. Direct methylation route involve use of *n*-Butyllithium, it reacts violently with water hence require great amount of safety during handling, storage and transport. Low temperature is another requirement for this route, reaction with methyl iodide or methyl bromide in an ethereal solvent is carried out at -60 to -25 C.

Merck & Co., in United States Patent 4,582,915, described a process for the preparation of simvastatin involving only one chemical step and resulting in overall yields much higher than those realized by the prior art process, with the expenditure of much less time, labor and materials.

This process comprises C-methylation at the 2-position of the 2-methylbutyryloxy group of lactone compound (I). The lactone compound is first converted to an alkali metal salt by adding a substantially stoichiometric amount of aqueous potassium hydroxide to a solution of the lactone starting material in a hydrocarbon solvent containing a small amount of a C1-3 alcohol. The dry alkali metal salt is dissolved in an ethereal solvent, cooled to about -50 to about -25 C and treated with an excess of a strong base such as an alkali metal amide in an ethereal solvent in a dry inert environment followed by addition of a methyl halide to the mixture while maintaining the low temperature, this mixture of base and methyl halide is added in lots till the completion of reaction. To isolate the product the aqueous phase is adjusted to pH 3-6 with a strong mineral acid, extracted with cyclohexane or toluene, dried, filtered, refluxed and finally concentrated, and filtered [22].

Merck & Co., in United States Patent 4,820,850, disclosed another process for alkylating the alpha carbon of the 8'-C-ester side chain of mevinolin and analogs thereof with only a single charge of base and alkyl halide to form a product in substantially higher yield. The starting lactone is converted into an amide by reaction with an n-butylamine and the hydroxyl groups are protected with tert-butyldimethylsilyl chloride (TBDMSCl). Tert-butyldimethylsilyl protected amide was treated with a base (pyrrolidine, THF and n-butyllithium) and methyl halide to get alkylated tert-butyldimethylsilyl protected amide. The tert-butyldimethylsilyl protecting groups are removed by treatment with aqueous hydrofluoric acid. Simvastatin is recovered by amide group removal followed by ammonium salt formation and lactonization in toluene at 100°C [23]. Apotex Inc., in United States Patent 5,393,893, described the preparation of simvastatin through cyclohexylamidephenylboronate intermediate (III) which enables a selective alkylation of the C-8 acyl side chain.

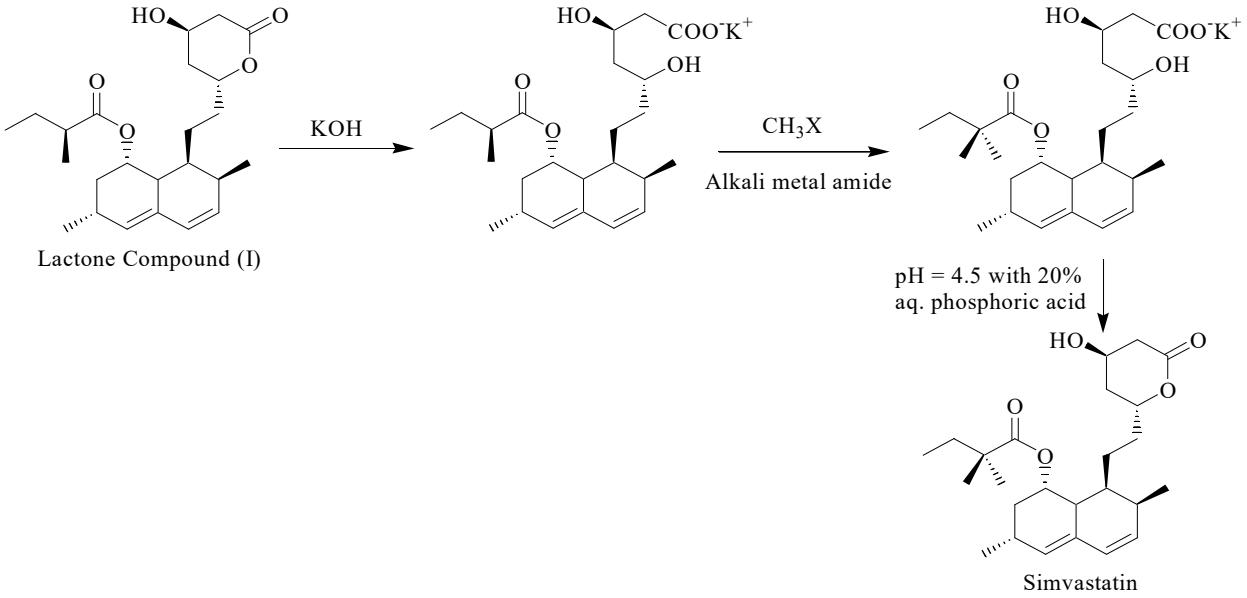

Fig. 14. Synthesis of simvastatin as described in U S Patent 4,582,915.

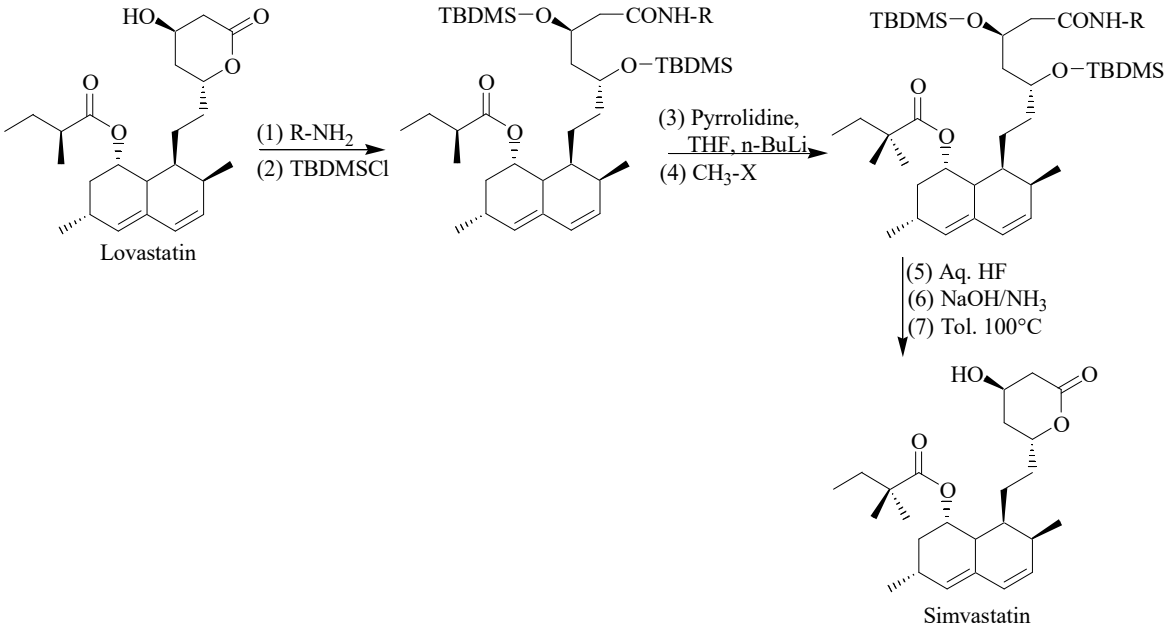

Fig. 15. Synthesis of simvastatin as described in U S Patent 4,820,850.

