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(54) **Title:** PROCESS FOR THE PREPARATION OF AZETIDINONES

(57) **Abstract:** A process for preparing an azetidinone such as ezetimibe of formula (I) is disclosed using an alcohol of formula (III) as starting material.

PROCESS FOR THE PREPARATION OF AZETIDINONES

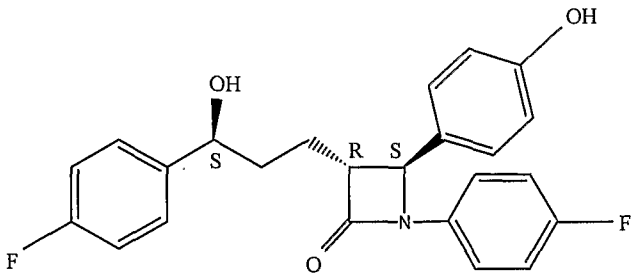
BACKGROUND OF THE INVENTION

1. Technical Field

[0001] The present invention generally relates to an improved process for the preparation of azetidinones.

2. Description of the Related Art

[0002] The present invention relates to a process for the preparation of azetidinones such as ezetimibe (also known as 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone) of Formula I:



(I)

[0003] Ezetimibe is sold under the commercial name Zetia®. Ezetimibe is a lipid-lowering compound in the class of azetidinones that selectively inhibits the intestinal absorption of cholesterol and related phytosterols. Ezetimibe acts by diminishing the absorption of dietary cholesterol through the intestines by getting localized in the brush border of small intestinal endocytes and blocks the uptake of cholesterol. Ezetimibe is ordinarily used as an adjunctive therapy to a diet for the reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), and apolipoprotein B (Apo B) in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.

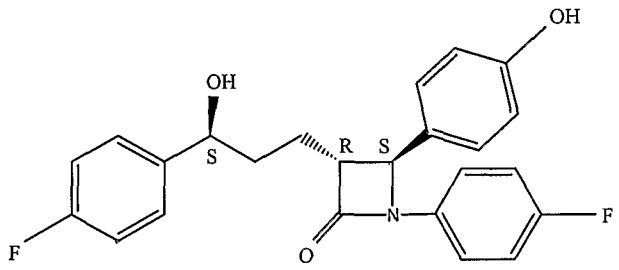
[0004] U.S. Patent No. 5,631,365 ("the '365 patent") discloses a process for preparing ezetimibe. In the '365 patent, the process for preparing ezetimibe includes: (1) treating a lactone with a strong base in an anhydrous organic solvent; (2) reacting the product of (1) with an imine; (3) quenching the reaction with an acid; and (4) removing any necessary protecting groups.

[0005] Several drawbacks are associated with the processes of the prior art. These drawbacks include using pyrophoric bases, such as n-butyl lithium and a metalamide, e.g., LDA, and low temperatures, e.g., below -50°C, which lead to difficulties when trying to prepare ezetimibe on a commercial scale. Further, butyl lithium is a hazardous, corrosive reagent which limits its usefulness.

[0006] Accordingly, there remains a need for improved processes for preparing ezetimibe that eliminates and reduces the drawbacks of the prior art in a convenient and cost efficient manner on a commercial scale.

SUMMARY OF THE INVENTION

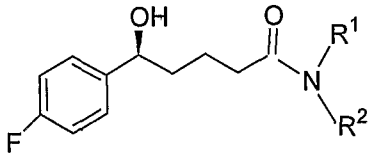
[0007] In one embodiment of the present invention, a process for preparing a compound of formula I is provided:



(I),

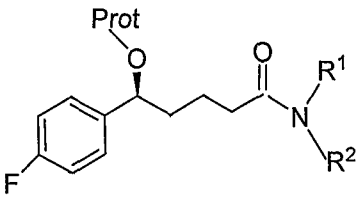
the process comprising

(a) reacting an alcohol of formula III:



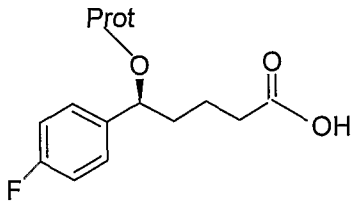
(III)

wherein R^1 and R^2 are as described herein, with a protecting group to provide a protected amide of formula IV:



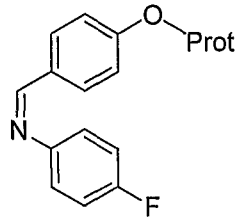
(IV);

(b) hydrolyzing the protected amide of step (a) with a strong base to provide a protected carboxylic acid of formula V:



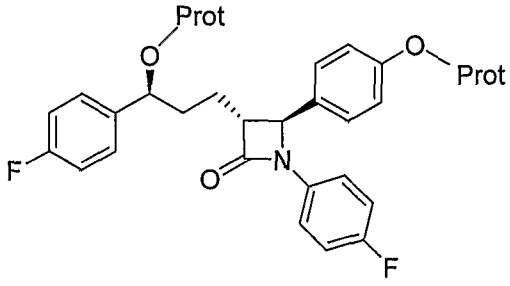
(V);

