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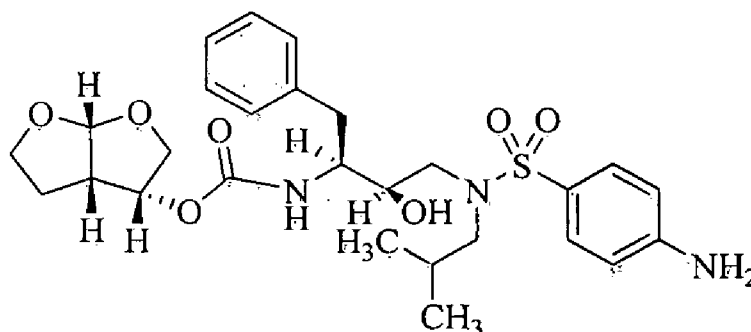
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(54) Title: PROCESS FOR THE PREPARATION OF [(1 S,2R)-3-[[[4-AMINOPHENYL]SULFONYL] (2-METHYLPROPYL)AMINO]-2-HYDROXY-1-(PHENYLMETHYL)PROPYL]-CARBAMIC ACID (3R,3aS,6aR)HEXAHYDRO FURO[2,3-b]FURAN-3-YL ESTER AND ITS AMORPHOUS FORM



Formula-1

(57) Abstract: The present invention relates to an improved process for the preparation of [(1 S,2R)-3-[[[4-aminophenyl]sulfonyl] (2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl ester compound of formula- 1 represented by the following structural formula:

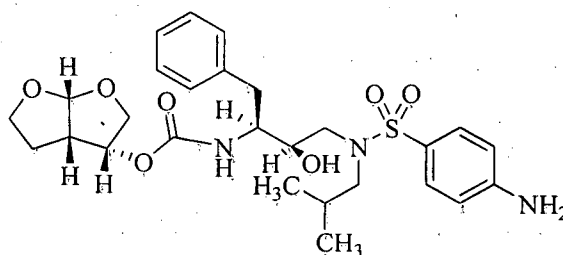
Process for the preparation of [(1S,2R)-3-[[[(4-aminophenyl) sulfonyl](2-methyl propyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl ester and its amorphous form

5 Related Applications:

This application claims the benefit of priority of our Indian patent application number 3197/CHE/2015 filed on 25th June 2015 which is incorporated herein by reference.

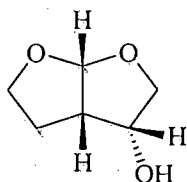
Field of the Invention:

The present invention relates to an improved process for the preparation of [(1S,2R)-3-[[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]-carbamic acid (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl ester compound of formula-1 represented by the following structural formula:



Formula-1

The present invention also provides an improved process for the preparation of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2,



Formula-2

which is a key intermediate and is useful in the preparation of compound of formula-1.

Background of the Invention:

[(1S,2R)-3-[[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenyl

methyl)propyl]-carbamic acid (3R,3aS,6aR)hexahydrofuro[2,3-b]furan-3-yl ester is commonly known as Darunavir. The Darunavir is a protease inhibitor drug used to treat HIV infection. Prezista is an OARAC recommended treatment option for treatment-naïve and treatment-experienced adults and adolescents.

5 Darunavir was first generically disclosed in U.S. Patent No. 5,843,946 and specifically disclosed in U.S. Patent No. 6,248,775.

US pat. No 7,126,015 discloses process for the preparation of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol. The disclosed process involves cyclisation of 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutan-1-ol in presence of potassium tert-butoxide in isopropanol followed by reaction with concentrated hydrochloric acid to give mixture of compound of formula-2 i.e. (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol in a ratio of 78:22 which results in the formation of final product with low yield and low purity. Further the final compound of formula-2 was purified by column chromatography, which is a laborious and time consuming process and also it is not suitable for commercial scale purpose.

15 Hence, there is a need in the art to develop an improved, economical viable and efficient, simple process for the preparation of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2 with high yield and purity.

Brief description of the Invention:

20 The first aspect of the present invention is to provide an improved process for the preparation of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2.

The second aspect of the present invention is to provide an improved process for the preparation of (R,E)-ethyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate compound of formula-
25 8.

The third aspect of the present invention is to provide an improved process for the preparation of ethyl-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate compound of formula-9.

30 The fourth aspect of the present invention is to provide an alternate process for the preparation of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2.

The fifth aspect of the present invention is to provide a process for the preparation of Amorphous [(1S,2R)-3-[[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl ester compound of formula-1.

5

The sixth aspect of the present invention is to provide a one-pot process for the preparation of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2.

Brief description of Drawings:

10 **Figure 1:** Illustrates the PXRD pattern of amorphous [(1S,2R)-3-[[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl ester compound of formula-1.

Figure 2: Illustrates the IR pattern of [(1S,2R)-3-[[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid (3R,3aS,6aR)-
15 hexahydrofuro[2,3-b]furan-3-yl ester compound of formula-1.

Detailed description of the Invention:

The term "suitable solvent" used in the present invention includes, but not limited to "ester solvents" such as ethyl acetate, methyl acetate, isopropyl acetate, n-butyl acetate and
20 the like; "ether solvents" such as tetrahydrofuran, dimethyl ether, diethyl ether, diisopropyl ether, methyl tert-butyl ether, 1,4-dioxane and the like; "hydrocarbon solvents" such as toluene, hexane, heptane, pet ether, benzene, xylene, cyclohexane and the like; "polar aprotic solvents" such as dimethyl acetamide, dimethylsulfoxide, dimethylformamide, N-methyl-2-pyrrolidone and the like; "ketone solvents" such as acetone, methyl ethyl ketone, methyl
25 isobutyl ketone and the like; "alcoholic solvents" such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, tert-butanol and the like; "chloro solvents" such as dichloromethane, chloroform, dichloroethane, carbon tetrachloride and the like; "nitrile solvents" such as acetonitrile, butyronitrile, isobutyronitrile and the like; "protic solvent" such as acetic acid; "polar solvent" such as water or mixtures thereof.

30 The term "base" used herein the present invention until unless specified is selected from inorganic bases like "alkali metal hydroxides" such as lithium hydroxide, sodium

hydroxide, potassium hydroxide and the like; "alkali metal carbonates" such as sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate and the like; "alkali metal bicarbonates" such as sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, cesium bicarbonate and the like; "alkali metal hydrides" such as sodium hydride, potassium hydride, lithium hydride and the like; "alkali metal alkoxides" such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium methoxide, potassium ethoxide, potassium tert-butoxide and the like; ammonia; and organic bases such as triethyl amine, methyl amine, ethyl amine, 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU), Tetra-*n*-butylammonium fluoride (TBAF), 1,5-Diazabicyclo(4.3.0)non-5-ene (DBN), lithium diisopropylamide (LDA), *n*-butyl lithium, tribenzylamine, isopropyl amine, diisopropylamine, diisopropylethylamine, N-methylmorpholine, N-ethylmorpholine, piperidine, dimethylaminopyridine, morpholine, pyridine, 2,6-lutidine, 2,4,6-collidine, imidazole, 1-methylimidazole, 1,2,4-triazole, 1,4-diazabicyclo[2.2.2]octane (DABCO) or mixtures thereof.

The "suitable oxidizing agent" used herein the present invention is selected from peroxides such as oxygen, oxygen/Pt, ozone, hydrogen peroxide, hydrogen peroxide/HCl in presence of hydroxyl amine hydrochloride, peroxydisulfuric acid, peroxy mono sulfuric acid; nascent oxygen, chlorite, chlorate, perchlorates of alkali and alkaline earth metals such as sodium chlorite, sodium chlorate, sodium hypochlorite, calcium chlorite, sodium chlorite/H₂O₂, calcium hypochlorite and the like; oxalyl chloride in combination with dimethyl sulfoxide, trichloroisocyanuric acid in combination with TEMPO, nitric acid, silver nitrate, potassium nitrate, silver oxide, copper (II) oxide, sodium perborate, hypochlorous acid, tollen's reagent (silver nitrate/ammonia), lithium bromide/ triethylamine, Br₂/sodium acetate/ acetic acid; hexavalent chromium compounds such as chromic and dichromic acids and chromium trioxide, chromium trioxide/H₂SO₄ pyridinium chlorochromate (PCC), chromyl chlorite, chromate/dichromate compounds such as potassium dichromate, sodium dichromate optionally in presence of sulfuric acid; permanganate compounds such as potassium permanganate and the like; manganate compounds such as potassium manganate and the like; peracids such as perbenzoic acid, Peroxy acetic acid, *m*-chloroperbenzoic acid, trifluoro peracetic acid and the like; chromium complexes such as

(1,10-phenanthroline) H_2CrOCl_5 (1,10-phenanthroline) $CrOCl_3$, (α , α' -bipyridyl) H_2CrOCl_5 , (α , α' -bipyridyl) $CrOCl_3$ and other well-known oxidizing agents.

The suitable "reducing agent" is selected from Lithium aluminum hydride ($LiAlH_4$), Nascent (atomic) hydrogen, hydroquinone, sodium amalgam, diborane, sodium borohydride, lithium borohydride, compounds containing the Sn^{+2} ion such as tin(II)chloride, sulfite compounds, hydrazine, zinc-mercury amalgam, diisobutylaluminum hydride (DIBAL-H), Lindlar catalyst, oxalic acid, formic acid, ascorbic acid, phosphites, hypophosphites and phosphorous acid, dithiothreitol (DTT), compounds containing Fe^{+2} ion such as iron(II)sulfate, carbon monoxide and the like.

The term "acid" used in the present invention refers to inorganic acid selected from hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, sulfamic acid and the like; organic acid such as formic acid, acetic acid, trifluoro acetic acid, methane sulfonic acid, ethane sulfonic acid, benzene sulfonic acid, trifluoromethane sulfonic acid, p-toluene sulfonic acid, tartaric acid, mandelic acid, malic acid, maleic acid, succinic acid, malonic acid, oxalic acid, dibenzoyl tararic acid, lactic acid, cinnamic acid and the like.

The first aspect of the present invention provides an improved process for the preparation of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2, comprising of:

- a) Reacting L-Ascorbic acid compound of formula-3 with 2,2-dimethoxypropane in a suitable solvent to provide 5,6-O-isopropylidene-L-ascorbic acid compound of formula-4,
- b) oxidizing compound of formula-4 with a suitable oxidizing agent in presence of calcium carbonate in a suitable solvent to provide calcium salt of 3,4-O-isopropylidene-L-threonic acid compound of formula-5,
- c) reacting compound of formula-5 with sodium hypochloride in presence of acetic acid and sodium acetate in a suitable solvent to provide (S)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde compound of formula-6,
- d) reacting compound of formula-6 with ethyl-2-(diethoxyphosphoryl)acetate compound of formula-7 in presence of a base in a suitable solvent to provide α,β -unsaturated ester (R,E)-ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate compound of formula-8,

- e) reacting ester compound of formula-8 with nitromethane in presence of a base in a suitable solvent to provide ethyl 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate compound of formula-9,
- f) reducing compound of formula-9 with a suitable reducing agent in presence of lithium bromide in a suitable solvent to provide 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutan-1-ol compound of formula-10,
- g) cyclization of compound of formula-10 in presence of a suitable base and a suitable inorganic acid in a suitable solvent to provide (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2.