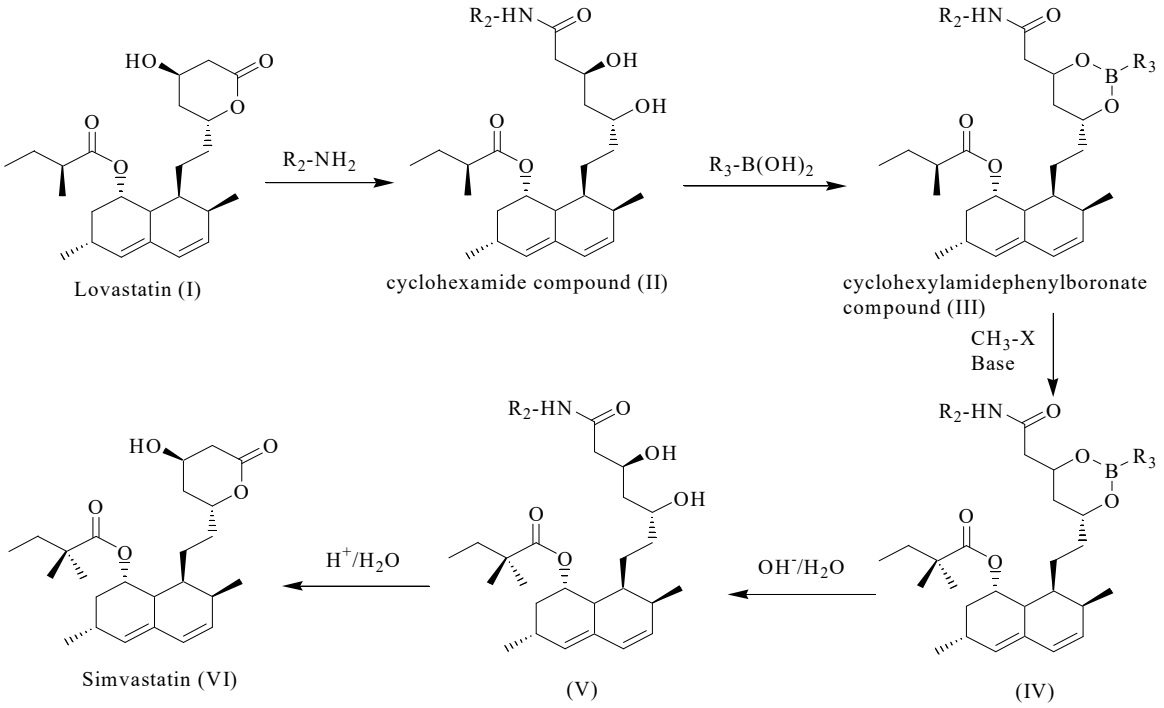

Fig. 16. Synthesis of simvastatin as described in U S Patent 5,393,893.

The lactone ring in lovastatin (I) is converted into an amide by reaction with cyclohexylamine to get cyclohexamide compound (II). The hydroxyl groups of cyclohexamide compound are protected with phenylboronic acid to get cyclohexylamidephenylboronate compound (III) in nearly quantitative yield. The c-alkylation of the protected amide derivative is carried out in the presence of a base an alkali metal amide which is prepared by combination of n-butyllithium and pyrrolidine in an etheral solvent. Deprotection of borylidene group followed by removal of amide group and lactonization with an aqueous organic acid to get simvastatin (VI) [24].

Brantford Chemicals Inc., in United States Patent 6,307,066 B1, described a process for preparing simvastatin from lovastatin by reacting lovastatin with an organic boronic acid to produce a derivative of lovastatin (lovastatin phenylboronate) methylating the 2-methylbutyryloxy group on the lovastatin derivative to form a 2,2-dimethylbutyryloxy group on the lovastatin derivative and thereafter removing the boronate group to produce Simvastatin.

Lovastatin (I) is heated together with an equimolar amount of an aryl or alkyl boronic acid like phenylboronic acid, in a no polar solvent like toluene and the lovastatin boronate (II) formed is isolated by concentration of the reaction mixture and crystallization with a suitable solvent. Lovastatin boronate (II) subsequently alkylated with lithium pyrrolidide followed by treatment with methyl iodide to get simvastatin boronate (III). Simvastatin boronate (III) is heated in the presence of a diol solvent like ethylene glycol and 1,3-propanediol, under thermal conditions. Simvastatin is isolated by concentration of the reaction mixture, dilution with water, and extraction with an organic solvent. The organic Solvent is concentrated to a minimum volume and simvastatin is isolated by the addition of a co solvent and filtration. [25].

Ranbaxy, in United States Patent 5,763,653, described a process for preparing simvastatin from lovastatin or mevinolinic acid in salt form comprises treating either starting material with cyclopropyl or butyl amine, the pyranone ring thereby being opened when lovastatin is the starting material, adding a methyl group to the 2-methylbutyrate side chain, and thereafter closing the open pyranone ring to produce simvastatin. The process is performed without protecting and deprotecting the two hydroxyl groups of the open pyranone ring.

