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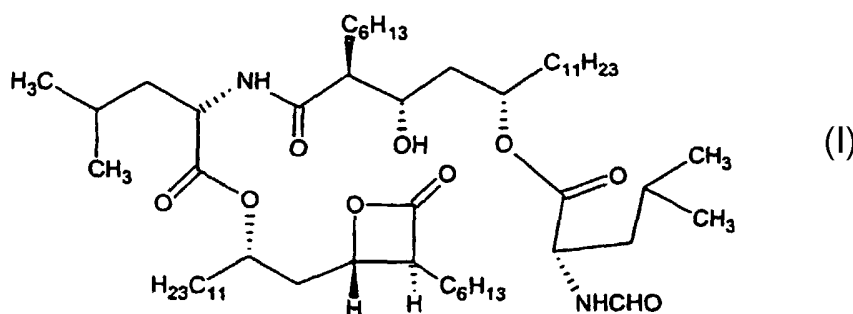
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(54) Title: PROCESS FOR THE PREPARATION OF AN ORLISTAT DERIVATIVE USEFUL AS REFERENCE STANDARD
IN THE DETERMINATION OF THE PURITY OF ORLISTAT AND PROCESS FOR THE PREPARATION OF ORLISTAT



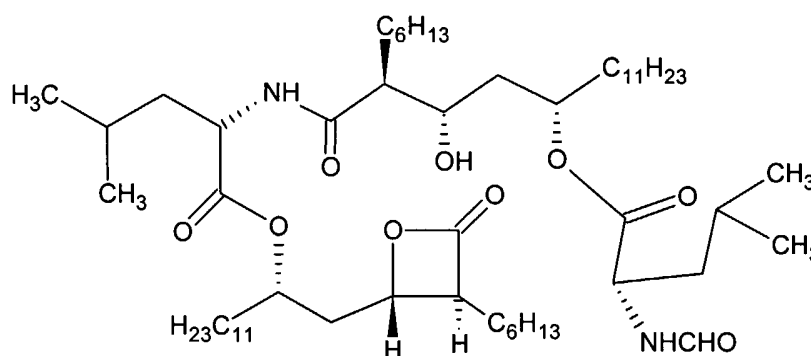
(57) Abstract: The invention relates to a leucine derivative, N-2[(S)-2-N-formylamino-4-methyl pentanoic acid (S)-1-[[3(S)-hy-
droxy-5-oxo-4-hexyl methyl]dodecyl ester] amino-4-methyl pentanoic acid (S)-1-[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl]methyl do-
decyl ester of Formula (I), and process for isolating it. More particularly, it relates to the preparation of pure orlistat, which is
(S)-2-Formylamino-4-methyl pentanoic acid (S)-1-[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl ester. The invention also re-
lates to the use of the Compound of Formula (I) as reference standard or reference marker for checking the purity of orlistat.

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PROCESS FOR THE PREPARATION OF AN ORLISTAT DERIVATIVE USEFUL AS REFERENCE STANDARD IN THE DETERMINATION OF THE PURITY OF ORLISTAT AND PROCESS FOR THE PREPARATION OF ORLISTAT

Field of the Invention

The field of the invention relates to a leucine derivative, 2-N-[(S)-2-N-formylamino-4-methyl pentanoic acid (S)-1-[[3(S)-hydroxy-5-oxo-4-hexyl methyl]dodecyl ester]amino-4-methyl pentanoic acid (S)-1-[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl]methyl] dodecyl ester of Formula I,



Formula I

and process for producing it. More particularly, it relates to the preparation of pure orlistat and pharmaceutical compositions that include the pure orlistat.

The invention also relates to use of pure orlistat or dodecyl ester as reference standards or reference markers for checking the purity of orlistat.