(c) reacting an organic halide with the protected carboxylic acid of step (b) and an imine of formula VI:



(VI);

wherein Prot is a protecting group to provide an azetidinone of formula VII

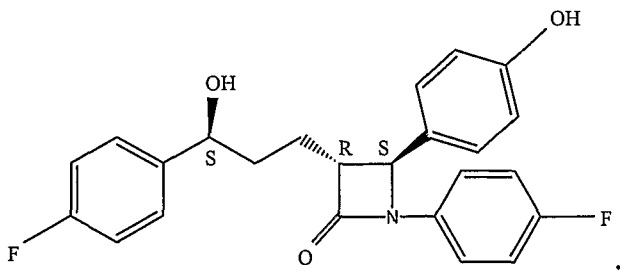


(VII); and

(d) removing the protecting groups.

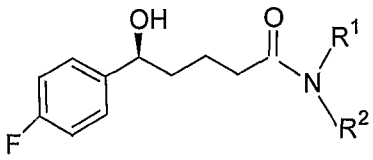
DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0008] The present invention is directed to a process for preparing a compound of formula I:



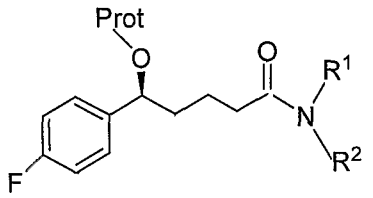
.

[0009] In step (a) of the process of the present invention, an alcohol of formula III:



(III)

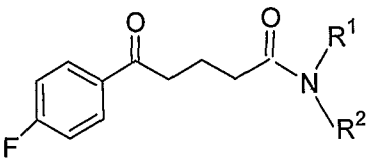
is reacted with a protecting group to provide a protected amide of the formula IV:



(IV)

R^1 and R^2 can independently be hydrogen, hydrocarbons of from 1 to 20 carbon atoms or R^1 and R^2 together with the nitrogen atom to which they are bonded are joined together to form a substituted or unsubstituted heterocyclic group optionally containing one or more additional heterocyclic atoms. Preferably, only one of R^1 and R^2 are hydrogen. Representative examples of R^1 and R^2 are independently methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, cyclohexyl, heptyl, octyl, 2-ethylhexyl, nonyl, decyl, dodecyl, stearyl, oleyl, phenyl, benzyl, and the like, containing, e.g., up to about 20 carbon atoms, preferably no more than about 18 carbon atoms and more preferably no more than about 12 carbon atoms. Representative groups in the case where R^1 and R^2 together with the nitrogen atom to which they are bonded are joined together to form a heterocyclic compound include substituted or unsubstituted cyclic amines such as pyrrolidines, piperidines, piperazines, morpholines, and the like. R^1 and R^2 can also independently be alkyl groups substituted with one or more heterocyclic substituents.

[0010] Representative of the starting alcohols of formula III are known in the art. See, e.g., U.S. Patent No. 6,207,822. In general, the starting alcohol can be prepared by first amidating p-fluorobenzoyl butyric acid with an amine of the formula HNR^1R^2 wherein R^1 and R^2 have the aforestated meanings optionally in the presence of a suitable solvent to provide a keto amide of formula II:



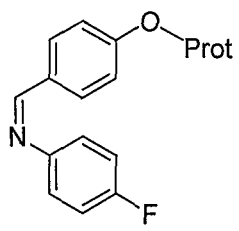
(II).

Examples of suitable amines include, but are not limited to, pyrrolidines such as 2-(2-aminoethyl)-1-methylpyrrolidine, 1-(2-aminoethyl)pyrrolidine, and the like; morpholines such as 4-(2-aminoethyl)-morpholine and the like; piperidines such as 1-(2-aminoethyl)-piperidine, 4-dimethyl-amino pyridine and the like; piperazines such as 1-(2-aminoethyl)piperazine, and the like and mixtures thereof. Other useful amines are (aminoalkyl)alkylamines such as N-alkylethylene diamines, N-alkyl-1,3-propane diamines, and the like. Suitable solvents include, but are not limited to, C_1 to C_4 alcohols such as methanol, ethanol, iso-propanol and butanol, lower ketones such as acetone, amides such as dimethylformamide ("DMF") and N,N'-carbonyl diimidazole and the like and mixtures thereof. Next, the keto amide is reduced to the corresponding alcohol of formula III under conditions well known in the art, for example, by using a reagent such as $BH_3.S(CH_3)_2$ in the presence of a chiral promoting agent such as, for example, a chiral borane (e.g., (R)-methyl oxazaborilidine).

[0011] Useful protecting groups to provide a protected amide of formula IV include, but are not limited to, aromatic protecting groups such as, for example, benzyl bromide, benzyl chloride and benzyl iodide, and the like. If desired, the reaction can be carried out in the presence of a base to provide a protected amide of formula IV. Useful bases include, but are not limited to, sodium t-butoxide, potassium t-butoxide, diisopropylamide, sodium hydride, potassium hydride, sodium methoxide, potassium methoxide and the like and mixtures thereof.

