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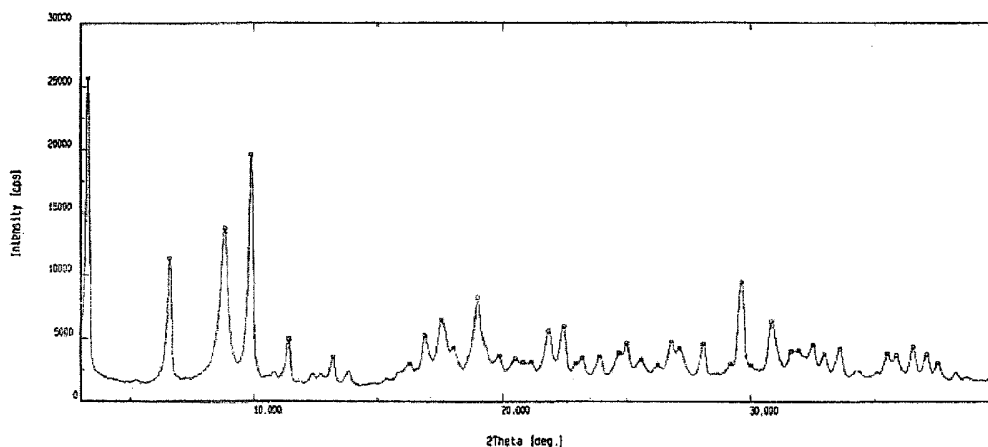
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(54) Title: PROCESS FOR PREPARATING ENANTIOMERICALLY PURE FLUVASTATIN SODIUM AND A NOVEL POLYMORPHIC FORM THEREOF



(57) Abstract: The present invention provides processes for preparing enantiomerically pure fluvastatin sodium. The present invention also provides pharmaceutical compositions comprising the enantiomerically pure fluvastatin sodium for antagonizing HMG-CoA. In addition the present invention provides a novel polymorphic form of enantiomerically pure fluvastatin sodium.

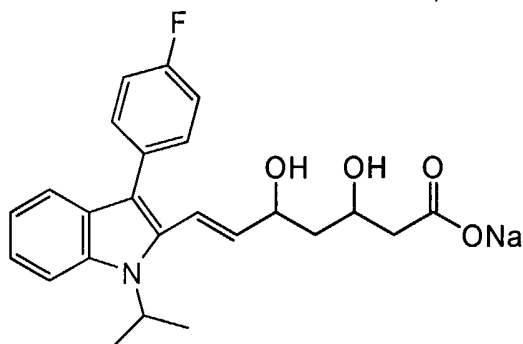
PROCESSES FOR PREPARING ENANTIOMERICALLY PURE FLUVASTATIN SODIUM AND A NOVEL POLYMORPHIC FORM THEREOF

Field of the Invention

5 Provided are processes for preparing enantiomerically pure fluvastatin sodium. Also provided are pharmaceutical compositions comprising enantiomerically pure fluvastatin sodium. In addition, provided is a novel polymorphic form of enantiomerically pure fluvastatin sodium.

Background of the Invention

10 Fluvastatin sodium is the monosodium salt of a racemic mixture 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 A.



FORMULA A

15 Fluvastatin sodium is a cholesterol lowering agent, which acts through the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. It 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
20 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.

A process for preparing racemic fluvastatin sodium, which involves lyophilization of an aqueous solution of fluvastatin sodium, has been reported. Also previously reported is a process for 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.

Processes of forming enantiomerically pure fluvastatin sodium have also been reported. Crystalline hydrates of enantiomerically enriched (3R,5S) or (3S,5R) of fluvastatin sodium referred to as Forms A, B1, B2, C, D and E have also been reported.

However, previously reported processes to prepare enantiomerically pure fluvastatin sodium involve purification through column chromatography, use of large quantity of solvents and toxic reagents which generate significant amount of toxic effluents and side-products. The yields obtained are low and the processes are not viable on commercial scale. Accordingly, there remains a need for novel forms of fluvastatin sodium, as well as improved processes of preparing enantiomerically pure fluvastatin sodium.

Brief Description of the Figures

Figure 1 is an XRD spectrum of Form I of the enantiomerically pure (3R,5S) enantiomer of fluvastatin sodium.

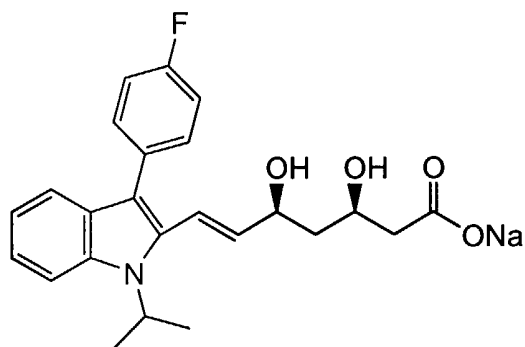
Figure 2 is an FTIR spectrum of Form I of the enantiomerically pure (3R,5S) enantiomer of fluvastatin sodium.

Summary of the Invention

Enantiomerically pure (3R,5S) *E*-fluvastatin sodium can now be prepared in excellent yields and in fewer steps by processes which do not utilize toxic reagents, as compared to previously known processes. The processes are easily scalable on commercial scale. Also provided is novel Form I of the enantiomerically pure (3R,5S) fluvastatin sodium.

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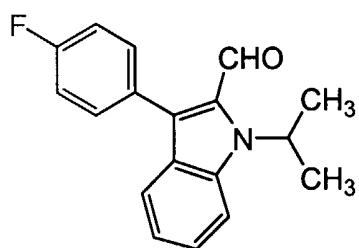
Thus in one aspect, provided are processes for preparing (3R,5S) enantiomer of fluvastatin sodium of Formula I,



FORMULA I

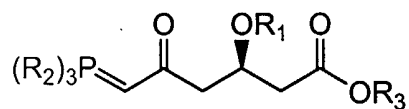
which comprises:

- 5 a) reacting an aldehyde of Formula Ia



FORMULA Ia

with a β -hydroxyester of Formula Ib,

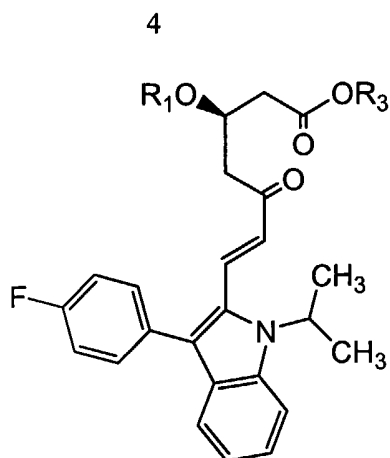


FORMULA Ib

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to form a compound of Formula Ic,

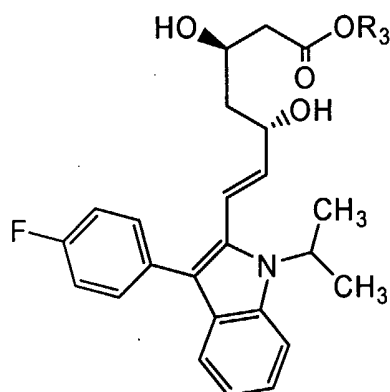
15



FORMULA Ic

wherein R_1 is hydrogen or a hydroxy protecting group, R_2 is aryl, aralkyl or alkyl and R_3 is hydrogen or C_{1-4} alkyl;

- b) (i) reducing the compound of Formula Ic, wherein R_1 is hydrogen and R_3 is hydrogen or C_{1-4} alkyl, to form a diol of Formula Id,

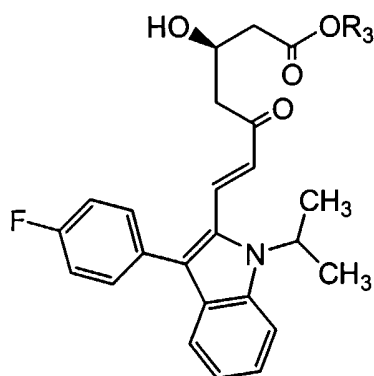


FORMULA Id

or

- (ii) deprotecting the compound of Formula Ic, wherein R_1 is a hydroxy protecting group and R_3 is hydrogen or C_{1-4} alkyl, to form a compound of Formula Ic'