In this process simvastatin is prepared in a four steps which does not include the protection and deprotection of the two

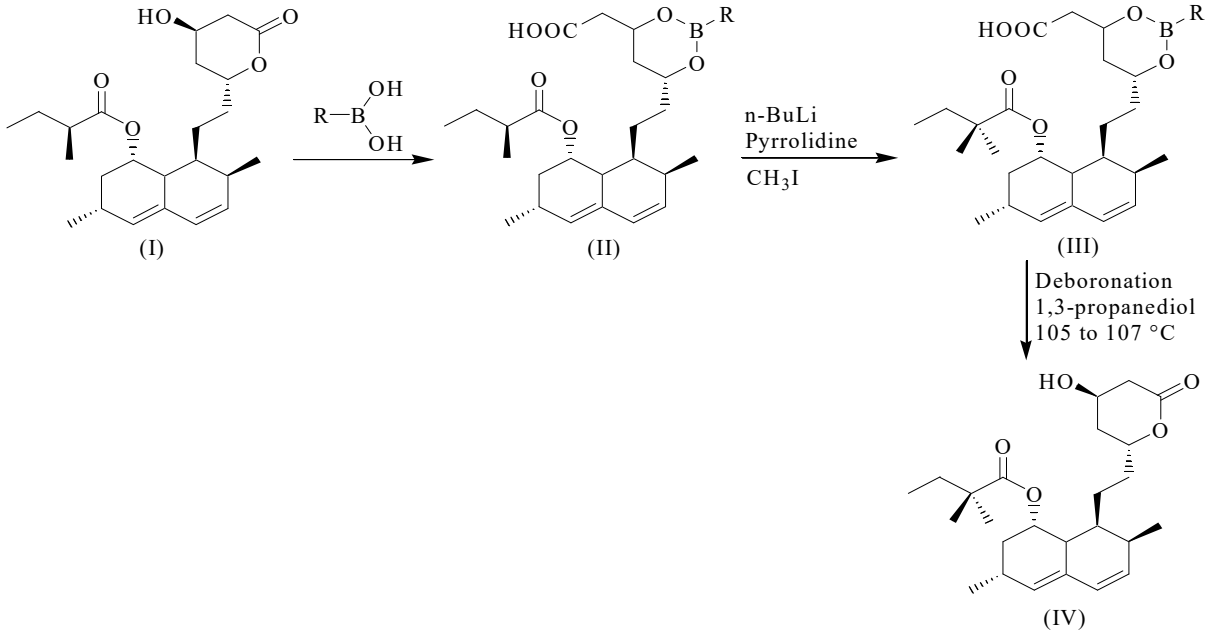

Fig. 17. Synthesis of simvastatin as described in U S Patent 6,307,066 B1.

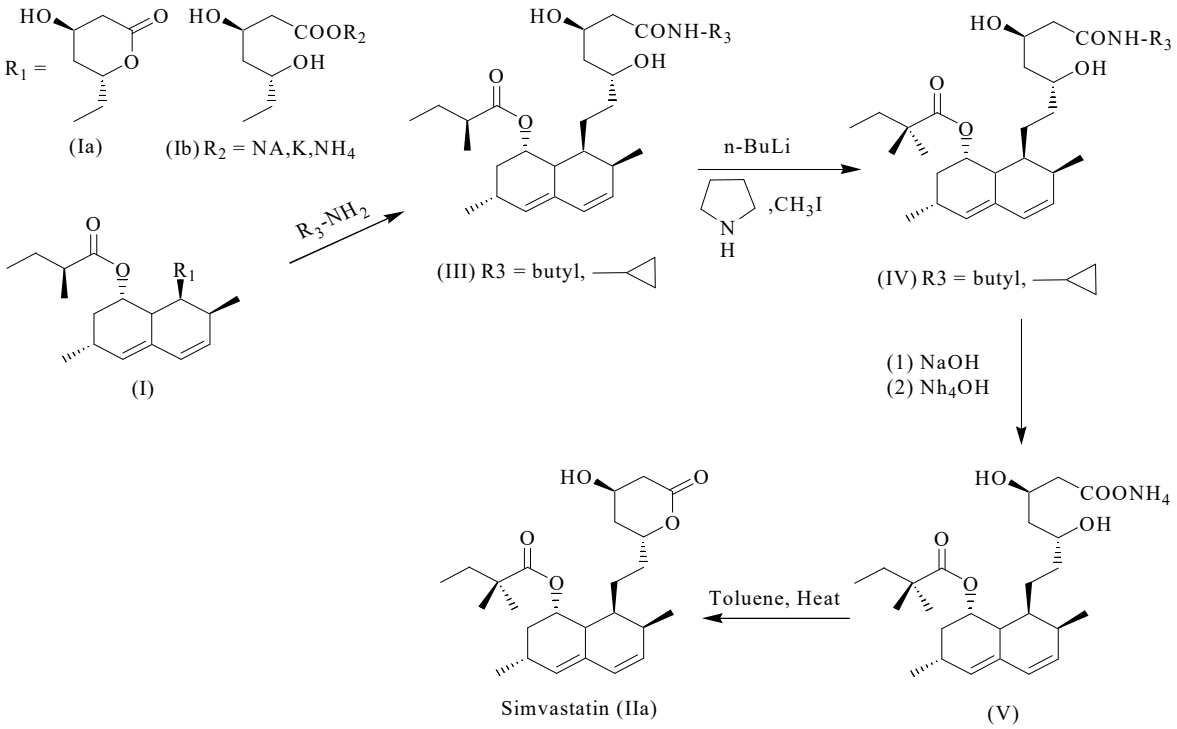

Fig. 18. Synthesis of simvastatin as described in U S Patent 5,763,653.

hydroxy groups of the open pyranone ring, before this process all the processes have reported protection and deprotection of the hydroxy groups as essential steps for the preparation of simvastatin [26, 27].

Sython B.V., in United States Patent 6,100,407, described a direct acylation process for the production of simvastatin and its analogues that is efficient, economical and convenient involves the use of ether-based hydroxyl protected intermediates. These intermediates allow for direct alkylation of the butyrate side chain followed by deprotection and reformation of the lactone ring.

The amide compounds of formula (II) are formed by carrying out a ring opening reaction of lovastatin with an amine of the formula R-NH2. The hydroxyl groups of the amide of formula (II) are then protected with carbon-terminated protective groups to form ether or cyclic ether (acetal or ketal) intermediate (III). Direct methylation of ether intermediates carried out by adding an alkylating agent in the presence of a base. Deprotection of the hydroxyl groups in compounds (IV) to form simvastatin amide of formula (V) is achieved by acid hydrolysis. Finally amide group is removed by refluxing in 2N NaOH and ring closed in concentrated HCl to get simvastatin (VI) [28, 29, 30].

