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(71) Applicant: AMNEAL PHARMACEUTICALS COMPANY GMBH [CH/CH]; Turmstrasse 30, 6312 Steinhausen (CH).

(72) Inventors: AGARWAL, Virendra Kumar; A14, Vishal residency, Anandnagar char-rasta, Satellite, Ahmedabad, Gujarat (IN). **KOILPILLAI, Joseph Prabahar;** H-56, TNHB phase-II, Perumalpuram, Tirunelveli, Tamil Nadu (IN). **MAHETA, Abhay Subodhbhai;** F-302, Binori Sonnet, Nr. Govt. tubewell, Opp. Rangsagar Society, Bopal, Ahmedabad, Gujarat (IN). **KANERIA, Ankur Amrutbhai;** 603,Mansi Residence, Ahmedabad, Gujarat (IN). **SAVALIYA, Bhavesh Laljibhai;** 50, Satyanarayan Society, Ahmedabad, Gujarat (IN). **BHESANIYA, Kapil Dhanjibhai;** H-302, Sarovar-5, Ahmedabad, Gujarat (IN).

(74) Agent: ZIMMERMANN & PARTNER PATENTANWÄLTE MBB; Josephspitalstr. 15, 80331 Munchen (DE).

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(54) Title: PROCESS FOR PREPARATION OF DAPAGLIFLOZIN AND INTERMEDIATES THEREOF

(57) Abstract: Processes for the preparation of dapagliflozin reduce or eliminate impurities in dapagliflozin, preferably individual impurities are not more than 0.15% by HPLC.

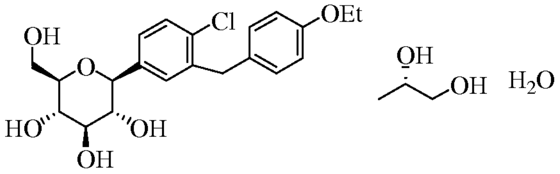
PROCESS FOR PREPARATION OF DAPAGLIFLOZIN AND INTERMEDIATES THEREOF

FIELD OF INVENTION

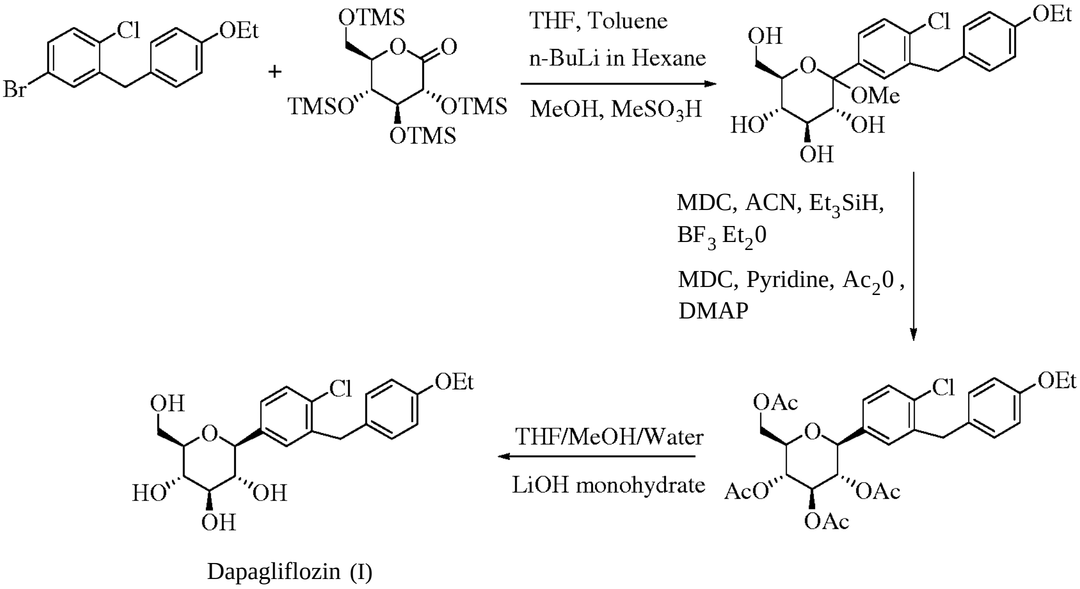
The present invention relates to processes for the preparation of dapagliflozin. The present invention also relates to a novel intermediate and its use in the preparation of dapagliflozin.

BACKGROUND OF THE INVENTION

Dapagliflozin is a potent, highly selective and orally-active inhibitor of human renal sodium-glucose co-transporter 2 (SGLT2), the major transporter responsible for renal glucose reabsorption. Dapagliflozin propanediol monohydrate is chemically designated as (2R,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol, (2S)-l,2-propanediol, monohydrate and is marketed as Farxiga® by AstraZeneca for the treatment of type 2 diabetes mellitus. Its chemical structure is represented by following structure formula.

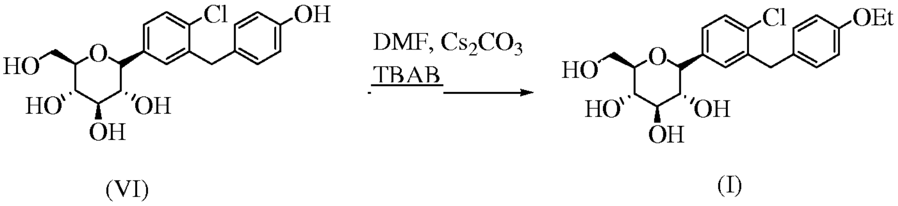


U.S. Patent No. 6,515,117 first disclosed process for the preparation of dapagliflozin and its purification by making tetraacetylated dapagliflozin using pyridine and then deprotecting tetraacetylated dapagliflozin using lithium hydroxide monohydrate to provide dapagliflozin as an off-white solid with purity 94%. This process results in a final product of low purity which makes multiple purification steps unavoidable which results desired product in a very low yield. Hence, there is a need in the art to develop dapagliflozin with high purity and yield. The process for preparation of dapagliflozin described in U.S. Patent No. 6,515,117 is given in the below Scheme-I.



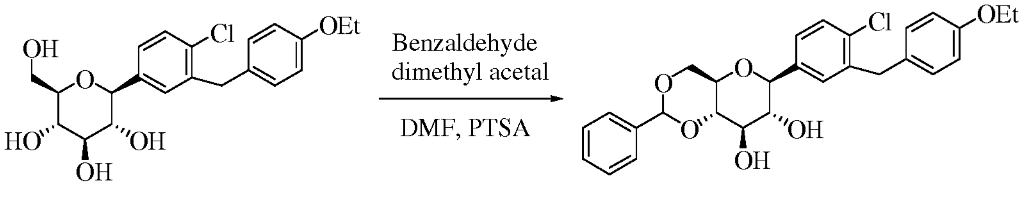
Scheme-I

JMC, 2014, 57, 4, 1236-1251 discloses reaction of (2R,3R,4R,5S,6R)-2-(4-chloro-3-(4-hydroxybenzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2/-/-pyran-3,4,5-triol of formula (VI) with ethyl p-toluenesulfonate using DMF, cesium carbonate and TBAB to provide dapagliflozin as a residue which was purified by preparative TLC to provide dapagliflozin as a white solid with purity 99.8%. This process involves purification of dapagliflozin by preparative TLC which is not feasible on an industrial scale.



Scheme-II

US2011/0059910 AI and Medicinal Chemistry, 2014, 10, 3, 304-317 discloses reaction of dapagliflozin with benzaldehyde dimethyl acetal using DMF in presence of catalyst such as para toluenesulfonic acid and camphorsulfonic acid to provide (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2-phenylhexahydropyrano[3,2-d] [l,3]dioxine-7,8-diol of formula (VIII) followed by purification using column chromatography.



(I) (VIII)

Scheme-III

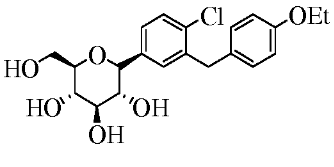
In view of the above disadvantages associated with the processes known in the art for the preparation of dapagliflozin, there is a need to develop an improved process for the preparation of dapagliflozin, which is industrially feasible and can avoid multiple purification steps. Moreover, an improved process should avoid formation of isomeric and other process related impurities, while providing the desired product in high yield and purity.

The problem is solved by the present invention by preparing a dapagliflozin using a novel intermediate which substantially eliminates the formation of impurities and thereby provides dapagliflozin with enhanced yield and purity.

SUMMARY OF THE INVENTION

The present invention provides processes for reducing or eliminating the impurities in dapagliflozin (I).