[0012] In step (b) of the process of the present invention, the protected amide of formula IV is hydrolyzed under conditions well known in the art, for example, by hydrolyzing the protected amide with a strong base in an alcoholic solution, e.g., an ethanolic solution, to provide a protected carboxylic acid of formula V.

[0013] In step (c) of the process of the present invention, an organic halide, e.g., thionyl chloride, is reacted with the protected carboxylic acid of formula V and an imine of formula VI:

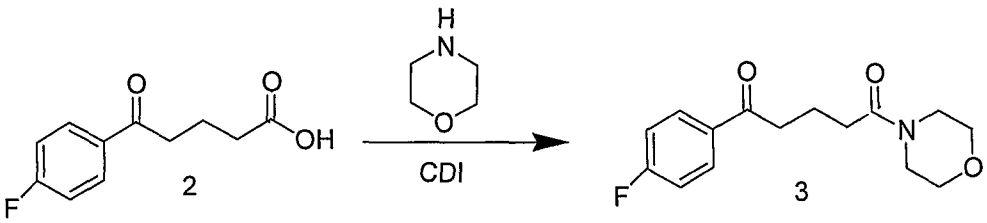


(VI);

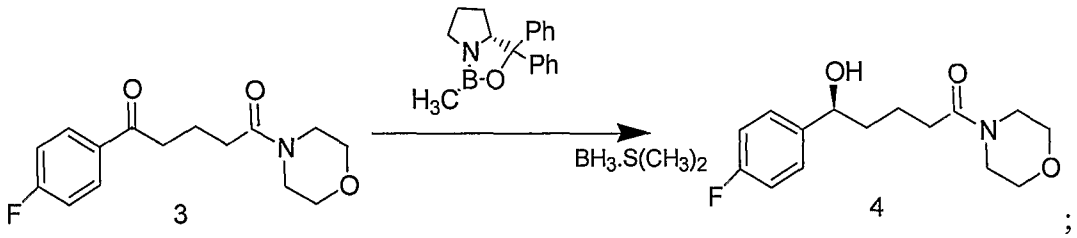
wherein Prot is a protecting group in the presence of one or more inert organic solvents to provide the azetidinone of the formula VII. Suitable protecting groups include, but are not limited to, aromatic protecting groups such as a benzyl containing group, e.g., a substituted or unsubstituted benzyl group as described above. Preferably, the organic halide is reacted with a mixture of the carboxylic acid of formula V and the imine. Suitable inert organic solvents for use herein can be, for example, a hydrocarbon having from 5 to about 12 carbon atoms such as an aromatic hydrocarbon or an aliphatic hydrocarbon solvent. Examples of aromatic hydrocarbons include, but are not limited to, xylene, benzene, toluene, chlorobenzene and the like. The reaction is ordinarily carried out at reflux in the presence of one or more bases. Representative bases for use herein include, but are not limited to, an organic amine, an alkoxide, a hydroxide of an alkali metal or an alkaline earth metal. Specific examples of bases include, but are not limited to, N,N'-diisopropyl ethylamine, triethylamine, sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide. Preferably, at least two bases are employed in this step.

[0014] In step (d) of the process of the present invention, the protecting groups on the azetidinone of the formula VI are removed by methods well known in the art, for example, by hydrogenating an alcoholic solution, e.g., a methanolic solution, of the compound of formula VI with Pd/C under H_2 at a suitable pressure, e.g., a pressure of about 6.5 Kg/cm2, to provide the compound of formula I.

[0015] In a preferred reaction scheme, the compound of formula I can be obtained by at least (a) providing an alcohol by first reacting p-fluorobenzoyl butyric acid (2) with morpholine in the presence of N,N'-carbonyl diimidazole (CDI) to form a keto amide (3):

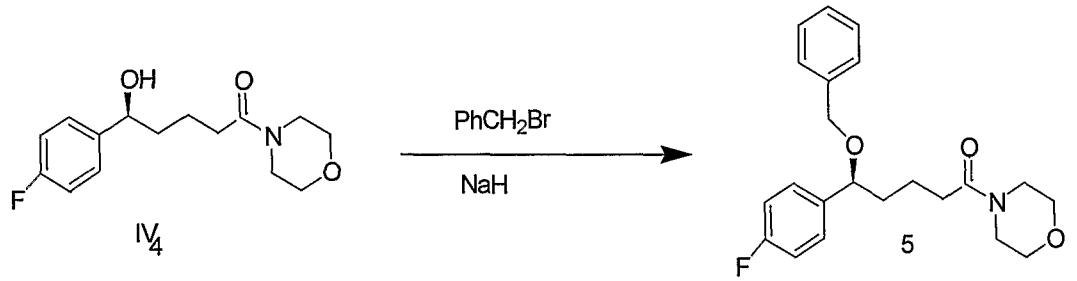


and then reducing the keto amide (3) with $BH_3.S(CH_3)_2$ in the presence of a chiral catalyst (R)-methyl oxazaborilidine to provide an alcohol of formula (4)

