

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
31 August 2006 (31.08.2006)

PCT

(10) International Publication Number
WO 2006/090256 A1

(51) International Patent Classification:
C07C 221/00 (2006.01) C07C 223/02 (2006.01)

(21) International Application Number:
PCT/IB2006/000395

(22) International Filing Date:
27 February 2006 (27.02.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
431/DEL/2005 28 February 2005 (28.02.2005) IN

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

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.

(54) Title: PROCESS FOR THE PREPARATION OF N-METHYL ANILINO ACROLEIN

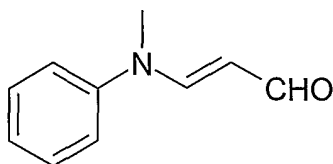
(57) Abstract: This present invention relates to processes for the preparation of 3-N-methyl-N-phenylaminoacrolein.



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PROCESS FOR THE PREPARATION OF N-METHYL ANILINO ACROLEINField of the Invention

Processes for the preparation of 3-N-methyl-N-phenylaminoacrolein of Formula I as provided.



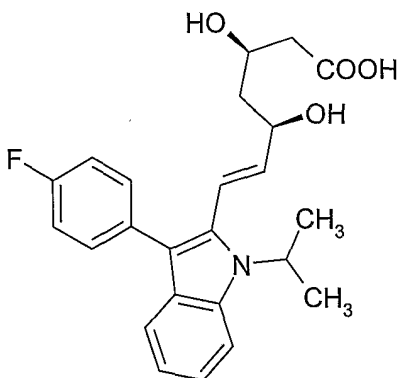
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Formula I

Processes for the preparation of fluvastatin or a pharmaceutically acceptable salt thereof ester or lactone form thereof is also provided using the compound of Formula I.

Background of the Invention

10 Fluvastatin is a racemate of (3R,5S) and (3S,5R) erythro-7-[3-(4-fluorophenyl)-1-(1-methylethyl)-1H-indol-2-yl]-3,5-dihydroxy-6-heptenoic acid of Formula II.

**Formula II**

15 Fluvastatin is available commercially in the form of its monosodium salt which is indicated as an adjunct to diet to reduce elevated total cholesterol (Total-C), LDL-C, TG and Apo B levels, and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia (Fredrickson Type IIa and IIb) whose response to dietary restriction of saturated fat and cholesterol and other non-pharmacological measures has not been adequate.

It is also indicated to slow the progression of coronary atherosclerosis in patients with coronary heart disease as part of a treatment strategy to lower total and LDL cholesterol to target levels. Fluvastatin sodium is the first entirely synthetic HMG-CoA reductase inhibitor, and is in part structurally distinct from the fungal derivatives of this therapeutic class.

5 GB Specification 945536 and U.S. Patent No. 5,118,853 disclose synthesis of 3-N-methyl-N-phenylaminoacrolein using N-methylformanilide and ethyl vinyl ether in the presence of phosgene or oxalyl chloride followed by hydrolysis of the resultant complex.

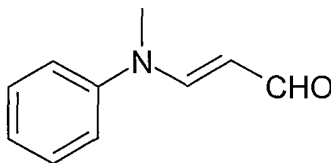
U. S. Application No. 2004/0229958 discloses the preparation of 3-N-methyl-N-phenylaminoacrolein by a similar procedure reported in U.S. Patent No. 5,118,853, except
10 that dioxane is used as a solvent in place of chlorinated hydrocarbons.

German Patent Specification Nos. 944,852 and 948,871 disclose processes for preparation of beta-aminoacroleins but do not exemplify the preparation of 3-N-methyl-N-phenylaminoacrolein.

U.S. Patent No. 4,739,073 ("the '073 Patent") and US Patent No. 5,354,772 provide a
15 process for preparation of racemic fluvastatin sodium, which involves lyophilization of an aqueous solution of fluvastatin sodium. The '073 Patent further provides a process for the preparation of enantiomerically pure (3S, 5R) or (3R, 5S) forms of fluvastatin sodium which comprises resolution of racemic fluvastatin sodium by High Performance Liquid Chromatography (HPLC) and by using chiral auxiliaries.

20 Summary of the Invention

The present inventors have now prepared N-methyl-N-phenylaminoacrolein of structural Formula I, by a process using cheap and easily available propargyl alcohol and N-methyl aniline. The process can readily and desirably be carried out in a single step.