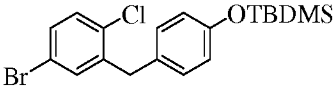
In one aspect, the present invention provides a process for the preparation of dapagliflozin (I)



(I)

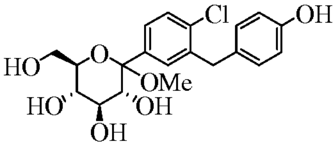
comprising the steps of:

a) reacting (4-(5-bromo-2-chlorobenzyl)phenoxy)(tert-butyl)dimethylsilane of formula (II)



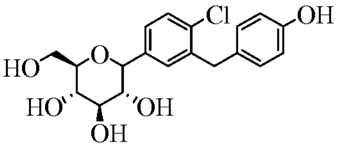
(II)

with (3R,4S,5R,6R)-3,4,5-tris((trimethylsilyl)oxy)-6-(((trimethylsilyl)oxy) methyl)-tetrahydro-2/-/-pyran-2-one followed by *in situ* reaction with an alcohol and an acid to provide (3R,4S,5S,6R)-2-(4-chloro-3-(4-hydroxybenzyl)phenyl)-6-(hydroxy-methyl)-2-methoxytetrahydro-2H-pyran-3,4,5-triol of formula (III);



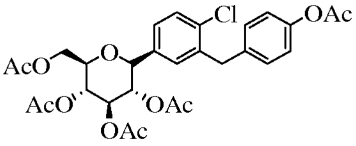
(III)

b) reacting compound of formula (III) with suitable reducing agent in presence of solvent to provide compound of formula (IV);



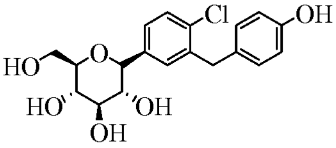
(IV)

c) protecting compound of formula (IV) with suitable acetylating agent to provide (2S,3S,4R,5R,6R)-2-(3-(4-acetoxybenzyl)-4-chlorophenyl)-6-(acetoxymethyl)-tetrahydro-2/-/-pyran-3,4,5-triyl triacetate of formula (V); optionally purifying compound of formula (V);



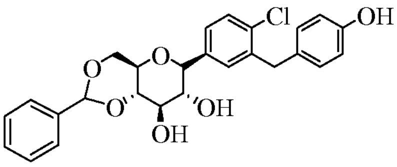
(V)

d) deprotecting compound of formula (V) to provide (2R,3R,4R,5S,6R)-2-(4-chloro-3-(4-hydroxybenzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2/-/-pyran-3,4,5-triol of formula (VI), optionally purifying compound of formula (VI);



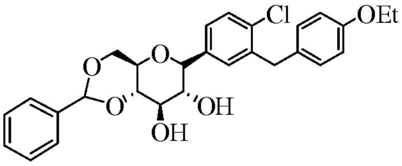
(VI)

e) protecting compound of formula (VI) with substituted or unsubstituted benzaldehyde acetal to provide (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-hydroxybenzyl)phenyl)-2-phenylhexahydropyrano[3,2-d] [l,3]dioxine-7,8-diol of formula (VII);



(VII)

f) reacting compound of formula (VII) with a suitable ethylating agent in presence of suitable solvent and base to provide (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-ethoxy-benzyl)phenyl)-2-phenylhexahydropyrano[3,2-d] [l,3]dioxine-7,8-diol of formula (VIII), optionally purifying compound of formula (VIII); and

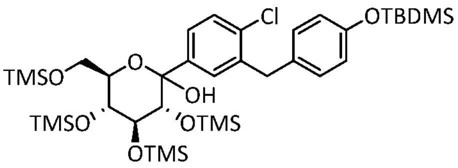


(VIII)

g) deprotecting compound of formula (VIII) to provide dapagliflozin (I).

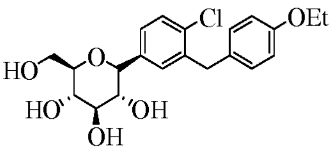
Optionally in another aspect, compound of formula (IV) can be purified directly to compound of formula (VI).

Optionally in another aspect, step (a) may involve isolation of intermediate IIa before getting compound of formula III.



(Ha)

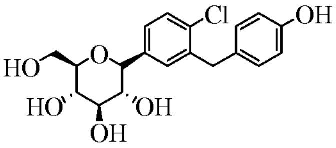
In another aspect, the present invention provides a process for the preparation of dapagliflozin (I):



(I)

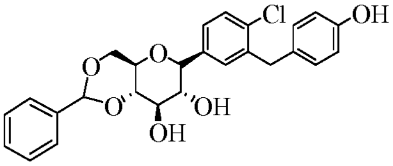
comprising the steps of:

a) protecting compound of formula (VI)



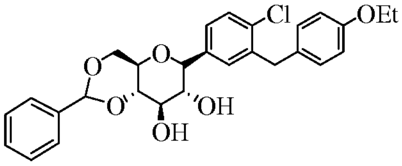
(VI)

with substituted or unsubstituted benzaldehyde acetal to provide (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-hydroxybenzyl)phenyl)-2-phenylhexahydropyrano[3,2-d] [l,3]-dioxine-7,8-diol of formula (VII);



(VII)

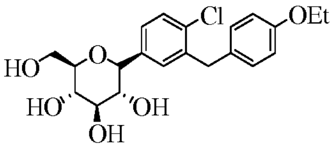
b) reacting compound of formula (VII) with a suitable ethylating agent in presence of suitable solvent and base to provide (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2-phenylhexahydropyrano[3,2-d] [l,3] dioxine-7,8-diol of formula (VIII), optionally purifying compound of formula (VIII); and



(VIII)

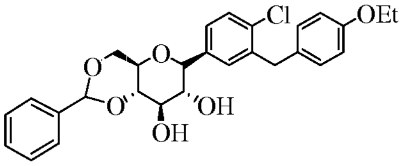
c) deprotecting compound of formula (VIII) to provide dapagliflozin (I).

In yet another aspect, the present invention provides a process for the preparation of dapagliflozin (I):



(I)

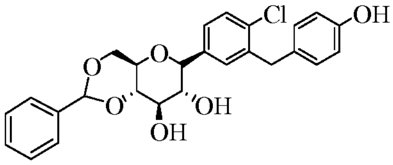
comprising a step of deprotecting compound of formula (VIII)



(VIII)

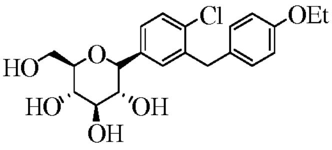
to provide dapagliflozin (I).

In yet another aspect, the present invention provides a novel intermediate of formula (VII) and their pharmaceutically acceptable salts, solvates and hydrates thereof; process for their preparation; and their uses for the preparation of dapagliflozin (I).



(VII)

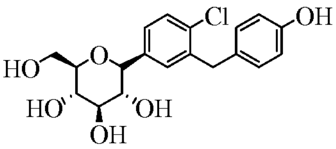
According to another aspect, the present invention provides a process for the preparation of dapagliflozin (I)



(I)

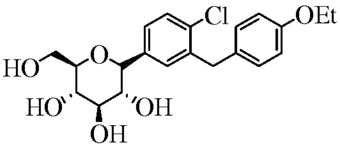
comprising the steps of:

a) reacting compound of formula (VI)



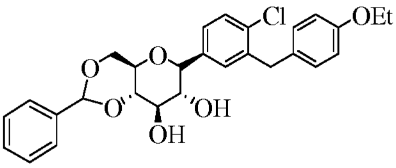
(VI)

with a suitable ethylating agent in presence of suitable solvent and base to provide dapagliflozin (I);



(I)

b) protecting dapagliflozin (I) with substituted or unsubstituted benzaldehyde acetal to provide (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2-phenyl-hexahydropyrano[3,2-d] [l,3]dioxine-7,8-diol of formula (VII I), optionally purifying compound of formula (VII I); and



(VIII)

c) deprotecting compound of formula (VIII) to provide dapagliflozin (I).

In yet another aspect, the present invention provides processes for preparing dapagliflozin having an improved impurity profile.

DETAILED DESCRIPTION OF THE INVENTION

The term "about", as used herein, when used along with values assigned to certain measurements and parameters means a variation of 10% from such values, or in case of a range of values, means a 10% variation from both the lower and upper limits of such ranges.

The term "acetylation", as used herein, refers to the addition of acetyl group(s) to a given compound.

The term "deacetylation", as used herein, refers to the removal of acetyl group(s) from a given compound.

As used herein, the term "alkyl" by itself or as part of another substituent, means, unless otherwise stated, a saturated straight or branched chain, or cyclic hydrocarbon radical, or combination thereof having the number of carbon atoms designated (e.g. C_{1-10} means one to ten carbons). Examples of saturated hydrocarbon radicals include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, t-butyl, isobutyl and the like.

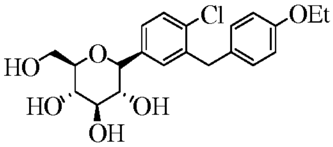
As used herein, the term "aryl" by itself or as part of another substituent, means, unless otherwise stated, a polyunsaturated, aromatic, hydrocarbon substituent which can be a single ring or multiple rings (often from 1 to 3 rings) which are fused together or linked covalently. "Aryl" includes, but is not limited to, heteroaryl groups. Non-limiting examples of aryl and heteroaryl groups include: phenyl, 1-naphthyl, 2-naphthyl, 4-biphenyl, pyrrolyl, pyrazolyl, imidazolyl, pyrazinyl, oxazolyl and isoxazolyl.

The term "substituted" as used herein means that the groups in question are substituted with one or more of the substituents selected from nitro, hydroxy, cyano, sulfanyl, oxo, halogen, amino, sulfo, alkyl, alkenyl, aryl and heteroaryl. When the groups in question are substituted with more than one substituent, the substituents may be the same or different.

TBDMS is tert-butyldimethyl silyl.

As used herein, the term "halogen" refers to an atom selected from the group consisting of F, Cl, Br and I.