5



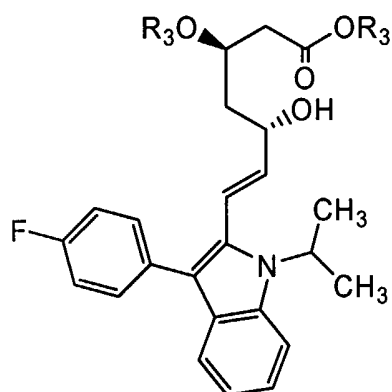
FORMULA Ic'

and reducing the compound of Formula Ic' to form a diol of Formula Id,

or

(iii) reducing the compound of Formula Ic, wherein R₁ is a hydroxy protecting group and R₃ is hydrogen or C₁₋₄ alkyl, to form a compound of Formula Ic''

5



FORMULA Ic''

and deprotecting the compound of Formula Ic'' to form a diol of Formula Id,

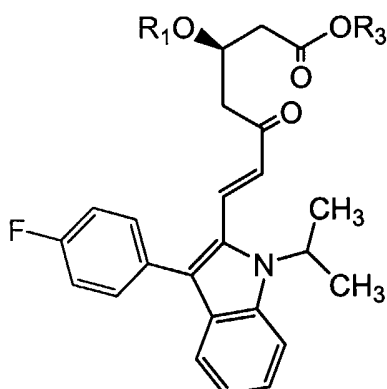
and

10

- c) converting the diol of Formula Id to enantiomerically pure (3R,5S) enantiomer of fluvastatin sodium of Formula I by contacting the diol of Formula Id with one or more sodium-containing compounds.

The processes can include one or more of the following embodiments. For example, the reduction of the compound of Formula Ic or the compound of Formula Ic' in step b)(i) or b)(iii) can be carried out in the presence of one or more reducing agent selected from one or more borohydride. Suitable borohydrides can be selected from sodium borohydride, potassium borohydride, calcium borohydride or mixtures thereof.

In another aspect, provided are compounds of Formula Ic,

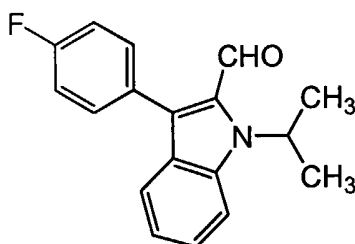


FORMULA Ic

wherein R₁ is hydrogen or a hydroxy protecting group and R₃ is hydrogen or C₁₋₄ alkyl group.

In yet another aspect, provided are processes for preparing compounds of Formula Ic or compounds of Formula Ic' comprising the steps of:

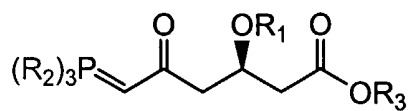
- a) reacting an aldehyde of Formula Ia



FORMULA Ia

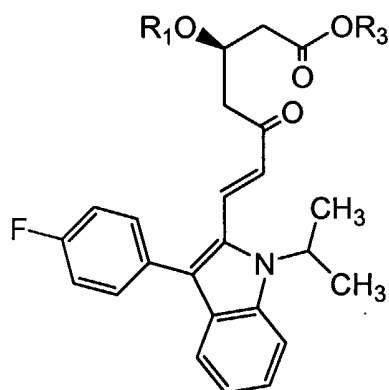
with a β -hydroxyester of Formula Ib

7



FORMULA Ib

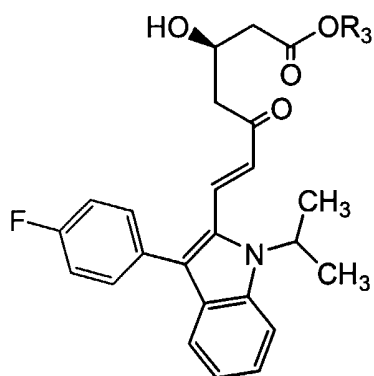
to form a condensation product of Formula Ic,



FORMULA Ic

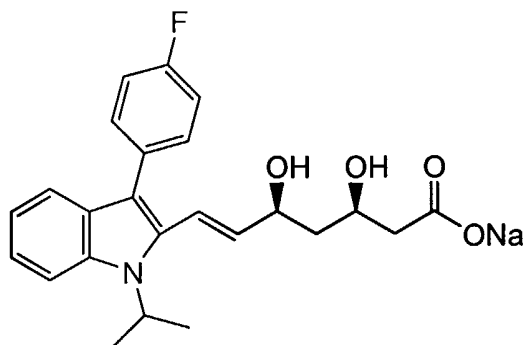
wherein R_1 is hydrogen or a hydroxy protecting group, R_2 is aryl, aralkyl or alkyl, and R_3 is hydrogen or C_{1-4} alkyl; and

- b) optionally deprotecting the compound of Formula Ic, wherein R_1 is a hydroxy protecting group, to form a compound of Formula Ic'.



FORMULA Ic'

2 In another aspect, provided are processes for preparing enantiomerically pure (3R,5S)-
3 fluvastatin sodium of Formula I,

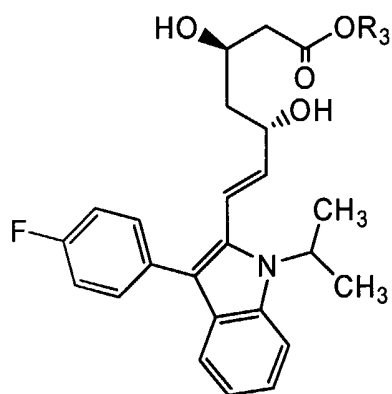


FORMULA I

4

5 comprising the steps of:

6 a) (i) reducing the compound of Formula Ic, wherein R_1 is hydrogen and R_3
7 is hydrogen or C_{1-4} alkyl, to form a diol of Formula Id,



FORMULA Id

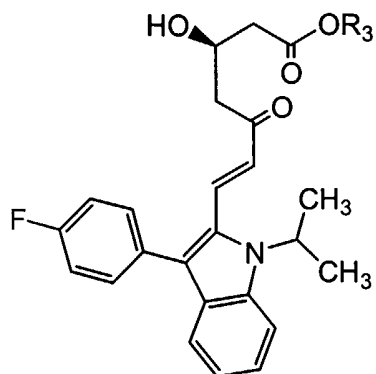
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9

or

10 (ii) deprotecting the compound of Formula Ic, wherein R_1 is a hydroxy
11 protecting group and R_3 is hydrogen or C_{1-4} alkyl, to form a compound of
12 Formula Ic'

9

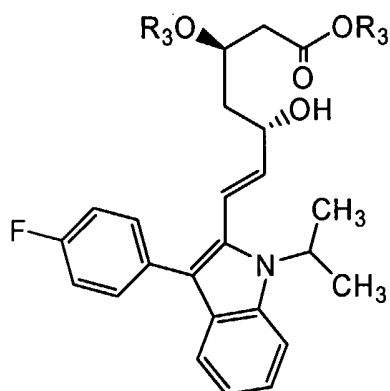


FORMULA Ic'

and reducing the compound of Formula Ic' to form a diol of Formula Id,

or

(iii) reducing the compound of Formula Ic, wherein R₁ is a hydroxy protecting group and R₃ is hydrogen or C₁₋₄ alkyl, to form a compound of Formula Ic''



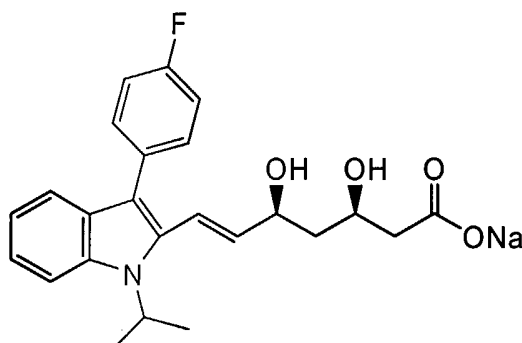
FORMULA Ic''

and deprotecting the compound of Formula Ic'' to form a diol of Formula Id,

and

b) converting the diol of Formula Id to enantiomerically pure (3R,5S) enantiomer of fluvastatin sodium of Formula I

10



FORMULA I

24

25 by contacting the diol of Formula Id with one or more sodium-containing compounds.