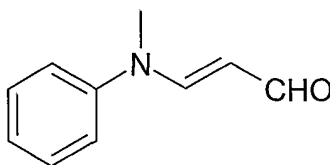


25 **Formula I**

The present process affords 3-N-methyl-N-phenylaminoacrolein of Formula I in high yield and high purity and also avoids the use of toxic reagents.

Detailed Description of the Invention

In one aspect, a process for the preparation of 3-N-methyl-N-phenylaminoacrolein of
5 Formula I is provided.



Formula I

wherein the process comprises:

- a) reacting N-methylaniline and propargyl alcohol in presence of an oxidizing agent; and
- 10 b) isolating 3-N-methyl-N-phenylaminoacrolein of Formula I from the resulting reaction mass.

N-methylaniline and propargyl alcohol are dissolved in an organic solvent until a clear solution is obtained. The solution so obtained is oxidized with an oxidizing agent at about 15 to about 60°C by stirring for about 5 to about 25 h. The reaction can be readily monitored by
15 thin layer chromatography (TLC), followed by filtration. The residual solid is washed with an organic solvent and de-ionized water. The combined filtrate is taken and the aqueous layer discarded. The organic layer can be is treated with activated charcoal. The solvent can be completely recovered, for example, under reduced pressure, and the product can be recrystallized from solvent or a mixture of solvents to afford pure 3-N-methyl-N-
20 phenylaminoacrolein of Formula I.

The organic solvent can be chosen from aromatic hydrocarbons, chlorinated hydrocarbons, ethers, polar aprotic solvents, ketones or mixtures thereof. The aromatic hydrocarbon can be, for example, toluene, benzene or xylene. The chlorinated hydrocarbon can be, for example, chloroform, dichloromethane, 1,2-dichloroethane and the like. The ether
25 can be, for example tetrahydrofuran, 1,4-dioxane and the like. The ketone can be, for

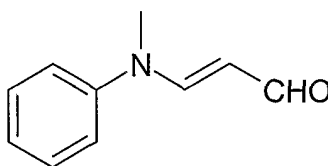
example, acetone, ethyl methyl ketone, methyl isobutyl ketone, diisobutyl ketone and the like. The polar aprotic solvent can be, for example, N,N-dimethylformamide, N,N-dimethylacetamide, dimethylsulphoxide, acetonitrile, N-methylpyrrolidone and the like.

5 The oxidizing agent which can be used is one that can convert $-CH_2OH$ (a primary alcohol) group to $-CHO$ (an aldehyde) group and is known to a person of ordinary skill in the art. Some of the oxidizing agents that can be used are exemplified hereinafter but they do not limit the scope of the invention. The oxidizing agent can be selected from, for example, manganese dioxide, potassium dichromate, potassium permanganate, chromium trioxide, Jones reagent, ceric ammonium nitrate, oxalyl chloride/dimethylsulphoxide and the like.

10 Solvents for recrystallization can be selected from, for example, hydrocarbons, ketones or mixtures thereof. The hydrocarbon can be, for example, petroleum ether, hexane, cyclohexane, cyclopentane, cycloheptane, toluene, benzene, xylene and the like. The ketone can be, for example, acetone, ethyl methyl ketone, methyl isobutyl ketone, diisobutyl ketone and the like.

15 3-N-methyl-N-phenylaminoacrolein of Formula I as obtained by processes described herein can have purity greater than about 98%. More preferably the purity is greater than about 99.8%. Most preferably the purity is greater than about 99.94%.

In another aspect, processes for the preparation of 3-N-methyl-N-phenylaminoacrolein of Formula I are provided.



Formula I

20 wherein the process comprises:

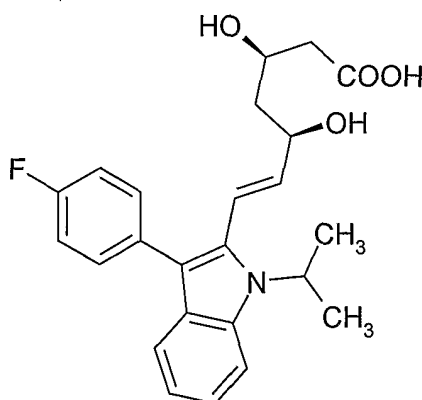
- a) oxidizing propargyl alcohol;
- b) treating the solution of step a) in situ with N-methylaniline; and
- 25 c) isolating 3-N-methyl-N-phenylaminoacrolein of Formula I from the reaction mass thereof.