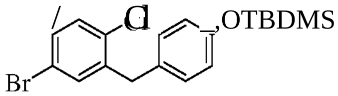
In one aspect, the present invention provides a process for the preparation of dapagliflozin (I)



(I)

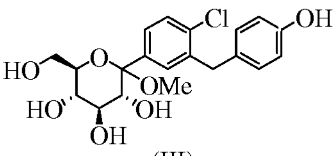
comprising the steps of:

a) reacting (4-(5-bromo-2-chlorobenzyl)phenoxy)(tert-butyl)dimethylsilane of formula (II)



(II)

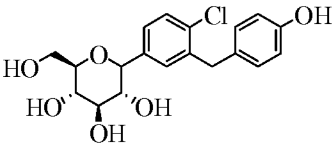
with (3R,4S,5R,6R)-3,4,5-tris((trimethylsilyl)oxy)-6-(((trimethylsilyl)oxy) methyl) tetrahydro-2H-pyran-2-one followed by *in situ* reaction with an alcohol and an acid to provide (3R,4S,5S,6R)-2-(4-chloro-3-(4-hydroxybenzyl)phenyl)-6-(hydroxyl-methyl)-2-methoxytetrahydro-2H-pyran-3,4,5-triol of formula (III);



(III)

wherein an alcohol is selected from methanol, ethanol and the like; and an acid is selected from organic and inorganic acid such as hydrochloric acid, sulfuric acid, methanesulphonic acid, camphorsulfonic acid, p-toluenesulfonic acid and the like. Preferably the acid used is methanesulphonic acid;

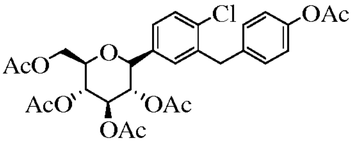
b) reacting compound of formula (III) with suitable reducing agent in presence of solvent to provide compound of formula (IV);



(IV)

wherein reducing agent is selected from silane reagent such as triethylsilane and the like;

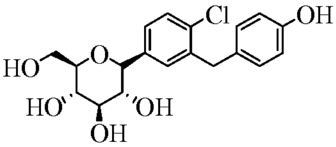
c) protecting compound of formula (IV) with suitable acetylating agent to provide (2S,3S,4R,5R,6R)-2-(3-(4-acetoxybenzyl)-4-chlorophenyl)-6-(acetoxymethyl) tetrahydro-2/-/-pyran-3,4,5-triyl triacetate of formula (V); optionally purifying compound of formula (V);



(V)

wherein acetylating agents are selected from acetic anhydride, acetyl chloride and the like. This step carried out in presence of suitable solvent optionally in presence of catalyst;

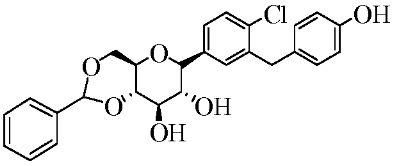
d) deprotecting compound of formula (V) to provide (2R,3R,4R,5S,6R)-2-(4-chloro-3-(4-hydroxybenzyl)phenyl)-6-(hydroxymethyl)tetrahydro-2/-/-pyran-3,4,5-triol of formula (VI), optionally purifying compound of formula (VI);



(VI)

wherein deprotection carried out using base in presence of suitable solvent;

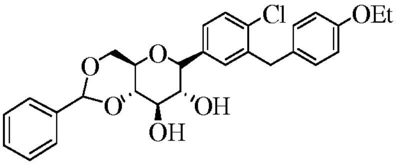
e) protecting compound of formula (VI) with substituted or unsubstituted benzaldehyde acetal to provide (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-hydroxybenzyl) phenyl)-2-phenylhexahydropyrano[3,2-d] [l,3]dioxine-7,8-diol of formula (VII);



(VII)

wherein protection carried out in suitable solvent optionally in presence of catalyst.

f) reacting compound of formula (VII) with a suitable ethylating agent in presence of suitable solvent and base to provide (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-ethoxy-benzyl)phenyl)-2-phenylhexahydropyrano[3,2-d] [l,3]dioxine-7,8-diol of formula (VIII), optionally purifying compound of formula (VIII); and

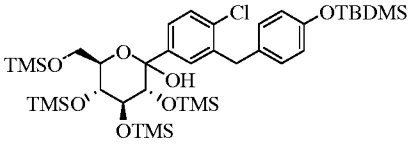


(VIII)

g) deprotecting compound of formula (VIII) to provide dapagliflozin (I).

Step a) involves coupling of (4-(5-bromo-2-chlorobenzyl)phenoxy)(tert-butyl)dimethylsilane of formula (II) with protected gluconolactone in presence of a suitable solvent and a base followed by *in situ* reaction with an alcohol and an acid to provide (3R,4S,5S,6R)-2-(4-chloro-3-(4-hydroxybenzyl)phenyl)-6-(hydroxymethyl)-2-methoxytetrahydro-2/-/-pyran-3,4,5-triol of formula (III). Solvents that may be used for this step include, but are not limited to, hydrocarbons such as toluene, xylene; ethers such as tetrahydrofuran (THF), diethyl ether or mixtures thereof. Base that may be used for this step selected from, but are not limited to, n-butyl lithium, sec-butyl lithium, sodium hydride, potassium hydride and isopropylmagnesium chloride lithium chloride complex. Preferably, the base used is n-butyl lithium. The coupling of the compound of formula (II) with protected gluconolactone may be carried out at a temperature of about -80 to 0°C. Preferably, the reaction is carried out at a temperature of about -60 to about -80°C.

Optionally in another aspect, step (a) may involve isolation of intermediate IIa before getting compound of formula III.



(IIa)

Step b) involves reaction of compound of formula (III) with suitable reducing agent in presence of solvent to provide (3R,4S,5S,6R)-2-(4-chloro-3-(4-hydroxybenzyl)phenyl)-6-(hydroxymethyl)-2-methoxytetrahydro-2/-/-pyran-3,4,5-triol of formula (IV). Solvents that may be used for this step include, but are not limited to, esters such as ethyl acetate, methyl acetate, n-butyl acetate, isobutyl acetate, sec-butyl acetate, isopropyl acetate and the like; halogenated hydrocarbons such as dichloromethane, chlorobenzene, chloroform and the like; nitriles such as acetonitrile, propionitrile, butyronitrile, isobutyronitrile and the like or mixtures thereof. Preferably, the solvent is a mixture of methylene dichloride and acetonitrile. This reduction reaction is carried out in the presence of a lewis acid such as boron trifluoride diethyl ether complex, boron trifluoride tetrahydrofuran complex, aluminium chloride, zinc chloride and the like. Preferably, the compound of formula III is converted to the compound of formula IV by treating with triethylsilane in the presence of boron trifluoride diethyl ether complex. The reaction may be carried out at temperature ranging from 0°C to 40°C. Preferably, the reaction carried out at a temperature of about 0°C to about 10°C over a period of 3 to 5 h.

Step c) involves protection of compound of formula (IV) with suitable acetylating agent in presence of suitable solvent, base and optionally in presence of catalyst to provide (2S,3S,4R,5R,6R)-2-(3-(4-acetoxybenzyl)-4-chlorophenyl)-6-(acetoxymethyl) tetrahydro-2/-/-pyran-3,4,5-triyl triacetate of formula (V). In this process, the compound of formula IV is not isolated in step 'b' and converted *in situ* to the compound of formula V. Solvents that may be used for this step include, but are not limited to, halogenated hydrocarbons such as dichloromethane, chlorobenzene, chloroform and the like; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone, diisopropyl ketone, methyl isopropyl ketone and the like or mixtures thereof. Base that may be used for this step selected from, but are not limited to, amines, alkali or alkaline earth metal carbonate, bicarbonate, amide, hydride or phosphate or mixtures thereof. Examples include, but are not limited to, pyridine, diisopropylethylamine (DIPEA), triethylamine

(TEA), diethylamine (DEA), l,8-diazabicyclo[5.4.0]undec-7-ene (DBU), imidazole, N,N-dimethyl aniline, 1,5- diazabicyclo[4.3.0]non-5-ene (DBN), potassium carbonate, sodium carbonate, lithium carbonate, sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, sodium hydride, lithium hydride or potassium hydride, sodium or potassium methoxide or ethoxide and sodium or potassium tertiary butoxide (KTB). The acetylation of formula (IV) may be performed in the presence of a catalyst. Examples of catalyst include, but are not limited to, N,N-dimethyl aminopyridine (DMAP), N-methyl piperazine (NMP) and the like. The reaction can be carried out at any temperature ranging from about 10°C to about 40°C. Preferably, acetylation of compound formula (IV) carried out using acetic anhydride in presence of dichloromethane, pyridine and DMAP at a temperature of about 25°C to about 35°C over a period of 1 to 3 h. The compound of formula (V) may be purified in alcohol such as methanol, ethanol, isopropanol, n-propanol, butyl alcohol and the like or mixtures thereof. Preferably, purification of compound of formula (V) carried out in ethanol.

Step d) involves deprotection of compound of formula (V) in presence of suitable solvent and base to provide (2R,3R,4R,5S,6R)-2-(4-chloro-3-(4-hydroxy benzyl)phenyl)-6-(hydroxy-methyl) tetrahydro-2/-/-pyran-3,4,5-triol of formula (VI). Example of solvents that can be used for this step include, but are not limited to, ethers such as tetrahydrofuran, diethyl ether, diisopropylether, dimethoxyethane and the like; alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol, t-butanol and the like; ketones such as acetone, ethyl methyl ketone, diethyl ketone, methyl tert-butyl ketone, isopropyl ketone, methyl isobutyl ketone and the like; chlorinated hydrocarbons such as methylene chloride, ethylene dichloride, carbon tetra chloride, chloroform, chlorobenzene and the like; polar solvents such as water; polar aprotic solvents such as N,N-dimethylformamide (DMF), dimethyl acetamide (DMAc), dimethyl sulfoxide (DMSO) and the like or mixtures thereof. Base that may be used for this step include, but are not limited to, sodium hydroxide, potassium hydroxide, lithium hydroxide and the like. Preferably, deacetylation of compound formula (V) carried out in a mixture of tetrahydrofuran, methanol and water using an aqueous solution of potassium hydroxide at a temperature of about 30-40°C over a period of 4 to 5 h. The compound (2R,3R,4R,5S,6R)-2-(4-chloro-3-(4-hydroxybenzyl)phenyl)-6-(hydroxymethyl) tetrahydro-

2H-pyran-3,4,5-triol (V) obtained after deacetylation can be further purified in ketone such as methyl ethyl ketone. Preferably, compound of formula (V) purified in methyl ethyl ketone.

