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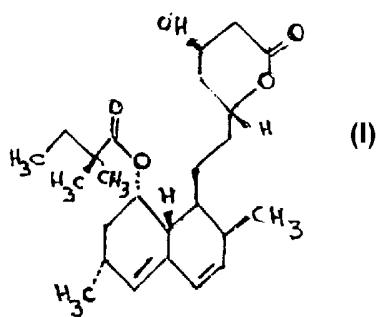
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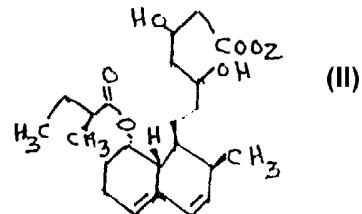
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[Continued on next page]

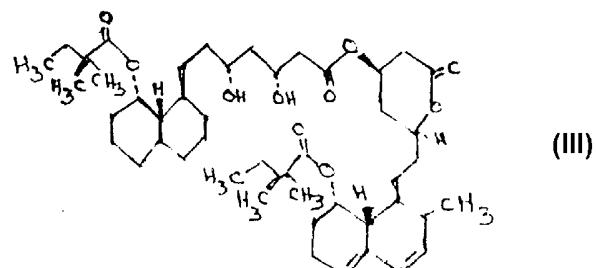
(54) Title: A PROCESS FOR LACTONIZATION TO PRODUCE HIGHLY PURE SIMVASTATIN



(I)



(II)



(III)

WO 02/094803 A1

(57) Abstract: There is disclosed, a process for lactonization to produce highly pure simvastatin of Formula 1 [F. I] which comprises lactonization of a compound of the Formula II, [F.II] where Z is H or NH₄ in a mixture of acetonitrile and glacial acetic acid to provide anhydrous conditions at a temperature of 65-70° C and wherein the dimer impurity of formula III formed is less than 0.1, thereafter adding water to the reaction mixture thereby causing simvastatin of formula I to precipitate from the reaction mixture. [F. III]



(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

- *as to the identity of the inventor (Rule 4.17(i)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*
- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*
- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP,*

KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

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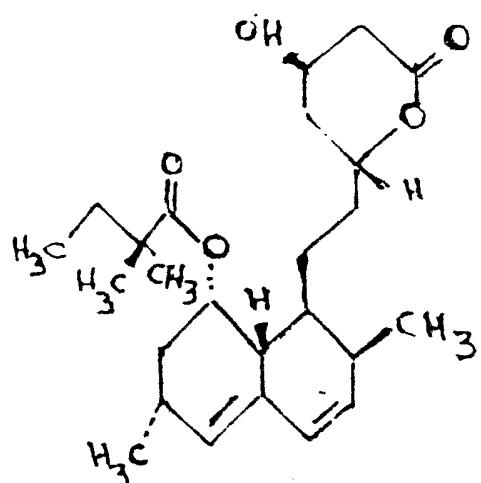
For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

Title:

A process for lactonization to produce simvastatin

Field of the Invention:

1. A process for lactonization to produce highly pure simvastatin of Formula 1.



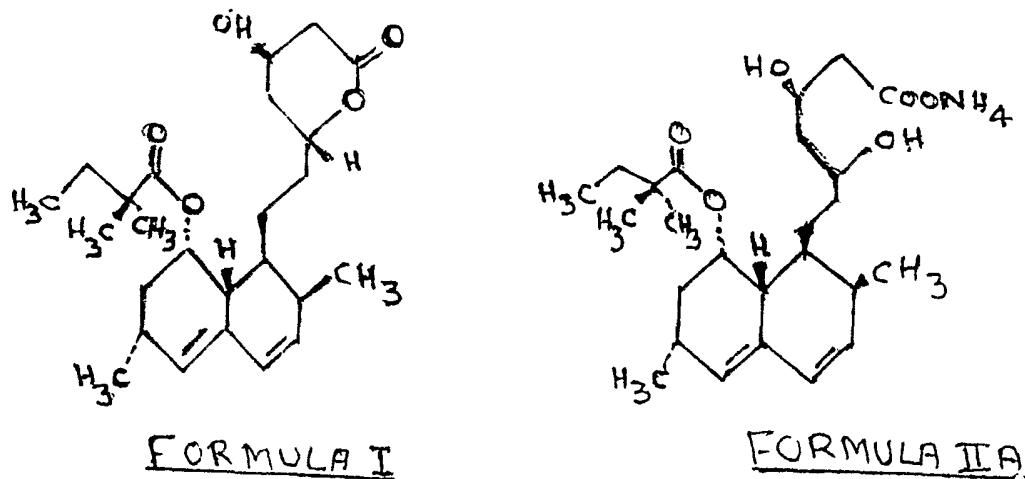
FORMULA I

Background of the Invention:

This invention relates to a process for lactonization to produce highly pure simvastatin.