A solution of an oxidizing agent in de-ionized water can be cooled to about -10 to about 30°C and added to a solution of propargyl alcohol in an organic solvent at about -10 to about 30°C . The reaction mixture can be quenched, for example, with methanol, and filtered. The residue can be washed with an organic solvent. The organic solvent can be completely recovered from the filtrate. The reaction mass can be extracted with an organic solvent, dried and treated with N-methylaniline. The reaction can be easily monitored by thin layer chromatography (TLC), followed by treatment with activated charcoal. The solvent can be completely recovered, under reduced pressure and the product recrystallized from solvent or a mixture of solvents, to afford pure 3-N-methyl-N-phenylaminoacrolein of Formula I.

The oxidizing agent, organic solvent and solvent for recrystallization can be chosen as discussed herein.

3-N-methyl-N-phenylaminoacrolein of Formula I obtained by the process of the present invention can be converted to statins by processes known in the art. For example it can be converted to fluvastatin by the process disclosed, for example, in U.S. Patent No. 2004/0229958, U. S. Patent No. 4,739,073 or U.S. Patent No. 5,354,772, which are incorporated herein as reference in their entireties.

In yet another, aspect processes for the preparation of fluvastatin of Formula II, or salt, ester or lactone form thereof are provided,



Formula II

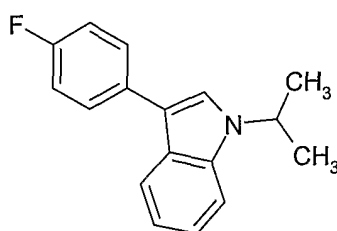
wherein the process comprises:

a) reacting N-methylaniline and propargyl alcohol in presence of an oxidizing agent;

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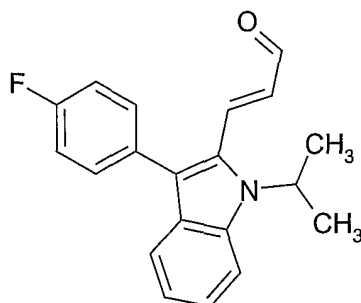
b) optionally isolating 3-N-methyl-N-phenylaminoacrolein of Formula I, from the reaction mixture of step a);

c) treating the reaction mixture or the product of step b) with a compound of structural Formula V



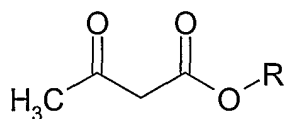
Formula V

in the presence of phosphorous oxychloride to obtain a compound of structural Formula VI;



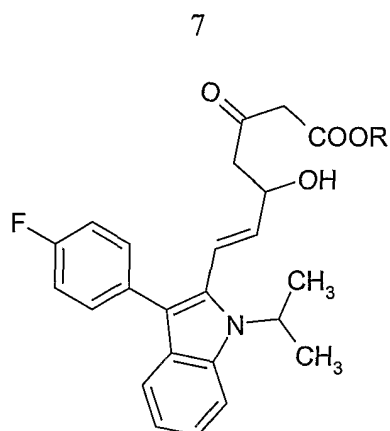
Formula VI

d) treating the reaction mixture of step c) with alkyl acetoacetate of Formula VII,

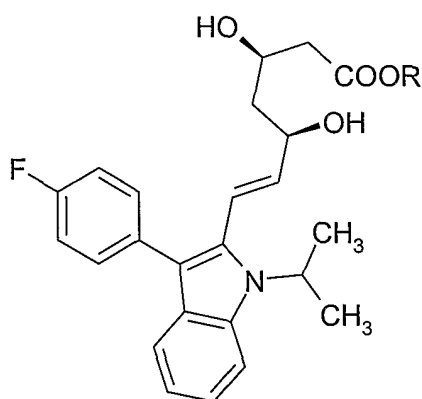


Formula VII

wherein R is alkyl group of 1 to 4 carbon atoms, in the presence of a base, to obtain a compound of structural Formula VIII wherein R is as described above;

**Formula VIII**

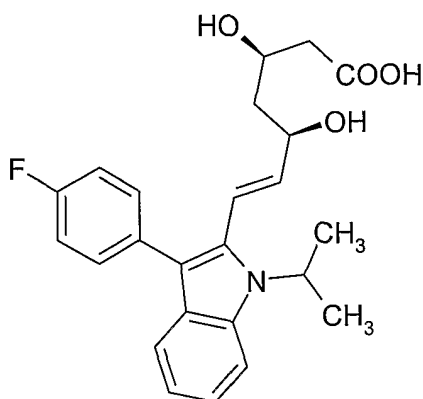
- e) reducing the reaction mixture of step d) using diethylmethoxyborane and sodium
 5 borohydride to obtain a compound of Formula IX wherein R is as described above; and

**Formula IX**

- f) hydrolyzing the solution of step e) in the presence of sodium hydroxide to obtain fluvastatin
 10 of Formula II or salt, ester or lactone form thereof.