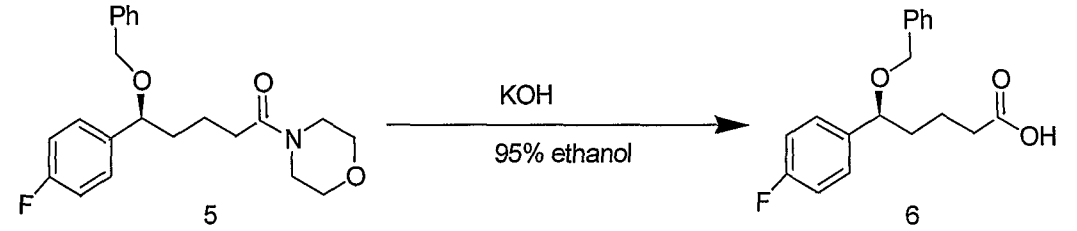


;

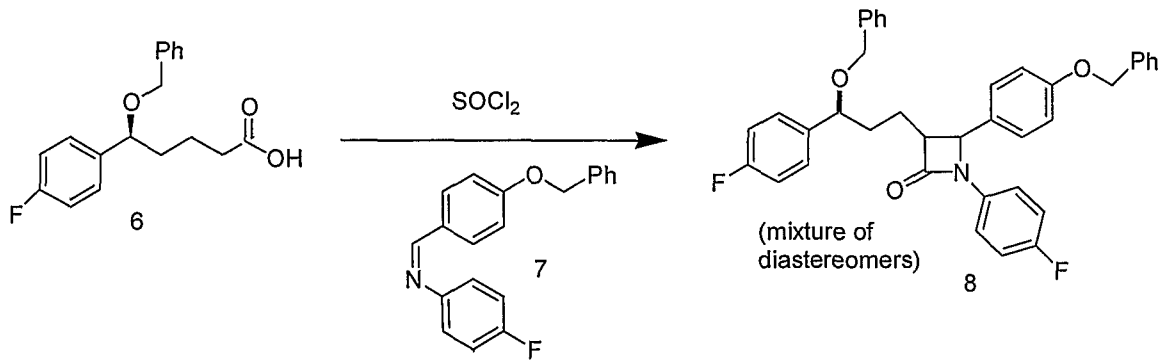
(b) reacting the alcohol (4) with a benzyl contaning halide in the presence of sodium hydride to provide a benzyl protected amide (5):



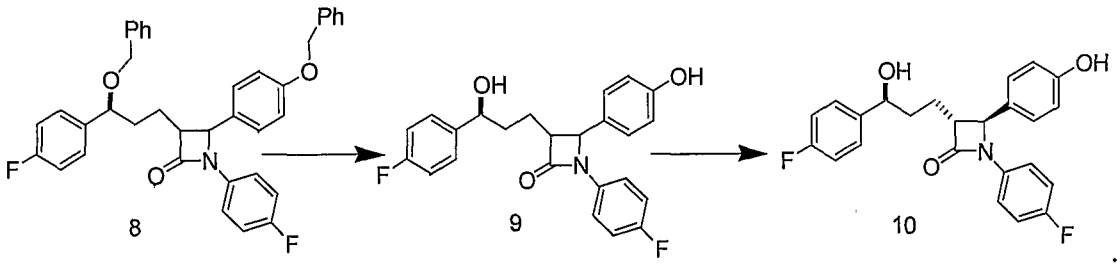
(c) hydrolyzing the benzyl protected amide (5) with a strong base in about 95% ethanol to provide a carboxylic acid (6):



(d) reacting thionyl chloride with a mixture of the carboxylic acid (6) and an imine (7) wherein Ph is phenyl in toluene at reflux in the presence of one or more bases to provide an azetidinone (8):



(d) deprotecting the azetidinone (8) by hydrogenation in the presence of Pd/C to provide an ezetimibe precursor (9); and (e) purifying the ezetimibe precursor (9) to form ezetimibe (10):



[0016] The following examples are provided to enable one skilled in the art to practice the invention and are merely illustrative of the invention. The examples should not be read as limiting the scope of the invention as defined in the claims.

EXAMPLE 1

Step I: Synthesis of the Keto Amide

[0017] A solution of p-fluorobenzoyl butyric acid (50.0g, 0.24 mol) in DMF (500.0 ml) and N,N'-Carbonyl diimidazole (50.0g, 0.31 mol) was stirred under nitrogen at about room temperature (from about 25°C to about 30°C) for three hours. Morpholine (40.0 ml, 0.46 mol) was added to the reaction mass dropwise. The reaction mass was stirred at a temperature ranging from about 40°C to about 45°C for about 10 hours. After completion of the reaction as determined by TLC, the reaction mass was cooled to a temperature ranging from about 0°C to about 5°C and adjusted to a pH of about 2.0 with 2N HCl and extracted with ethyl acetate (2 X 500.0 ml). The ethyl acetate layer was washed with saturated sodium bicarbonate solution (200.0 ml), water (200.0 ml) and brine (200.0 ml). The ethyl acetate layer on evaporation gave a residue. The residue on crystallization from ethyl acetate/hexane yielded 55.0g of the keto amide III.