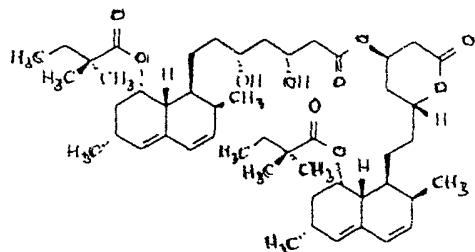
Lovastatin, simvastatin, pravastatin, atorvastatin and mevastatin are well known potent antihypercholesterolemic agents that function by limiting cholesterol biosynthesis by inhibiting the enzyme, HMG-CoA reductase. This class of compounds referred to generally as statins are produced either by natural 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. The use of highly pure simvastatin is exceedingly desirable in preparation of a pharmaceutical product as it would avoid accumulation of impurities during prolonged usage and would reduce the possible side effects during medical treatment.

In most of the synthetic methods known to manufacture simvastatin (Formula 1) shown below, the compound of formula II also shown below, is the common intermediate, which is cyclized to obtain simvastatin and thus lactonization constitutes an essential step of the synthesis.



It is of considerable importance to employ an efficient method for the lactonization that can produce simvastatin of high purity in good yield.

The process disclosed in the US Patent 4,820,850 involves heating of hydroxyacid ammonium salt in toluene at 100° C under a purge of nitrogen. The lactonization completion requires 6-8 hours refluxing and results in formation of increased amounts of dimer (Formula III).



Formula III

This dimer impurity is difficult to separate from the desired lactone even with repeated crystallization. Efforts to minimize the formation of the dimer have led to the use of high dilution during lactonization reaction. Nevertheless, this technique results in lower efficiency and is disadvantageous at commercial scale.

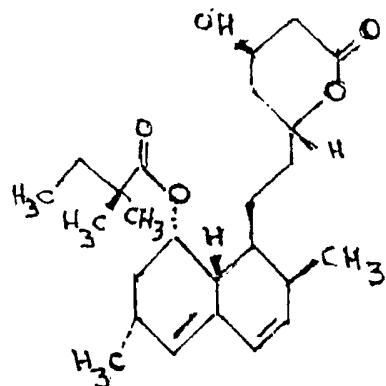
US Patent 4,916,239 describes another process where the lactonization reaction has been carried out by treating hydroxyacid ammonium salt in a mixture of acetic acid and water, and in the presence of a strong acid catalyst. This process requires gradual addition of water in several lots to effect crystallization of the lactonized product from the reaction medium to shift the equilibrium to the lactone side and this drives the lactonization to completion. This process is not amenable to industrial scale due to effluent generation and low purity of simvastatin product even though dimer content obtained is reported to be less than 0.2%.

US Patent 5,917,058 provides an alternate process to lactonize hydroxyacid or its salt by treatment with acetic acid under anhydrous conditions. However, the purity of the final product obtained by this procedure is not more than 99%. Furthermore, in this patent, there is no reference to the level of dimeric impurity produced in the process.

The aim of the present invention is to obtain highly pure simvastatin that contains dimeric impurity less than 0.1%. An example where simvastatin of greater than 99.5% purity has been achieved is cited in WO 99/42601 wherein the product was purified by successive crystallizations from aqueous acetone and from ethyl acetate.

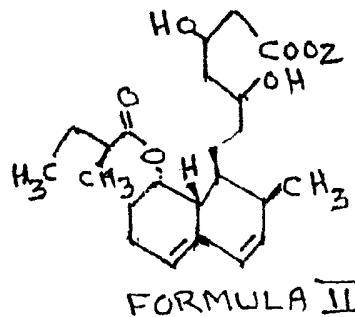
Brief Statement of the Invention:

According to this invention, there is provided a process for lactonization to produce highly pure simvastatin of Formula 1