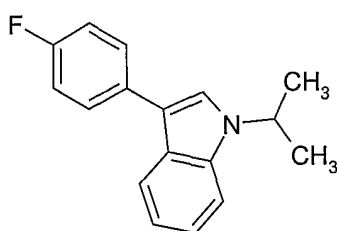
3-N-methyl-N-phenylaminoacrolein of Formula I can be prepared, for example, by
 any of the processes described above. 3-N-methyl-N-phenylaminoacrolein of Formula I can
 be optionally isolated from the reaction mass thereof and used for the preparation of
 fluvastatin or salt, ester or lactone form thereof. Compound of Formula VI (obtained by
 15 reaction of 3-N-methyl-N-phenylaminoacrolein of Formula I with compound of Formula V)
 can be converted to fluvastatin, salt or ester or lactone form thereof essentially by the process
 described in, for example, Examples 5 and 6 of U.S. Patent No. 4,739,073 or U.S. Patent No.
 5,354,772.

In still another aspect, processes for the preparation of fluvastatin of Formula II, or salt, ester or lactone form thereof are provided,



Formula II

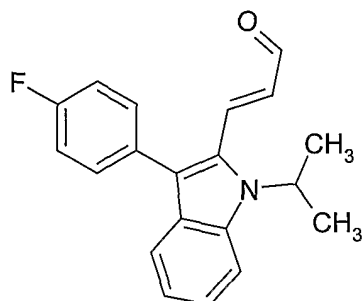
- 5 wherein the process comprises:
- a) oxidizing propargyl alcohol;
 - b) treating the reaction mixture of step a) with N-methylaniline;
 - c) optionally isolating 3-N-methyl-N-phenylaminoacrolein of Formula I from the reaction mixture of step b);
 - 10 d) treating the reaction mixture or the product of step c) with a compound of structural Formula V



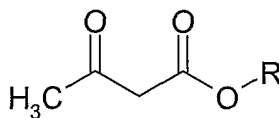
Formula V

- 15 in the presence of phosphorous oxychloride to obtain a compound of structural Formula VI;

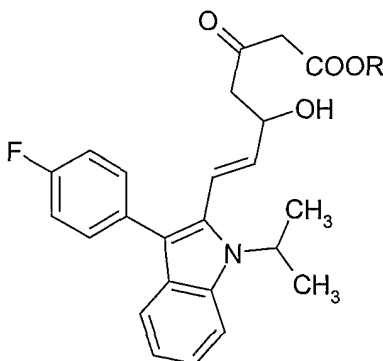
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**Formula VI**

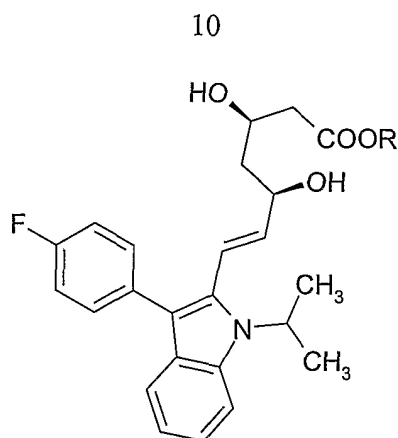
e) treating the reaction mixture of step d) with alkyl acetoacetate of Formula VII

**Formula VII**

wherein R is alkyl group of 1 to 4 carbon atoms, in the presence of a base, to obtain a compound of structural Formula VIII wherein R is as described above;

**Formula VIII**

f) reducing the reaction mixture of step e) using diethylmethoxyborane and sodium borohydride to obtain a compound of Formula IX wherein R is as defined earlier; and

**Formula IX**

g) hydrolyzing the solution of step f) in the presence of sodium hydroxide to obtain fluvastatin
 5 of Formula II or salt, ester or lactone form thereof.