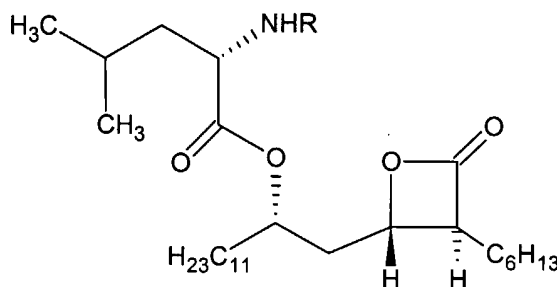
Background of the Invention

Orlistat, a tetrahydrolipstatin is a useful pancreatic lipase-inhibiting agent and can be used for the prevention and treatment of obesity and hyperlipaemia. Chemically, orlistat is (S)-2-Formylamino-4-methyl pentanoic acid (S)-1-[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl]methyl] dodecyl ester and is known from U.S. Patent No. 4,598,089.

Several processes have been reported for the preparation of orlistat for example, in U.S. Patent Nos. 4,202,824; 4,983,746; *J. Org. Chem.* 1988, 53, 1218; *Tetrahedron Lett.* 1990, 31, 3645; *Synlett*, 1991, 11, 781; *J. Org. Chem.* 1991, 56, 4714; 1993, 58, 7768; and *J. Chem. Soc., Perkin Trans. 1*, 1998, 17, 2679.

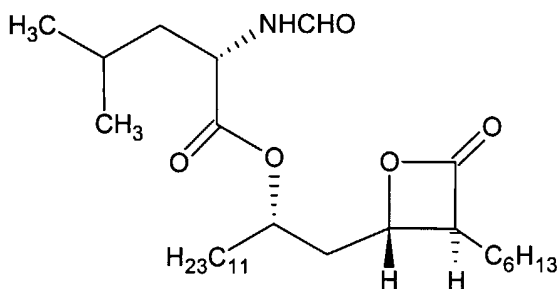
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U.S. Patent No. 4,983,746; *J. Chem. Soc., Perkin Trans. 1*, 1998, 17, 2679; and *J. Org. Chem.* 1991, 56, 4714 disclose the preparation of orlistat by deprotection of compound of Formula II,



Formula II

- 5 wherein R is benzyloxycarbonyl. The process includes hydrogenating the compound of Formula II with palladium black using tetrahydrofuran as a solvent followed by the addition of formic acetic anhydride to obtain orlistat of Formula III.



Formula III

- 10 In order to secure marketing approval for a new drug product, a drug manufacturer must submit detailed evidence to the appropriate regulatory authorities to show that the product is suitable for release on to the market. The regulatory authorities must be satisfied, inter alia that the active agent is acceptable for administration to humans and that the particular formulation, which is to be marketed, is free from impurities at the time of release and has an appropriate shelf-life.

- 15 Submissions made to regulatory authorities therefore typically include analytical records, which demonstrate:

- (a) that impurities are absent from the drug at the time of manufacture, or are present only at negligible level, and

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(b) that the storage stability i.e. shelf-life of the drug is acceptable.

These details are usually obtained by testing the drug against an external standard, or reference marker, which is a pure sample of a potential impurity or a potential degradation product. Dodecyl ester has a possibility of being used as a reference marker
5 compound in identifying the purity of the orlistat. There is no reference of this impurity in the literature.

Summary of the Invention

In one general aspect there is provided a substantially pure compound of formula I, which is chemically N-2[(S)-2-N-formylamino-4-methyl pentanoic acid (S)-1-[[3(S)-
10 hydroxy-5-oxo-4-hexyl methyl]dodecyl ester]amino-4-methyl pentanoic acid (S)-1-[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl]methyl] dodecyl ester (hereinafter referred to as dodecyl ester).

In another general aspect there is provided use of dodecyl ester as a reference standard for determination of the purity of orlistat.