Biocon India Ltd., in United States Patent 6,573,392 B1, described a process for preparing simvastatin from lovastatin by converting the lovastatin to lova amide using a secondary amine and subsequent reaction with a metal amide base generated from n-butyl lithium and pyrrolidine and followed by treatment with methyl iodide to give desired C-methylated intermediate. This intermediate was further transformed to the final product, simvastatin. According to the Biocon process the absence of the hydrogen in the amide nitrogen produced by using secondary amine prevents side reactions and thereby resulting in purer products. The hydrogen in the amide nitrogen reacts with lithium amide base thereby necessitating the need for larger equivalent of the amide base and the hydrogen in the amide nitrogen can react with the methyl iodide and lithium amide base and thus lead to side reactions and overall low yield [31, 32].

Biocon India Ltd., in WO2002024675A1, described another direct methylation process for preparing simvastatin from lovastatin by protecting the hydroxy group of the lactone ring and then converting to lovastatin amide using an amine and subsequent reaction with a metal amide base generated from n-butyl lithium and pyrrolidine and followed by treatment with methyl iodide to give desired C-methylated intermediate. This intermediate was further transformed to the final product, simvastatin. Lovastatin following protection is reacted with a diamine (secondary amine). The amide thus prepared is dissolved in dry tetrahydrofuran and cooled to -45°C to -20°C. The metal amide base is prepared by adding n-BuLi to pyrrolidine and is cooled to -45°C to -20°C. After about 1 hour, the alkyl halide, methyl iodide, is added and the contents are stirred for 30min. Water is added to the reaction mixture and the layers separated. The organic layer is washed with brine solution and concentrated under reduced pressure to give an oily residue, which contains the intermediate. The crude intermediate is then hydrolyzed to give the free acid which is converted to the ammonium salt and is cyclized to give the final product, simvastatin **[33]**.

Fermic de, in United States Patent 6,472,542 B1, described a direct methylation process for the synthesis of simvastatin by forming an amide of lovastatin and protecting the free hydroxyl groups of the lovastatin amide with hexamethyidisilazane (HMDS) to form a protected lovastatin amide. The α-carbon of the 2-methylbutyrate secondary chain of the protected lovastatin amide then methylated to form a protected simvastatin amide. The protecting groups removed therefrom by quenching the methylation reaction with water. The simvastatin amide which is obtained hydrolyzed to form simvastatin acid, followed by forming a simvastatin ammonium salt, lactonizing the salt to form simvastatin, and recrystallizing the thus formed crude Simvastatin to a high degree of purity. The HMDS protecting agent for the lactone hydroxyl groups of lovastatin is selected so as to result in a reaction that does not produce acid so that a base, such as imidazole, is not required to neutralize the acidity of the reaction medium. Another advantage of using HMDS as a protecting agent is that the removal of the protecting agent after the methylation reaction is carried out simply by water quenching. The lactonization reaction is carried out using a low boiling point solvent such as methylene chloride in the presence of inorganic acids such as sulfuric, hydrochloric, methanesulfonic or phosphoric acid as catalyst [34].

Eos Eczacibasi Istanbul, in WO2003000673A2, described a 04 step direct methylation process for preparing simvastatin from lovastatin. Preparation of simvastatin starts with the protection of hydroxy group on lovastatin, and then the carboxyl group in the lactone ring is protected as an ortho ester derivative. The methylation of 2-methylbutyrate-side chain is performed then the protecting group of the lactone hydroxyl is simultaneously removed by adding water at the end of this reaction. Finally carboxyl-protecting group of the lactone ring is removed with diluted hydrochloric acid to give desired simvastatin. The main feature of this process is the carbonyl group protection of lactone ring as an ortho ester derivative. This pathway overcomes the formation of dimer of simvastatin since the lactone ring is not opened which is not so in the -lactone opening and closing-methods [35].

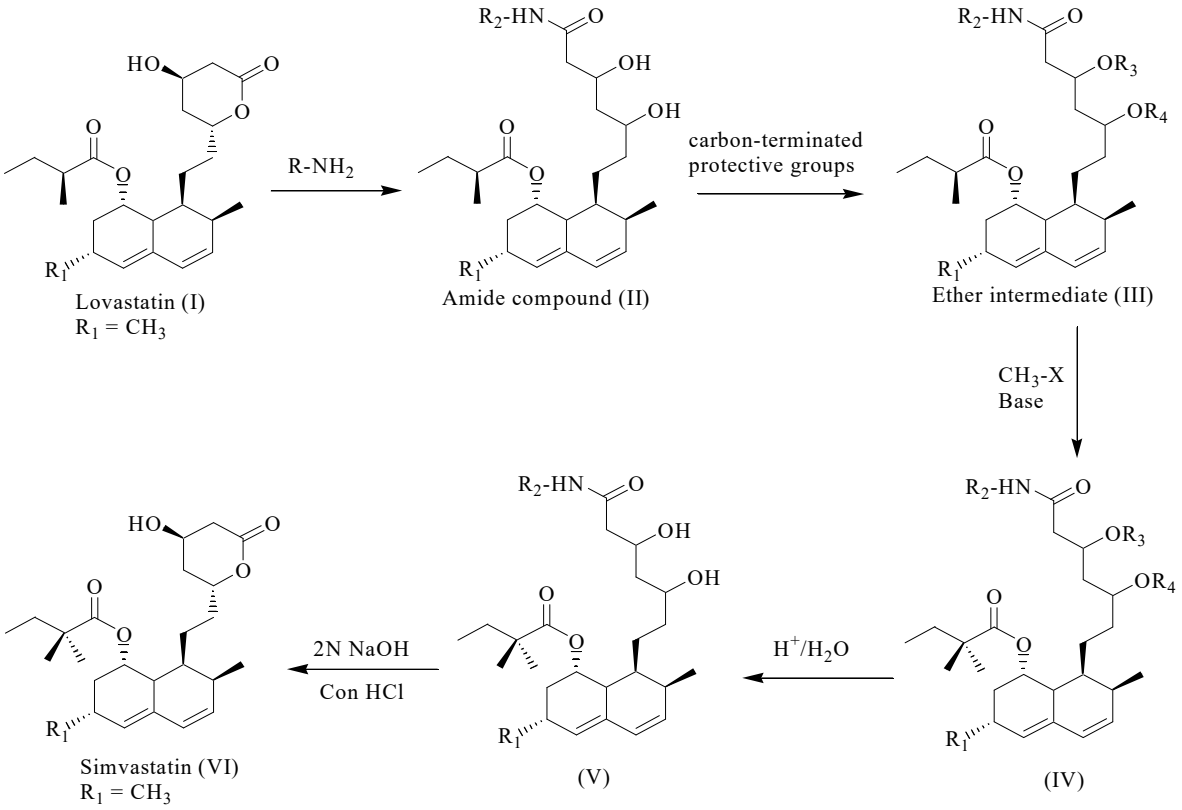

Fig. 19. Synthesis of simvastatin as described in U S Patent 6,100,407.