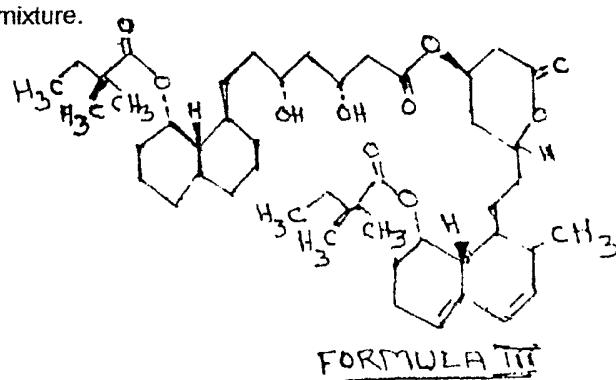
FORMULA I

which comprises lactonization of a compound of the Formula II,



FORMULA II

where Z is H or NH₄ in a mixture of acetonitrile and glacial acetic acid to provide anhydrous conditions at a temperature of 65-70° C and wherein the dimer impurity of formula III formed is less than 0.1, thereafter adding water to the reaction mixture thereby causing simvastatin of formula I to precipitate from the reaction mixture.



FORMULA III

In this process in Formula II above, preferably Z is NH₄.

The process further comprises adding water to the reaction mixture, thereby causing simvastatin of Formula 1 to precipitate from the reaction mixture.

Detailed Description of the Invention:

The instant invention relates to a novel process for lactonization of simvastatin hydroxyacid or its salt that avoids the use of strong corrosive acids and drastic heat conditions. This process allows lactonization reaction to proceed in a mixture of acetic acid and acetonitrile at moderate temperatures and consistently provides simvastatin of greater than 99.5% purity with dimer content less than 0.1%.

Specifically, the process of this invention comprises heating a solution of simvastatin hydroxyacid in its salt form, most preferably the ammonium salt (Formula II) in a mixture of acetic acid and acetonitrile under anhydrous conditions at a temperature that vary from 50° C to 80° C and preferably at 65-70° C.

The lactonization reaction is typically accomplished within about 5 to 7 hours. The amount of acetic acid used is at least 3 to 5 parts by volume per part of the starting material. The amount of acetonitrile is 10 to 20 parts by volume per part of the starting material and preferably 15 parts by volume may be used. The lactonized product is isolated after completion of reaction by addition of water.

Major advantage of the present invention as compared to the prior art procedures is the high product purity where the level of dimer impurity has been greatly reduced to less than 0.1%. The addition of water to the reaction mixture directly provides lactone as a homogeneous slurry that makes the filtration operation very easy at large scale and work up involves no solvent concentration or neutralization step prior to product isolation.

The invention will now be more fully described with reference to the following examples which are only illustrative and are not be construed as any limitation thereof.

Example 1

PREPARATION OF (1S, 3R, 7S, 8S, 8aR) -3, 7-DIMETHYL-8- [2- [(2R, 4R) -4-HYDROXY-6-OXO-3, 4, 5, 6-TETRAHYDRO-2H-PYRAN-2-YL] ETHYL] -1, 2, 3, 7, 8, 8a-HEXAHYDRO NAPHTHALIN-1-YL 2, 2-DIMETHYLBUTANOATE

Lactonization

Ammonium 7- [1, 2, 6, 7, 8, 8a (R) -hexahydro-2 (S), 6 (R) -dimethyl-8 (S) - (2, 2-dimethylbutyryloxy) -1 (S) -naphthyl] -3 (R), 5 (R)-dihydroxyheptanoate (Formula II) (10 g., 0.022 moles) was dissolved in a mixture of acetonitrile (150 ml.) and glacial acetic acid (30 ml.). The solution was then heated to 65-70° C and was maintained at this temperature for 6 hours. At the end of the reaction, HPLC showed simvastatin 97.4%, unreacted starting material 0.69% and dimer 0.07%. The reaction mass was cooled to 15-20° C and water (350 ml.) was added over a period of 30 minutes. The precipitated product was cooled further to 10-15° C and stirring continued for 1 hour. Product was filtered and washed with water (2x10 ml.), 1:2 v/v acetonitrile-water (2x10 ml.) and dried in vacuo at 45-50° C. The product thus obtained was dissolved in cyclohexene (200 ml.) at 80-85° C and then cooled over 1 hour to 10-12° C. Product was filtered and washed with chilled cyclohexene (10 ml.) and dried in vacuo at 45-50° C to yield highly pure 8.2 g. (89%) of the title compound with HPLC purity 99.63% and dimer impurity 0.04%.