[0018] Mp: 54-55°C. IR(cm^{-1}) :3044, 3061, 1636, 1677, 1599, 1441, 1278, 1241, 1114, 1030, 988, 960. ^1H NMR ($CDCl_3$) (δ ppm): 2.1(2H), 2.4(2H), 3.1(2H), 3.5(2H), 3.7(6H), 7.1(2H), 8.0(2H). (M+1):280.2

EXAMPLE 2

Step II: Synthesis of the Alcohol

[0019] To a solution of borane dimethyl sulfide (16.0 ml, 0.17 mol) in dichloromethane (100 ml) maintained at a temperature of -5°C under nitrogen atmosphere was added (R)-methyl oxazaborilidine catalyst in toluene (1M, 8.0 ml, 0.0078 mol) and maintained for 15 minutes. To the above mixture, a solution of the keto amide prepared in step I (40.0g, 0.143 mol) in dichloromethane (300.0 ml) was added slowly over a period of four hours at a temperature ranging from about -5°C to about 0°C. The reaction mass was stirred for two hours. After completion of the reaction as determined by TLC, methanol was added dropwise to the reaction mass. Subsequently 5% hydrogen peroxide solution (80.0 ml) and 4N sulfuric acid (6.0 ml) were added to the reaction mixture and stirred for 15 minutes. The separated organic layer was washed with 2N sulfuric acid (80.0 ml) and 5% sodium sulfite (100.0 ml) water (100.0 ml) and brine solution (100.0ml). The organic layer was dried over anhydrous sodium sulfate and distilled under reduced pressure to provide the alcohol as an oil (38.0g).

[0020] IR(cm^{-1}): 3375, 2967, 2909, 2862, 1622, 1507, 1439, 1280, 1244, 1210, 1160, 1116, 1028, 852. ^1H NMR ($CDCl_3$) (δ ppm): 1.8(4H), 2.4(2H), 3.4(2H), 3.6(6H), 4.8(1H), 7.0(2H), 7.3(2H). (M+1): 282.2.

EXAMPLE 3

Step III: Synthesis of the Benzyl Protected Amide

[0021] To a solution of the alcohol prepared in step II (30.0g, 0.11 mol) in tetrahydrofuran (THF) (240.0 ml) maintained under nitrogen atmosphere, sodium hydride (5.5g, 0.138 mol) was added at a temperature of about 0°C. Benzyl bromide (20.4g, 0.12 mol) was added slowly to the reaction mass at a temperature of about 0°C. After completion of the addition, the reaction mass was stirred for 24 hours at room temperature. After completion of the reaction as determined by TLC, the reaction mass was cooled to 0°C and water (30.0 ml) was added slowly. The reaction mixture was brought to room temperature and the solvent was distilled off under reduced pressure to get a residue. Water (200.0 ml) was added to the residue and extracted with ethyl acetate (3 X 200.0 ml). The ethyl acetate layer was washed with water (250.0 ml), brine (250.0 ml) and dried over

anhydrous sodium sulfate. The organic layer was evaporated to yield the benzyl protected amide (38.0g).

[0022] IR(cm^{-1}): 3400, 3008, 2925, 2860, 2398, 1640, 1508, 1435, 1219, 1116, 837, 756, 699. ^1H NMR ($CDCl_3$) (δ ppm): 1.-6-2.0(4H), 2.3(2H), 3.4(2H), 3.6(6H), 4.2-4.6(3H), 7.0(2H), 7.3(7H). (M+1):372.3.

EXAMPLE 4

Step IV: Synthesis of the Carboxylic Acid

[0023] The benzyl protected amide prepared in step III (40.0g, 0.11 mol), 95% ethanol (600.0 ml) and potassium hydroxide (30.0g, 0.54 mol) were taken in a 1L round-bottom flask and refluxed at a temperature of about 78°C for about 48 hours. After completion of the reaction as determined by TLC, the solvent was distilled out under reduced pressure. Water (400.0 ml) was added to the residue and extracted with dichloromethane (200.0 ml) to remove the organic impurities. The aqueous layer was cooled to a temperature ranging from about 0°C to about 5°C and adjusted the pH to about 2.0 with concentrated HCl. The aqueous layer was extracted with ethyl acetate (2 X 200.0 ml). The ethyl acetate layer was washed with water (200.0 ml) and brine (200.0 ml). The organic layer was dried over anhydrous sodium sulfate. The organic layer was evaporated to yield the carboxylic acid as a liquid (17.0g).