10 Wherein

in step-c), d), e) and f) the suitable solvent is selected from ester solvents, ether solvents, chloro solvents, hydrocarbon solvents, ketone solvents and alcohol solvents or mixture thereof;

in step-g) the suitable solvent is selected from ester solvents, ether solvents, chloro solvents,

15 hydrocarbon solvents and ketone solvents or mixture thereof;

in step-d), e) and g) the suitable base is selected from organic or inorganic base;

in step-f) a suitable reducing agent is selected from Lithium aluminum hydride (LiAlH_4),

hydroquinone, sodium amalgam, diborane, sodium borohydride, lithium borohydride, compounds containing the Sn^{+2} ion such as tin(II)chloride, sulfite compounds, hydrazine, zinc-mercury amalgam, diisobutylaluminum hydride (DIBAL-H), Lindlar catalyst, dithiothreitol (DTT), compounds containing Fe^{+2} ion such as iron(II)sulfate, carbon monoxide and the like,

in step-g) a suitable inorganic acid is selected from hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, sulfamic acid and the like.

25

The preferred embodiment of the present invention provides an improved process for the preparation of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2, comprising of:

- a) Reacting L-Ascorbic acid compound of formula-3 with 2,2-dimethoxypropane in acetone provides 5,6-O-isopropylidene-L-ascorbic acid compound of formula-4,

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- b) oxidizing compound of formula-4 with hydrogen peroxide in presence of calcium carbonate in water followed by treatment with manganese dioxide provides calcium salt of 3,4-O-isopropylidene-L-threonic acid compound of formula-5,
- c) reacting compound of formula-5 with sodium hypochloride in presence of acetic acid and sodium acetate in water provides (S)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde compound of formula-6,
- d) reacting compound of formula-6 with ethyl-2-(diethoxyphosphoryl)acetate compound of formula-7 in presence of potassium tert-butoxide in dichloromethane provides α,β -unsaturated ester (R,E)-ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate compound of formula-8,
- e) reacting ester compound of formula-8 with nitromethane in presence of 1,8-Diazabicyclo[5.4.0]undec-7-ene in acetonitrile provides ethyl 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate compound of formula-9,
- f) reducing compound of formula-9 with sodium borohydride in presence of lithium bromide in tetrahydrofuran provides 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutan-1-ol compound of formula-10,
- g) cyclization of compound of formula-10 in presence of potassium tert-butoxide and sulfuric acid in et and water provides (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2.

Alternatively, the compound of formula-10 of step-f) can be prepared by reducing compound of formula-9 in presence of lithium borohydride in tetrahydrofuran.

The compound of formula-2 of step-g) can also be prepared by cyclization of compound of formula-10 in presence of sodium hydroxide and sulfuric acid in water.

US7126015 B2 discloses the cyclisation of compound of formula-10 in presence of potassium tert-butoxide in isopropanol followed by reaction with concentrated hydrochloric acid in isopropanol results in the formation of mixture of compound of formula-2 in a ratio of 78:22. Whereas, the process of the present invention involves the cyclisation of 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutan-1-ol compound of formula-10 in presence of sodium hydroxide or potassium tert-butoxide in presence of sulfuric acid in water results in

the formation of required specific isomer i.e. (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2 with good yield and purity which makes the process more simple, economically viable and advantageous over the process disclosed in US7126015 B2. Hence, the process of the present invention is advantageous over the process disclosed in prior-art
5 such as US7126015 B2.

The second aspect of the present invention is to provide an improved process for the preparation of (R,E)-ethyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate compound of formula-8, comprising of reacting the compound of formula-6 with ethyl-2-(diethoxyphosphoryl) acetate compound of formula-7 in presence of a base in a suitable solvent to provide α,β -unsaturated ester (R,E)-ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate compound of formula-8.
10

Wherein, the suitable base and solvent used are same as defined in step-d) of the first aspect of the present invention.

The preferred embodiment of the present invention provides an improved process for the preparation of (R,E)-ethyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate compound of formula-8, comprising of reacting compound of formula-6 with ethyl-2-(diethoxyphosphoryl) acetate compound of formula-7 in presence of potassium tert-butoxide in dichloromethane provides α,β -unsaturated ester i.e, (R,E)-ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate compound of formula-8.
15
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The third aspect of the present invention is to provide an improved process for the preparation of ethyl-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate compound of formula-9, comprising of reacting ester compound of formula-8 with nitromethane in presence of a base in a suitable solvent to provide ethyl 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate compound of formula-9.
25

Wherein, the suitable base and solvent used are same as defined in step-e) of the first aspect of the present invention.

The preferred embodiment of the present invention provides an improved process for the preparation of ethyl-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate compound
30

of formula-9, comprising of reacting ester compound of formula-8 with nitromethane in presence of tetrabutylammonium fluoride in tetrahydrofuran provides ethyl 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate compound of formula-9.

5 The forth aspect of the present invention is to provide an alternate process for the preparation of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2, comprising of:

- a) Treating ethyl 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate compound of formula-9 with a suitable inorganic acid in a suitable solvent to provide (5S)-5-(hydroxymethyl)-4-(nitromethyl)dihydrofuran-2(3H)-one compound of formula-11,
10
- b) reducing compound of formula-11 in presence of a suitable reducing agent in a suitable solvent to provide (2S)-3-(nitromethyl)pentane-1,2,5-triol compound of formula-12,
- c) cyclizing of compound of formula-12 in presence of a suitable base and a suitable
15 inorganic acid in a suitable solvent to provide (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2.

Wherein,

in step-a), b) and c) the suitable solvent is selected from ester solvents, ether solvents, chloro solvents, hydrocarbon solvents, ketone solvents and alcohol solvents or mixture thereof;
20

in step-a) and c) the suitable inorganic acid is selected from hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, sulfamic acid and the like;

in step-b) a suitable reducing agent is same as defined in step-f) of first aspect of the present invention.

25 in step-c) a suitable base is selected from organic or inorganic base.

The above process can be prepared by one pot process without isolating compounds of formula-11 and formula-12.

The preferred embodiment of the present invention provides a process for the preparation of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2, comprising of:

- a) Treating ethyl 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate compound of formula-9 with concentrated hydrochloric acid in methanol provides (5S)-5-(hydroxymethyl)-4-(nitromethyl)dihydrofuran-2(3H)-one compound of formula-11,
- b) reducing compound of formula-11 in-situ in presence of sodium borohydride in a mixture of tetrahydrofuran and methanol provides (2S)-3-(nitromethyl)pentane-1,2,5-triol compound of formula-12,
- c) cyclizing compound of formula-12 in-situ in presence of potassium tert-butoxide and concentrated hydrochloric acid in methanol followed by treating with triethylamine provides (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2.

The fifth aspect of the present invention is to provide a process for the preparation of amorphous [(1S,2R)-3-[[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl ester compound of formula-1, comprising of:

- a) Reacting (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2 with N,N'-disuccinimidyl carbonate compound of formula-13 in presence of suitable base in a suitable solvent to provide 2,5-dioxopyrrolidin-1-yl (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl carbonate compound of formula-14,
- b) reacting compound of formula-14 with 4-amino-N-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-isobutylbenzenesulfonamide compound of formula-15 in presence of a base in a suitable alcohol solvent to provide [(1S,2R)-3-[[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl ester compound of formula-1,
- c) purifying the compound of formula-1 in a suitable solvent provides amorphous [(1S,2R)-3-[[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl ester compound of formula-1.

Wherein,

in step-b) a suitable solvent is selected from methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, tert-butanol and the like or mixture thereof.

5 The preferred embodiment of the present invention provides a process for the preparation of Amorphous [(1S,2R)-3-[[[4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl ester compound of formula-1, comprising of:

a) Reacting (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2 with
10 N,N'-disuccinimidyl carbonate compound of formula-13 in presence of pyridine in dichloromethane provides 2,5-dioxopyrrolidin-1-yl (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl carbonate compound of formula-14,

b) reacting compound of formula-14 with 4-amino-N-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-isobutylbenzenesulfonamide compound of formula-15 in presence of
15 triethylamine in methanol provides [(1S,2R)-3-[[[4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl ester compound of formula-1,

c) purifying the compound of formula-1 in a mixture of dichloromethane and methanol provides amorphous [(1S,2R)-3-[[[4-aminophenyl)sulfonyl](2-methylpropyl)amino]-
20 2-hydroxy-1-(phenylmethyl)propyl]carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl ester compound of formula-1.

The another preferred embodiment of the present invention provides a process for the preparation of Amorphous [(1S,2R)-3-[[[4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-
25 hydroxy-1-(phenylmethyl)propyl]carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl ester compound of formula-1, comprising of:

a) Reacting (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2 with
30 N,N'-disuccinimidyl carbonate compound of formula-13 in presence of pyridine in dichloromethane provides 2,5-dioxopyrrolidin-1-yl (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl carbonate compound of formula-14,

- b) purifying the obtained compound using n-hexane and methanol provides pure compound of formula-14,
- c) reacting compound of formula-14 with 4-amino-N-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-isobutylbenzenesulfonamide compound of formula-15 in presence of triethylamine in methanol provides [(1S,2R)-3-[[[4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl ester compound of formula-1,
- d) purifying the compound of formula-1 in a mixture of dichloromethane and methanol and followed by slurrying the obtained compound from cyclohexane provides pure amorphous [(1S,2R)-3-[[[4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl ester compound of formula-1.

The sixth aspect of the present invention provides a one-pot process for the preparation of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2, comprising of:

- a) Reacting L-Ascorbic acid compound of formula-3 with 2,2-dimethoxypropane in a suitable solvent to provide 5,6-O-isopropylidene-L-ascorbic acid compound of formula-4,
- b) oxidizing compound of formula-4 in-situ with a suitable oxidizing agent in presence of sodium hydroxide in a suitable solvent to provide sodium salt of 3,4-O-isopropylidene-L-threonic acid compound of formula-16,
- c) reacting compound of formula-16 in-situ with a suitable alkylating agent in presence of a suitable base in a suitable solvent to provide (R)-methyl-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxyacetate compound of formula-17,
- d) reducing compound of formula-17 with a suitable reducing agent in a suitable solvent to provide (S)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol compound of formula-18,
- e) reacting compound of formula-18 in-situ with sodium periodate in presence of suitable base in a suitable solvent to provide (S)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde compound of formula-6,

- f) reacting compound of formula-6 in-situ with ethyl-2-(diethoxyphosphoryl)acetate compound of formula-7 in presence of a base in a suitable solvent to provide α,β -unsaturated ester (R,E)-ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate compound of formula-8,
- 5 g) reacting ester compound of formula-8 in-situ with nitromethane in presence of a base in a suitable solvent to provide ethyl 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate compound of formula-9,
- h) reducing compound of formula-9 in-situ with a suitable reducing agent in presence of lithium bromide in a suitable solvent to provide 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutan-1-ol compound of formula-10,
- 10 i) cyclization of compound of formula-10 in-situ in presence of a suitable base and a suitable inorganic acid in a suitable solvent to provide (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2.