In another aspect, provided is Form I of enantiomerically pure (3R,5S) fluvastatin sodium. Form I of enantiomerically pure (3R,5S) fluvastatin sodium can include one or more of the following embodiments. For example, Form I of enantiomerically pure (3R,5S) fluvastatin sodium can exhibit an XRD spectrum having 2θ values at about: 6.6, 9.9, 11.4, and 30.9. Form I of enantiomerically pure (3R,5S) fluvastatin sodium can also exhibit an XRD pattern having 2θ values at about 3.3, 6.6, 8.8, 9.9, 11.4, 13.2, 19.0, 21.9, 29.6 and/or 30.9. Form I of enantiomerically pure (3R,5S) enantiomer of fluvastatin sodium can exhibit an FTIR spectrum as depicted in Figure 2. The Form I of enantiomerically pure (3R,5S) enantiomer of fluvastatin sodium can have a moisture content of below about 5 % w/w.

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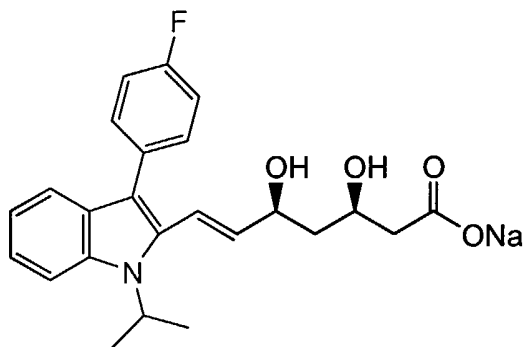
In another aspect, provided are pharmaceutical compositions comprising a therapeutically effective amount of Form I of enantiomerically pure (3R, 5S) fluvastatin sodium and optionally one or more pharmaceutically acceptable diluents or excipients.

In yet another aspect, provided are methods of antagonizing HMG-CoA in mammal, which comprises administering to the mammal a therapeutically effective amount of Form I of enantiomerically pure (3R,5S) fluvastatin sodium.

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Detailed Description of the Invention

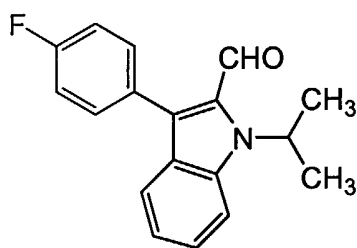
Processes for preparing (3R,5S) enantiomer of fluvastatin sodium of Formula I are provided.



FORMULA I

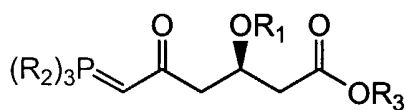
5 The process comprises the steps of:

- a) reacting an aldehyde of Formula Ia



FORMULA Ia

with a β -hydroxyester of Formula Ib,

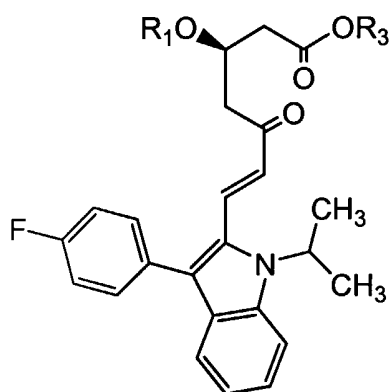


FORMULA Ib

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to form a compound of Formula Ic,

12

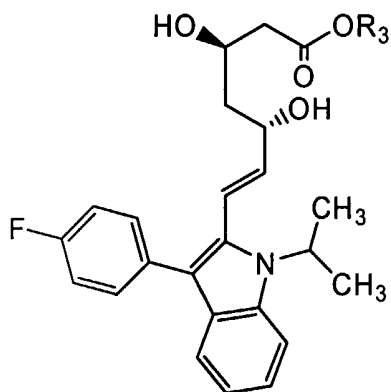


FORMULA Ic

wherein R_1 is hydrogen or a hydroxy protecting group, R_2 is aryl,
 aralkyl or alkyl and R_3 is hydrogen or C_{1-4} alkyl;

5

- b) (i) reducing the compound of Formula Ic, wherein R_1 is hydrogen and R_3 is hydrogen or C_{1-4} alkyl, to form a diol of Formula Id,



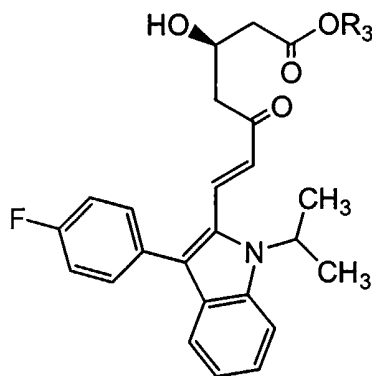
FORMULA Id

or

10

- (ii) deprotecting the compound of Formula Ic, wherein R_1 is a hydroxy protecting group and R_3 is hydrogen or C_{1-4} alkyl, to form a compound of Formula Ic'

13

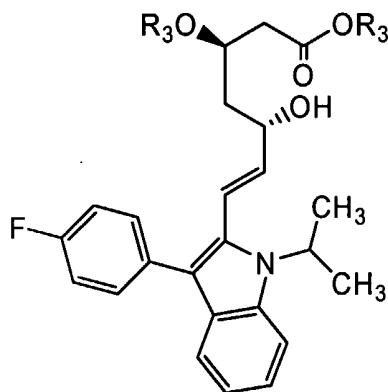


FORMULA Ic'

and reducing the compound of Formula Ic' to form a diol of Formula Id,

or

(iii) reducing the compound of Formula Ic, wherein R₁ is a hydroxy protecting group and R₃ is hydrogen or C₁₋₄ alkyl, to form a compound of Formula Ic''



FORMULA Ic''

and deprotecting the compound of Formula Ic'' to form a diol of Formula Id,

and

- 10 c) converting the diol of Formula Id to enantiomerically pure (3R,5S) enantiomer of fluvastatin sodium of Formula I by contacting the diol of Formula Id with one or more sodium-containing compounds.

The aldehyde of Formula Ia can be prepared by previously reported methods (for example, U.S. Patent Nos. 4,739,073 and 5,354,772). The aldehyde of Formula I can be condensed with a β -hydroxyester of Formula Ib (wherein R_1 can be hydrogen or a hydroxy protecting group, R_2 can be aryl, aralkyl or alkyl, and R_3 can be hydrogen or C_{1-4} alkyl) to form a compound of Formula Ic. The condensation reaction can be carried out in presence of one or more organic solvents, for example, polar aprotic solvents, aromatic hydrocarbon solvents, halogenated hydrocarbon solvents, acetonitrile, ethers or mixtures thereof. The reaction can be carried out at temperatures between about 40 °C to the reflux temperature of the one or more solvents used. After completion of the condensation reaction, the one or more solvents can be removed, and the product thus obtained can be contacted with one or more antisolvents, for example, cyclohexane, to yield a compound of Formula Ic, wherein R_1 and R_3 are as defined earlier.

In one embodiment, the compound of Formula Ic, wherein R_1 can be hydrogen and R_3 can be hydrogen or C_{1-4} alkyl, can be reduced to form a diol of Formula Id. In another embodiment, the compound of Formula Ic, wherein R_1 can be a hydroxy protecting group and R_3 can be hydrogen or C_{1-4} alkyl, can be deprotected to form a compound of Formula Ic' and the compound of Formula Ic' can then be reduced to form a diol of Formula Id. In yet another embodiment, the compound of Formula Ic, wherein R_1 can be a hydroxy protecting group and R_3 can be hydrogen or C_{1-4} alkyl, can be reduced to form a compound of Formula Ic'' and the compound of Formula Ic'' can then be deprotected to form a diol of Formula Id.