3-N-methyl-N-phenylaminoacrolein of Formula I can be prepared, for example, by
 any of the processes described above. 3-N-methyl-N-phenylaminoacrolein of Formula I can
 be optionally isolated from the reaction mass thereof and used for the preparation of
 fluvastatin or salt or ester or lactone form thereof. Compound of Formula VI (obtained by
 10 reaction of 3-N-methyl-N-phenylaminoacrolein of Formula I with compound of Formula V)
 can be converted to fluvastatin, salt or ester or lactone form thereof essentially by the process
 described, for example, in Examples 5 and 6 of U.S. Patent No. 4,739,073 or U.S. Patent No.
 5,354,772. 3-N-methyl-N-phenylaminoacrolein of Formula I can also be used as an
 intermediate in the preparation of other statins by processes known to one skilled in the art.

15 While the present invention has been described in terms of its specific embodiments,
 certain modifications and equivalents will be apparent to those skilled in the art and do not
 limit the scope of the present invention.

Example 1: Preparation of 3-N-methyl-N-phenylaminoacrolein

20 Into a 1000 ml three neck round bottom flask was added toluene (300 ml), propargyl
 alcohol (25 g, 446.43 mmole) and N-Methylaniline (25 g, 233.64 mmole) at 20-25°C. The
 resultant mixture was stirred to get clear solution and then manganese dioxide (200 g, 3.57
 mole) was added at 20-25°C. The reaction mixture was stirred for 15 hours. After monitoring

the reaction, the reaction mixture was filtered and the residual solid washed with toluene (3 x 50 ml) and deionized water (100 ml). The combined filtrate was charged in another round bottom flask, the lower aqueous layer was discarded and the toluene layer was treated with activated carbon (3 g). The residual carbon was filtered through hyflo supercel. Toluene was recovered completely under reduced pressure and product was crystallized from toluene: petroleum ether (25 ml : 75 ml respectively) to afford the title compound.
Yield: 25 g (66.7%); Purity: 99.8% (by HPLC).

Example 2: Preparation of 3-N-methyl-N-phenylaminoacrolein

Into a 1000 ml three neck round bottom flask was added toluene (350 ml), propargyl alcohol (19.6 g, 350.46 mmole) and N-Methylaniline (25 g, 233.64 mmole) at 20-25°C. The resultant mixture was stirred to get clear solution and then manganese dioxide (122 g, 1.40 mole) was added at 15-20°C. The reaction mixture was stirred for 20 hours. After monitoring the reaction, the reaction mixture was filtered and the residual solid washed with toluene (3 x 50 ml) and deionized water (100 ml). The combined filtrate was charged in another round bottom flask, the lower aqueous layer was discarded and the toluene layer was treated with activated carbon (3 g). The residual carbon was filtered through hyflo supercel. Toluene was recovered under reduced pressure leaving 25 ml toluene. The residual material in toluene was crystallized from hexanes (100 ml) to afford the title compound.
Yield: 30 g (80%); Purity: 98.2% (by HPLC).

Example 3: Preparation of 3-N-methyl-N-phenylaminoacrolein

Into a 1000 ml three neck round bottom flask was added dioxane (300 ml), propargyl alcohol (25 g, 446.43 mmole) and manganese dioxide (200 g, 3.57 moles). The reaction mixture was stirred for 10 hours and N-Methylaniline (47.77 g, 446.43 mmole) was added at 20-25°C. The reaction mixture was stirred and monitored. The reaction mixture was filtered and the residual solid washed with dioxane (3 x 50 ml) and deionized water (100 ml). The filtrate was recovered completely under reduced pressure and the product was extracted with dichloromethane (2 x 150 ml). Dichloromethane was recovered completely under reduced

pressure and product crystallized from toluene: hexanes (25 ml : 75 ml respectively) to afford the title compound.

Yield: 61.62 g (86 %); Purity: 98.17%.

Example 4: Preparation of 3-N-methyl-N-phenylaminoacrolein

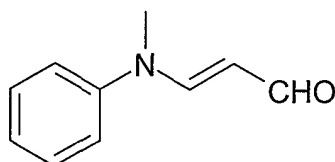
5 Into a 500 ml three neck round bottom flask containing a solution of chromium trioxide (60.70 gm, 607.47 m mole) and 325 ml deionized water cooled to 0-5°C, was added sulphuric acid (86 g). This reagent was slowly added into a solution of propargyl alcohol (31.40 g, 560.71 mmole) in acetone (500 ml) at 0-5°C. The reaction mixture was stirred and quenched with methanol. The reaction mixture was filtered and the residue washed with
10 acetone. Acetone was recovered completely under reduced pressure and the propargyl aldehyde was extracted with toluene (2 x 150 ml). The toluene layer was dried over sodium sulphate and N-methylaniline (50 g, 467.29 mmole) was added. After monitoring the reaction it was treated with activated carbon (3 g) and the carbon filtered through hyflo supercel. Toluene was recovered completely under reduced pressure and the product was crystallized
15 from toluene: hexanes (25 ml : 100 ml respectively) to afford the title compound.
Yield: 62.25 g (83 %); Purity: 98.0%.