Wherein

- 15 in step-a) to i) the suitable solvent is selected from ester solvents, ether solvents, chloro solvents, hydrocarbon solvents, ketone solvents, alcohol solvents, polar solvents such as water or mixture thereof;
- in step-c), e), f), g) and i) the suitable base is selected from organic or inorganic base;
- in step-d) & h) the suitable reducing agent is selected from Lithium aluminum hydride
- 20 (LiAlH₄), hydroquinone, sodium amalgam, diborane, sodium borohydride, lithium borohydride, compounds containing the Sn⁺² ion such as tin(II)chloride, sulfite compounds, hydrazine, zinc-mercury amalgam, diisobutylaluminum hydride (DIBAL-H), Lindlar catalyst, dithiothretol (DTT), compounds containing Fe⁺² ion such as iron(II)sulfate, carbon monoxide and the like,
- 25 in step-i) a suitable inorganic acid is selected from hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, sulfamic acid and the like.

The preferred embodiment of the present invention provides a one-pot process for the preparation of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2,

30 comprising of:

- a) Reacting L-Ascorbic acid compound of formula-3 with 2,2-dimethoxypropane in acetone to provide 5,6-O-isopropylidene-L-ascorbic acid compound of formula-4,
- b) oxidizing compound of formula-4 in-situ with hydrogen peroxide in presence of sodium hydroxide in water to provide sodium salt of 3,4-O-isopropylidene-L-threonic acid compound of formula-16,
- 5 c) reacting compound of formula-16 in-situ with dimethyl sulfate in presence of sodium bicarbonate in dichloromethane to provide (R)-methyl-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxyacetate compound of formula-17,
- d) reducing the compound of formula-17 with sodium borohydride in a mixture of dichloromethane and methanol to provide (S)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol compound of formula-18,
- 10 e) reacting compound of formula-18 in-situ with sodium periodate in presence of sodium bicarbonate in dichloromethane to provide (S)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde compound of formula-6,
- 15 f) reacting compound of formula-6 in-situ with ethyl-2-(diethoxyphosphoryl)acetate compound of formula-7 in presence of potassium tert-butoxide in dichloromethane provides α,β -unsaturated ester (R,E)-ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate compound of formula-8,
- g) reacting ester compound of formula-8 in-situ with nitromethane in presence of tetrabutylammoniumfluoride in tetrahydrofuran provides ethyl 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate compound of formula-9,
- 20 h) reducing compound of formula-9 in-situ with sodium borohydride in presence of lithium bromide in tetrahydrofuran provides 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutan-1-ol compound of formula-10,
- 25 i) cyclization of compound of formula-10 in-situ in presence of potassium tert-butoxide and sulfuric acid in tetrahydrofuran and water provides (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2.

The compounds of formula-7 and formula-13 can be prepared by the process known
30 in the art.

We have repeated the process for the preparation of Darunavir which was analogously disclosed in US pat. No. US6248775 B2 and characterized the PXRD and IR of the obtained compound of formula-1. We have found that, the PXRD and IR patterns of compound of formula-1 obtained from the present invention are well matching with the PXRD and IR patterns of compound of formula-1 as per the process disclosed in US6248775 B2. The said PXRD & IR patterns have been depicted in figure-1 & figure-2.

The amorphous compound of formula-1 obtained according to the present invention can be useful in the preparation of pharmaceutical composition.

P-XRD Method of Analysis:

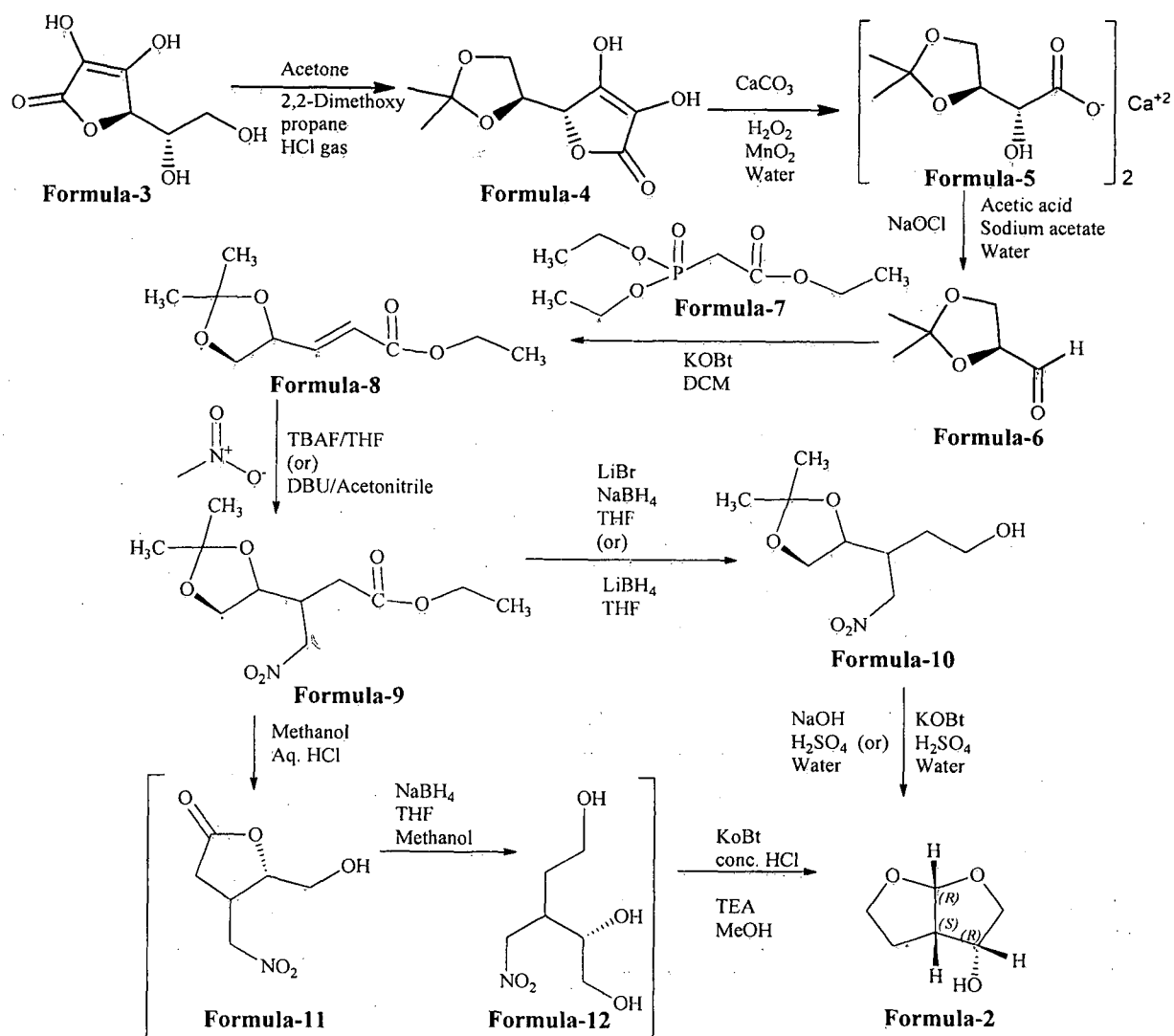
PXRD analysis of compound of formula-1 produced by the present invention can be carried out using BRUKER/AXS X-Ray diffractometer using Cu K α radiation of wavelength 1.5406 Å and continuous scan speed of 0.03°/min.

IR spectra of compound of formula-1 was recorded on a Perkin-Elmer FTIR spectrometer

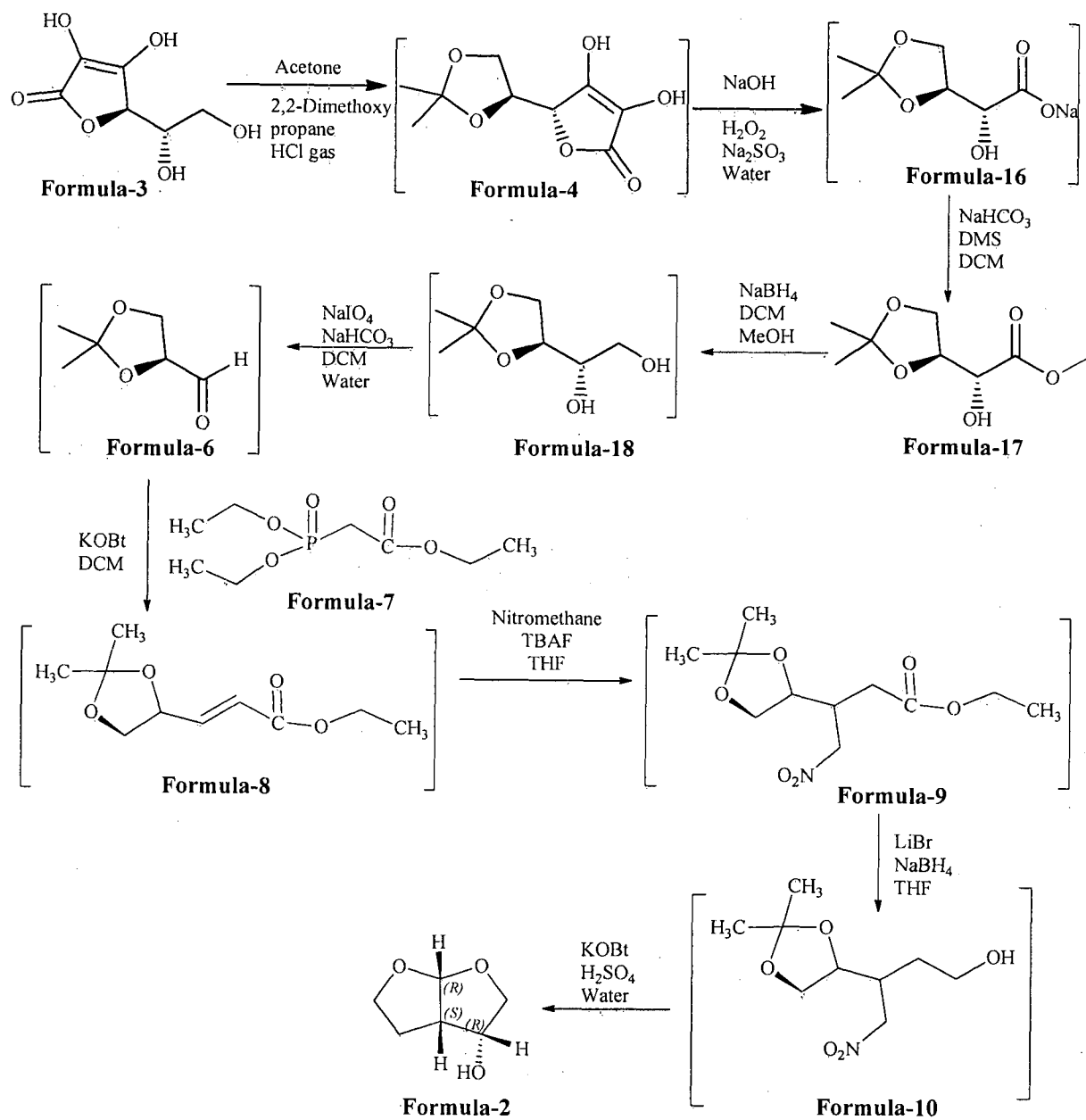
The compound of formula-1 produced by the present invention can be further micronized or milled to get the desired particle size to achieve desired solubility profile based on different forms of pharmaceutical composition requirements. Techniques that may be used for particle size reduction include, but not limited to ball, roller and hammer mills, and jet mills. Milling or micronization may be performed before drying, or after the completion of drying of the product.