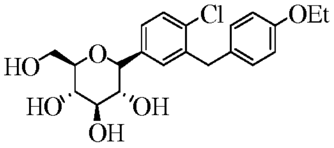
Step e) involves protection of compound of formula (VI) with substituted or unsubstituted benzaldehyde acetal in presence of suitable solvent optionally in presence of catalyst to provide (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-hydroxybenzyl)phenyl)-2-phenylhexahydro-pyrano[3,2-d] [l,3]dioxine-7,8-diol of formula (VII). Solvents that may be used for this step include, but are not limited to, nitriles such as acetonitrile, propionitrile, butyronitrile, isobutyronitrile and the like; esters such as ethyl acetate, methyl acetate, n-butyl acetate, isobutyl acetate, sec-butyl acetate, isopropyl acetate and the like; ethers such as diethyl ether, diisopropylether, tetrahydrofuran, dimethoxyethane and the like; halogenated hydrocarbons such as dichloromethane, chlorobenzene, chloroform and the like; hydrocarbon such as toluene, xylene and the like; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone, diisopropyl ketone, methyl isopropyl ketone and the like; polar aprotic solvents such as N,N-dimethylformamide (DMF), dimethyl acetamide (DMAc), dimethyl sulfoxide (DMSO) and the like or mixtures thereof. The protection step can be carried out in presence of catalyst such as para toluene sulfonic acid, camphor sulfonic acid and the like. Preferably, the protection of compound of formula (VI) with benzaldehyde dimethyl acetal carried out in N,N-dimethylformamide in presence of para toluenesulfonic acid monohydrate at temperature of about 20-60°C. The compound of formula (VII) may be purified in ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone, diisopropyl ketone, methyl isopropyl ketone and the like or mixtures thereof. Preferably, purification of compound of formula (V) carried out in acetone.

Step f) involves reaction of compound of formula (VII) with a suitable ethylating agent in presence of suitable solvent and base to provide (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2-phenylhexahydro pyrano[3,2-d] [l,3]dioxine-7,8-diol of formula (VIII). Solvents that may be used for this step include, but are not limited to, nitriles such as acetonitrile, propionitrile, butyronitrile, isobutyronitrile and the like; ethers such as tetrahydrofuran, diethyl ether, diisopropylether, dimethoxyethane and the like; halogenated hydrocarbons such as dichloromethane, chlorobenzene, chloroform and the like; hydrocarbon such as toluene, xylene and the like; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone, diisopropyl ketone, methyl isopropyl ketone and the like; polar aprotic solvents such as N,N-dimethylformamide (DMF), dimethyl acetamide (DMAc), dimethyl sulfoxide (DMSO), N-methyl-2-pyrrolidone and the like or mixtures thereof. The ethylation step can be carried out in presence of ethyl halides such as ethyl iodide, ethyl chloride, ethyl bromide and the like; diethyl sulphate, ethyl para toluene sulfonate and the like. Base that may be used for this step include, but are not limited to, alkali or alkaline earth metal carbonate or bicarbonate such as potassium carbonate, sodium carbonate, lithium carbonate, sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, cesium carbonate and the like or mixtures thereof. The compound (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-ethoxybenzyl) phenyl)-2-phenylhexahydropyrano[3,2-d] [l,3]dioxine-7,8-diol (VIII) can be purified in alcohols such as methanol, ethanol, n-propanol, isopropanol, n-butanol, t-butanol and the like; hydrocarbon such as toluene, xylene and the like; water or mixtures thereof.

Step g) involves deprotection of protected dapagliflozin of formula (VIII) in the presence of suitable solvent and an acid to provide dapagliflozin. Acid that may be used for this step include, but are not limited to, hydrochloric acid, sulfuric acid, orthophosphoric acid, para toluenesulfonic acid, camphorsulfonic acid, ascorbic acid, trifluoroacetic acid, methanesulfonic acid and borane trifluoride etherate. Solvents that may be used for this step include, but are not limited to, ethers such as tetrahydrofuran, diethyl ether, diisopropylether, dimethoxyethane and the like; halogenated hydrocarbons such as dichloromethane, chlorobenzene, chloroform and the like; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone, diisopropyl ketone, methyl isopropyl ketone and the like; esters such as ethyl acetate, methyl acetate, n-butyl acetate, isobutyl acetate, sec-butyl acetate, isopropyl acetate and the like; alcohols such as methanol, ethanol, n-butanol, t-butanol and the like; water or mixtures thereof. Preferably, the deprotection step can be carried out in alcohol, such as methanol in presence of camphor sulfonic acid at temperature of about 30-60 °C using a suitable solvents.

In another aspect, compound of formula (IV) can be purified directly to compound of formula (VI) in presence of suitable solvent. Solvents that may be used for this step include, but are not limited to, ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone, diisopropyl ketone, methyl isopropyl ketone and the like; esters such as ethyl acetate, methyl acetate, n-butyl acetate, isobutyl acetate, sec-butyl acetate, isopropyl acetate and the like or mixtures thereof. In a purification process, the compound of formula (IV) dissolved in suitable solvent. To obtain the solution, the solvent may have to be heated. Heating is preferably carried out to a temperature of about 40 °C to about 100 °C, and more preferably to a temperature of about 40 °C to about 60 °C. The solution is then preferably allowed to cool, such to a temperature of about 0 °C to about 10 °C, or at about room temperature. The solution may then be seeded. When the solution is cooled to obtain a suspension, the suspension is preferably maintained for a period of about 1 h to about 12 h, more preferably about 1 h to about 2 h, to obtain a precipitate of the compound of formula VI. Optionally, the compound of formula (VI) can be recrystallized to achieve the desired purity.

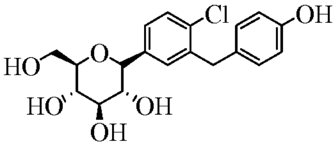
In another aspect, the present invention provides a process for the preparation of dapagliflozin (I)



(I)

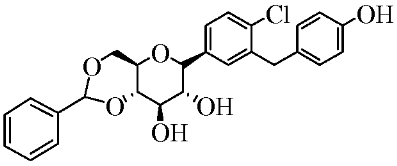
comprising the steps of:

a) protecting compound of formula (VI)



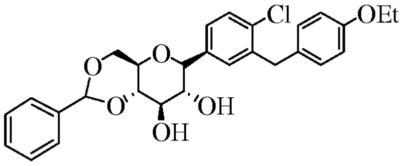
(VI)

with substituted or unsubstituted benzaldehyde acetal to provide (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-hydroxybenzyl)phenyl)-2-phenylhexa hydropyrano[3,2-d] [l,3]-dioxine-7,8-diol of formula (VI I);



(VII)

b) reacting compound of formula (VII) with a suitable ethylating agent in presence of suitable solvent and base to provide (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2-phenylhexahydropyrano[3,2-d] [l,3]dioxine-7,8-diol of formula (VIII), optionally purifying compound of formula (VIII);



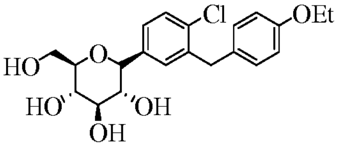
(VIII)

c) deprotecting compound of formula (VIII) to provide dapagliflozin (I).

The compound (2R,3R,4R,5S,6R)-2-(4-chloro-3-(4-hydroxybenzyl)phenyl)-6-(hydroxyl-methyl)tetrahydro-2/-/-pyran-3,4,5-triol (VI) reacted with substituted or unsubstituted benzaldehyde acetal in presence of suitable solvent optionally in presence of catalyst to provide (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-hydroxybenzyl)phenyl)-2-phenylhexahydro-pyrano[3,2-d] [l,3]dioxine-7,8-diol (VII). Benzylidene acetals can be used to selectively protect 1,3-diols in the presence of other hydroxy groups. The compound of formula (VII) reacted with ethylating agent in presence of suitable solvent and base to provide (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2-phenylhexahydro pyrano[3,2-d] [l,3]dioxine-7,8-diol of formula (VIII) followed by deprotection carried out in presence of suitable solvent and an acid to provide dapagliflozin.

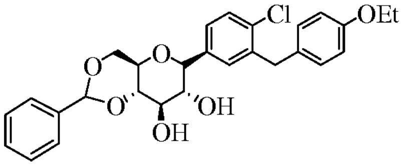
Dapagliflozin obtained by this process is substantially free of impurities; preferably individual impurities are not more than 0.15% by HPLC.

In yet another aspect, the present invention provides a process for the preparation of dapagliflozin (I)



(I)

comprising a step of deprotecting compound of formula (VIII),

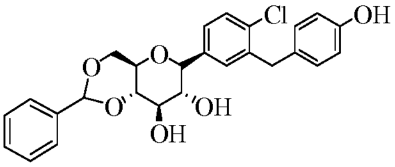


(VIII)

to provide dapagliflozin (I).