15 In another general aspect there is provided a process for the isolation of dodecyl ester.

In another aspect there is provided a process for preparing pure orlistat. The process includes deprotecting the compound of Formula II, wherein R is an amino protecting group, in the presence of methylene dichloride; adding formic acetic anhydride;
20 and recovering the pure orlistat. It has been observed by the inventors that the solvent used in the deprotection reaction has a great impact on the purity of orlistat obtained. Different solvents used in the deprotection reaction results in different amounts of compound of Formula I, as an impurity and therefore different purity of orlistat. It has been observed that the use of methylene dichloride as a solvent in the deprotection reaction minimizes the
25 formation of the impurity of Formula I and thus results in better purity of orlistat.

The process may include further drying of the product obtained.

The process may produce pure orlistat having less than 0.15% dodecyl ester. In particular, it may produce pure orlistat having less than 0.05% dodecyl ester.

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In another general aspect there is provided pure orlistat containing less than 0.15% dodecyl ester.

In another general aspect there is provided pure orlistat having less than 0.05% dodecyl ester.

5 In another aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of pure orlistat having less than 0.15% dodecyl ester; and one or more pharmaceutically acceptable, carriers, excipients or diluents.

In another aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of pure orlistat having less than 0.05% dodecyl ester; and
10 one or more pharmaceutically acceptable, carriers, excipients or diluents.

In another aspect there is provided a method of preventing and treating obesity and hyperlipaemia using therapeutically effective amount of pure orlistat having less than 0.15% dodecyl ester.

In another aspect there is provided a method of preventing and treating obesity and
15 hyperlipaemia using therapeutically effective amount of pure orlistat having less than 0.05% dodecyl ester.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects and advantages of the invention will be apparent from the description and claims.

20 Detailed Description of the Invention

The inventors have identified that the dodecyl ester is formed as an impurity during the synthesis of orlistat. The inventors have isolated dodecyl ester, which can be used as a reference standard for determination of the purity of orlistat.

The process involves:

- 25 a) stirring a mixture of crude orlistat in one or more solvents;
b) adding water and separating orlistat enriched with dodecyl ester;

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- c) subjecting the orlistat enriched with dodecyl ester to preparative HPLC and eluting with a gradient mobile phase to get eluent containing dodecyl ester; and
- d) isolating the substantially pure dodecyl ester from the eluent.

5 The term “substantially pure” herein refers to dodecyl ester having a purity of at least 92% by HPLC.

 The crude orlistat may contain from about 20% to about 25 % of the dodecyl ester. The mixture of crude orlistat and suitable solvent may be stirred by sonication for about 1 to 5 minutes. The suitable solvent here represents any inert solvent, which does not react
10 under reaction conditions. The addition of water may be carried out till haziness appears and may be allowed to settle at the bottom. The above step may be repeated twice or thrice for enrichment of dodecyl ester. The enriched material may be loaded on to 8 μ HS silica (250 x 21.1 mm) column. Mobile phase used may be a gradient of isopropyl alcohol and hexane. The fractions containing the dodecyl ester may be further combined and
15 concentrated to dryness. The substantially pure dodecyl ester can then be further purified by crystallization or column chromatography.

 The inventors also have developed a process for preparing pure orlistat by deprotecting the compound of Formula II, wherein R is an amino protecting group, in the presence of methylene dichloride; adding formic acetic anhydride; and recovering the pure
20 orlistat.

 The orlistat may be recovered by a technique which includes, for example, distillation, distillation under vacuum, cooling, evaporation, filtration, filtration under vacuum, decantation and centrifugation.

 The orlistat thus recovered may be further purified or additionally purified, by
25 employing commonly practiced recrystallization techniques using solvent / antisolvent mixture to obtain pure orlistat.

 The inventors also developed pharmaceutical compositions that contain the pure orlistat having less than 0.15% dodecyl ester, for example, less than 0.05% dodecyl ester, in admixture with one or more solid or liquid pharmaceutical diluents, carriers and/or

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excipients. These pharmaceutical compositions may be used for preventing and treating obesity and hyperlipaemia.

The compound of formula II can be obtained by methods known in the art including methods described in U.S. Patent No. 4,983,746; *J. Chem. Soc. Perkin. Trans. I*, 1998, 17, 2679; and *J. Org.Chem.* 1991, 56, 4714, which are incorporated herein by reference.