Example 5: Preparation of 3-N-methyl-N-phenylaminoacrolein

 In to a 1000 ml three neck round bottom flask was added toluene (300 ml), propargyl alcohol (25 g, 446.43 mmole) and N-Methylaniline (25 g, 233.64 mmole) at 20-25°C. The
20 reaction mixture was stirred to get clear solution and then manganese dioxide (200 g, 3.57 mole) was added at 20-25°C. The reaction mixture was stirred for 15 hours. After monitoring the reaction the reaction mixture was filtered and the residual solid washed with toluene (3 x 50 ml) and deionized water (100 ml). The combined filtrate was charged in another round bottom flask, the lower aqueous layer was discarded and the toluene layer was treated with
25 activated carbon (3 g). The residual carbon was filtered through hyflo supercel. Toluene was recovered under reduced pressure and the product was crystallized from toluene (75 ml) at – 10 to –15°C to afford the title compound.
Yield: 20 g (53.3%); Purity: 99.94%.

We Claim:

- 1 1. A process for the preparation of 3-N-methyl-N-phenylaminoacrolein of Formula I,

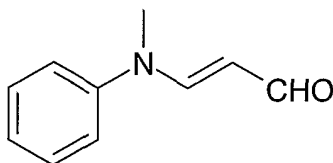


2
3 **Formula I**

4 wherein the process comprises:

- 5 a) reacting N-methylaniline and propargyl alcohol in presence of an oxidizing agent; and
6 b) isolating 3-N-methyl-N-phenylaminoacrolein of Formula I from the reaction mass.

- 1 2. A process for the preparation of 3-N-methyl-N-phenylaminoacrolein of Formula I,

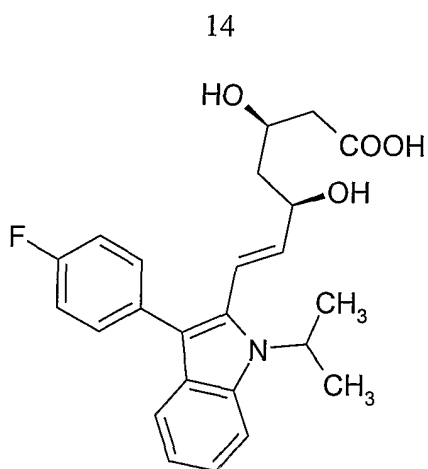


2
3 **Formula I**

4 wherein the process comprises:

- 5 a) oxidizing propargyl alcohol ;
6 b) treating the solution of step a) in situ with N-methylaniline ; and
7 c) isolating 3-N-methyl-N-phenylaminoacrolein of Formula I from the reaction mass thereof.

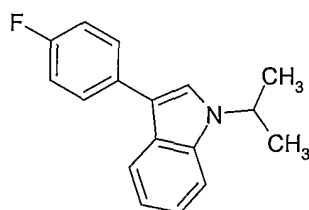
- 1 3. A process for the preparation of fluvastatin of Formula II, or salt, ester or lactone,



Formula II

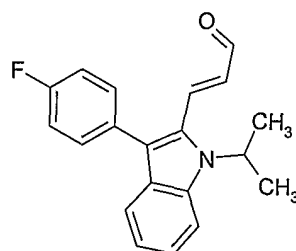
wherein the process comprises:

- a) reacting N-methylaniline and propargyl alcohol in presence of an oxidizing agent;
- b) optionally isolating 3-N-methyl-N-phenylaminoacrolein of Formula I from the reaction mixture of step a);
- c) treating the reaction mixture or the product of step b) with a compound of structural Formula V



Formula V

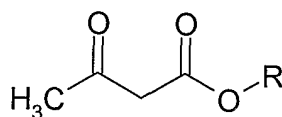
in the presence of phosphorous oxychloride to obtain a compound of structural Formula VI;



Formula VI

15

17 d) treating the reaction mixture of step c) with alkyl acetoacetate of Formula VII,