Compounds of Formula Ic or Formula Ic'', wherein R_1 is a hydroxy protecting group, can be deprotected by conventional processes (for example, by addition of one or more acids) to form compounds of Formula Ic' or compounds Formula Id respectively. When trialkylsilyl groups are used as protecting agents, acid hydrolysis of the product can be conveniently carried out in order to deprotect trialkylsilyl groups.

Compounds of Formula Ic (wherein R_1 is hydrogen) or Formula Ic' can be reduced using one or more trialkylboranes and optionally one or more metal borohydrides to form compounds of Formula Ic'' or compounds Formula Id respectively. Such reduction reactions

can also be carried out in presence of one or more organic solvents, for example, one or more C₃₋₆ ethers (*e.g.*, tetrahydrofuran, 1,4-dioxane, diethylether or mixture thereof), one or more C₁₋₄ alcohols (*e.g.*, methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, *tert*-butanol or mixtures thereof), or mixtures thereof. The reactions can also be carried out at low
5 temperatures, for example, from about -10 to about -80 °C. Suitable borohydrides include, for example, one or more of sodium borohydride, potassium borohydride, calcium borohydride, or mixtures thereof. Borohydride, if used in excess, can be quenched (using, for example one or more lower alcohols, *e.g.*, methanol, ethanol) after completion of the reduction reaction. The reaction mixture can then be basified and extracted with one or more suitable organic
10 solvents (*e.g.*, ethyl acetate, toluene, dichloromethane, dichloroethane, chloroform, hydrocarbons, including lower alkanes and cycloalkanes, such as cyclohexane). The organic layer can be dried and concentrated under vacuum to obtain a residue, which can be purified by crystallization or column chromatography to yield enantiomerically pure (3R,5S)-diol of Formula Id.

15 The (3R,5S)-diol of Formula Id can be contacted with one or more sodium-containing compounds, for example, sodium hydroxide, to form enantiomerically pure (3R,5S)-fluvastatin sodium of Formula I. This reaction can also be carried out in presence of one or more organic solvents and water. Suitable organic solvents include, for example, one or more C₁₋₄ alcohols (*e.g.*, methanol, ethanol, n-propanol, isobutanol, n-butanol, isobutanol, *tert*-
20 butanol or mixtures thereof).

Compounds of Formula Ic, wherein R₁ is hydrogen or a hydroxy protecting group and R₃ is hydrogen or C₁₋₄ alkyl group, are also provided.

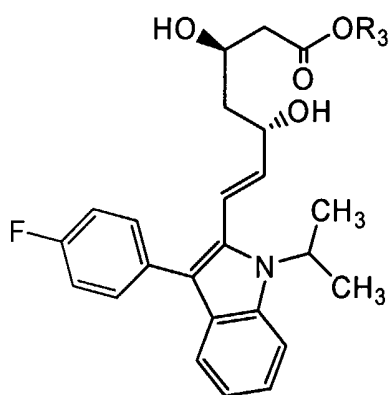
Also provided are processes for preparing compounds of Formula Ic or compounds of Formula Ic' comprising the steps of:

- 25 a) reacting an aldehyde of Formula Ia with a β -hydroxyester of Formula Ib to form a condensation product of Formula Ic,
wherein R₁ is hydrogen or a hydroxy protecting group, R₂ is aryl, aralkyl or alkyl, and R₃ is hydrogen or C₁₋₄ alkyl; and

- b) optionally deprotecting the compound of Formula Ic, wherein R_1 is a hydroxy protecting group, to form a compound of Formula Ic'.

In yet a further aspect, provided are processes for preparation of enantiomerically pure (3R,5S)-fluvastatin sodium comprising the steps of:

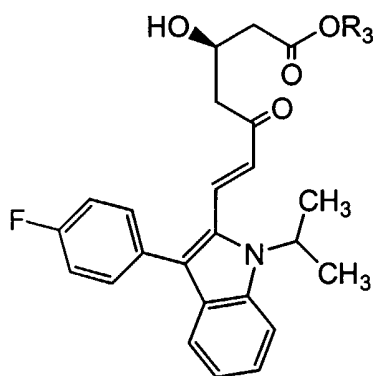
- 5 a) (i) reducing the compound of Formula Ic, wherein R_1 is hydrogen and R_3 is hydrogen or C_{1-4} alkyl, to form a diol of Formula Id,



FORMULA Id

or

- 10 (ii) deprotecting the compound of Formula Ic, wherein R_1 is a hydroxy protecting group and R_3 is hydrogen or C_{1-4} alkyl, to form a compound of Formula Ic'



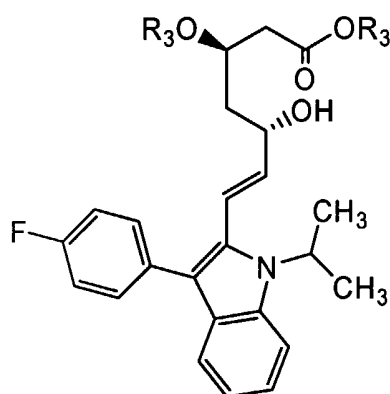
FORMULA Ic'

and reducing the compound of Formula Ic' to form a diol of Formula Id,

17

or

- (iii) reducing the compound of Formula Ic, wherein R_1 is a hydroxy protecting group and R_3 is hydrogen or C_{1-4} alkyl, to form a compound of Formula Ic''



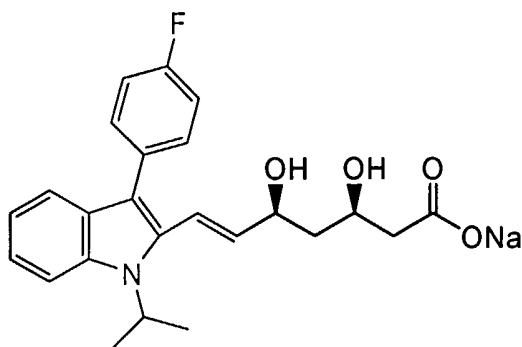
FORMULA Ic''

5

and deprotecting the compound of Formula Ic'' to form a diol of Formula Id,

and

- b) converting the diol of Formula Id to enantiomerically pure (3R,5S) enantiomer of fluvastatin sodium of Formula I



FORMULA I

10

by contacting the diol of Formula Id with one or more sodium-containing compounds.

In yet another aspect, Form I of enantiomerically pure (3R,5S) fluvastatin sodium is provided. Form I of enantiomerically pure (3R,5S) fluvastatin sodium can exhibit an XRD spectrum having one or more 2θ values at about: 6.6, 9.9, 11.4, and/or 30.9. Form I of enantiomerically pure (3R,5S) fluvastatin sodium can also exhibit an XRD spectrum having one or more 2θ values at about: 3.3, 6.6, 8.8, 9.9, 11.4, 13.2, 19.0, 21.9, 29.6 and/or 30.9. Form I of enantiomerically pure (3R,5S) fluvastatin sodium can also exhibit an XRD spectrum having one or more 2θ values at about: 3.3, 6.6, 8.8, 9.9, 11.4, 13.2, 16.3, 16.9, 17.6, 18.1, 19.0, 19.9, 20.5, 20.8, 21.2, 21.9, 22.5, 22.9, 23.2, 23.9, 24.7, 25.0, 25.6, 26.3, 26.8, 27.1, 28.1, 29.2, 29.6, 30.0, 30.9, 31.6, 32.0, 32.5, 33.0, 33.0, 35.5, 35.9, 36.5, 37.1 and/or 37.5. An example of an XRD spectrum of Form I of enantiomerically pure (3R,5S) fluvastatin sodium is depicted in Figure 1.

Form I of enantiomerically pure (3R,5S) fluvastatin sodium can also have a moisture content below about 5 % w/w. An example of an FTIR spectrum of Form I of enantiomerically pure (3R,5S) fluvastatin sodium is depicted in Figure 2.

In yet another aspect, pharmaceutical compositions comprising therapeutically effective amounts of Form I of enantiomerically pure (3R, 5S) fluvastatin sodium optionally containing one or more pharmaceutically acceptable diluents or excipients are provided.