Examples of amino protecting group include alkyl, alkoxy, aralkyl, alkoxyalkyl, trialkylsilyl, benzyloxy, benzyloxycarbonyl, p-nitrobenzyloxycarbonyl, t-butoxycarbonyl, 9-fluorenylmethoxycarbonyl, alkyl-aminocarbonyloxy, phthalimides and sulfonamides.

Examples of alkyl groups include methyl, ethyl, n-propyl, isopropyl, and tert-butyl groups. Examples of aralkyl include benzyl or substituted benzyl. Examples of substituted benzyl include p-nitro benzyl, p-methoxy benzyl, o-nitro benzyl, p-bromo benzyl or 2,4,6-trimethyl benzyl groups. Examples of alkoxy include methoxy and ethoxy, isopropoxy, and tert-butoxy. Examples of alkoxyalkyl include methoxymethyl, ethoxycarbonyl, isopropoxycarbonyl, and tert-butoxycarbonyl. Examples of trialkylsilyl include trimethylsilyl and tert-butyldimethylsilyl groups. Examples of alkyl-amino carbonyloxy include methyl aminocarbonyloxy and dimethyl aminocarbonyloxy.

When the protecting group is benzyl, benzyloxy, benzyloxycarbonyl, p-nitrobenzyloxycarbonyl or t-butoxycarbonyl, the deprotection may be carried out by hydrogenation in the presence of a catalyst. The hydrogenation catalysts are the customary hydrogenation catalysts known in organic chemistry, such as transition metal compounds. Examples of transition metal compounds include palladium compounds such as palladium/carbon and palladium hydroxide, platinum compounds such as platinum oxide and platinum/carbon, ruthenium compounds such as ruthenium oxide, rhodium compounds such as rhodium/carbon and nickel compounds such as Raney nickel.

The hydrogenation reaction may be carried out at normal pressure, or at elevated pressure depending on the choice of a catalyst. In general, it may be carried out at a hydrogen pressure in the range from about 1 kg/cm² to about 10 kg/cm², for example at a hydrogen pressure in the range from about 2 kg/cm² to about 4 kg/cm².

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The hydrogenation temperature may be varied depending on the choice of a catalyst and/or pressure employed. For example, the hydrogenation may be carried out at a temperature range from about -20°C to about 120°C, or at a temperature range from about 0°C to about 80°C. In particular, it may be carried out at a temperature range from about
5 10°C to about 35°C.

When the protecting group is 9- fluorenylmethoxycarbony, it may be deprotected by a base catalyzed reaction. Examples of base include ammonia, piperidine, morpholine and 1,8- diazacyclo [5.4.0] undec-7-ene (DBU). When the protecting group is silyl-protecting groups, it may be removed by treatment with fluoride.

10 Other protecting groups may be removed by hydrolysis. The hydrolysis is a reaction in which the protecting group is removed in the presence of water and acid or a base (alkali). Accordingly, hydrolysis may be acid or alkali hydrolysis.

Alkali hydrolysis may be carried out in the presence of organic and inorganic bases. Examples of organic base include trimethylamine, triethylamine, tributylamine, triisopropylamine, diisopropylethylamine, 1,8-diazabicyclo- [5.4.0]-undec-7-ene (DBU),
15 1,5-diazabicyclo-[4.3.0]-non-5-ene (DBN), 4-dimethylamino pyridine, morpholine, thiomorpholine, piperidine, pyrrolidine and mixtures thereof. Examples of inorganic base include alkali metal carbonate, bicarbonate, hydroxide and mixtures thereof. Examples of alkali metal carbonate include lithium carbonate, sodium carbonate and potassium
20 carbonate. Examples of alkali metal bicarbonate include sodium bicarbonate and potassium bicarbonate. Examples of alkali metal hydroxide include sodium hydroxide and potassium hydroxide.