Example 2

PREPARATION OF (1S, 3R, 7S, 8S, 8aR) -3, 7-DIMETHYL-8- [2- [(2R, 4R) -4-HYDROXY-6-OXO-3, 4, 5, 6-TETRAHYDRO-2H-PYRAN-2-YL] ETHYL] -1, 2, 3, 7, 8, 8a-HEXAHYDRO NAPHTHALIN-1-YL 2, 2-DIMETHYLBUTANOATE

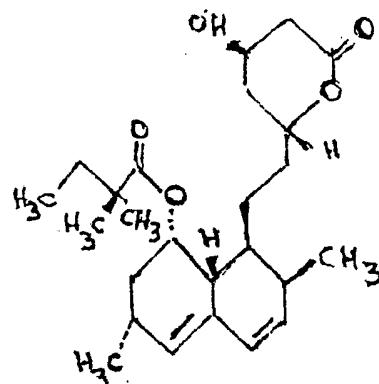
Lactonization

Ammonium 7- [1, 2, 6, 7, 8, 8a (R) -hexahydro-2 (S), 6 (R) -dimethyl-8 (S) - (2, 2-dimethylbutyryloxy) -1 (S) -naphthyl] -3 (R), 5 (R)-dihydroxyheptanoate (Formula II) (10 g., 0.022 moles) was dissolved in a mixture of acetonitrile (150 ml.) and glacial acetic acid (30 ml.). The reaction mixture was heated to 65-70° C under anhydrous conditions for 6 hours. Progress of reaction was checked by HPLC. At the end of the reaction, simvastatin was 97.55%, unreacted starting material 0.66% and dimer impurity 0.07%. Thereafter, reaction mixture was cooled to 10-15° C and water (350 ml.) was added slowly over a period of 30 minutes and stirring was continued for 30 minutes. The product was filtered, washed with water (2x10 ml.) and dissolved in

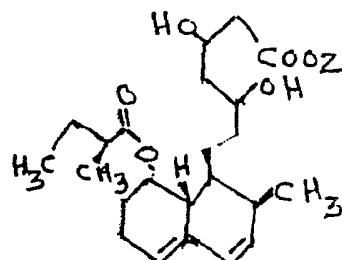
methanol (90 ml.) at 25-30° C. The solution was cooled to 5-10° C and water (82 ml.) was added in 30 minutes. The product thus crystallized was stirred at 5-10° C, filtered and washed with cold methanol/water mixture (1:1 v/v, 8 ml.). Product was dried to constant weight in vacuo at 45-50° C to obtain simvastatin (8.3 g., 90%). Chromatographic purity (HPLC) 99.55% and dimer impurity 0.07%.

We Claim:

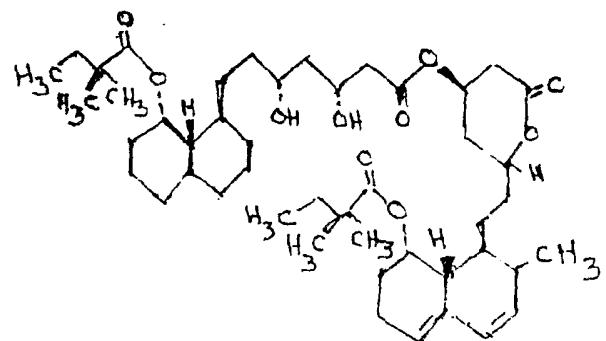
1. A process for lactonization to produce highly pure simvastatin of Formula 1.

**FORMULA I**

which comprises lactonization of a compound of the Formula II

**FORMULA II**

where Z is H or NH₄ in a mixture of acetonitrile and glacial acid to provide anhydrous conditions at a temperature of 65-70° C and wherein the dimer impurity of formula III formed is less than 0.1%, thereafter adding water to the reaction mixture, thereby causing simvastatin of Formula 1 to precipitate from the reaction mixture.

**FORMULA III**

2. The process according to Claim 1 wherein Z is NH₄.
3. A process for lactonization to produce highly pure simvastatin of formula I substantially as herein described.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IN 02/00121

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D309/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 917 058 A (Y.KUMAR) 29 June 1999 (1999-06-29) cited in the application column 1 -column 5 ---	1-3
Y	US 5 939 564 A (Y.KUMAR) 17 August 1999 (1999-08-17) column 1 -column 6 ---	1-3
Y	WO 01 30773 A (MERCK) 3 May 2001 (2001-05-03) page 1 -page 12; claims ---	1-3

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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Date of the actual completion of the international search

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11 September 2002

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/IN 02/00121

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5917058	A 29-06-1999	NONE	
US 5939564	A 17-08-1999	NONE	
WO 0130773	A 03-05-2001	AU 8030900 A 08-05-2001 EP 1228057 A2 07-08-2002 WO 0130773 A2 03-05-2001 US 6380401 B1 30-04-2002	