The present invention is schematically represented as below:

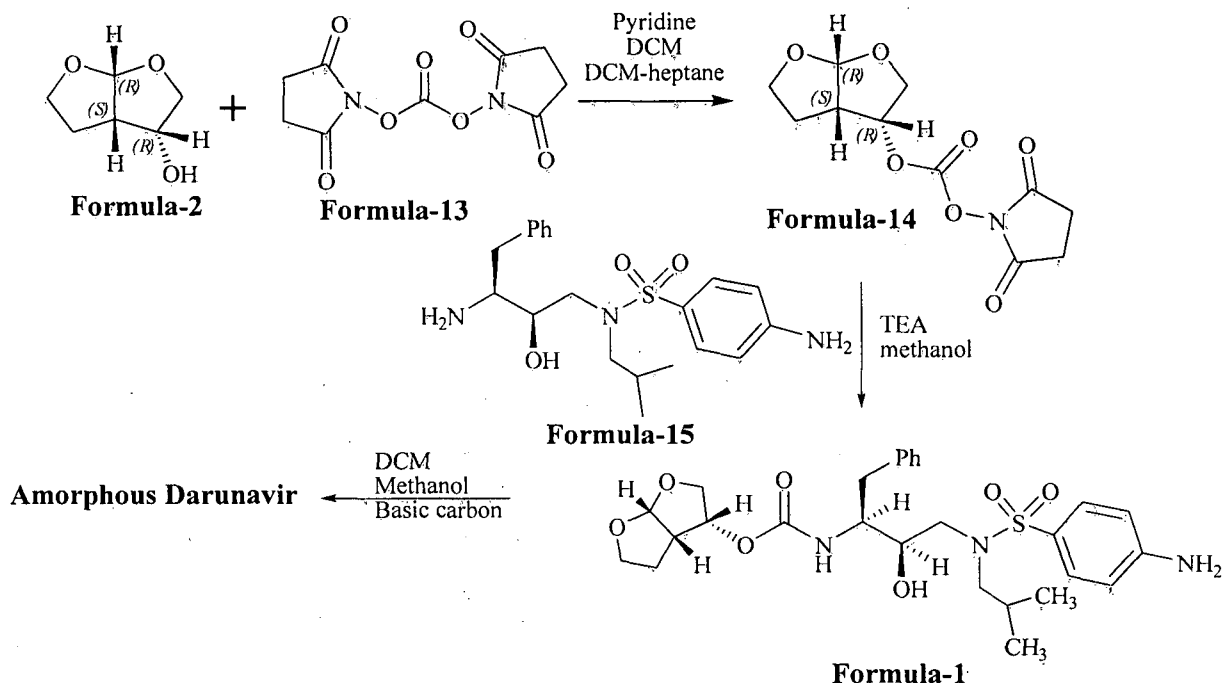
Scheme-I:



Scheme-II:



Scheme-III:



The process described in the present invention was demonstrated in examples illustrated below. These examples are provided as illustration only and therefore should not be construed as limitation of the scope of the invention.

5

Examples:

Example-1: Preparation of 5,6-O-isopropylidene-L-ascorbic acid (Formula-4)

A mixture of L-Ascorbic acid compound of formula-3 (50 gm) and acetone (250 ml) was stirred for 15 minutes. 2,2-Dimethoxy propane (62.5 ml) was added to the reaction mixture. Acidified the reaction mixture by using HCl gas and stirred for 4 hrs at 25-30°C. Cooled the reaction mixture to 5-10°C and stirred for 45 minutes at the same temperature. The precipitated solid was filtered, washed with acetone and dried to get the title compound. Yield: 50 gm; M.R: 205-210°C.

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Example-2: Preparation of Calcium-3,4-O-isopropylidene-L-threonic acid (Formula-5)

Calcium carbonate (115.5 gm) was added lot wise to the mixture of 5,6-O-isopropylidene-L-ascorbic acid compound of formula-4 (100 gm) and water (300 ml). Aqueous hydrogen peroxide (126 ml and water 84 ml) was added slowly to the reaction

mixture at 25-30°C and stirred for 5 hrs at the same temperature. Heated the reaction mixture to 55-60°C and stirred for 2 hrs at the same temperature. Manganese dioxide (1.2 gm) was added to the reaction mixture at 55-60°C and stirred for 2 hrs at the same temperature. Cooled the reaction mixture to 25-30°C. Filtered the undissolved salts through hyflow bed and washed with water. Some portion of water was distilled off from the filtrate. Cooled the reaction mixture to 25-30°C. Acetone was slowly added to the reaction mixture. Cooled the reaction mixture to 0-5°C and stirred for 4 hrs at the same temperature. The precipitated solid was filtered, washed with acetone and dried to get the title compound.

Yield: 55 gm; M.R: 260-266°C, SOR = +29.311 (c=0.9% water).

Example-3: Preparation of (S)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (Formula-6)

Sodium acetate (99 gm) and acetic acid (119.8 gm) were added to the mixture of calcium salt of 3,4-O-isopropylidene-L-threonic acid compound of formula-5 (65 gm) and water (520 ml). Heated the reaction mixture to 50-55°C. Sodium hypochlorite (284 ml) was slowly added to the reaction mixture at 50-55°C and stirred for 4 hrs at the same temperature. Cooled the reaction mixture to 25-30°C. Basify the reaction mixture by slowly adding sodium carbonate (105 gm) and stirred at 25-30°C for 15 minutes. The unwanted salt formed was filtered and washed with the mixture of dichloromethane and methanol. Both the organic and aqueous layers were separated from the filtrate. Sodium chloride (130 gm) was added to aqueous layer and extracted the aqueous layer with the mixture of dichloromethane and methanol. Combined the organic layers and distilled off the solvent completely from the organic layer under reduced pressure to get the title compound. Yield: 25 gm.

Example-4: Preparation of (R,E)-ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate (Formula-8)

Potassium tert-butoxide (20 gm) was added to the mixture of dichloromethane (200 ml) and triethyl phosphonoacetate compound of formula-7 (27.5 gm) at 0-5°C under nitrogen atmosphere. A solution of (S)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde compound of formula-6 (20 gm in 50 ml) in dichloromethane was slowly added to the reaction mixture at 0-5°C and stirred the reaction mixture for 4 hrs. Distilled off the solvent from the reaction mixture completely under reduced pressure at the same temperature. Ethyl acetate (50 ml)

followed by aqueous sodium bicarbonate solution (4 gm dissolved in 50 ml water) were added to the reaction mixture. Both the organic and aqueous layers were separated. Distilled off the solvent completely from the organic layer under reduced pressure to get the title compound. Yield: 18 gm, SOR = -30.24° (c=1% chloroform)

5

Example-5: Preparation of ethyl 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate (Formula-9)

A mixture of (R,E)-ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate compound of formula-8 (2 gm) and acetonitrile (20 ml) was cooled to 0-5°C. Nitromethane (0.67 gm) was added to the reaction mixture at 0-5°C and stirred for 10 minutes. 1,8-Diazabicyclo[5.4.0]undec-7-ene solution (2.3 gm in 6 ml of acetonitrile) was slowly added to the reaction mixture and stirred for 25 hrs at 25-30°C. Solvent from the reaction mixture was evaporated by purging nitrogen. Ethyl acetate and water was added to the reaction mixture. Both the organic and aqueous layers were separated. The aqueous layer was extracted with ethyl acetate. Combined the organic layers and washed with aq.HCl solution followed by with aqueous sodium bicarbonate solution. The solvent from the organic layer was evaporated by purging nitrogen to get the title compound. Yield: 2 gm

Example-6: Preparation of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol (Formula-2)

A mixture of sodium borohydride (0.7 gm), lithium bromide (1.6 gm) and tetrahydrofuran (50 ml) was cooled to 0-5°C. Ethyl 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate compound of formula-9 (5 gm) was added to the reaction mixture at 0-5°C. Raised the temperature of the reaction mixture to 25-30°C and stirred for 35 hrs at the same temperature. Potassium tert-butoxide (2 gm) was added to the above reaction mixture at 25-30°C under nitrogen atmosphere and stirred for 20 minutes. The reaction mixture was slowly added to the sulfuric acid solution (2.7 ml in 6 ml of water) at 0-5°C and stirred for 20 minutes. Raised the temperature of the reaction mixture to 25-30°C and stirred for 5 hrs at the same temperature. Cooled the reaction mixture to 0-5°C. Neutralized the reaction mixture by adding triethylamine. Filtered the reaction mixture through hyflow bed, washed with tetrahydrofuran. Distilled off the solvent from the filtrate under reduced pressure. Ethyl acetate was added to the obtained compound at 25-30°C and stirred for 5 minutes. Filtered

the undissolved salt through hyflow bed and washed with ethyl acetate. Distilled off the filtrate completely under reduced pressure to get the title compound. Yield: 1.5 gm

Example-7: Preparation of ethyl 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate (Formula-9)