In yet another aspect, methods of antagonizing HMG-CoA in mammal, which comprises administering to the mammal therapeutically effective amounts of Form I of enantiomerically pure (3R, 5S) fluvastatin sodium are also provided.

Powder XRD spectra of the samples can be determined by using a X-Ray Diffractometer manufactured by Rigaku Corporation, RU-H3R, Goniometer CN2155A3, X-Ray tube with Cu target anode, Divergence slits 1°, Receiving slit 0.15mm, Scatter slit 1°, Power: 40 KV, 100 mA, Scanning speed: 2 deg/min step: 0.02 deg, Wave length: 1.5406 Å.

FT-IR spectra of the samples can be determined by using a Perkin Elmer instrument, 16 PC, SCAN: 16scans, 4.0 cm^{-1} , according to the USP 25, general test methods page 1920, infrared absorption spectrum by potassium bromide pellet method.

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 are included within the scope of the present invention. The examples are provided to illustrate particular aspects of the disclosure and do not limit the scope of the present invention as

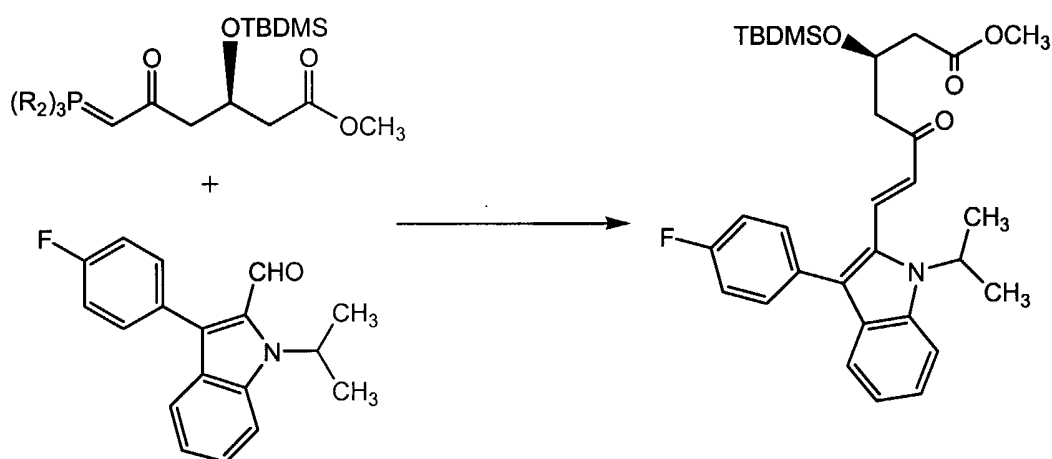
5 defined by the claims.

Examples

Example 1: Synthesis of Methyl (3S,6E)-7-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]3-[(*tert*-butyl-dimethylsilyl)oxy]-5-oxohept-6-enoate

The title compound is a compound of Formula Ic, wherein R₁ is *tert*-

10 butyldimethylsilyl and R₃ is methyl.



A mixture of 3-(4'-fluorophenyl)-1-isopropyl indole-2-carboxyaldehyde (1.0 g) and 1-methyl-(3R)-3-[(*tert*-butyl-dimethylsilyl)oxy]-5-oxo-6-triphenylphosphoranylidene-hexanate (3.0 g) in acetonitrile (60 mL) was refluxed at 81 to 83 °C for 48 hours, cooled to room temperature and concentrated under vacuum (40-100 mmHg) at 40 to 45 °C to yield a crude oil. The crude oil was suspended in cyclohexane (30 mL) and concentrated, forming a residue. The residue was suspended in cyclohexane (30 mL) and stirred for 1 hour. The solids thus obtained were filtered, washed with cyclohexane (20 mL) and the combined

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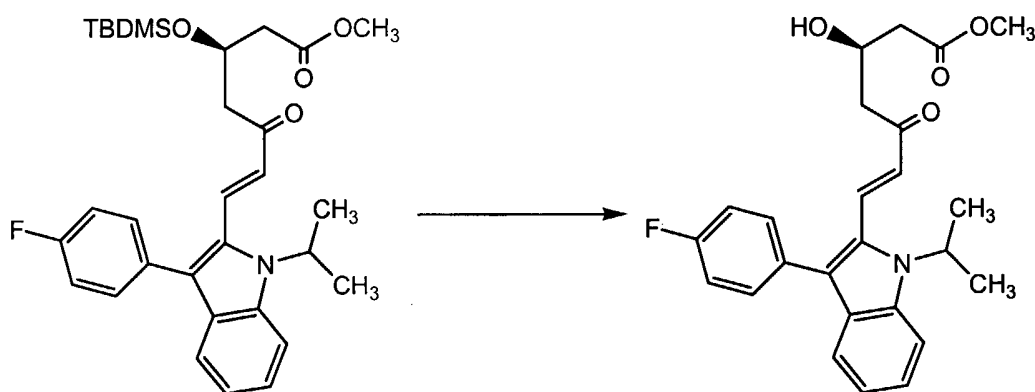
20 filtrate and washings were concentrated to yield the title compound as an oil.

Yield: 1.53 g.

^{13}C NMR (δ , CDCl_3): 199.94, 172.11, 163.1, 140.12, 131.88, 123.45, 64.58, 51.432, 25.98, 20.77, 18.52. ^1H NMR (δ , CDCl_3): 0.07 [$(\text{CH}_3)_2\text{Si}$, 6H, s], 0.90 [$(\text{CH}_3)_3\text{C}$ -, 9H, s], 1.74 to 1.77 [$(\text{CH}_3)_2\text{C}$ -, 6H, two singlets], 2.60 [$-\text{CH}_2-$, 2H, m], 2.82 [$-\text{CH}_2-$, 2H, m], 3.61 (OCH_3 , 3H, s), 4.6 [$-\text{CH}(\text{CH}_2)_2-$, 1H, m], 4.72 to 5.0 [$-\text{CH}(\text{CH}_3)_2$, 1H, m], 6.37 to 6.47 [$-\text{CH}=\text{CH}-\text{CO}-$, 1H, dd], 7.76 to 7.73 [$-\text{CH}=\text{CH}-\text{CO}-$, 1H, dd], 7.58 to 7.20 [ArH , 8 H, m]. MS m/z : $[\text{M}+1]^+$ 538.6, 421, 279. For $\text{C}_{31}\text{H}_{40}\text{FNO}_4\text{Si}$, Found: C 69.32; H 7.47; F 3.47; N 2.67; O 11.52; Si 5.55

10 Example 2: Synthesis of Methyl (3S,6E)-7-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]3-hydroxy-5-oxohept-6-enoate

The title compound is a compound of Formula Ic', wherein R_3 is methyl.



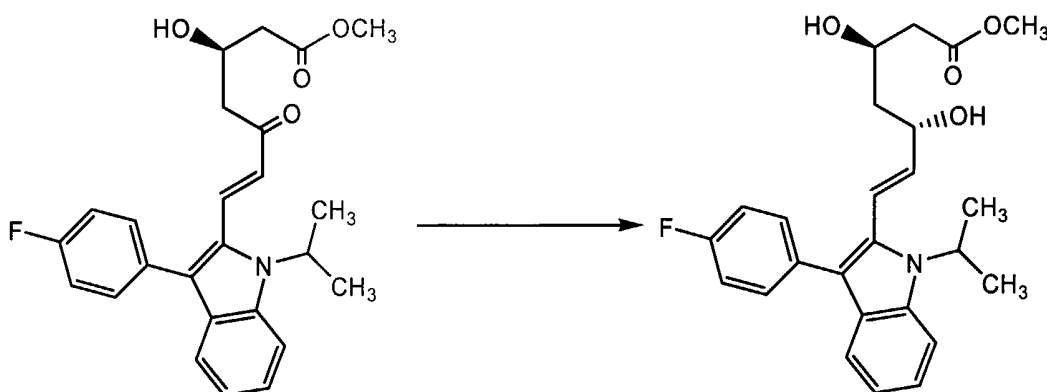
15 A solution of methanesulphonic acid (0.25 mL) in water (5.0 mL) was added to (3S,6E)-7-[3-(4-fluorophenyl)-1-isopropyl-1H-indol-2-yl]3-[(*tert*-butyl-dimethylsilyl) oxy]-5-oxohept-6-enoate (2.0 g) in methanol (30 mL) at 15 °C. The reaction mixture was stirred for 6 hours at 30 to 35°C and concentrated under vacuum. The residue thus obtained was extracted with dichloromethane (100 mL), and washed with water (50 mL) and then with aqueous sodium bicarbonate (1% w/v; 30 mL). The solution was concentrated under vacuum to yield the title compound as thick oil.