The compound (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-ethoxybenzyl) phenyl)-2-phenyl hexahydropyrano[3,2-d] [l,3]dioxine-7,8-diol (VIII) deprotected in the presence of suitable solvent and an acid to provide dapagliflozin. The compound of formula (VIII) was purified in suitable alcohol solvent before final deprotection step to get dapagliflozin substantially free of impurities. Dapagliflozin obtained by this process having HPLC purity greater than about 99%, preferably greater than about 99.5%, more preferably greater than about 99.9%. For example, the total purity of dapagliflozin obtained by the process disclosed herein can be about 99.5% to about 99.9% as measured by HPLC.

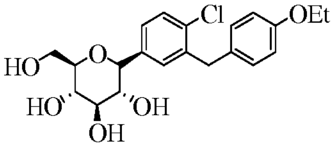
In yet another aspect, the present invention provides a novel intermediate of formula (VII) and their pharmaceutically acceptable salts, solvates and hydrates thereof; process for their preparation; and their uses for the preparation of dapagliflozin (I).



(VII)

The compound of formula (VII) prepared by selectively protection of 1,3-diols using substituted or unsubstituted benzaldehyde acetal. Examples of substituted or unsubstituted benzaldehyde acetal include; but are not limited to, benzaldehyde dimethyl acetal, anisaldehyde dimethyl acetal, 4-chlorobenzaldehyde dimethyl acetal, 3,4,5-trimethoxybenzaldehyde dimethyl acetal, 3-nitrobenzaldehyde dimethyl acetal, acetaldehyde dimethyl acetal, acetaldehyde diethyl acetal and the like. Compound of formula (VII) selectively protects reactive primary hydroxy group, hence, ethylation of compound of formula (VII) provide protected dapagliflozin having minimum amount of impurities. The purification of compound of formula (VII) in alcohol, such as methanol provide compound of formula (VII) having HPLC purity greater than about 99%, preferably greater than about 99.5%, more preferably greater than about 99.9%. For example, the total purity of protected dapagliflozin obtained by using compound of formula (VII) can be about 99.5% to about 99.9% as measured by HPLC.

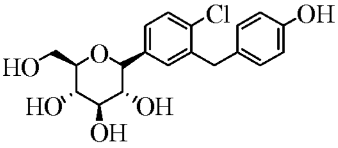
According to another aspect, the present invention provides a process for the preparation of dapagliflozin (I)



(I)

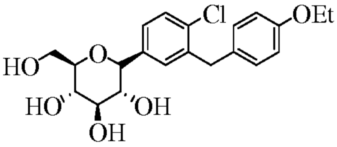
comprising the steps of:

a) reacting compound of formula (VI)



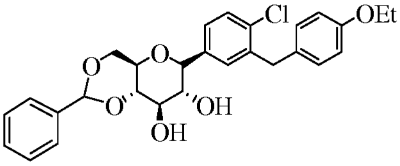
(VI)

with a suitable ethylating agent in presence of suitable solvent and base to provide dapagliflozin (I);



(I)

b) protecting dapagliflozin (I) with substituted or unsubstituted benzaldehyde acetal to provide (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2-phenyl hexahydropyrano[3,2-d] [l,3]dioxine-7,8-diol of formula (VIII), optionally purifying compound of formula (VIII); and



(VIII)

c) deprotecting compound of formula (VIII) to provide dapagliflozin (I).

Step a) involves reaction of compound of formula (VI) with a suitable ethylating agent in presence of suitable solvent and base to provide dapagliflozin of formula (I). Solvents that may be used for this step include, but are not limited to, ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone, diisopropyl ketone, methyl isopropyl ketone and the like; polar aprotic solvents such as N,N-dimethylformamide (DMF), dimethyl acetamide (DMAc), dimethyl sulfoxide (DMSO), N-methyl-2-pyrrolidone and the like or mixtures thereof. The ethylation step can be carried out in presence of ethyl halides such as ethyl iodide, ethyl chloride, ethyl bromide and the like; diethyl sulphate, ethyl para toluenesulfonate and the like. Base that may be used for this step include, but are not limited to, alkali or alkaline earth metal carbonate or bicarbonate such as potassium carbonate, sodium carbonate, lithium carbonate, sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, cesium carbonate and the like or mixtures thereof.

Step b) involves protection of dapagliflozin (I) with substituted or unsubstituted benzaldehyde acetal in presence of suitable solvent optionally in presence of catalyst to provide (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2-phenylhexahydro-pyrano[3,2-d] [l,3]dioxine-7,8-diol of formula (VIII). Solvents that may be used for this step include, but are not limited to, nitriles such as acetonitrile, propionitrile, butyronitrile, isobutyronitrile and the like; halogenated hydrocarbons such as dichloromethane, chlorobenzene, chloroform and the like; hydrocarbons such as toluene, xylene and the like; polar aprotic solvents such as N,N-dimethylformamide (DMF), dimethyl acetamide (DMAc), dimethyl sulfoxide (DMSO) and the like or mixtures thereof. The protection step can be carried out in presence of catalyst such as para toluenesulfonic acid, camphorsulfonic acid and the like. Preferably, the protection of compound of formula (I) with benzaldehyde dimethyl acetal carried out in acetonitrile in presence of para toluene sulfonic acid monohydrate at temperature of about 20-40°C, or about 25-35°C.

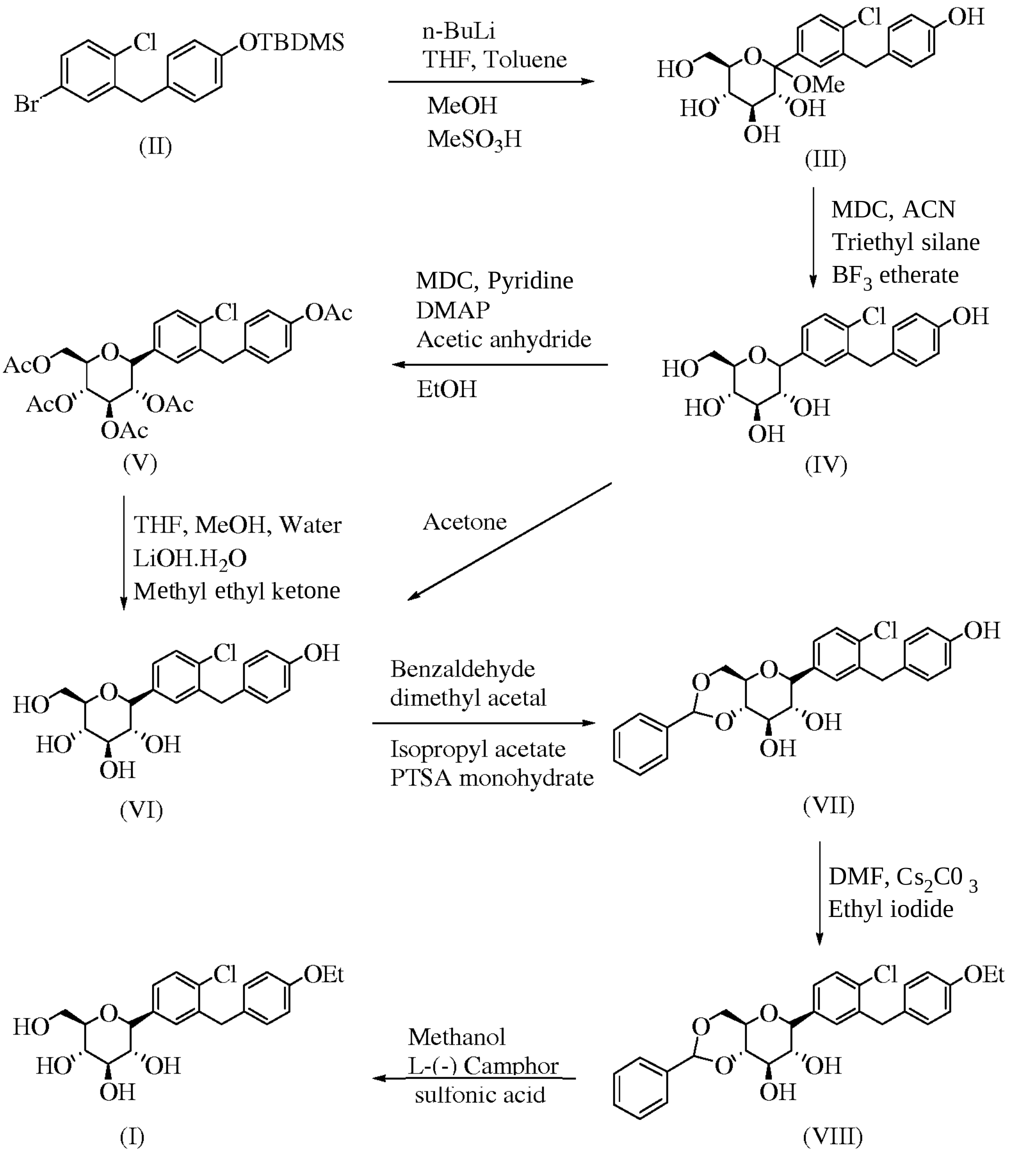
Step c) involves deprotection of protected dapagliflozin of formula (VIII) in the presence of suitable solvent and an acid to provide dapagliflozin. The reaction is done in the same manner as described above in earlier aspect in step g.

In order to obtain dapagliflozin substantially free of impurities, the present invention provides two different aspects to get the protected dapagliflozin intermediate of formula (VIII), which can be purified in suitable alcohol such as methanol to get the penultimate step having HPLC purity greater than about 99%, preferably greater than about 99.5%, more preferably greater than about 99.9%. Therefore, dapagliflozin obtained by deprotection of formula (VIII) is substantially free of impurities; preferably individual impurities are not more than 0.15% by HPLC. Moreover, the process of the present invention involves simple procedure for deprotection of acetal group at penultimate step.