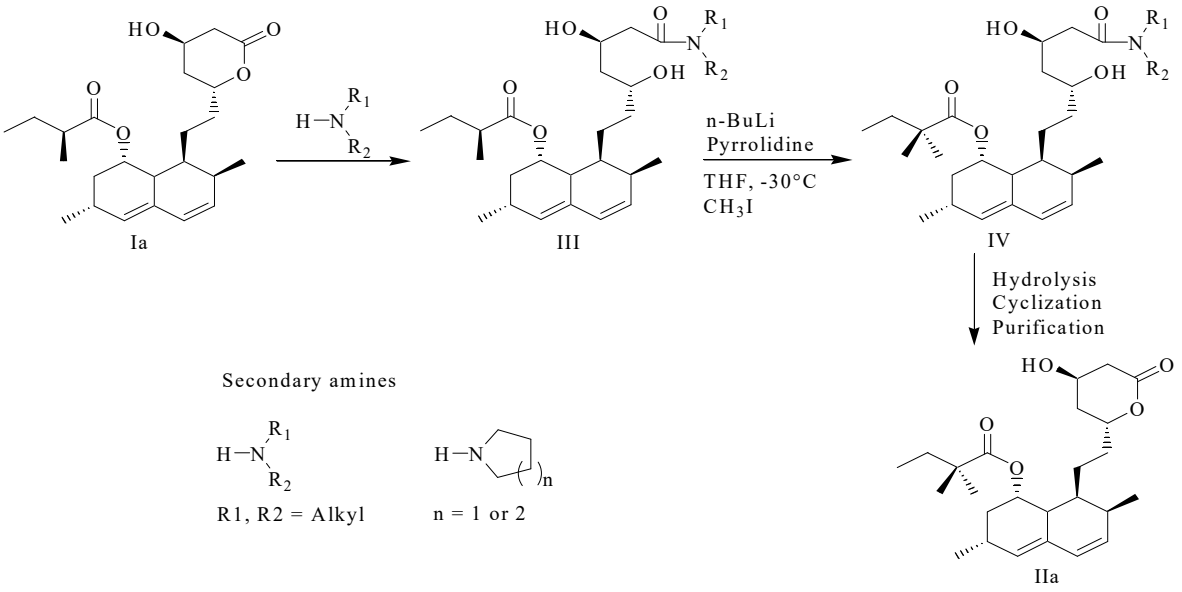

Fig. 20.Synthesis of simvastatin as described in U S Patent 6,573,392 B1.

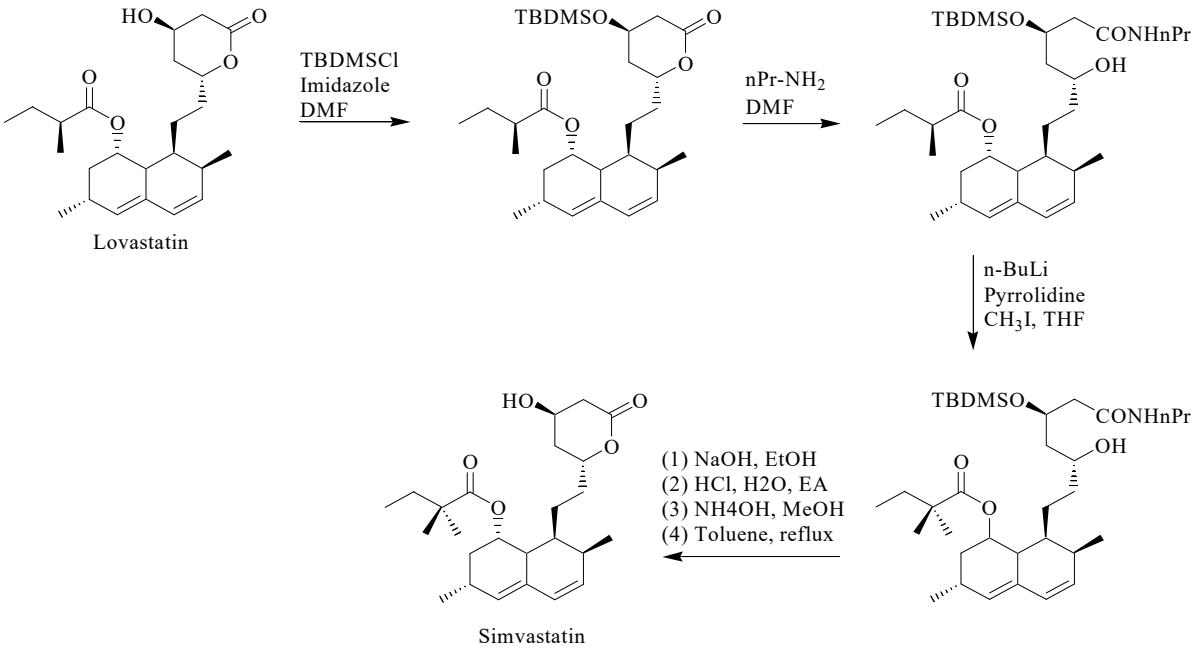

Fig. 21. Synthesis of simvastatin as described in WO2002024675A1.