20 Yield: 1.5 g.

¹³ CNMR (δ , CDCl₃): 200.76, 172.23, 165.33, 141.38, 131.78, 126.19, 123.6, 121.53, 64.35, 51.58, 48.27, 20.72. ¹HNMR (δ , CDCl₃): 1.63 to 1.67 [(CH₃)₂C-, 6H, two singlets], 2.55 to 2.67 (CH₂, 2H, m), 2.82 to 2.95 [-CH₂-, 2H, m], 3.72 (OCH₃, 3H, s), 4.12 [-CHOH-, 1H, m], 4.67 [-CH(CH₃)₂, 1H, m], 5.65 [-OH, 1H, broad] 6.51 to 6.55 [-CH=CH-CO-, 1H, dd], 7.76 to 7.73 [-CH=CH-CO-, 1H, dd], 7.58 to 7.20 [ArH, 8H, m]. MS m/z: [M+1]⁺ 424. For C₂₅H₂₆FNO₄, Found: C 70.95; H 6.24; F 4.52; N 3.27; O 15.02

Example 3: Synthesis of Methyl (3*R*,5*S*)-7-[3-(4-fluorophenyl)-1-isopropyl-1*H*-indol-2-yl]-3,5-dihydroxyheptanoate

The title compound is a compound of Formula Id, wherein R₃ is methyl.



10

To a solution of methyl (3*S*,6*E*)-7-[3-(4-fluorophenyl)-1-isopropyl-1*H*-indol-2-yl]-3-hydroxy-5-oxohept-6-enoate (1.5 g) in anhydrous tetrahydrofuran (20 mL) and (6 mL) of methanol, was added a solution of diethylmethoxyborane (2 mL, 1M in tetrahydrofuran) at -78°C, and the mixture was stirred at the same temperature for 30 minutes. To the mixture was added sodium borohydride (0.5 g) and the mixture was stirred for another 3 hours. Acetic acid (2.5 mL) was added thereto, and the mixture was adjusted to pH 8 with saturated sodium bicarbonate and extracted with ethyl acetate. The organic layer was washed with water, dried and evaporated ethyl acetate under reduced pressure. To the resulting residue, methanol was added and the mixture was evaporated under reduced pressure. The resulting residue was subjected to column chromatography of silica gel eluting with methylene

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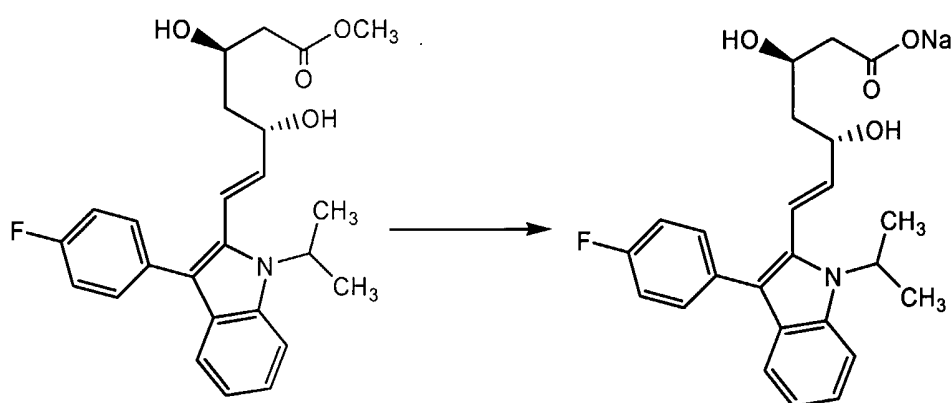
chloride/ ether (3:1) to give (1.5 g) of title compound as oil which was finally purified by column chromatography, to give a yield of 1.2 g.

IR (KBr) (cm^{-1}): 3468, 3458, 3391, 1707, 1535, 1258, 1216, 1118. ^{13}C NMR (δ , CDCl_3): 173.7, 164.8, 140.7, 136.6, 134.9, 120.4, 116.4, 115.6, 112.8, 71.4, 52.1, 48.27, 43.3, 21.9.

- 5 ^1H NMR (δ , CDCl_3): 1.53 to 1.61 [$(\text{CH}_3)_2\text{C}$ -, 6H, two singlets], 1.95 to 2.01 (CH_2 -, 2H, m), 2.45 to 2.61 [$-\text{CH}_2$ -, 2H, m], 3.60 (OCH_3 , 3H, s), 4.27 [$-\text{CH}(\text{OH})\text{C}(\text{H})=\text{C}(\text{H})$ -, 1H, m], 4.33 [$-\text{CH}_2\text{CH}(\text{OH})\text{CH}_2$ -, 1H, m], 4.7 [$-\text{CH}(\text{CH}_3)_2$, 1H, m], 5.8 [$-\text{CH}=\text{CH}-\text{CHOH}$ -, 1H, dd], 6.89 [$-\text{CH}=\text{CH}-\text{CHOH}$ -, 1H, dd], 7.38 to 7.57 [ArH , 8 H, m]. MS m/z : $[\text{M}+1]^+$ 426. For $\text{C}_{25}\text{H}_{28}\text{F}_4\text{NO}$, Found: C 70.66; H 66.56; O 15.03; N 32.98; F 4.45.

10 Example 4: Synthesis of sodium (3*R*,5*S*)-7-[3-(4-fluorophenyl)-1-isopropyl-1*H*-indol-2-yl]-3,5-dihydroxyheptanoate

The title compound is a compound of Formula I.



- 15 Aqueous sodium hydroxide (6 mL, 0.25N) was added to a solution of methyl (3*R*,5*S*)-7-[3-(4-fluorophenyl)-1-isopropyl-1*H*-indol-2-yl]-3,5-dihydroxyheptanoate (0.60 g) in methanol (20 mL) at room temperature and stirred for 2 hours. The solution was concentrated to remove the organic solvent under vacuum at 35 to 40 °C, forming a residue. Water (20 mL) was added to the residue and the mixture was stirred. The aqueous layer was washed
- 20 with ethyl acetate (2 x 50 mL) and filtered through a celite bed. The aqueous layer was then concentrated under vacuum at 40 °C to yield title compound as a white solid.
- Yield: 0.4 g.

Moisture content: below 5 % w/w.

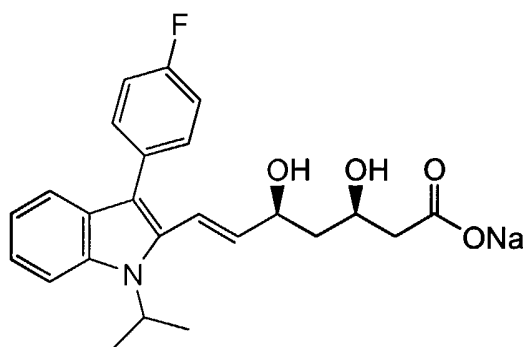
IR (KBr) (cm⁻¹): 3407, 1573, 1346, 1216, 1107. ¹³CNMR (δ, CD₃OD): 180.6, 166.43, 141.0, 136.6, 129.8, 122.7, 120.6, 119.98, 71.8, 68.5, 48.5, 44.8, 24.3, 22.0. ¹HNMR (δ, CD₃OD):
1.53 to 1.59 [(CH₃)₂C-, 6H, two singlets], 1.97 to 2.12 (CH₂, 2H, m), 2.34 to 2.55 [-CH₂-, 2H,
5 m], 2.35 [OH, 1H, broad], 3.09 [OH, 1H, broad], 4.34 [-CHOHC(H)=C(H)-, 1H, m], 4.23 [-
CH₂CHOHCH₂-, 1H, m], 4.68 [-CH(CH₃)₂-, 1H, m], 6.34 [-CH=CH-CHOH-, 1H, dd], 6.76 [-
CH=CH-CHOH-, 1H, dd], 7.28 to 7.59 [ArH, 8H, m]. MS m/z: [M⁺-Na] 412.1, [M - H₂O]
394.2. For C₂₄H₂₅O₄FN, Found: C 66.57; H 5.9; O 14.7; N 32.24; F.