Acid hydrolysis may be carried out in the presence of an acid. Examples of acid include hydrochloric acid, hydrobromic acid, sulfuric acid and nitric acid.

25 The addition of formic acetic anhydride may be carried out in the presence of a suitable solvent. Suitable solvents are inert organic solvents, which do not react under the reaction conditions. Examples of such solvents include chlorinated hydrocarbons such as methylene chloride, ethylene dichloride and carbon tetrachloride; alcohols such as methanol, ethanol, isopropanol and butanol; ketones such as acetone and methyl isobutyl
30 ketone; esters such as ethylacetate and isopropylacetate; nitriles such as acetonitrile and

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benzonitrile; dipolar aprotic solvents such as dimethylsulfoxide and dimethylformamide; alkyl ethers such as diethylether, diisopropylether and dimethoxyethane; cyclic ethers such as dioxane and tetrahydrofuran, and mixtures thereof.

5 The addition of formic acetic anhydride may be performed at temperatures of from about -20°C to about 20°C for 30 minutes to 2 hours. The addition may be carried out at about -10°C to about -5°C for 30 minutes to 40 minutes. In particular, the reaction may be carried out at about -20°C to about 20°C for 30 minutes to 4 hours. The reaction mixture may be stirred at about 0°C to about -5°C for 1 to 2 hours in some particular embodiments.

10 Formic acetic anhydride may be prepared by adding acetic anhydride to formic acid.

The pure orlistat may have purity of more than 99% having less than 0.15% by HPLC of compound of Formula I.

15 The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

Example-1: Synthesis of (S)-2-Formylamino-4-methyl pentanoic acid (S)-1-[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl]methyl] dodecyl ester (Orlistat)

10 10 % palladium on charcoal (1.0 g) was added to a solution of N-(benzyloxycarbonyl)-L-leucine(1S)-1-[[[(2S,3S)-3-hexyl-4-oxo-2-oxetanyl]methyl]dodecyl ester (cbz-orlistat) (50 g; 83.19 mmol) in methylene dichloride (200 ml). The reaction mixture was stirred at 25-30°C for 90 minutes under hydrogen pressure of about 2.5 - 3 Kg. 10 % Palladium on charcoal (0.25 g) was again added to the reaction mixture and the reaction mixture was stirred for another 3 to 4 hours till cbz-orlistat is not more than 0.8 %. The reaction was
25 monitored by high performance liquid chromatography. After the completion of reaction, the catalyst was filtered and washed with methylene dichloride (100 ml).

The filtrate obtained from above was added to methylene dichloride (200 ml), which was cooled at -10°C. To this reaction mixture, freshly prepared acetic formic anhydride (28.02 g; 269.4 mmol) was added slowly at -10 to -5°C within 30 to 40
30 minutes. The reaction mixture was stirred at 0 to -5°C for 60 to 120 minutes. After the

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completion of reaction, it was quenched in distilled water (500 ml) at 20 to 25°C. The aqueous layer was extracted with methylene dichloride (50 ml). The combined organic layers were washed with aqueous sodium bicarbonate solution (5% solution) twice (200 ml each) and distilled water (250 ml each). Activated carbon (1 g) was then added to the methylene dichloride layer and stirred for 30 minutes. The reaction mixture was filtered through hyflow bed and the bed was washed with methylene dichloride (50 ml). The solvent was recovered completely under reduced pressure at 25 to 30°C. To the oily residue, hexane (25 ml) was added and degassed completely under reduced pressure at 30 to 35°C. The reaction mass was cooled at 20 to 25°C and the product was crystallized from hexane (350 ml). The solid obtained was filtered and recrystallized twice from hexane (350 ml each) at 0 to 5°C to get pure orlistat.

HPLC Purity: 99.55%

Dodecyl ester: 0.00%

Example-2: Synthesis of formic acetic anhydride

Acetic anhydride (27.5 g) was added to formic acid (50 g) and the mixture was stirred at 45 to 50°C till acetic anhydride content was not more than 5%.