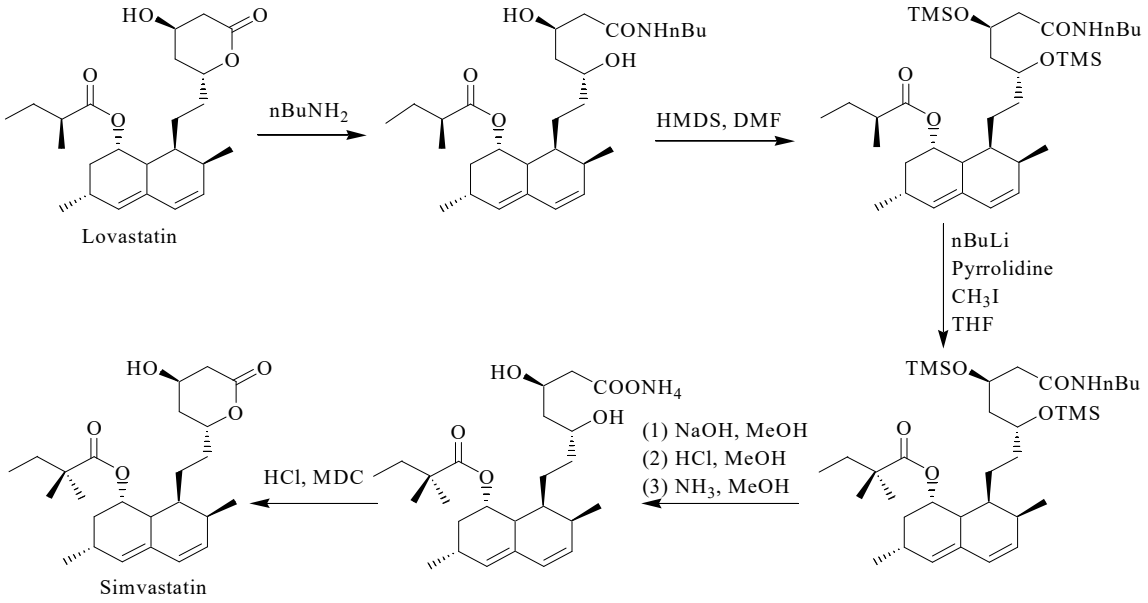

Fig. 22. Synthesis of simvastatin as described in U S Patent 6,472,542 B1.

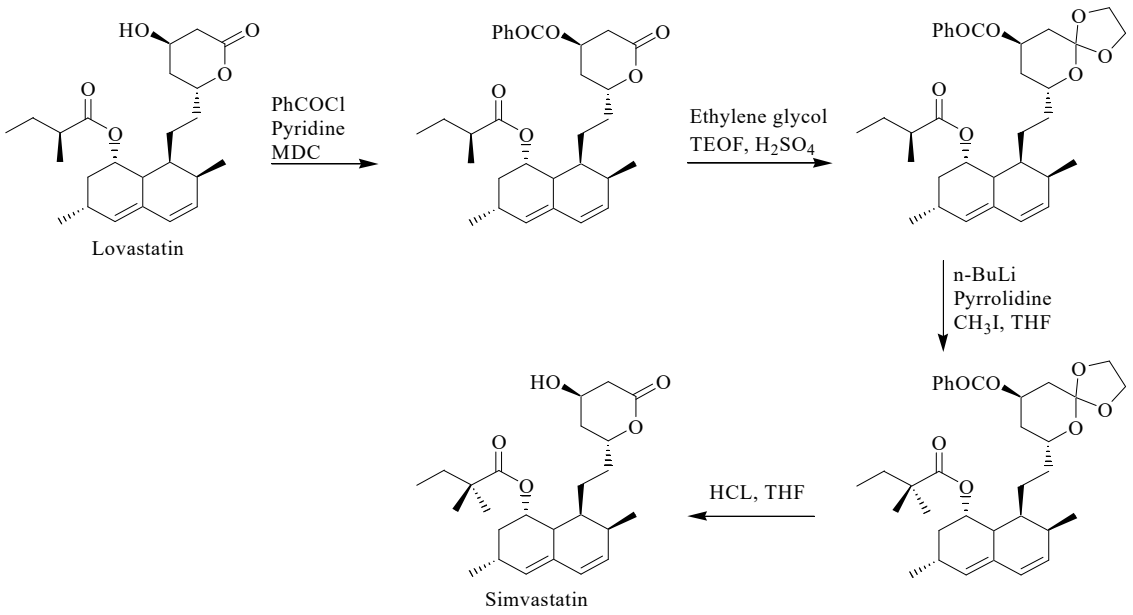

Fig. 23. Synthesis of simvastatin as described in WO2003000673A2.

Hetero Drugs, in United States Patent 7,205,415 B2, described a process for manufacturing simvastatin is provided using novel intermediates. Lovastatin (II) or its open chain compound (III) is reacted with methoxyethyl amine in the media of tetrahydrofuran to get amide compound of formula (V). Two hydroxyl groups of formed amide compound are optionally protected before methylation, compound thus formed is methylated to get a compound of formula (VIIa) followed by removal of amide group by hydrolysis in sodium hydroxide solution under heating conditions, pH of the solution is than adjusted to adjusted to 5 with 2N hydrochloric acid at 25° C., ethyl acetate is added and the pH is again adjusted to 3.5 with 2N hydrochloric acid solution. The layers are separated and the aqueous layer is washed with ethyl acetate. The combined organic layer is dried on Sodium Sulfate. Ammonia solution, prepared by mixing aqueous ammonia and methanol, is added to the reaction mass for 15 minutes at about 25°C to get of simvastatin ammonium salt (VIII). The ammonium salt of simvastatin is suspended in toluene and heated at 100° C under a constant sweep of nitrogen for 5 hours to get simvastatin (I) [36].

Jubilant Organosys Limited, in WO2005069741 A3, described a process for producing simvastatin by treating lovastatin or lovastatin ammonium salt with hydrazine or hydrazine derivatives to produce hydrazide intermediate, which is further converted into simvastatin. Process involve treating lovastatin or lovastatin ammonium salt with hydrazine or hydrazine derivatives like phenyl hydrazine to obtain lovastatin hydrazide, methylating the lovastatin hydrazide intermediate with methyl halide to prepare simvastatin hydrazide which is hydrolyzed and lactonized to get simvastatin [37].

Teva Pharmaceuticals USA Inc, in US20070129437A1, described a process for preparation of simvastatin and intermediates of the simvastatin which include the preparation of lovastatin amide, protected lovastatin amide derivatives, simvastatin dihydroxy acid amide derivatives, alkali salts, simvastatin dihydroxy acids, simvastatin ammonium salts, and simvastatin. Process involves treating lovastatin, lovastatin acid or salt of lovastatin acid with an amine of formula HNR1R2 to get lovastatin amide intermediate. Converting lovastatin amide intermediate to simvastatin by reacting lovastatin amide intermediate with a silylation catalyst and hexamethyldisilazane (HMDS) to obtain bis (TMS)-lovastatin amide derivative, direct methylation of bis (TMS)-lovastatin amide derivative followed by deprotection to get simvastatin dihydroxy acid. Once the simvastatin dihydroxy acid of is obtained, it may be, further converted into simvastatin ammonium salt, which is then lactonized to get simvastatin [38, 39].