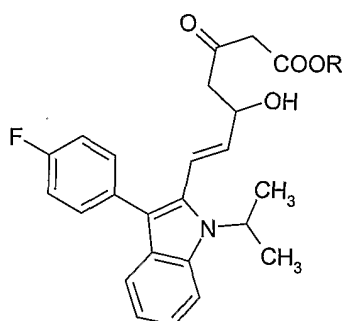


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Formula VII

20 wherein R is alkyl group of 1 to 4 carbon atoms, in the presence of a base, to obtain a
21 compound of structural Formula VIII wherein R is as described above;



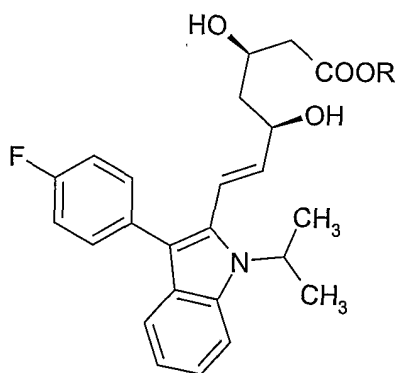
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Formula VIII

25 e) reducing the reaction mixture of step d) using diethylmethoxyborane and sodium
26 borohydride to obtain a compound of Formula IX wherein R is as defined earlier; and



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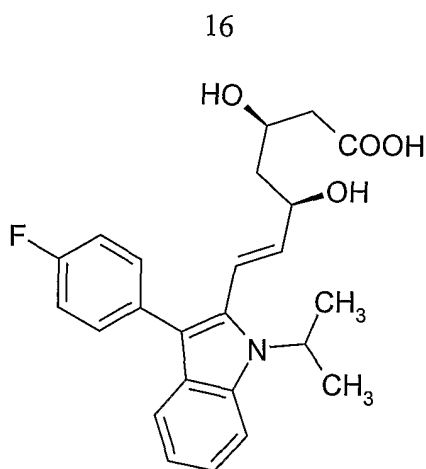
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Formula IX

30 f) hydrolyzing the solution of step e) in the presence of sodium hydroxide to obtain fluvastatin
31 of Formula II or salt, ester or lactone.

1 4. A process for the preparation of fluvastatin of Formula II, or salt, ester or lactone,

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**Formula II**

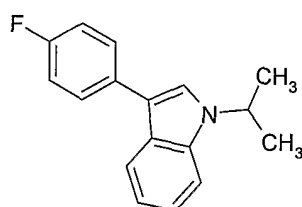
wherein the process comprises:

a) oxidizing propargyl alcohol ;

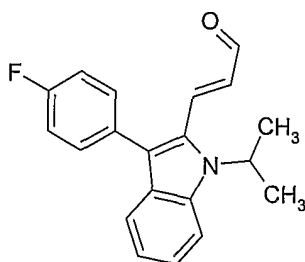
b) treating the reaction mixture of step a) with N-methylaniline;

c) optionally isolating 3-N-methyl-N-phenylaminoacrolein of Formula I from the reaction mixture of step b);

d) treating the reaction mixture or the product of step c) with a compound of structural Formula V

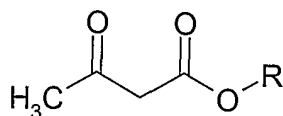
**Formula V**

in the presence of phosphorous oxychloride to obtain a compound of structural Formula VI;

**Formula VI**

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18 e) treating the reaction mixture of step d) with alkyl acetoacetate of Formula VII,

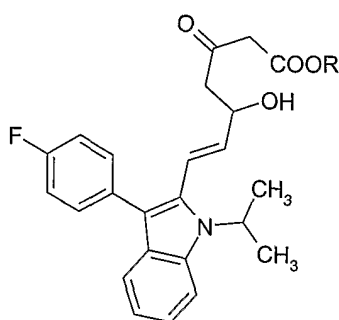


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Formula VII

21 wherein R is alkyl group of 1 to 4 carbon atoms, in the presence of a base, to obtain a
22 compound of structural Formula VIII wherein R is as described above;



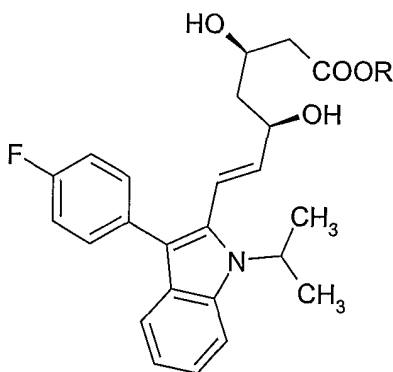
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Formula VIII

26 f) reducing the reaction mixture of step e) using diethylmethoxyborane and sodium
27 borohydride to obtain a compound of Formula IX wherein R is as defined earlier; and



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Formula IX

32 g) hydrolyzing the solution of step f) in the presence of sodium hydroxide to obtain fluvastatin
33 of Formula II or salt, ester or lactone form thereof.