A mixture of (R,E)-ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate compound of formula-8 (25 gm) and tetrahydrofuran (50 ml) was cooled to 0-5°C. Nitromethane (9 gm) was added to the reaction mixture at 0-5°C and stirred for 5 minutes. Tetrabutyl ammonium fluoride solution (39 gm in 250 ml tetrahydrofuran) was slowly added to the reaction mixture at 0-5°C and stirred the reaction mixture for 4 hrs at the same temperature. The solvent from the reaction mixture was evaporated by purging nitrogen. Ethyl acetate followed by aqueous sodium bicarbonate solution (4 gm in 30 ml of water) were added to the reaction mixture. Both the organic and aqueous layers were separated. The solvent from the organic layer was evaporated by purging nitrogen and purified by column chromatography using cyclohexane and ethylacetate as eluent to get the title compound. Yield: 25 gm

Example-8: Preparation of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol (Formula-2)

Hydrochloric acid (4 ml) was added to the mixture of ethyl 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate compound of formula-9 (10 gm) and methanol (100 ml) at 25-30°C and stirred for 3 hrs at the same temperature. Sodium bicarbonate (12 gm) was added to the reaction mixture at 25-30°C and stirred for 15 minutes at 25-30°C. Filtered the reaction mixture and washed with methanol. Distilled off the solvent completely under reduced pressure. Sodium borohydride (4.3 gm) and tetrahydrofuran (50 ml) were added to the obtained compound at 25-30°C. Heated the reaction mixture to 65-70°C. Methanol (25 ml) was added to the reaction mixture at 65-70°C and stirred for 3 hrs at the same temperature. Cooled the reaction mixture to 25-30°C. Methanol (25 ml) and potassium tert-butoxide (5 gm) were added to the reaction mixture at 25-30°C and stirred for 10 minutes. The reaction mixture was added to the pre-cooled mixture of methanol (25 ml) and hydrochloric acid (10 ml) at 0-5°C. Raised the reaction mixture temperature to 25-30°C and stirred for 3 hrs at the same temperature. Cooled the reaction mixture to 0-5°C. Neutralized the reaction mixture by adding triethylamine at 0-5°C. Raised the reaction mixture

temperature to 25-30°C. Filtered the reaction mixture through hyflow bed and washed with ethyl acetate. Distilled off the solvent from the filtrate. Ethyl acetate was added to the obtained compound and stirred for 5 minutes. Filtered the reaction mixture through hyflow bed and washed with ethyl acetate. Distilled off the solvent from the reaction mixture to get the title compound. Yield: 2.5 gm

Example-9: Preparation of Preparation of 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutan-1-ol (Formula-10)

A mixture of ethyl 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate compound of formula-9 (20 gm) and tetrahydrofuran (200 ml) was cooled to 0-5°C under nitrogen atmosphere. Lithium borohydride (60 ml) was added to the reaction mixture at 0-5°C. Raised the temperature of the reaction mixture to 25-30°C and stirred for 18 hrs at the same temperature. Cooled the reaction mixture to 0-5°C. Aqueous ammonium chloride solution (30 gm in 100 ml water) was added to the reaction mixture at 0-5°C. Raised the temperature of the reaction mixture to 25-30°C. Ethyl acetate was added to the reaction mixture. Both the organic and aqueous layers were separated. The aqueous layer was extracted with ethyl acetate. Combined the organic layers and washed with aq.sodium chloride solution. The solvent from the organic layer was evaporated by purging nitrogen to get the title compound. Yield: 9 gm

Example-10: Preparation of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol (Formula-2)

A mixture of sodium hydroxide (0.4 gm) and water (7 ml) was cooled to 5-10°C. 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutan-1-ol compound of formula-10 (1.8 gm) was added to the reaction mixture at 0-5°C. Sulfuric acid solution (1.2 ml in 8 ml of water) was slowly added to the reaction mixture at 5-10°C and stirred for 15 minutes at the same temperature. Raised the temperature of the reaction mixture to 25-30°C and stirred for 2 hrs at the same temperature. Sodium chloride (10 gm) and dichloromethane were added to the reaction mixture. The organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane. Distilled off the solvent completely from the organic layer under reduced pressure to get the title compound. Yield: 0.6 gm

Example-11: Preparation of 2,5-dioxopyrrolidin-1-yl (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl carbonate (Formula-14)

N,N'-Disuccinimidyl carbonate compound of formula-13 (148 gm) was added to the mixture of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2 (50 gm) and dichloromethane (500 ml) at 25-30°C. Pyridine (78 ml) was added to the reaction mixture at 25-30°C. Heated the reaction mixture at 40-45°C and stirred the reaction mixture for 17 hrs at the same temperature. Washed the reaction mixture with water followed by with sodium chloride solution. Distilled off the solvent under reduced pressure. Cooled the obtained compound to 25-30°C. Dichloromethane (100 ml) was added to the obtained compound at 25-30°C. Heated the reaction mixture to 35-40°C. N-heptane (100 ml) was slowly added to the reaction mixture. Cooled the reaction mixture to 0-5°C and stirred for 1.5 hrs at the same temperature. Filtered the precipitated solid, washed with n-heptane and dried to get the title compound. Yield: 83 gm

Example-12: Preparation of [(1S,2R)-3-[[4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl ester (Formula-1)

2,5-dioxopyrrolidin-1-yl (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl carbonate compound of formula-14 (25 gm) was added to the mixture of 4-amino-N-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-isobutylbenzenesulfonamide compound of formula-15 (36.8 gm) and methanol (125 ml) and stirred for 15 minutes. Triethylamine (13 ml) was added to the reaction mixture at 25-30°C and stirred for 3 hrs at the same temperature. Cooled the reaction mixture to 0-5°C and stirred for 1.5 hrs at the same temperature. Filtered the reaction mixture, washed with methanol and dried to get the title compound. Yield: 45 gm

Example-13: Preparation of Amorphous [(1S,2R)-3-[[4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl ester (Formula-1)

[(1S,2R)-3-[[4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl ester (50 gm) was added to a mixture of dichloromethane (27 ml) and methanol (150 ml). Carbon (5 gm in

23 ml of methanol) was added to the reaction mixture. Heated the reaction mixture to 55-60°C and stirred for 20 minutes at the same temperature. Filtered the reaction mixture and washed with a mixture of methanol (40 ml) and dichloromethane (6 ml). The filtrate was cooled to 0-5°C under nitrogen atmosphere and stirred for 4 hrs at the same temperature. 5 Filtered the precipitated solid under nitrogen atmosphere, washed with chilled methanol and dried under reduced pressure to get the title compound. Yield: 44 gm.

The PXRD & IR patterns of the obtained compound is well matching with the PXRD & IR patterns of compound of formula-1 as per the process disclosed in US6248775 B2 10 which is depicted in figure-1 & figure-2.

Example-14: Preparation of 4-Amino-N-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-isobutyl benzenesulfonamide:

Ethyl acetate (250 ml) was added to 2R-hydroxy-3-[[[(4-nitro phenyl)sulfonyl](2-methoxypropyl)amino]-1S-(phenyl methyl)propyl carbonic acid phenylmethyl ester (50 gms) 15 at 25-30°C. Palladium carbon (2.5 gms) was added to the reaction mixture at 25-30°C under hydrogen pressure. Heated the reaction mixture to 40-45°C and stirred for 6 hours at the same temperature. Filtered the reaction mixture through hyflow bed and washed with ethyl acetate then followed by water. Distilled off the solvent completely from the organic layer 20 under reduced pressure.

Isopropanol (200 ml) was added to the obtained solid at 25-30°C. Heated the reaction mixture to 70-75°C and stirred for 20 minutes at the same temperature. Slowly cooled the reaction mixture to 25-30°C further cooled to 0-5°C and stirred for 3 hours at the same temperature. Filtered the precipitated solid, washed with isopropanol and dried to get the title 25 compound. Yield: 26.1 gms.

Example-15: Preparation of (R)-methyl-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxyacetate:

Acetone (1000 ml) was added to L-ascorbic acid (200 gms) at 25-30°C and stirred for 30 10 minutes at the same temperature. 2,2-dimethoxy propane (212.5 gms) was added to the reaction mixture at 25-30°C. Acidifying the reaction mixture by using hydrochloric acid gas

at 25-30°C and stirred for 4 hours at the same temperature. Cooled the reaction mixture to 0-5°C and stirred for 45 minutes at the same temperature. Filtered the precipitated solid and washed with acetone.

Water (900 ml) and sodium hydroxide (18.2 gms) were added to the obtained solid at 25-30°C and stirred for 10 minutes at the same temperature. Sodium bicarbonate (190.7 gms) was added portion wise to the reaction mixture at 25-30°C. Heated the reaction mixture to 45-50°C. Hydrogen peroxide (566 ml) was slowly added to the reaction mixture at 45-50°C within 7 hours and stirred for 24 hours at the same temperature. Sodium sulfite (57.2 gms) was added to the reaction mixture at 45-50°C and stirred for 45 minutes at the same temperature. Sodium bicarbonate (467.4 gms) was added to the reaction mixture at 25-30°C and heated to 45-50°C. Dimethylsulphate (701.1 gms) was slowly added to the reaction mixture at 50°C within 6 hours and stirred for 4 hours at the same temperature. Cooled the reaction mixture to 25-30°C. Filtered the reaction mixture through hyflow bed and washed with water. Obtained filtrate was extracted twice with dichloromethane. Distilled off the solvent completely from the organic layer under reduced pressure and dried to get the title compound. Yield: 148 gms.

Example-16: Preparation of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol:

Dichloromethane (1500 ml) was added to (R)-methyl-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxyacetate (150 gms) at 25-30°C and stirred for 10 minutes at the same temperature. Sodium borohydride (45 gms) was added to the reaction mixture at 0-5°C. Methanol (150 ml) was slowly added to the reaction mixture at 0-5°C and stirred for 30 minutes at the same temperature. Raised the temperature of the reaction mixture to 25-30°C and stirred for 6 hours at the same temperature. Acetic acid (71 gms) was slowly added the reaction mixture at 0-5°C and stirred for 90 minutes at the same temperature. Filtered the reaction mixture through hyflow bed and washed with dichloromethane.

Sodium bicarbonate solution (10 gm dissolved in 234 ml water) was added to the obtained filtrate at 25-30°C. Sodium periodate (308.7 gms) was added portion wise to the reaction mixture at 25-30°C and stirred for 6 hours at the same temperature. Filtered the reaction mixture through hyflow bed and washed with dichloromethane. Distilled off the solvent completely from the obtained filtrate under reduced pressure. Dichloromethane (330

ml) was added to the reaction mixture and added to a pre-cooled mixture of triethyl phosphonoacetate (227.3 gms), potassium tertiary butoxide (113.8 gms) and dichloromethane at 0-5°C and stirred for 5 hours at the same temperature. Sodium chloride solution (99 gm dissolved in 330 ml of water) was added to the reaction mixture at 0-5°C. Filtered the
5 reaction mixture through hyflow bed and washed with dichloromethane. Both the organic and aqueous layers were separated and distilled off the solvent completely from the organic layer under reduced pressure.