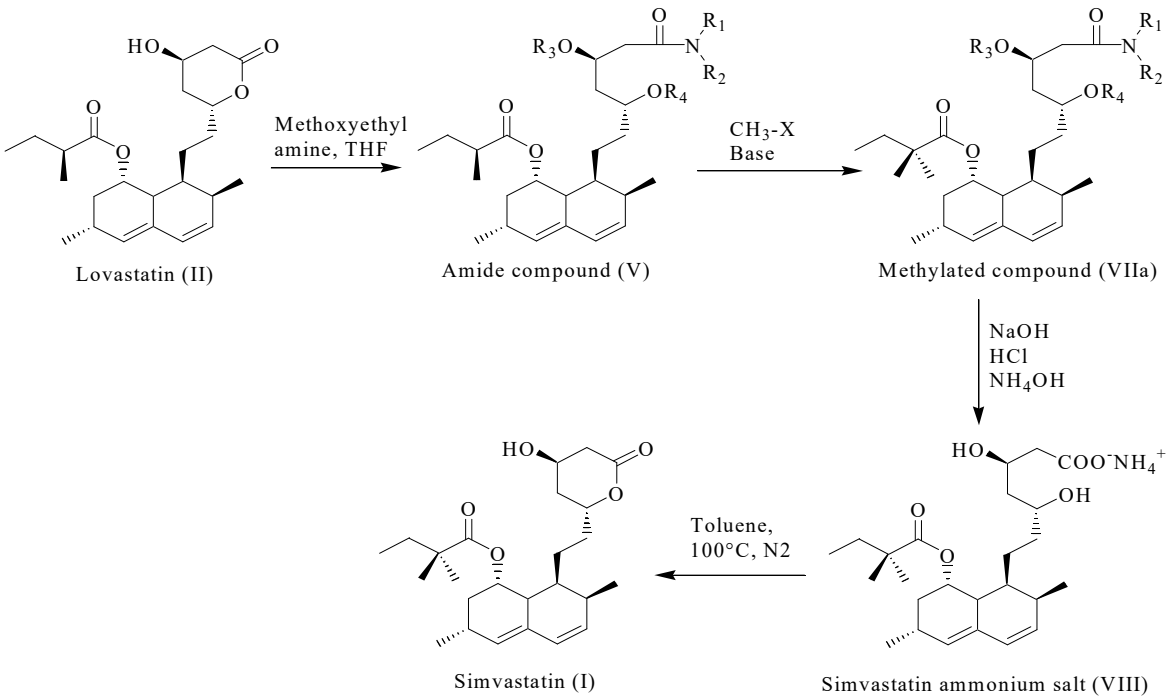

Fig. 24. Synthesis of simvastatin as described in U S Patent 7,205,415 B2.