Example-3: Synthesis of N-2[(S)-2-N-formylamino-4-methyl pentanoic acid (S)-1-[[3(S)-hydroxy-5-oxo-4-hexyl methyl]dodecyl ester]amino-4-methyl pentanoic acid (S)-1-[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl]methyl] dodecyl ester

The mixture of crude orlistat (5g, dodecyl ester: 23%) and acetonitrile (5ml) was sonicated for 2 minutes. Further, 0.5 ml water was added to the mixture and shaken, as the haziness appeared, it was allowed to settle. An oily mass appeared at the bottom, which was separated by pipette. The sample (dodecyl ester: 40 to 45%) so obtained was subjected to the above step twice for enrichment of dodecyl ester to about 65 to 70%. The sample obtained was loaded on 8 μ HS silica (250 x 21.1 mm) column. Mobile phase used was gradient of hexane and isopropyl alcohol in 98:2 ratios. The fractions containing the dodecyl ester were combined and concentrated to dryness.

HPLC Purity: 92.72%

Weight: 600mg

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The spectral data of the isolated dodecyl ester are as follows:

¹H-NMR (300 MHz) in CDCl₃: 8.207 (s, 1H, -NH-CHO); 6.30 (d, 1H, -NH); 6.07 (d, 1H, -NH); 5.07-5.11 (m, 1H, -C4''-H) 5.01 (m, 1H, -C2'H); 4.70 (ddd, 1H, -C3'-H); 4.69 (ddd, 1H, -C5''-H); 4.30 (m, 1H, -C4-H); 3.70 (m, 3H, -C2''-H & OH); 3.21 (ddd, 1H, -C3-H); 2.17 (ddd, 1H, -C1'-H_AH_B, -C3''-H & -C1''-H); 2.12 (ddd, 1H, -C1'-H_AH_B & -C3''-H); 1.77-1.25 (m, 64H, -(CH₂)₁₅); 0.98-0.93 (m, 12H, -(CH₃)₂C); 0.88-0.85 (distorted t, 12H, 2 x CH₃)

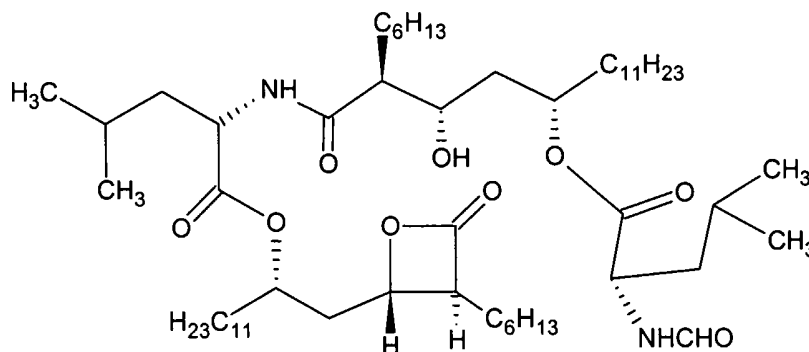
IR (Perkin Elmer, Spectrum-one) in CCl₄: 3317 (NH & OH stretching); 2924 (CHO stretching); 1823 (β-lactone ring (COO) stretching); 1738 (NHCHO (CONH stretching); 1657 (COO stretching).

Mass: 963.8 (M)

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 intended to be included within the scope of the present invention.