Methods

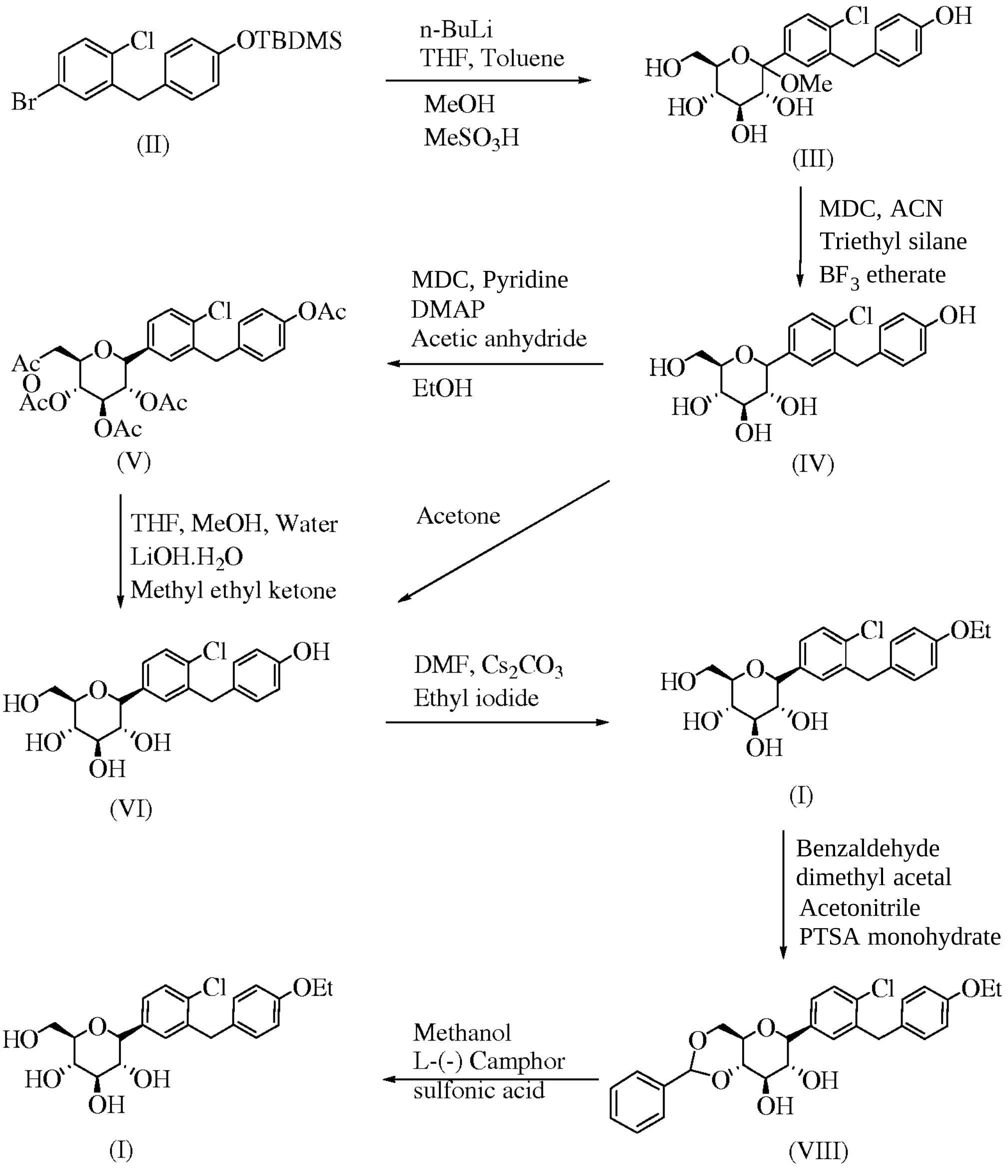
The HPLC purity of dapagliflozin was determined using YMC ODS AQ (150 x 4.6 mm), 3μιτι column with a flow rate of 0.7 ml/min; column oven temperature: 30°C; sample tray temperature: 10°C; detector: UV at 240 nm; injection volume: 10 μΙ; run time: 45 min.

In one embodiment, the synthetic reaction scheme of the present invention is as shown in Scheme-V.



Scheme-IV

In another embodiment, the synthetic reaction scheme of the present invention is as shown in Scheme-VI.



Scheme-V

The following examples are given for the purpose of illustrating the present invention and should not be considered as limiting the scope of the invention.

Example-1: Preparation of (4-(5-bromo-2-chlorobenzyl)phenoxy)(tert-butyl) dimethylsilane (II)

To a stirred solution of 4-(5-bromo-2-chlorobenzyl)phenol (100 g), imidazole (45.75 g) and dichloromethane (250 ml), a solution of tert. butyl dimethylsilyl chloride (55.72 g) in dichloromethane (250 ml) was slowly added at 25-35°C. Reaction mixture was stirred at 25-35°C for 2-3 h. The progress of reaction was monitored by TLC. After completion of reaction, water (500 ml) was added to the reaction mixture and then stirred for 15 min. Organic layer was separated and washed with 20% aqueous sodium dihydrogen phosphate solution (500 ml) followed by water (500 ml). The organic layer was distilled out under vacuum at 50-60°C to give title compound (135 g) as light yellow colour liquid. Yield: 97.54%

Example-2: Preparation of (3R,4S,5S,6R)-2-(4-chloro-3-(4-hydroxybenzyl) phenyl)-6-(hydroxy methyl)-2-methoxytetrahydro-2H-pyran-3,4,5-triol (III)

To a stirred solution of (4-(5-bromo-2-chlorobenzyl)phenoxy)(tert-butyl)dimethylsilane (50 g), tetrahydrofuran (100 ml) and toluene (200 ml) at -60 to -70°C, 1.6 M n-butyl lithium solution in n-hexane (114 ml) was added drop wise under nitrogen. The reaction mixture was stirred for 1 h at -60 to -70°C. A solution of (3R,4S,5R,6R)-3,4,5-tris((trimethylsilyl)oxy)-6-(((trimethylsilyl)oxy) methyl)tetrahydro-2H-pyran-2-one (73.7 g) in toluene (100 ml) was cooled to 0-10 °C and then added drop wise to the above reaction mixture within 1-2 h. The reaction mixture was stirred at -60 to -70°C for 2-3 h. The progress of reaction was monitored by TLC. After completion of reaction, a solution of methanesulfonic acid (23.4 g) in methanol (200 ml) was added drop wise to the reaction mixture. Reaction mixture was heated to 30-40°C, stirred for 15 h and then 20% aqueous solution of potassium bicarbonate (250 ml) was slowly added and then further stirred 15 min. Separate the layers and then aqueous layer was extracted with ethyl acetate (3x250 ml). Combine the organic layers; washed with brine solution (250 ml) and distilled out under vacuum to give title compound (32 g) as light yellow colour solid. Yield: 64%. HPLC Purity: 85.65%

Example-3: Preparation of (2S,3S,4R,5R,6R)-2-(3-(4-acetoxybenzyl)-4-chloro phenyl)-6-(acetoxy-methyl)tetrahydro-2H-pyran-3,4,5-triyl triacetate (V)

A mixture of (3R,4S,5S,6R)-2-(4-chloro-3-(4-hydroxybenzyl) phenyl)-6-(hydroxymethyl)-2-methoxytetrahydro-2/-/-pyran-3,4,5-triol (140 g), acetonitrile (700 ml) and dichloromethane (700 ml) was cooled to 0-10°C. Triethylsilane (79.24 g) followed by boron trifluoride diethyl etherate solution (161 g) was added to the reaction mixture at 0-10°C. The reaction was stirred at 0-10°C for 4 h. The pH of reaction mixture was adjusted to 7-8 by 20% aqueous potassium bicarbonate solution. Organic solvent was distilled out from the reaction mixture under vacuum at 50-60°C. Reaction mixture was extracted with ethyl acetate (2x700 ml). Combine ethyl acetate layers; washed with brine solution (700 ml) and distilled out under vacuum at 50-60°C. The residue was dissolved in a mixture of dichloromethane (840 ml), pyridine (243 g) and dimethyl amino pyridine (2. 1 g) at 25-35°C. Acetic anhydride (314 g) was added drop wise to the reaction mixture at 25-35°C and stirred for 2 h. The progress of reaction was monitored by TLC. After completion of reaction, 4% aqueous hydrochloric acid (1400 ml) solution was added and stirred for 30 min. The layers were separated and organic layer was washed with 4% aqueous hydrochloric acid (1400 ml) solution. Organic layer was distilled out under vacuum below 50-60°C. The obtained residue was stirred with ethanol (420 ml) for l h at 25-35°C. The solid material was filtered and washed with ethanol (4x70 ml). The solid was dried at 45-55°C for 4-5 h to give the title compound as white to off-white solid (109 g). Yield: 54%. HPLC Purity: 98.67%

Example-4: Preparation of (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-hydroxybenzyl) phenyl)-6-(hydroxy-methyl) tetrahydro-2H-pyran-3,4,5-triol (VI)