Tetrahydrofuran (168 ml) was added to the above obtained compound at 25-30°C and cooled to 0-5°C. Nitromethane (38.3 gms) was added to the reaction mixture at 0-5°C and
10 stirred for 10 minutes at the same temperature. Tetrabutyl ammoniumfluoride solution (164.5 gm dissolved in 840 ml of tetrahydrofuran) was slowly added to the reaction mixture at 0-5°C and stirred for 5 hours at the same temperature. Dichloromethane (252 ml) and sodium bicarbonate solution (21 gm dissolved in 420 ml of water) were added to the reaction mixture at 0-5°C and stirred for 10 minutes at the same temperature. Both the organic and aqueous
15 layers were separated and washed the organic layer with sodium chloride solution and distilled off the solvent completely from organic layer under reduced pressure.

Tetrahydrofuran (840 ml) was added to the reaction mixture at 25-30°C and slowly added to a mixture of sodium borohydride (36.6 gms), lithium bromide (82.9 gms) and tetrahydrofuran at 25-30°C. Stirred the reaction mixture for 60 minutes at 25-30°C. Heated
20 the reaction mixture to 45-50°C and stirred for 24 hours at the same temperature. Cooled the reaction mixture to 0-5°C and ammonium chloride solution (147 gm dissolved in 420 ml of water) was slowly added to the reaction mixture at the same temperature. Filtered the reaction mixture through hyflow bed and washed with tetrahydrofuran. Both the organic and aqueous layers were separated. Potassium tertiarybutoxide (39.2 gms) was added to the
25 organic layer at 25-30°C and stirred for 20 minutes at the same temperature. Reaction mixture was slowly added to pre-cooled aqueous sulfuric acid solution at 0-5°C and stirred for 20 minutes at the same temperature. Raised the temperature of the reaction mixture to 25-30°C and stirred for 5 hours at the same temperature.

Triethylamine (46.46 gms) was added to the reaction mixture at 0-5°C and stirred for
30 30 minutes at the same temperature. Filtered the reaction mixture through hyflow bed and

washed with tetrahydrofuran. Distilled off the solvent completely from the obtained filtrate under reduced pressure. Ethylacetate (320 ml) was added to the reaction mixture at 25-30°C. Filtered the reaction mixture through hyflow bed and washed with ethyl acetate. Distilled off the solvent completely from the obtained filtrate under reduced pressure. Ethylacetate (64 ml) was again added to the reaction mixture at 25-30°C and distilled off the solvent completely from the reaction mixture under reduced pressure.

Yield: 22 gms.

Example-17: Preparation of 2,5-dioxopyrrolidin-1-yl-((3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl) carbonate:

N,N-disuccinimidyl carbonate (44.28 gms) and pyridine (23.3 ml) were added to a mixture of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol (15 gms) and dichloromethane (150 ml) at 25-30°C and stirred for 10 minutes at the same temperature. Heated the reaction mixture to 40-45° and stirred for 17 hours at the same temperature. Distilled off the solvent completely from the reaction mixture under reduced pressure. Dichloromethane (150 ml) and water (75 ml) were added to the reaction mixture at 25-30°C and stirred for 15 minutes at the same temperature. Filtered the reaction mixture through hyflow bed and washed with dichloromethane. Both the organic and aqueous layers were separated from the obtained filtrate. Organic layer was washed with citric acid solution (0.75 gm dissolved in 30 ml of water) then followed by with water. Distilled off the solvent completely from the organic layer under reduced pressure. n-hexane (45 ml) was added to the reaction mixture and distilled off the solvent completely from the reaction mixture. n-hexane (45 ml) was again added to the reaction mixture and distilled off the solvent completely from the reaction mixture.

Pre-cooled methanol (75 ml) was added to the reaction mixture at 0-5°C and stirred for 45 minutes at the same temperature. Filtered the precipitated solid, washed with methanol and dried to get the title compound. Yield: 25 gms.

Example-18: Preparation of Darunavir:

4-Amino-N-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-isobutylbenzene sulfonamide (159 gms) was added to a mixture of 2,5-dioxopyrrolidin-1-yl-((3R,3aS,6aR)-

hexahydrofuro[2,3-b]furan-3-yl) carbonate (100 gms) and methanol (500 ml) at 25-30°C. Triethylamine (37.2 gms) was slowly added to the reaction mixture at 25-30°C and stirred for 3 hours at the same temperature. Cooled the reaction mixture to 0-3°C and stirred for 2 hours at the same temperature. Filtered the precipitated solid, washed with pre-cooled methanol and dried to get the title compound.

Yield: 182 gms.

Example-19: Preparation of Amorphous form of Darunavir:

A mixture of Darunavir (80 gms), dichloromethane (53 ml) and methanol (346 ml) were stirred for 10 minutes at 25-30°C. Heated the reaction mixture to 50-55°C and stirred for 20 minutes at the same temperature. Cooled the reaction mixture to 0-3°C and stirred for 4 hours at the same temperature. Filtered the precipitated solid and washed with methanol.

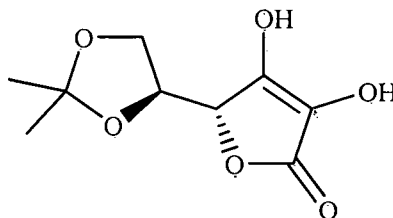
Methanol (249 ml) and dichloromethane (38.4 ml) were added to the obtained wet compound at 25-30°C and stirred for 15 minutes at the same temperature. Heated the reaction mixture to 50-55°C and stirred for 20 minutes at the same temperature. Carbon (8 gms) was added to the reaction mixture at 50-55°C and stirred for 30 minutes at the same temperature. Filtered the reaction mixture through hyflow bed and washed with a mixture of methanol and dichloromethane. Cooled the obtained filtrate to 0-3°C and stirred for 4 hours at the same temperature. Filtered the reaction mixture and washed with methanol.

Methanol (1.6 ml) and dichloromethane (160 ml) were added to the obtained wet compound at 25-30°C and stirred for 20 minutes at the same temperature. Filtered the reaction mixture through hyflow bed and washed with dichloromethane. Distilled off the solvent completely from the reaction mixture under reduced pressure. Cyclohexane (160 ml) was added to the obtained solid at 25-30°C and stirred for 4 hours at the same temperature. Filtered the precipitated solid, washed with cyclohexane and dried to get the title compound. Yield: 65 gms.

We Claim:

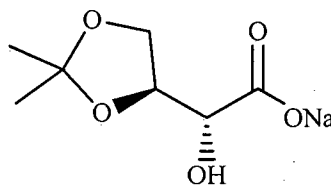
1. A process for the preparation of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2, comprising of:

- 5 a) Reacting the L-Ascorbic acid compound of formula-3 with 2,2-dimethoxypropane in a suitable solvent to provide 5,6-O-isopropylidene-L-ascorbic acid compound of formula-4,



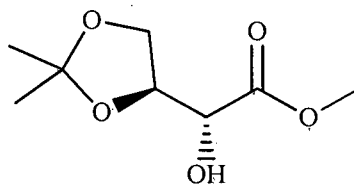
Formula-4

- 10 b) oxidizing the compound of formula-4 in-situ with a suitable oxidizing agent in presence of sodium hydroxide in a suitable solvent to provide sodium salt of 3,4-O-isopropylidene-L-threonic acid compound of formula-16,



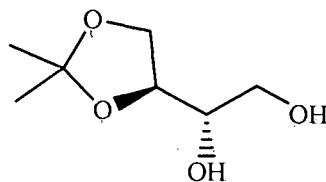
Formula-16

- 15 c) reacting the compound of formula-16 in-situ with a suitable alkylating agent in presence of a suitable base in a suitable solvent to provide (R)-methyl-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxyacetate compound of formula-17,



Formula-17

- 20 d) reducing the compound of formula-17 with a suitable reducing agent in a suitable solvent to provide (S)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol compound of formula-18,



Formula-18

- e) reacting compound of formula-18 in-situ with sodium periodate in presence of suitable base in a suitable solvent to provide (S)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde compound of formula-6,
- f) reacting compound of formula-6 in-situ with ethyl-2-(diethoxyphosphoryl)acetate compound of formula-7 in presence of a base in a suitable solvent to provide α,β -unsaturated ester i.e., (R,E)-ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate compound of formula-8,
- g) reacting ester compound of formula-8 in-situ with nitromethane in presence of a base in a suitable solvent to provide ethyl 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate compound of formula-9,
- h) reducing compound of formula-9 in-situ with a suitable reducing agent in presence of lithium bromide in a suitable solvent to provide 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutan-1-ol compound of formula-10,
- i) cyclization of compound of formula-10 in-situ in presence of a suitable base and a suitable inorganic acid in a suitable solvent with a proviso that the solvent is not an alcohol solvent to provide (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2.

2. The process according to claim-1, wherein,

in step-a) to g) the suitable solvent is selected from ester solvents, ether solvents, chloro solvents, hydrocarbon solvents, ketone solvents, alcohol solvents, polar solvents such as water or mixture thereof;

in step-h) to i) the suitable solvent is selected from ester solvents, ether solvents, chloro solvents, hydrocarbon solvents, ketone solvents, polar solvents such as water or mixture thereof;

in step-c), e), f), g) and i) the suitable base is selected from organic or inorganic base;

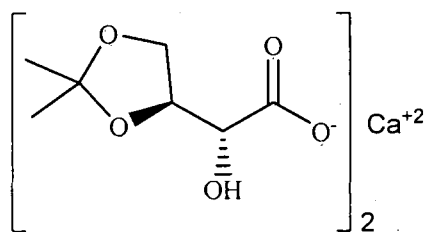
in step-d) & h) the suitable reducing agent is selected from Lithium aluminum hydride

(LiAlH₄), hydroquinone, sodium amalgam, diborane, sodium borohydride, lithium borohydride, compounds containing the Sn⁺² ion such as tin(II)chloride, sulfite compounds, hydrazine, zinc-mercury amalgam, diisobutylaluminum hydride
 5 (DIBAL-H), Lindlar catalyst, dithiothretol (DTT), compounds containing Fe⁺² ion such as iron(II)sulfate, carbon monoxide and the like,

in step-i) a suitable inorganic acid is selected from hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, sulfamic acid and the like.