We claim:

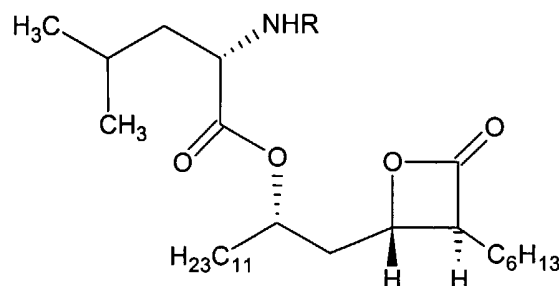
- 1 1. Substantially pure N-2 [(S)-2-N-Formylamino-4-methyl pentanoic acid (S)-1-
2 [[3(S)-hydroxy-5-oxo-4-hexyl methyl] dodecyl ester] amino-4-methyl pentanoic
3 acid (S)-1-[(2S, 3S)-3-hexyl-4-oxo-2-oxetanyl] methyl] dodecyl ester of Formula I,



Formula I

- 1 2. A method of determining purity of orlistat or a pharmaceutical composition
2 containing the orlistat, comprising use of dodecyl ester of Formula I as a reference
3 standard compound.
- 1 3. A process for the preparation of substantially pure dodecyl ester, the process
2 comprising:
 - 3 a) stirring a mixture of crude orlistat in one or more solvents;
 - 4 b) adding water and separating orlistat enriched with dodecyl ester;
 - 5 c) subjecting the orlistat enriched with dodecyl ester to preparative HPLC and
6 eluting with a gradient mobile phase to get eluent containing dodecyl ester;
7 and
 - 8 d) isolating the substantially pure dodecyl ester from the eluent.
- 1 4. The process of claim 3, wherein the enriched orlistat is loaded on 8 μ HS silica
2 (250 x 21.1 mm) column.
- 1 5. The process of claim 3, wherein the mobile phase used is gradient of isopropyl
2 alcohol and hexane.
- 1 6. A process for the preparation of pure orlistat, the process comprising:

a) deprotecting the compound of Formula II,



Formula II

wherein R is an amino protecting group, in the presence of methylene dichloride;

b) adding formic acetic anhydride; and

c) recovering the pure orlistat.

7. The process of claim 6, wherein the amino protecting group comprises one or more of alkyl, alkoxy, aralkyl, alkoxyalkyl, trialkylsilyl, benzyloxy, benzyloxy carbonyl, p-nitrobenzyloxycarbonyl, t-Butoxycarbonyl, 9-fluorenylmethoxycarbonyl, alkyl-aminocarbonyloxy, phthalimides, and sulfonamides.

8. The process of claim 6, wherein the deprotection is carried out by hydrogenation in the presence of a catalyst.

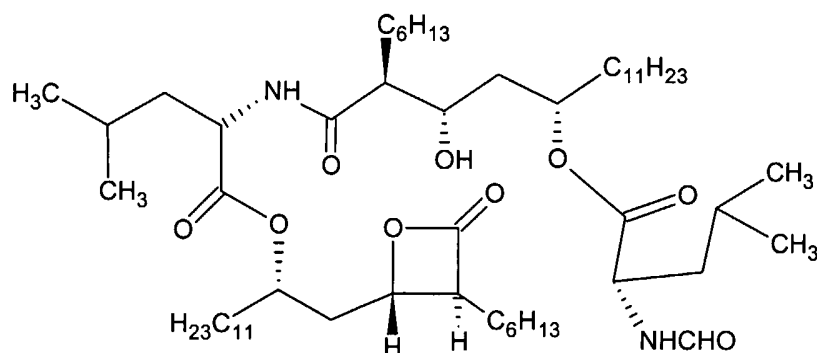
9. The process of claim 8, wherein the hydrogenation catalyst is a transition metal compound.

10. The process of claim 9, wherein the transition metal compound comprises one or more of palladium compounds, platinum compounds, ruthenium compounds, rhodium compounds and nickel compounds.