[0024] IR(cm^{-1}): 3064, 3032, 2929, 2867, 1709, 1604, 1508, 1454, 1413, 1222, 1156, 1096, 836, 736. ^1H NMR ($CDCl_3$) (δ ppm): 1.5-2.0(5H), 2.3(2H), 4.2-4.4(3H), 7.0(2H), 7.3(7H). (M-1):301.3.

EXAMPLE 5

Step V: Synthesis of the Azetidinone

Preparation of acid chloride

[0025] DMF (1.5 ml, 0.017mol) and thionyl chloride (1.5 ml, 0.017mol) were added to a solution of the carboxylic acid prepared in step IV (5.0g, 0.02 mol) in dichloromethane (20.0 ml) maintained at a temperature of about 0°C under nitrogen atmosphere. The reaction mass was stirred and raised to a temperature ranging from about 20°C to about 25°C and maintained for 2.0 hours.

Formation of β-Lactam

[0026] N,N'-Diisopropyl ethylamine (10.0ml, 0.06 mol) and triethylamine (1.0ml, 0.007 mol) were added to a solution of the imine of formula 7 above (2.5g, 0.008 mol) in toluene (100.0ml). The reaction mass was heated to reflux and the solution containing the acid chloride from above was added to the reaction mixture slowly over a period of about 2.0 hours. After completion of the addition, the reaction mass was maintained under reflux (a temperature ranging from about 110°C to about 112°C) for two hours. After completion of the reaction as determined by TLC, the reaction mass was cooled to a temperature of about 0°C and 1N HCl (100.0 ml) was added slowly and stirred for 15 minutes. The toluene layer was separated and washed with 1N HCl (100.0 ml), water (2 X 100.0 ml) and brine (100.0 ml). The organic layer was dried over anhydrous sodium sulfate and evaporated to yield the azetidinone as a mixture of diastereomers (3.0g).

[0027] IR(cm^{-1}): 2925, 2855, 1747, 1604, 1509, 1222, 1026. (M+1):590.8.

EXAMPLE 6

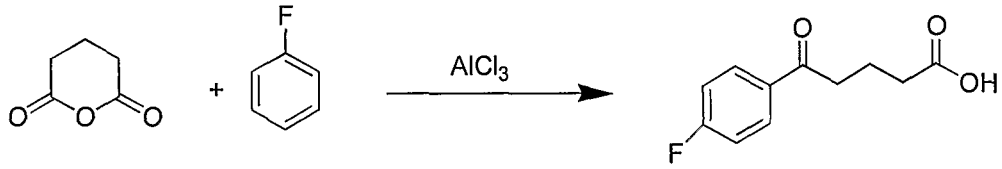
Step VI: Deprotection of Azetidinone to Yield Ezetimibe

[0028] A solution of the azetidinone prepared in step V (3.0g) in ethyl acetate (100.0 ml) and methanol (50.0 ml) was hydrogenated over 10% Pd-C (1.0g) for 10.0 hours. After completion of the reaction as determined by TLC, the reaction mass was filtered through a hy-flo bed. After evaporation, the ethyl acetate layer was recrystallized with methanol to yield ezetimibe.

[0029] IR(cm^{-1}): 3265, 2913, 1717, 1602, 1614, 1591, 1510, 1403, 1221, 1066, 831. ^1H NMR ($CDCl_3$) (δ ppm): 1.8-2.0(4H), 3.1(1H), 4.5(1H), 4.8(1H), 5.3(1H), 6.8(2H), 7.1-7.4(10H),9.6(1H).

EXAMPLE 7

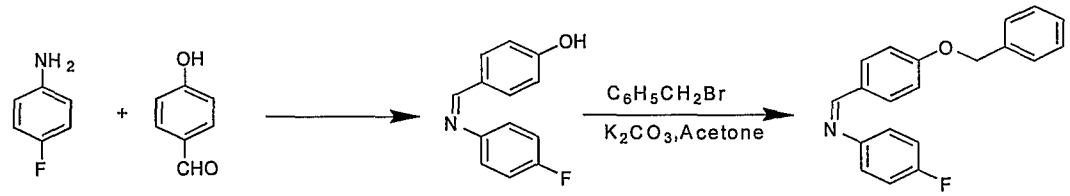
Preparation of 4-(4-fluorobenzoyl) butyric acid



[0030] To anhydrous $AlCl_3$ (250.0g, 1.87 mol) kept in a dry flask fluorobenzene (307.5 g:3.2 moles) was added. The reaction mass was cooled to a temperature of about 5°C and a suspension of glutaric anhydride (0.86 mol) in fluorobenzene (400.0 ml, 4.3 mol) was added dropwise. After completion of the addition, the reaction mass was brought to room temperature and maintained for 2 hours. On completion of the reaction as determined by NMR, the reaction mass was cooled to a temperature ranging from about 0°C to about 3°C and 1N HCl (715.0 ml) was added below a temperature of about 20°C. The reaction mixture was poured into 2.3L of ice-water suspension under stirring and the precipitated solids were filtered out. The solids were washed with water (500.0 ml) and treated with 5% $NaHCO_3$ (3.2L) and filtered through a hy-flo bed. The solids were acidified with concentrated HCl (pH of about 1.0) at a temperature ranging from about 0°C to about 5°C. The solids were precipitated out and the product was filtered and dried to yield 4-(4-fluorobenzoyl)-butyric acid (150.0g). Mp: 142-143°C. IR(cm^{-1}): 3073, 2967, 1698, 1672, 1597, 1509, 1414, 1258, 1241, 1165, 1075, 989, 839. ^1H NMR ($CDCl_3$) (δ ppm): 1.8(2H), 2.3(2H), 3.1(2H), 7.3(2H), 8.0(2H), 12.1(1H).