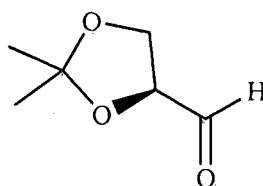
- 10 3. A process for the preparation of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2, comprising of:
 - a) Reacting L-Ascorbic acid compound of formula-3 with 2,2-dimethoxypropane in acetone to provide 5,6-O-isopropylidene-L-ascorbic acid compound of formula-4,
 - b) oxidizing compound of formula-4 in-situ with hydrogen peroxide in presence of
 15 sodium hydroxide in water to provide sodium salt of 3,4-O-isopropylidene-L-threonic acid compound of formula-16,
 - c) reacting compound of formula-16 in-situ with dimethyl sulfate in presence of sodium bicarbonate in dichloromethane to provide (R)-methyl-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxyacetate compound of formula-17,
 - 20 d) reducing the compound of formula-17 with sodium borohydride in a mixture of dichloromethane and methanol to provide (S)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol compound of formula-18,
 - e) reacting compound of formula-18 in-situ with sodium periodate in presence of sodium bicarbonate in dichloromethane to provide (S)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde compound of formula-6,
 25
 - f) reacting compound of formula-6 in-situ with ethyl-2-(diethoxyphosphoryl)acetate compound of formula-7 in presence of potassium tert-butoxide in dichloromethane provides α,β -unsaturated ester i.e., (R,E)-ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate compound of formula-8,

- g) reacting ester compound of formula-8 in-situ with nitromethane in presence of tetrabutylammoniumfluoride in tetrahydrofuran provides ethyl 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate compound of formula-9,
- h) reducing compound of formula-9 in-situ with sodium borohydride in presence of lithium bromide in tetrahydrofuran provides 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutan-1-ol compound of formula-10,
- i) cyclization of compound of formula-10 in-situ in presence of potassium tert-butoxide and aqueous sulfuric acid in tetrahydrofuran provides (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2.
4. A process for the preparation of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2, comprising of:
- a) Reacting the L-Ascorbic acid compound of formula-3 with 2,2-dimethoxypropane in a suitable solvent to provide 5,6-O-isopropylidene-L-ascorbic acid compound of formula-4,
- b) oxidizing the compound of formula-4 with a suitable oxidizing agent in presence of calcium carbonate in a suitable solvent to provide calcium salt of 3,4-O-isopropylidene-L-threonic acid compound of formula-5,



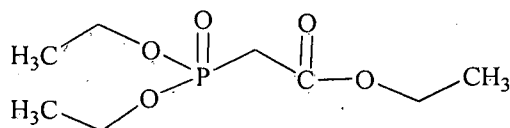
Formula-5

- c) reacting the compound of formula-5 with sodium hypochloride in presence of acetic acid and sodium acetate in a suitable solvent to provide (S)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde compound of formula-6,



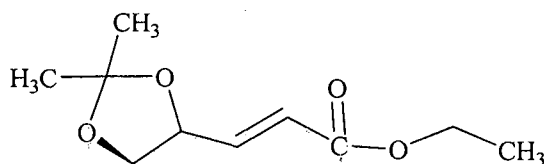
Formula-6

- d) reacting the compound of formula-6 with ethyl-2-(diethoxyphosphoryl)acetate compound of formula-7,



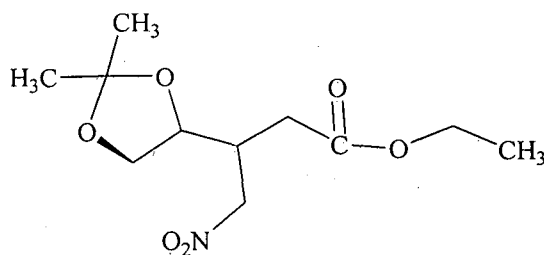
Formula-7

- 5 in presence of a base in a suitable solvent to provide α,β -unsaturated ester (R,E)-ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate compound of formula-8,



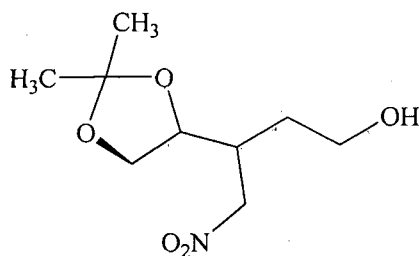
Formula-8

- 10 e) reacting the ester compound of formula-8 with nitromethane in presence of a base in a suitable solvent to provide ethyl 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate compound of formula-9,



Formula-9

- 15 f) reducing the compound of formula-9 with a suitable reducing agent in presence of lithium bromide in a suitable solvent to provide 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutan-1-ol compound of formula-10,



Formula-10

- 20 g) cyclization of compound of formula-10 in presence of a suitable base and a suitable inorganic acid in a suitable solvent with a proviso that the solvent is not an alcohol

solvent to provide (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2.

5. The process according to claim-4, wherein,

5 in step-c), d), e) and f) the suitable solvent is selected from ester solvents, ether solvents, chloro solvents, hydrocarbon solvents, ketone solvents and alcohol solvents or mixture thereof;

in step-g) the suitable solvent is selected from ester solvents, ether solvents, chloro solvents, hydrocarbon solvents, ketone solvents or mixture thereof;

10 in step-d), e) and g) the suitable base is selected from organic or inorganic base;

in step-f) a suitable reducing agent is selected from Lithium aluminum hydride (LiAlH_4), hydroquinone, sodium amalgam, diborane, sodium borohydride, lithium borohydride, compounds containing the Sn^{+2} ion such as tin(II)chloride, sulfite compounds, hydrazine, zinc-mercury amalgam, diisobutylaluminum hydride (DIBAL-H), Lindlar catalyst, dithiothretol (DTT), compounds containing Fe^{+2} ion such as iron(II)sulfate, carbon monoxide and the like,

in step-g) a suitable inorganic acid is selected from hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, sulfamic acid and the like.

20 6. A process for the preparation of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2, comprising of:

a) Reacting the L-Ascorbic acid compound of formula-3 with 2,2-dimethoxypropane in acetone provides 5,6-O-isopropylidene-L-ascorbic acid compound of formula-4,

25 b) oxidizing the compound of formula-4 with hydrogen peroxide in presence of calcium carbonate in water followed by treatment with manganese dioxide provides calcium salt of 3,4-O-isopropylidene-L-threonic acid compound of formula-5,

c) reacting the compound of formula-5 with sodium hypochloride in presence of acetic acid and sodium acetate in water provides (S)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde compound of formula-6,

30 d) reacting the compound of formula-6 with ethyl-2-(diethoxyphosphoryl)acetate compound of formula-7 in presence of potassium tert-butoxide in dichloromethane

provides α,β -unsaturated ester i.e., (R,E)-ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate compound of formula-8,

e) reacting ester compound of formula-8 with nitromethane in presence of 1,8-Diazabicyclo[5.4.0]undec-7-ene in acetonitrile provides ethyl 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate compound of formula-9,

f) reducing compound of formula-9 with sodium borohydride in presence of lithium bromide in tetrahydrofuran provides 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutan-1-ol compound of formula-10,

g) cyclization of compound of formula-10 in presence of potassium tert-butoxide and sulfuric acid in a mixture of tetrahydrofuran and water provides (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2.

7. A process for the preparation (R)-methyl-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxyacetate compound of formula-17, comprising of:

a) Reacting the L-Ascorbic acid compound of formula-3 with 2,2-dimethoxypropane in acetone to provide 5,6-O-isopropylidene-L-ascorbic acid compound of formula-4,

b) oxidizing the compound of formula-4 in-situ with hydrogen peroxide in presence of sodium hydroxide in water to provide sodium salt of 3,4-O-isopropylidene-L-threonic acid compound of formula-16,

c) reacting the compound of formula-16 in-situ with dimethyl sulfate in presence of sodium bicarbonate in dichloromethane to provide (R)-methyl-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-hydroxyacetate compound of formula-17.

8. A process for the preparation of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2, comprising of:

a) Reducing the compound of formula-17 with sodium borohydride in a mixture of dichloromethane and methanol to provide (S)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol compound of formula-18,

b) reacting compound of formula-18 in-situ with sodium periodate in presence of sodium bicarbonate in dichloromethane to provide (S)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde compound of formula-6,

- c) reacting compound of formula-6 in-situ with ethyl-2-(diethoxyphosphoryl)acetate compound of formula-7 in presence of potassium tert-butoxide in dichloromethane provides α,β -unsaturated ester i.e., (R,E)-ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate compound of formula-8,
- 5 d) reacting ester compound of formula-8 in-situ with nitromethane in presence of tetrabutylammoniumfluoride in tetrahydrofuran provides ethyl 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate compound of formula-9,
- e) reducing compound of formula-9 in-situ with sodium borohydride in presence of lithium bromide in tetrahydrofuran provides 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-
- 10 4-nitrobutan-1-ol compound of formula-10,
- f) cyclization of compound of formula-10 in-situ in presence of potassium tert-butoxide and aqueous sulfuric acid in tetrahydrofuran provides (3R,3aS,6aR)-hexahydro furo[2,3-b]furan-3-ol compound of formula-2.
- 15 9. A process for the preparation of (R,E)-ethyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate compound of formula-8, comprising of reacting the compound of formula-6 with ethyl-2-(diethoxyphosphoryl)acetate compound of formula-7 in presence of a base selected from alkoxide base preferably potassium tert-butoxide in a suitable solvent selected from chloro solvent preferably dichloromethane to provide α,β -unsaturated ester i.e., (R,E)-
- 20 ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate compound of formula-8.
10. A process for the preparation of ethyl-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate compound of formula-9, comprising of reacting ester compound of formula-8 with nitromethane in presence of a base in a suitable solvent to provide ethyl
- 25 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate compound of formula-9.
11. A process for the preparation of ethyl-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate compound of formula-9, comprising of reacting ester compound of formula-8 with nitromethane in presence of tetrabutylammonium fluoride in
- 30 tetrahydrofuran provides ethyl 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate compound of formula-9.

12. A process for the preparation of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2, comprising of:
- a) Reducing compound of formula-9 with a suitable reducing agent in presence of lithium bromide in a suitable solvent to provide 3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutan-1-ol compound of formula-10,
 - b) cyclizing the compound of formula-10 in presence of a suitable base and a suitable inorganic acid in a suitable solvent to provide (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2 with a proviso that the solvent is not alcohol solvent.
13. A process for the preparation of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2, comprising of cyclizing the compound of formula-10 in presence of potassium tert-butoxide and aqueous sulfuric acid in tetrahydrofuran to provide (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2.
14. A process for the preparation of Amorphous [(1S,2R)-3-[[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid (3R,3aS,6aR)-hexahydrofuro [2,3-b]furan-3-yl ester compound of formula-1, comprising of:
- a) Reacting (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2 obtained from any of the preceding claims with N,N'-disuccinimidyl carbonate compound of formula-13 in presence of pyridine in dichloromethane provides 2,5-dioxopyrrolidin-1-yl(3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ylcarbonate compound of formula-14,
 - b) purifying the obtained compound using n-hexane and methanol provides pure compound of formula-14,
 - c) reacting compound of formula-14 with 4-amino-N-((2R,3S)-3-amino-2-hydroxy-4-phenylbutyl)-N-isobutylbenzenesulfonamide compound of formula-15 in presence of triethylamine in methanol provides [(1S,2R)-3-[[[(4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl ester compound of formula-1,

d) purifying the compound of formula-1 in a mixture of dichloromethane and methanol and followed by slurrying the obtained compound from cyclohexane provides pure amorphous [(1S,2R)-3-[[4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl ester compound of formula-1.