XRD spectrum as per Figure 1

10 FTIR spectrum as per Figure 2.

We Claim:

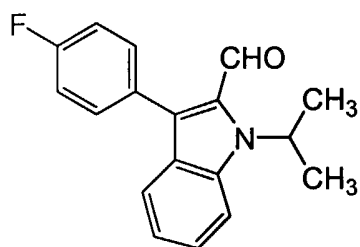
- 1 1. A process for preparing (3R,5S) enantiomer of fluvastatin sodium of Formula I,



FORMULA I

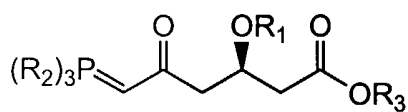
2 which comprises:

- 3 a) reacting an aldehyde of Formula Ia



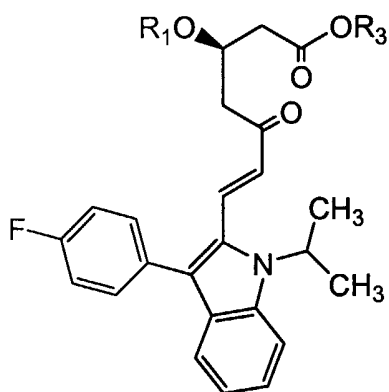
FORMULA Ia

4 with a β -hydroxyester of Formula Ib,



FORMULA Ib

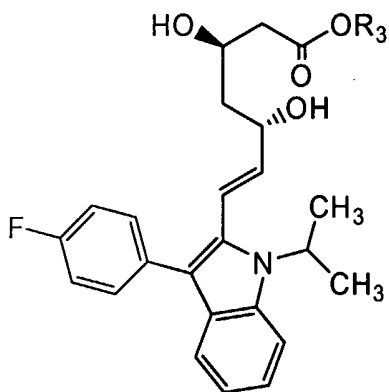
5 to form a compound of Formula Ic,



FORMULA Ic

wherein R_1 is hydrogen or a hydroxy protecting group, R_2 is aryl, aralkyl or alkyl and R_3 is hydrogen or C_{1-4} alkyl;

- b) (i) reducing the compound of Formula Ic, wherein R_1 is hydrogen and R_3 is hydrogen or C_{1-4} alkyl, to form a diol of Formula Id,

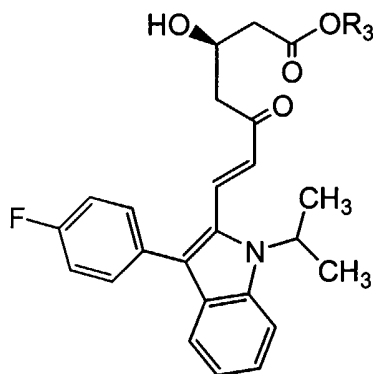


FORMULA Id

or

- (iv) deprotecting the compound of Formula Ic, wherein R_1 is a hydroxy protecting group and R_3 is hydrogen or C_{1-4} alkyl, to form a compound of Formula Ic'

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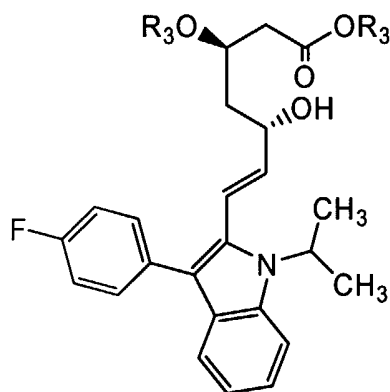


FORMULA Ic'

and reducing the compound of Formula Ic' to form a diol of Formula Id,

or

(v) reducing the compound of Formula Ic, wherein R₁ is a hydroxy protecting group and R₃ is hydrogen or C₁₋₄ alkyl, to form a compound of Formula Ic''



FORMULA Ic''

and deprotecting the compound of Formula Ic'' to form a diol of Formula Id,

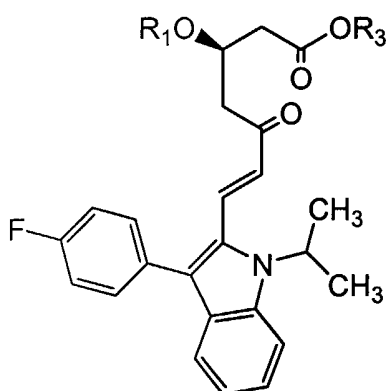
and

c) converting the diol of Formula Id to enantiomerically pure (3R,5S) enantiomer of fluvastatin sodium of Formula I by contacting the diol of Formula Id with one or more sodium-containing compounds.

1 2. The process of claim 1, wherein the reduction of the compound of Formula Ic or the
 2 compound of Formula Ic' in step b)(i) or b)(iii) is carried out in the presence of one or more
 3 reducing agent selected from one or more borohydrides.

1 3. The process of claim 2, wherein the one or more borohydride is selected from sodium
 2 borohydride, potassium borohydride, calcium borohydride or mixtures thereof.

1 4. A compound of Formula Ic,

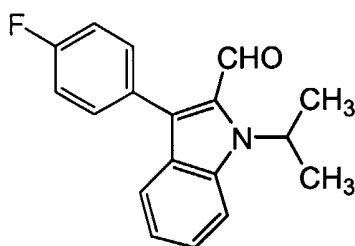


2 FORMULA Ic

3 wherein R₁ is hydrogen or a hydroxy protecting group and R₃ is hydrogen or C₁₋₄ alkyl group.

1 5. A process for preparation of a compound of Formula Ic or a compound of Formula Ic'
 2 comprising the steps of:

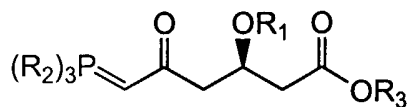
3 a) reacting an aldehyde of Formula Ia



4 FORMULA Ia

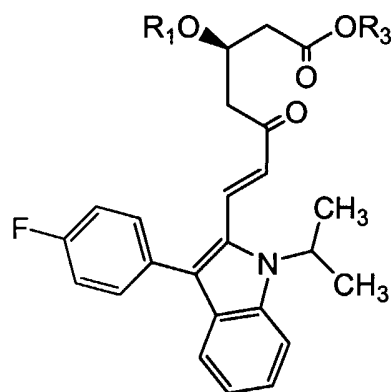
5 with a β -hydroxyester of Formula Ib

28



FORMULA Ib

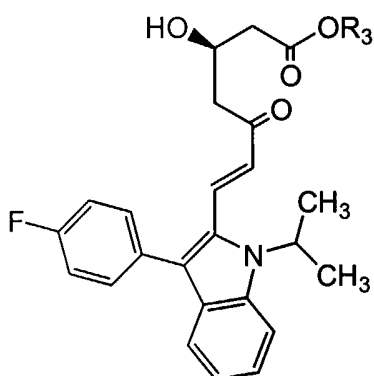
to form a condensation product of Formula Ic,



FORMULA Ic

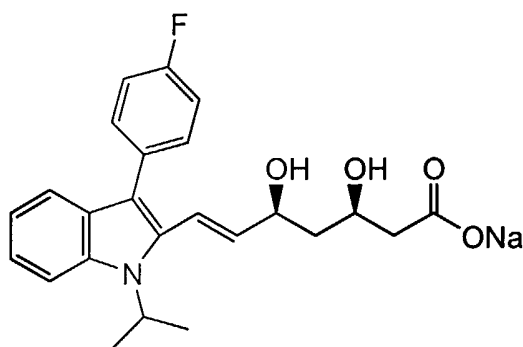
wherein R₁ is hydrogen or a hydroxy protecting group, R₂ is aryl, aralkyl or alkyl, and R₃ is hydrogen or C₁₋₄ alkyl; and

- b) optionally deprotecting the compound of Formula Ic, wherein R₁ is a hydroxy protecting group, to form a compound of Formula Ic'.