EXAMPLE 8

Step I: Preparation of the imine



Reaction of 4-fluoroaniline with 4-hydroxy benzaldehyde

[0031] 4-fluoroaniline (114.0 ml, 1.2 mol) was added dropwise to a solution of 4-hydroxy benzaldehyde (144.0g, 1.18 mol) in isopropyl alcohol (500.0 ml) maintained at 50°C. The reaction mass was maintained for 2.0 hours at 50°C. After the completion of the reaction as determined by TLC, the separated solid was filtered, and the cake was washed with IPA (150.0 ml). The cake was dried for 6 hours at a temperature of about 60°C to furnish the imine (220.0g). Mp: 181-182°C. ^{1}H NMR (DMSO d6) (δ ppm): 6.9(2H), 7.3(4H), 7.8(2H), 8.3(1H), 10.2(1H).

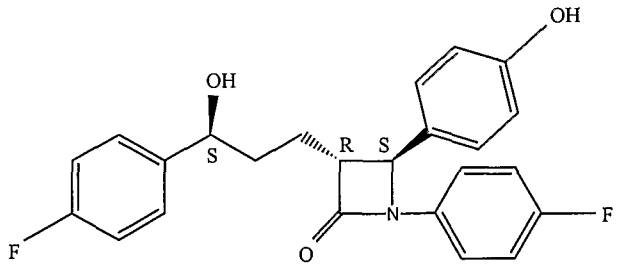
Step II: Protection of imine

[0032] Acetone (1200.0 ml), potassium carbonate (95.0g, 0.73 mol) and benzyl bromide (39.3g, 0.23 mol) were added to a dry 2L flask containing the imine prepared in step I (50.0g, 0.23 mol). The solution was maintained at reflux for 4.0 hrs. After completion of the reaction as determined by TLC, the reaction mass was brought to room temperature and filtered to separate the inorganic impurities. The solid obtained was washed with acetone (200.0 ml) and the washings were combined with the filtrate. The acetone layer was evaporated to get a residue which was dissolved in dichloromethane (600.0 ml). The dichloromethane layer was washed with water (2 X 250.0 ml). The dichloromethane layer on evaporation yielded the protected imine (58.0g). Mp: 135-137°C. IR(cm^{-1}): 3446, 2867, 1604, 1508, 1249, 1219, 1165, 1003, 836. ^{1}H NMR ($CDCl_3$) (δ ppm): 5.2(2H), 7.1(4H), 7.2(2H), 7.4(5H), 7.8(2H), 8.4(1H). ^{13}C NMR ($CDCl_3$) (δ ppm): 70.0, 115.0, 115.59, 115.88, 122.12, 122.23, 127.44, 128.11, 128.61, 129.25, 130.4, 136.34, 148.24, 148.28, 159.35, 161.36, 162.56. (M+1):306.2.

[0033] It will be understood that various modifications may be made to the embodiments disclosed herein. Therefore the above description should not be construed as limiting, but merely as exemplifications of preferred embodiments. For example, the functions described above and implemented as the best mode for operating the present invention are for illustration purposes only. Other arrangements and methods may be implemented by those skilled in the art without departing from the scope and spirit of this invention. Moreover, those skilled in the art will envision other modifications within the scope and spirit of the claims appended hereto.

WHAT IS CLAIMED IS:

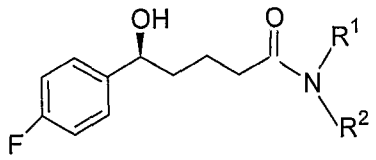
1. A process for preparing a compound of formula I:



(I),

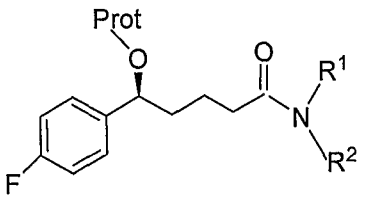
the process comprising

(a) reacting an alcohol of formula III:



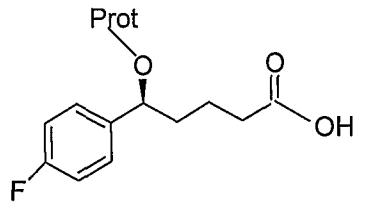
(III)

wherein R^1 and R^2 are independently hydrogen, hydrocarbons of from 1 to 20 carbon atoms or R^1 and R^2 together with the nitrogen atom to which they are bonded are joined together to form a substituted or unsubstituted heterocyclic group optionally containing one or more additional heterocyclic atoms, with a protecting group to provide a protected amide of formula IV:



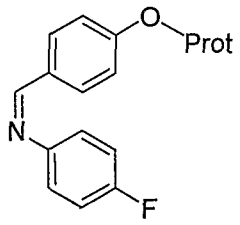
(IV);

(b) hydrolyzing the protected alcohol of step (a) with a strong base to provide a carboxylic acid of formula V:



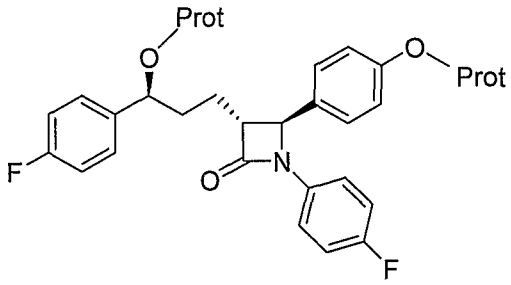
(V);

(c) reacting an organic halide with the carboxylic acid of step (b) and an imine of the formula VI:



(VI);

wherein Prot is a protecting group to provide an azetidinone of formula VII



(VII); and

(d) removing the protecting groups.

2. The process of Claim 1, comprising

(a) reacting the alcohol of formula III with a benzyl halide in the presence of a base to provide a benzyl protected amide;

(b) hydrolyzing the benzyl protected amide product of step (a) with a strong base to provide a carboxylic acid;

(c) reacting the carboxylic acid product of step (b) with thionyl chloride and one or more bases and an imine of the formula VI wherein Prot is phenyl to provide an azetidinone; and

(d) debenzylation of the product of step (c) by hydrogenation.

3. The process of Claims 1 and 2, wherein in the alcohol of formula III R^1 and R^2 together with the nitrogen atom to which they are bonded form a substituted or unsubstituted heterocyclic group optionally containing one or more additional heterocyclic atoms.

4. The process of Claim 3, wherein the heterocyclic compound is a morpholine group.

5. The process of Claims 1 and 2, wherein in the alcohol of formula III R^1 and R^2 are independently selected from the group consisting of methyl, ethyl, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, cyclohexyl, heptyl, octyl, 2-ethylhexyl, nonyl, decyl, dodecyl, stearyl, oleyl, and phenyl.

6. The process of Claims 1-5, wherein in step (a) the protecting group is selected from the group consisting of benzyl bromide, benzyl chloride, and benzyl iodide.

7. The process of Claims 1-6, wherein in step (b) the base is selected from the group consisting of sodium t-butoxide, potassium t-butoxide, diisopropylamide, sodium hydride, potassium hydride, sodium methoxide, potassium methoxide and mixtures thereof.

8. The process of Claims 1-7, wherein the protected amide of step (b) is hydrolyzed in an ethanolic solution.

9. The process of Claim 1, wherein the organic halide is thionyl chloride.

10. The process of Claims 1-9, wherein step (c) is carried out in the presence of an aromatic hydrocarbon solvent.

11. The process of Claim 10, wherein the aromatic hydrocarbon solvent is selected from the group consisting of xylene, benzene, toluene, chlorobenzene and mixtures thereof.

12. The process of Claims 1-11, wherein the reaction of step (c) is carried out at reflux in the presence of at least one base.

13. The process of Claim 12, wherein the at least one base is selected from the group consisting of an organic amine, an alkoxide, an alkali metal hydroxide, an alkaline earth metal hydroxide and mixtures thereof.

14. The process of Claim 12, wherein the at least one base is selected from the group consisting of N,N'-diisopropyl ethylamine, triethylamine, sodium hydroxide, potassium hydroxide, calcium hydroxide, magnesium hydroxide and mixtures thereof.

15. The process of Claims 1-14, wherein the reaction of step (c) is carried out at reflux in the presence of at least two bases.

16. The process of Claim 2, wherein the step of debenzylation of the azetidinone comprises hydrogenation with an alcoholic solution.

17. The process of Claim 16, wherein hydrogenation is with a methanolic solution and Pd/C under H_2 at a pressure of about 6.5 Kg/cm2.

International application No
PCT/IB2005/002393

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/397 C07D505/08

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

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, 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.
Y	WO 00/34240 A (SCHERING CORPORATION) 15 June 2000 (2000-06-15) the whole document	1-17
Y	WO 2005/044256 A (MERCK & CO., INC; SINGS, HEATHER, I; UJJAINWALLA, FEROZE; MACCOSS, MAL) 19 May 2005 (2005-05-19) claims; examples	1-17
Y	WO 2004/099132 A (RANBAXY LABORATORIES LIMITED; KAROOTI, KIRAN, KUMAR, GANAGAKHEDKAR, SH) 18 November 2004 (2004-11-18) the whole document	1-17

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

☒ See patent family annex.

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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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 April 2006	11/04/2006

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