1 5. A process according to claim 1, 2, 3 or 4 wherein oxidation is carried out in the
2 presence of an oxidizing agent selected from manganese dioxide, potassium dichromate,

3 potassium permanganate, chromium trioxide, Jones reagent, ceric ammonium nitrate, oxaly
4 chloride/dimethylsulphoxide or mixtures thereof.

1 6. A process according to claim 5 wherein the oxidizing agent is selected from
2 manganese dioxide and chromium trioxide or mixtures thereof.

1 7. A process according to claim 1, 2, 3 or 4 wherein the oxidation is carried out in the
2 presence of an organic solvent.

1 8. A process according to claim 7 wherein the organic solvent is selected from aromatic
2 hydrocarbons, chlorinated hydrocarbons, ethers, polar aprotic solvents, ketones or mixtures
3 thereof.

1 9. A process according to claim 8 wherein the aromatic hydrocarbon is selected from
2 toluene, benzene or xylene or mixtures thereof.

1 10. A process according to claim 9 wherein the aromatic hydrocarbon is toluene.

1 11. A process according to claim 8 wherein the ether is selected from tetrahydrofuran and
2 1,4-dioxane or mixtures thereof.

1 12. A process according to claim 11 wherein the ether is 1,4-dioxane.

1 13. A process according to claim 8 wherein the ketone is selected from acetone, ethyl
2 methyl ketone, methyl isobutyl ketone and diisobutyl ketone or mixtures thereof.

1 14. A process according to claim 13 wherein the ketone is acetone.

1 15. A process according to claims 1, 2, 3 or 4 further comprising recrystallization of 3-N-
2 methyl-N-phenylaminoacrolein of Formula I from an organic solvent selected from
3 hydrocarbons, ketones or mixtures thereof.

1 16. A process according to claim 15 wherein the hydrocarbon is selected from petroleum
2 ether, hexane, cyclohexane, cyclopentane, cycloheptane, toluene, benzene, xylene or mixtures
3 thereof.

1 17. A process according to claim 16 wherein the hydrocarbon is selected from hexane,
2 toluene or mixtures thereof.

- 1 18. A process according to claim 15 wherein the ketone is selected from acetone, ethyl
2 methyl ketone, methyl isobutyl ketone and diisobutyl ketone or mixtures thereof.
- 1 19. A process according to claims 1, 2, 3 or 4 wherein 3-N-methyl-N-
2 phenylaminoacrolein of Formula I obtained has a purity of 98% or more.
- 1 20. Use of 3-N-methyl-N-phenylaminoacrolein of Formula I obtained by the process
2 according to any of the preceeding claims as an intermediate to prepare fluvastatin.

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2006/000395

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C221/00 C07C223/02

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)
C07C

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)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2 808 437 A (PASEDACH HEINRICH ET AL) 1 October 1957 (1957-10-01) example 12 claims 11,12	1,2
Y	column 2, lines 9-24	3-19
X	DE 948 871 C (BADISCHE ANILIN- & SODA-FABRIK AKTIENGESELLSCHAFT) 6 September 1956 (1956-09-06) cited in the application	1,2
Y	column 1, line 24 - column 2, line 11 ----- -/--	3-19

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"&" document member of the same patent family

Date of the actual completion of the international search

29 June 2006

Date of mailing of the international search report

19/07/2006

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Goetz, G

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2006/000395

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; MAKIN, S. M. ET AL: "Synthesis and study of .beta.-alkyl(aryl)aminoacroleins" XP002387863 retrieved from STN Database accession no. 76:13712 abstract & ZHURNAL ORGANICHESKOI KHIMII , 7(10), 2120-4 CODEN: ZORKAE; ISSN: 0514-7492, 1971,	1,2
Y	US 5 118 853 A (LEE ET AL) 2 June 1992 (1992-06-02) cited in the application example 6 claim 1	3-19
X	abstract	20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2006/000395

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 2808437	A	01-10-1957	NONE	
DE 948871	C	06-09-1956	NONE	
US 5118853	A	02-06-1992	NONE	