FORMULA Ic'

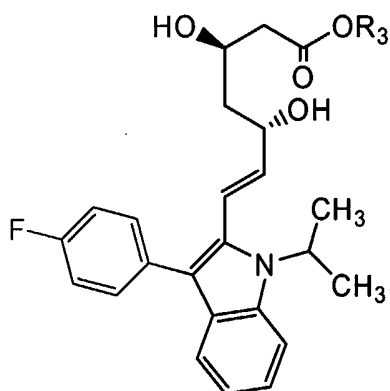
- 1 6. A process for preparation of the enantiomerically pure (3R,5S)-fluvastatin sodium of
2 Formula I,



FORMULA I

- 3
4 comprising the steps of:

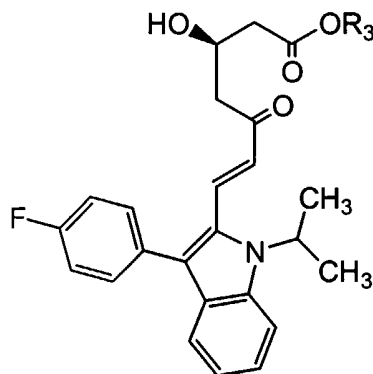
- 5 a) (i) reducing the compound of Formula Ic, wherein R_1 is hydrogen and R_3
6 is hydrogen or C_{1-4} alkyl, to form a diol of Formula Id,



FORMULA Id

- 7
8 or
9 (iii) deprotecting the compound of Formula Ic, wherein R_1 is a hydroxy
10 protecting group and R_3 is hydrogen or C_{1-4} alkyl, to form a compound of
11 Formula Ic'

30

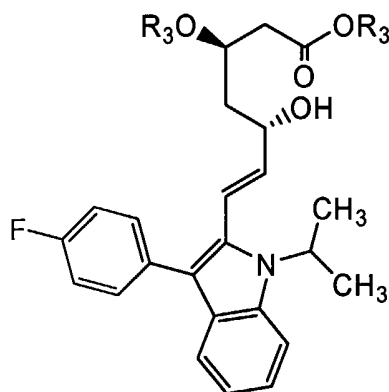


FORMULA Ic'

and reducing the compound of Formula Ic' to form a diol of Formula Id,

or

(iii) reducing the compound of Formula Ic, wherein R₁ is a hydroxy protecting group and R₃ is hydrogen or C₁₋₄ alkyl, to form a compound of Formula Ic''

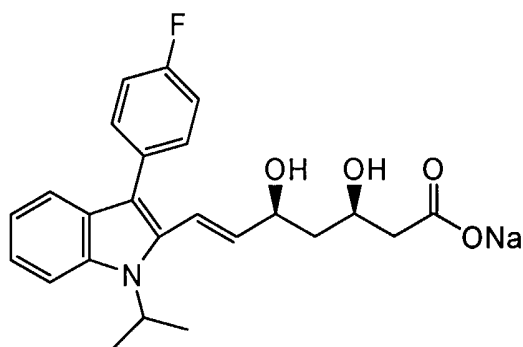


FORMULA Ic''

and deprotecting the compound of Formula Ic'' to form a diol of Formula Id,

and

b) converting the diol of Formula Id to enantiomerically pure (3R,5S) enantiomer of fluvastatin sodium of Formula I



FORMULA I

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24 by contacting the diol of Formula Id with one or more sodium-containing compounds.

1 7. Form I of enantiomerically pure (3R,5S) fluvastatin sodium.

1 8. The Form I of enantiomerically pure (3R,5S) fluvastatin sodium of claim 7 exhibiting
2 an XRD spectrum having 2θ values at about: 6.6, 9.9, 11.4, and 30.9.

1 9. The Form I of enantiomerically pure (3R,5S) enantiomer of fluvastatin sodium of
2 claim 7 exhibiting FTIR spectrum as depicted in Figure 2.

1 10. The Form I of enantiomerically pure (3R,5S) enantiomer of fluvastatin sodium of
2 claim 7 having a moisture content of below about 5 % w/w.

1 11. Form I of enantiomerically pure (3R,5S) fluvastatin sodium of claim 7 exhibiting an
2 XRD pattern having 2θ values at about 3.3, 6.6, 8.8, 9.9, 11.4, 13.2, 19.0, 21.9, 29.6 and/or
3 30.9.

1 12. A pharmaceutical composition comprising a therapeutically effective amount of Form
2 I of enantiomerically pure (3R, 5S) fluvastatin sodium and optionally one or more
3 pharmaceutically acceptable diluents or excipients.

13. A method of antagonizing HMG-CoA in mammal, which comprises administering to
5 the mammal a therapeutically effective amount of Form I of enantiomerically pure (3R,5S)
fluvastatin sodium.

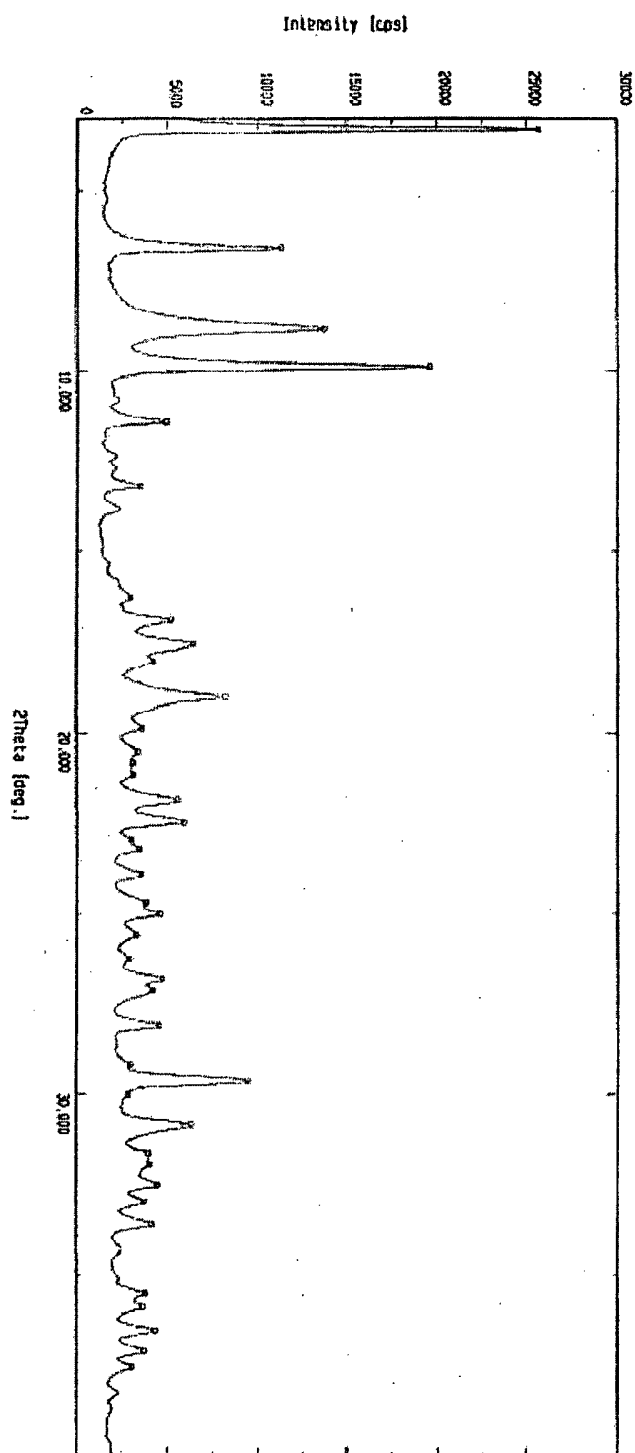


FIGURE 1