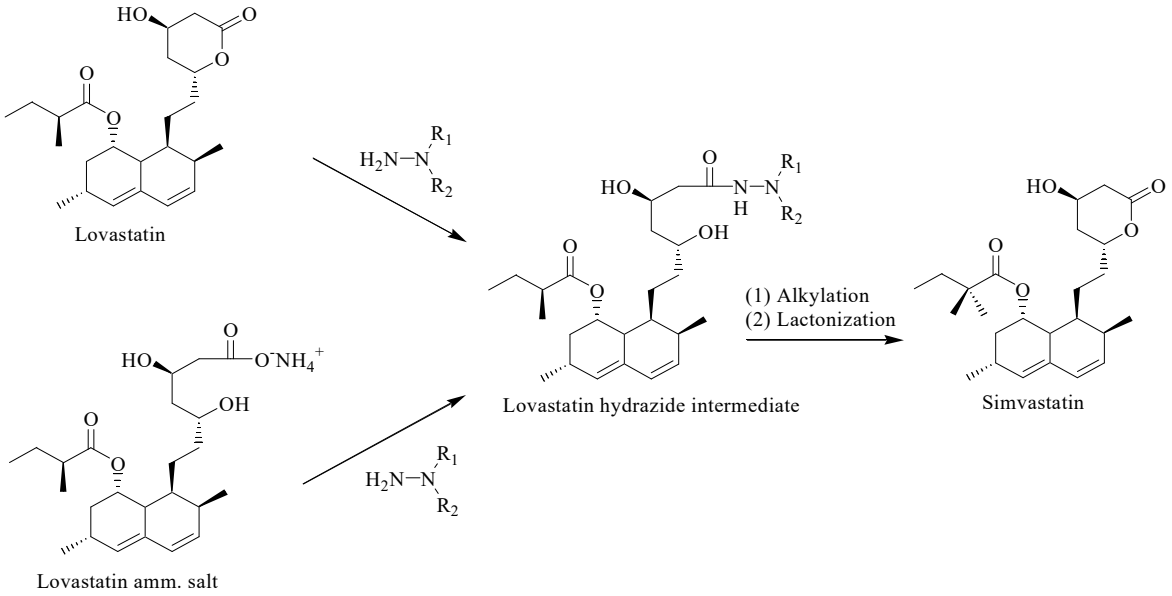

Fig. 25. Synthesis of simvastatin as described in WO2005069741 A3

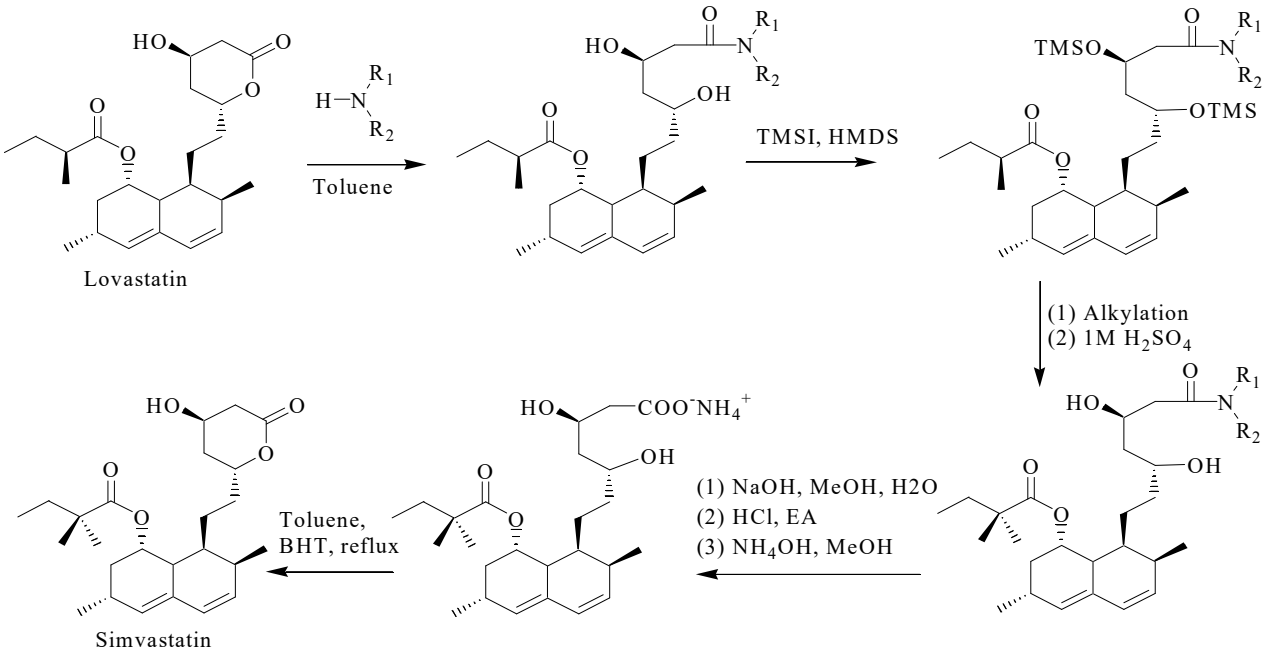

Fig. 26. Synthesis of simvastatin as described in US20070129437A1.

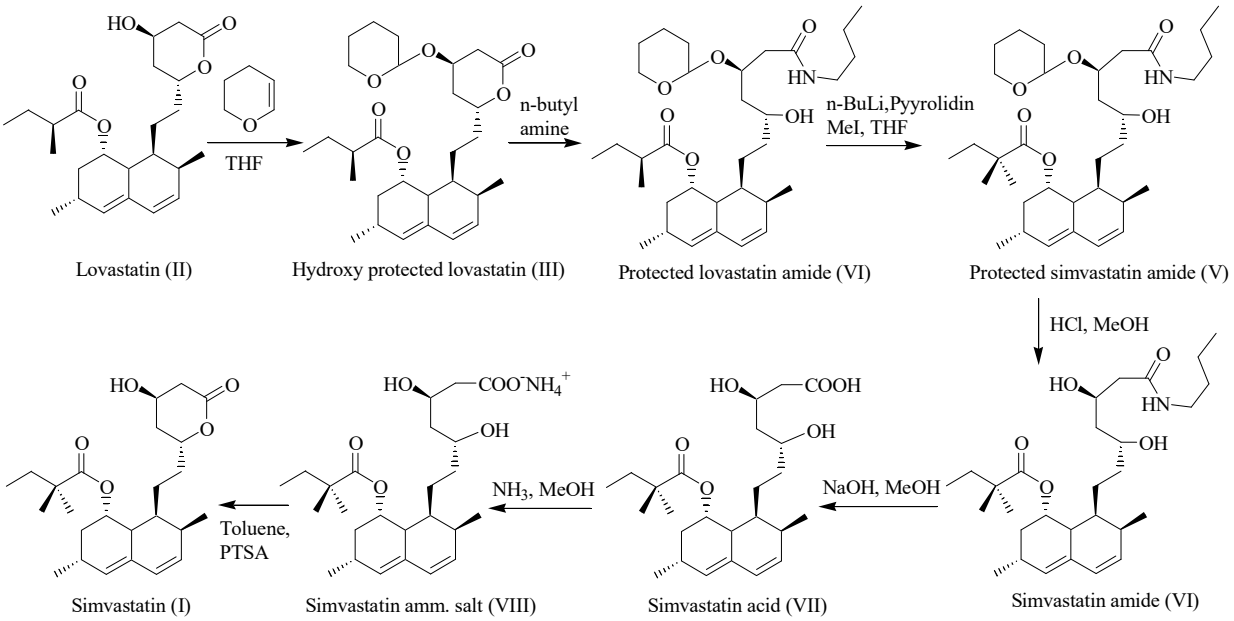

Fig. 27. Synthesis of simvastatin as described in US20070117996A1.

Dr Reddy's Laboratories Ltd., in US20070117996A1, described a process for preparation of simvastatin comprising of protecting the free hydroxyl group of lovastatin (II) with 3,4-dihydro-2H-pyran to afford the hydroxy-protected lovastatin (III) and, without isolating the hydroxy-protected lovastatin (III), forming an amide of lovastatin, thereby opening the lactone ring of the lovastatin to form a protected lovastatin amide(IV).

Methylating the α-carbon of the 2-methylbutyrate side chain of the hydroxy protected lovastatin amide (IV) to form hydroxyl protected simvastatin amide (V), removing the tetrahydropyran protecting group by reacting with an acid to afford simvastatin amide (VI). Hydrolyzing the simvastatin amide (VI) to form simvastatin acid (VII) and, without isolating the simvastatin acid (VII), forming a simvastatin ammonium salt (VIII) in an intermediate step. Finally lactonizing the simvastatin ammonium salt (VIII) to form simvastatin (I) [40].

3 Conclusions

Simvastatin is commercially synthesized from the naturally occurring lovastatin by introduction of an extra α methyl group in the 8-acyl side chain of lovastatin. In principle, there are two possible routes of synthesis of simvastatin from lovastatin, these are direct alkylation of the 2-methylbutyrate side chain, removal of the 2-methylbutyrate side chain and introduction of a 2,2-dimethylbutyrate chain.

Relatively high yield and fewer synthetic steps are the main advantages of adopting direct alkylation route in the synthesis of simvastatin. However, there are several drawbacks associated with this route. Apart from the use of pyrophoric hazardous substances like n-Butyllithium, direct methylation of unprotected lovastatin results in a rather impure simvastatin, containing a relatively high amount of unconverted lovastatin and many byproducts. Therefore, protection of the pyranone ring of lovastatin with t-butyl dimethylsilyl chloride prior to the alkylation reactive groups of the pyranone ring is required to minimize the formation of byproducts.

Re-esterification route, wherein the 2-methyl butyrate side chain is completely removed and 2,2-dimethylbutyrate side chain is introduced, gives better quality of simvastatin, as the separation of the hydrolyzed product and the esterified product is much easier to achieve compared to the unreacted starting material and the methylated product. Re-esterification route involves protection of the hydroxy group in the pyranone ring with t-butyl dimethylsilyl chloride, esterification with 2,2-dimethyl butyric acid or 2,2-dimethyl butyryl chloride and deprotection of the hydroxy group of the pyranone ring. Relatively low yield and use of an expensive protecting group are the main disadvantages of this route.

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