A mixture of (2S,3S,4R,5R,6R)-2-(3-(4-acetoxybenzyl)-4-chlorophenyl)-6-(acetoxymethyl) tetrahydro-2/-/-pyran-3,4,5-triyl triacetate (195 g), methanol (1755 ml), tetrahydrofuran (1170 ml) and water (585 ml) was cooled at 10-20°C. Lithium hydroxide (20.8 g) was added lot wise at 10-20°C. The reaction mixture was heated to 30-40°C and stirred for 4-5 h. After completion of reaction, organic solvent was distilled out from the reaction mixture under vacuum below 55°C. Aqueous sodium chloride solution (10%, 1000 ml) was added to the reaction mixture, stirred for 5-10 min. and then extracted with ethyl acetate (3x1000 ml). Combine the organic layers and washed with brine solution (1000 ml). Organic layer was distilled out under vacuum at 50-60°C. The obtained residue was stirred with methyl ethyl ketone (1000 ml) at 75-85°C for lh. Reaction mixture was cooled to 10-20°C and stirred for lh. The solid material was filtered and washed with methyl ethyl ketone (2x100 ml). The solid was dried at 45-55°C for 6-8 h to give the title compound as white solid (117 g). Yield: 93%. HPLC Purity: 98.28%

Example-5: Preparation of (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-hydroxybenzyl) phenyl)-6-(hydroxy methyl) tetrahydro-2H-pyran-3,4,5-triol (VI)

A mixture of (3R,4S,5S,6R)-2-(4-chloro-3-(4-hydroxybenzyl)phenyl)-6-(hydroxymethyl)-2-methoxytetrahydro-2/-/-pyran-3,4,5-triol (136 g), acetonitrile (272 ml) and dichloromethane (1088 ml) was cooled to 0-10°C. Triethylsilane (76.98 g) followed by boron trifluoride diethyl etherate solution (156 g) was added to the reaction mixture at 0-10°C. The reaction was stirred at 0-10°C for 4 h. The pH of reaction mixture was adjusted to 7-8 by 20% aq. potassium bicarbonate solution. Organic solvent was distilled out from the reaction mixture under vacuum at 50-60°C. Reaction mixture was extracted with ethyl acetate (3 X 680 ml). Combine ethyl acetate layers; washed with brine solution (680 ml) and distilled out under vacuum at 50-60°C. Residue was concentrated under vacuum to remove remaining water azeotropically with methyl ethyl ketone (136 ml). Methyl ethyl ketone (680 ml) was added to the residue and stirred for 30 min. at 40-50°C. Reaction mixture was cooled to 0-10°C, seeded with (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-hydroxybenzyl)phenyl)-6-(hydroxy methyl) tetrahydro-2H-pyran-3,4,5-triol (0.68 g) and stirred for 1 h. The solid material was filtered and washed with chilled methyl ethyl ketone (2 x 68 ml). The solid was dried at 45-55°C for 6-8 h to give the title compound as white solid (80.5 g). Yield: 64.33 %. HPLC Purity: 97.07%

Example-6: Preparation of (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-hydroxybenzyl) phenyl)-2-phenylhexahydropyrano[3,2-d][l,3]dioxine-7,8-diol (VII)

A mixture of (2S,3/?,4/?,5S,6/?)-2-(4-chloro-3-(4-hydroxybenzyl)phenyl)-6-(hydroxymethyl) tetrahydro-2/-/-pyran-3,4,5-triol (60 g), p-toluenesulphonic acid monohydrate (11.38 g) and N, N-dimethyl formamide (180 ml) was stirred at 25-35°C. A solution of benzaldehyde dimethylacetal (72 g) in N, N-dimethyl formamide (120 ml) was slowly added to the reaction mixture at 25-35°C. The reaction mixtures was stirred at 40-50°C for 4-5 h. Reaction mixture was cooled to 10-20°C and process water (900 ml) was added slowly to the reaction mixture. Reaction mixture warmed to 25-35°C & stirred for 1 h. The solid was filtered and washed with process water (2 X 60 ml). The solid was dried at 50-60°C in air tray drier for 3 h to give the crude product as white solid (68 g). The crude product was stirred in acetone (420 ml) at 45-55°C for 1 h and then cooled to 25-35°C. The solid was filtered and washed with acetone (2 X 60 ml). The product dry in air tray dryer at 45-55°C for 6-8 hours to give title compound as white solid (55.0 g). Yield: 74.52 %. HPLC Purity: 99.73 %

Example-7: Preparation of (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-hydroxybenzyl) phenyl)-2-phenyl-hexahydropyrano[3,2-d] [l,3]dioxine-7,8-diol (VII)

A mixture of (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-hydroxybenzyl)phenyl)-6-(hydroxymethyl) tetrahydro-2/-/-pyran-3,4,5-triol (10 g), p-toluenesulphonic acid monohydrate (1.6 g) and isopropyl acetate (120 ml) was stirred at 25-35°C. A solution of benzaldehyde dimethylacetal (9.7 g) in isopropyl acetate (30 ml) was slowly added to the reaction mixture at 25-35°C. The reaction mixture was stirred at 25-35°C for 4-5 h. Reaction mixture was cooled to 0-5°C and stirred for 1 h. The solid was filtered and washed with isopropyl acetate (4x10 ml). The solid was dried at 55-60°C in air tray drier for 3 h to give the title product as white solid (10 g). Yield: 85.98%. MP: 178-182°C. HPLC Purity: 81.42%. DSC: 110°C and 185.37°C

^{1}H NMR (DMSO-d^6)6ppm: 3.24-3.30 (1H, m), 3.05-3.54 (3H, bs), 3.66-3.71 (1H, m), 3.89-3.98 (2H, q), 4.17-4.23 (2H, m), 5.15-5.16 (1H, d), 5.33-5.34 (1H, d), 5.61 (1H, s), 6.66-6.69 (2H, m), 6.97-6.99 (2H, d), 7.19-7.26 (2H, m), 7.37-7.48 (6H, m), 9.22 (1H, s).

Mass: 467.1 [M-H]$^+$Cl^{35}, 469.2 [M-H]$^+$Cl^{37}

Example-8: Preparation of (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-ethoxybenzyl) phenyl)-2-phenylhexahydropyrano[3,2-d] [l,3]dioxine-7,8-diol (VIII)

A solution of (4a/?,6S,7/?,8/?,8aS)-6-(4-chloro-3-(4-hydroxybenzyl)phenyl)-2-phenyl hexahydropyrano[3,2-d] [l,3]dioxine-7,8-diol (115 g) in dimethyl sulfoxide (460 ml) was mixed with cesium carbonate (119.8 g) at 25-35°C. A solution of ethyl bromide (19.4 g) in dimethyl sulfoxide (115 ml) was added drop wise to the reaction mixture at 20-30°C. The reaction mixture was stirred at 25-35°C for 4-5 h. Reaction mixture was cooled to 10-20°C and water (1725 ml) was added at 10-20°C. Reaction mixture was warmed to 25-35°C and stirred for 1 h. The solid was filtered; washed with water (2 X 115 ml) and suck dry well. The wet product was stirred in Process water (700 ml) for 30 minutes. The solid was filtered; washed with water (2 X 115 ml) and suck dry well. The solid was dried at 40-50°C in air tray drier for 4 h to give the crude product as white solid (112 g). The crude product was stirred in toluene (784 ml) at 50-60°C for 1 h and then cooled to 0-10°C for 1 h. The solid was filtered; wash with chilled toluene (2 X 50 ml) and dried at 45-55°C for 4-5 h in air tray dryer to give product as white solid (103 g). The solid product was stirred in methanol (784 ml) at 50-60°C for 1 h and then cooled to 0-10°C for 1 h. The solid was filtered; wash with chilled methanol (2 X 50 ml) and dried at 45-55°C for 4-5 h in air tray dryer to give title compound as white solid (94 g). Yield: 77.84 %. HPLC Purity: 99.93 %

Example-9: Preparation of (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-ethoxybenzyl) phenyl)-2-phenyl-hexahydropyrano[3,2-d] [l,3]dioxine-7,8-diol (VIII)

A solution of (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-hydroxybenzyl)phenyl)-2-phenyl-hexahydropyrano[3,2-d] [l,3]dioxine-7,8-diol (10 g) in N,N-dimethylformamide (40 ml) was mixed with cesium carbonate (10.4 g) at 25-35°C. A solution of ethyl iodide (3.7 g) in N,N-dimethylformamide (10 ml) was added drop wise to the reaction mixture at 25-35°C. The reaction mixture was heated to 30-40°C and stirred for 3 h. Water (100 ml) was added to the reaction mixture and stirred at 25-35°C for 1 h. The solid was filtered; washed with water (2x10 ml) and suck dry well. The crude product stirred in methanol (100 ml) at 50-60°C for 1 h and then cooled to 25-35°C. The solid was filtered and dried to give title compound as white solid (8 g). Yield: 61.33%. HPLC Purity: 99.16%

^{1}H NMR (CDCl$_3$)6ppm: 1.38-1.42 (3H, t), 2.21-2.22 (1H, d), 2.82 (1H, s), 3.54-3.65 (3H, m), 3.74-3.79 (1H, m), 3.85-3.90 (1H, m), 3.98-4.03 (3H, m), 4.07-4.11 (1H, m), 4.22-4.24 (1H, d), 4.33-4.37 (1H, q), 5.57 (1H, s), 6.81-6.83 (2H, d), 7.08-7.11 (2H, d), 7.20-7.23 (2H, m), 7.37-7.7.40(41-1, m),7.50-7.52 (2H, m)

Mass: 495.2 [M-H] $^+$Cl^{35}, 497. 1 [M-H] $^+$Cl^{37}

Example-10: Preparation of (2R,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl) phenyl)-6-(hydroxy-methyl)tetrahydro-2H-pyran-3,4,5-triol (Dapagliflozin)

To a stirred mixture of (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2-phenylhexahydropyrano[3,2-d] [l,3]dioxine-7,8-diol (3 g) in methanol (30 ml), concentrated hydrochloric acid (3 ml) was slowly added at 25-35°C and stirred for 3 h. After completion of reaction, water (30 ml) was added to reaction mixture. The reaction mixture was washed with toluene (4x15 ml). The aqueous layer was extracted with isopropyl acetate (3x30 ml) and then combined isopropyl acetate layers. The combined organic layer washed with 20% aqueous potassium bicarbonate solution (2x30 ml), 20% aqueous sodium bisulphite solution (4x30 ml) followed by brine solution (30 ml). Organic layer was dried over sodium sulphate and distilled out under vacuum below 50°C to give glassy solid (2.16 g).