15. Use of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2 obtained from any of the preceding claims for the preparation of pure [(1S,2R)-3-[[4-aminophenyl)sulfonyl](2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-yl ester compound of formula-1.

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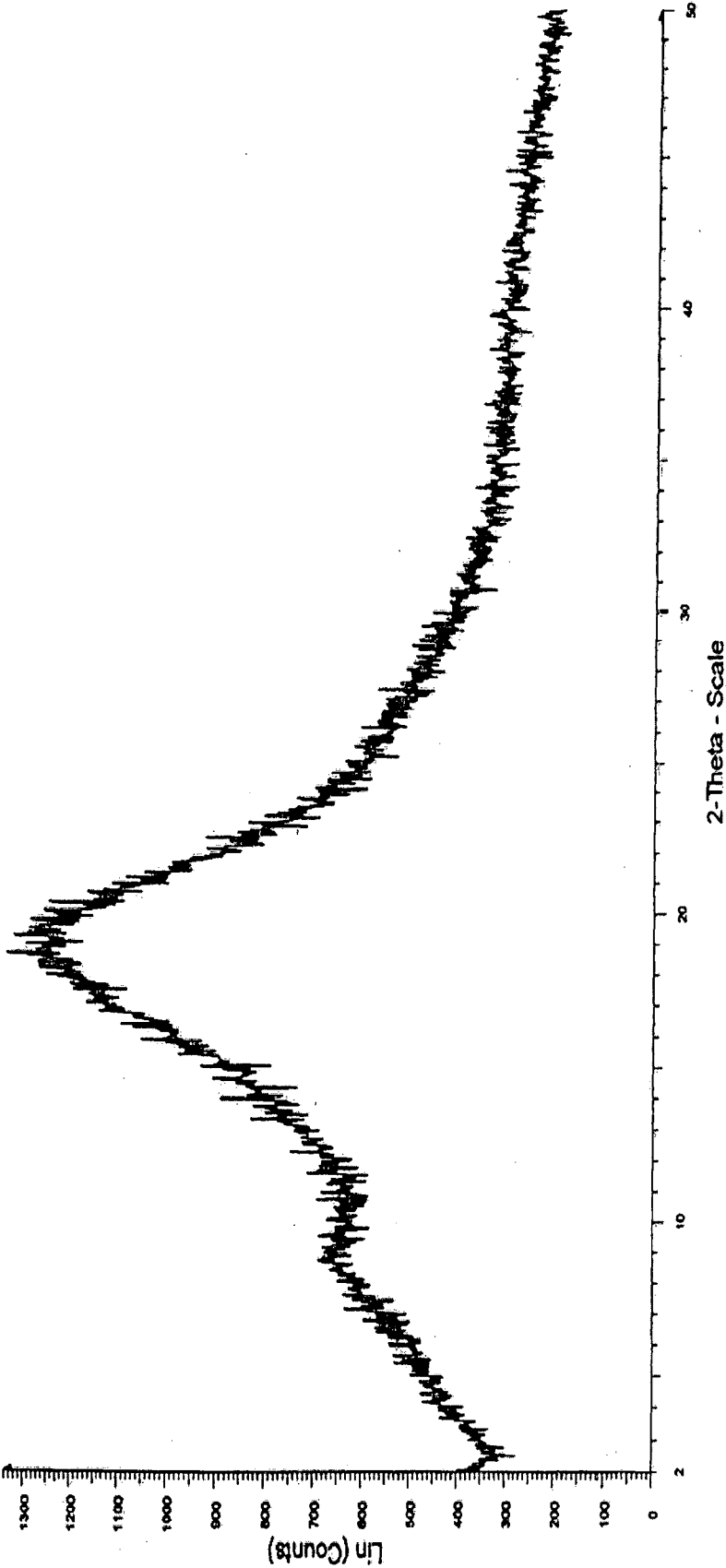


Figure-1

MSN Laboratories Private Limited

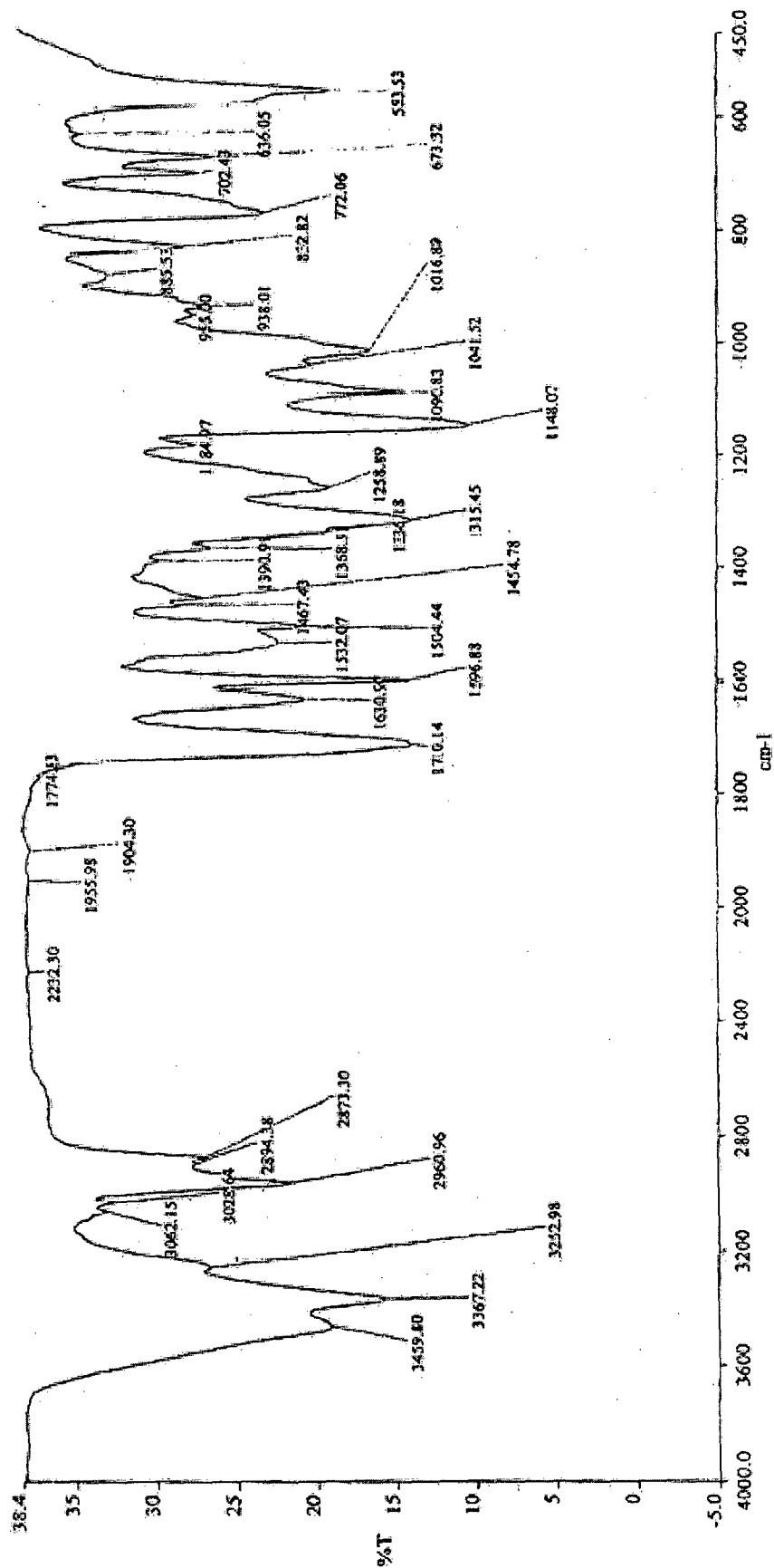


Figure-2

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2016/000168

A. CLASSIFICATION OF SUBJECT MATTER
C07D493/04 Version=2016.01

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 practicable, search terms used)

Patseer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO2008112286 A9; 18-09-2008; Jennifer Riggs-Sauthier Bo-Liang Deng Zhongxu Ren Wen Zhang Xuyuan Gu Franco J. Duarte Example 11; para [0212]	1-15
Y	----- CN104230877 A; 24-12-2014; ZENG XIUXIU; HE LIANG ; para [0018-0019]	1-15

☐ Further documents are listed in the continuation of Box C. ☒ See patent family 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 application or patent 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

"&" document member of the same patent family

Date of the actual completion of the international search

17-10-2016

Date of mailing of the international search report

17-10-2016

Name and mailing address of the ISA/

Indian Patent Office
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2016/000168

Box No. 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:

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 No. 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:
The International Searching Authority (ISA) found multiple inventions in this international application, as follows:

Group I: claims:1-6, 8,12-13 & 15; Process for the preparation of (3R,3aS,6aR)-hexahydrofuro[2,3-b]furan-3-ol compound of formula-2 using different-different reagents and alternative methods and use of formula 2,
Group II: claim 7: process for the preparation (R)-methyI-2-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)-2- hydroxyacetate compound of formula-17,
Group III: claim:9; process for the preparation of

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 additional fees, this Authority did not invite payment of additional fees.
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 and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2016/000168

Citation	Pub.Date	Family	Pub.Date
WO 2008112286 A9	18-09-2008	AU 2008226820 A1	18-09-2008
		CA 2679473 A1	18-09-2008
		CN 102816111 A	12-12-2014

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IN2016/000168

Continuation of Observations where unity of invention is lacking (Box III)

(R,E)-ethyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate compound of formula-8,

Group IV: claims 10-11 ; process for the preparation of ethyl-3-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-nitrobutanoate compound of formula-9 using two different alternatives method,

Group V: claim 14: process for the preparation of Amorphous [(1S,2R)-3-[[(4-aminophenyl)sulfonyl] (2-methylpropyl)amino]-2-hydroxy-1-(phenylmethyl)propyl]carbamic acid (3R,3aS,6aR)-hexahydrofuro [2,3-b]furan-3-yl ester compound of formula-1,

Claims 1-15 are drafted in such a way that they claiming the process for preparation of formula 1, 2 & different intermediates products, it does not constitute a special technical feature within the meaning of PCT Rule 13.2, because the common feature does not satisfy the requirement for being a special technical feature it follows that it cannot provide the necessary technical relationship between the identified inventions. Therefore the claims do not satisfy the requirement of unity of invention, a posteriori. Hence, ISA is of the opinion that claims 1-15 are not so linked as to form a single general inventive concept as per the requirement of Rule 13.1 of PCT and are non-unitary.