11. The process of claim 6, wherein the hydrogenation reaction is carried out at about 1 kg/cm² to about 10 kg/cm².

12. The process of claim 6, wherein the deprotection is carried out by acid or base hydrolysis.

- 1 13. The process of claim 12, wherein the acid hydrolysis is carried out in the presence
2 of a mineral acid comprising one or more of hydrochloric acid, hydrobromic acid,
3 sulfuric acid, nitric acid and mixtures thereof.
- 1 14. The process of claim 12, wherein the base hydrolysis is carried out in the presence
2 of organic or inorganic base.
- 1 15. The process of claim 14, wherein the organic base comprises one or more of
2 trimethylamine, triethylamine, tributylamine, triisopropylamine,
3 diisopropylethylamine, 1,8-diazabicyclo- [5.4.0]-undec-7-ene (DBU), 1,5-
4 diazabicyclo-[4.3.0]-non-5-ene (DBN), 4-dimethylamino pyridine, morpholine,
5 thiomorpholine, piperidine, pyrrolidine, and mixtures thereof.
- 1 16. The process of claim 14, wherein the inorganic base comprises one or more of
2 alkali metal carbonates, bicarbonates, hydroxides, and mixtures thereof.
- 1 17. The process of claim 6, wherein the addition of formic acetic anhydride is carried
2 out in the presence of a suitable solvent.
- 1 18.. The process of claim 17, wherein the suitable solvent comprises one or more of
2 chlorinated hydrocarbons, alcohols, ketones, esters, nitriles, dipolar aprotic
3 solvents, alkyl ethers, cyclic ethers, and mixtures thereof.
- 1 19. The process of claim 6, wherein the recovering comprises one or more of
2 distillation, distillation under vacuum, evaporation, cooling, filtration, filtration
3 under vacuum, decantation, and centrifugation.
- 1 20. Pure orlistat having less than 0.15% by HPLC of dodecyl ester of Formula I.



Formula I

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- 1 21. Pure orlistat of claim 20 having less than 0.05% of dodecyl ester by HPLC.
- 1 22. A pharmaceutical composition comprising a therapeutically effective amount of
2 pure orlistat having less than 0.15% of dodecyl ester; and one or more
3 pharmaceutically acceptable, carriers, excipients or diluents.
- 1 23. A method of preventing and treating obesity and hyperlipaemia, the method
2 comprising providing a dosage form that includes a therapeutically effective amount
3 of pure orlistat having less than 0.15% of dodecyl ester.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/IB2005/002864

A. CLASSIFICATION OF SUBJECT MATTER
C07D305/12 A61K31/365 A61P3/04

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)
C07D A61K A61P

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, WPI Data, PAJ, BIOSIS, BEILSTEIN Data, 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.
A	US 4 931 463 A (BARBIER ET AL) 5 June 1990 (1990-06-05) column 20; example 2.8 -----	1-5
P,X	WO 2005/005403 A (RANBAXY LABORATORIES LIMITED; KUMAR, YATENDRA; PRASAD, MOHAN; DEO, KES) 20 January 2005 (2005-01-20) in particular relevant page 11, line 31 page 11, line 29 - page 12, line 12; claims 25,26,33; examples 6,7 ----- -/--	6-11, 17-19

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

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

1 December 2005

Date of mailing of the international search report

02/01/2006

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/IB2005/002864

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	I.FLEMING, N.J. LAWRENCE: "Stereocontrol in organic synthesis using silicon-containing compounds. A synthesis of (-)-tetrahydrolipstatin using the alkylation of a beta-silyl ester and the hydroboration of an allylsilane" J. CHEM. SOC. PERKIN TRANS. 1, 1998, pages 2679-2686, XP002355692 cited in the application page 2686, column 1, line 9 - line 42	6-16
X	the whole document	6,17-21
Y	CHADHA ET AL: "Synthesis of tetrahydrolipstatin" J. ORG. CHEM., vol. 56, 1991, pages 4714-4718, XP002355693 cited in the application page 4718, column 2, line 28 - line 43; figure V; compound 4	6-16
X	the whole document	6,17-21
X	US 2002/035089 A1 (BARBIER PIERRE ET AL) 21 March 2002 (2002-03-21) the whole document	22,23
Y	T.W. GREENE, P. WUTS: "Protective groups in organic synthesis" 1991, WILEY&SONS, NEW YORK, XP002355761 page 315 - page 348	6-16

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2005/002864

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 23 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PC1/1B2005/002864

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