Yield: 87.51%.HPLC Purity: 99.6%

^{1}H NMR (DMSO d^{6})6: 1.28-1.31 (3H, t), 3.07-3.27 (4H, m), 3.40-3.46 (1H, m), 3.67-3.71 (1H, m), 3.93-4.04 (5H, m), 4.44-4.47 (1H, t), 4.83-4.85 (1H, d), 4.95-4.98 (2H, t), 6.81-6.84 (2H, d), 7.08-7.10 (2H, d), 7.21-7.24 (1H, dd), 7.32-7.38 (2H, m)

Mass: 407. 1 [M-H] $^{+}$Cl^{35}' 409.1 [M-H] $^{+}$Cl^{37}

Example-11: Preparation of (2R,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl) phenyl)-6-(hydroxy-methyl)tetrahydro-2H-pyran-3,4,5-triol (Dapagliflozin crude)

A solution of (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-hydroxybenzyl)phenyl)-6-(hydroxymethyl) tetrahydro-2H-pyran-3,4,5-triol (20 g) in N,N-dimethylformamide (60 ml) was mixed with cesium carbonate (20.52 g) at 25-35°C. Ethyl iodide (9.8 g) was added drop wise and then the reaction mixture was heated to 30-40°C for 4-5 h. After completion of reaction, reaction mixture was dumped into water (300 ml) and product was extracted with ethyl acetate (3x200 ml). Organic layers were combined and washed with brine solution (100 ml). Organic layer was dried over sodium sulphate and distilled out under vacuum below 55°C to give title compound as brown colour syrup (21.6 g). Yield: 98.5%. HPLC Purity: 88.07%.

Example-12: Preparation of (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-ethoxybenzyl) phenyl)-2-phenyl-hexahydropyrano[3,2-d] [I,3]dioxine-7,8-diol (VIII)

A solution of (2R,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl)phenyl)-6-(hydroxy-methyl)tetrahydro-2/-/-pyran-3,4,5-triol (20 g) in acetonitrile (200 ml) mixed with para toluene sulfonic acid (3.55 g) at 25-35°C. A solution of benzaldehyde dimethylacetal (22.32 g) in acetonitrile (160 ml) was added to the reaction mixture and stirred at 25-35°C for 2-3 h. After completion of reaction, organic solvent was distilled out from the reaction mixture under vacuum below 50°C. Aqueous potassium bicarbonate solution (20%, 160 ml) was added to the reaction mixture and product was extracted with dichloromethane (200 ml). Organic layer was distilled out to give a residue. To the residue was added methanol (200 ml) and the mixture was heated to 50-

60°C for 1 h. The mixture was cooled to 25-35°C, stirred for 1 h; filtered and dried at 50-60°C to give the title compound as white solid (15 g). Yield: 56.61%. HPLC Purity: 98.17%

Example-13: Preparation of (2R,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl) phenyl)-6-(hydroxy-methyl)tetrahydro-2H-pyran-3,4,5-triol (Dapagliflozin)

To a stirred mixture of (4a/?,6S,7/?,8/?,8aS)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2-phenyl-hexahydropyrano[3,2-d] [l,3]dioxine-7,8-diol (2 g) in methanol (20 ml), camphorsulfonic acid (0.93 g) was slowly added to the reaction mixture and stirred at 30-40°C for 3 h. After completion of reaction, water (20 ml) was added to reaction mixture. The reaction mixture was washed with toluene (3x20 ml). The aqueous layer was extracted with ethyl acetate (3x20 ml). Organic layers were combined and washed with 20% aqueous potassium bicarbonate solution (2x20 ml), 20% aqueous sodium bisulphite solution (2x20 ml) followed by brine solution (20 ml). Organic layer was dried over sodium sulphate and distilled out under vacuum below 50°C to give glassy solid (1.3 g). Yield: 79.13%. HPLC Purity: 99.5%

Example-14: Preparation of (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-hydroxybenzyl) phenyl)-2-phenyl-hexahydropyrano[3,2-d] [l,3]dioxine-7,8-diol (VII)

A mixture of (2S,3R,4R,5S,6R)-2-(4-chloro-3-(4-hydroxybenzyl)phenyl)-6-(hydroxymethyl) tetrahydro-2/-/-pyran-3,4,5-triol (10 g), p-toluenesulphonic acid monohydrate (1.6 g) and methyl ethyl ketone (80 ml) was stirred at 0-10°C. A solution of benzaldehyde dimethylacetal (9.7 g) in methyl ethyl ketone (20 ml) was slowly added to the reaction mixture at 0-10°C. The reaction mixture was stirred at 0-10°C for 4-5 h. After completion of reaction, reaction mixture was filtered and washed with methyl ethyl ketone (2x10 ml). The solid was dried at 50-60°C in air tray drier for 2 h to give the title compound as white solid (10.4 g). Yield: 84.45%

Example-15: Preparation of (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-ethoxy benzyl)phenyl)-2-phenyl-hexahydropyrano[3,2-d] [l,3]dioxine-7,8-diol (VIII)

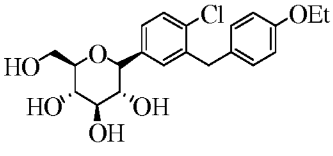
A solution of (4a/?,6S,7/?,8/?,8aS)-6-(4-chloro-3-(4-hydroxybenzyl)phenyl)-2-phenyl hexahydropyrano[3,2-d] [l,3]dioxine-7,8-diol (25 g) in dimethyl sulfoxide (100 ml) was mixed with cesium carbonate (26 g) at 25-35°C. A solution of ethyl iodide (9.14 g) in dimethyl sulfoxide (25 ml) was added drop wise to the reaction mixture at 25-35°C. The reaction mixture was stirred at 25-35°C for 3 h. After completion of reaction, water (375 ml) was added to the reaction mixture at 25-35°C and stirred for 1 h. The solid was filtered; washed with water (2x25 ml) and suck dry well. To the obtained crude product was added toluene (280 ml) and heated to 50-60°C for 1 h. The mixture was cooled to 0-10°C, filtered and dried at 50-60°C to give the title compound as white solid (18.7 g). Yield: 94.35%. HPLC Purity: 99.64%.

Example-16: Preparation of (2R,3R,4R,5S,6R)-2-(4-chloro-3-(4-ethoxybenzyl) phenyl)-6-(hydroxy-methyl)tetrahydro-2H-pyran-3,4,5-triol (Dapagliflozin)

To a stirred mixture of (4a/?,6S,7/?,8/?,8aS)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2-phenyl-hexahydropyrano[3,2-d] [l,3]dioxine-7,8-diol (10 g) in methanol (100 ml), a solution of camphorsulfonic acid (2.34 g) in water (10 ml) was slowly added to the reaction mixture and stirred at 35-45°C for 2 h. After completion of reaction, water (50 ml) and toluene (50 ml) was added to reaction mixture and stirred for 30 minutes. The layers were separated and aqueous layer was washed with toluene (6x30 ml). The aqueous layer was extracted with isopropyl acetate (140 ml) and then washed with 20% aqueous sodium chloride solution (50 ml), 20 % aqueous potassium bicarbonate solution (50 ml) followed by water (2x50 ml). Filter the organic layer through hyflo bed and distilled out under vacuum below 50°C to give residue. The obtained residue was stirred with isopropyl acetate (15 ml) at 35-45°C to get clear solution and then allowed to cool to 25-35°C. The obtained solution was added to the cooled n-hexane (100 ml) and then stirred for 6 h at 0-10°C. The resulting solid was filtered and washed with n-hexane (2X10 ml) to provide dapagliflozin. Yield: 73.2 %. HPLC Purity: 99.5%

CLAIMS:

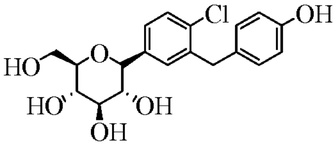
1. A process for the preparation of dapagliflozin (I)



(I)

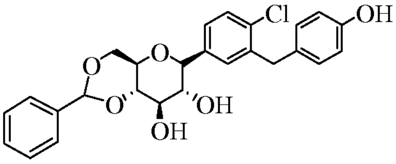
comprising the steps of:

a) reacting compound of formula (VI)



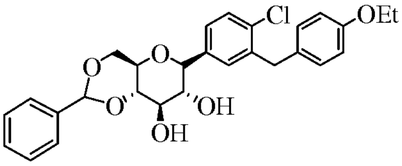
(VI)

with substituted or unsubstituted benzaldehyde acetal to provide (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-hydroxybenzyl)phenyl)-2-phenylhexahydropyrano[3,2-d] [l,3]dioxine-7,8-diol of formula (VII);



(VII)

b) reacting compound of formula (VII) with a suitable ethylating agent in presence of suitable solvent and base to provide (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-ethoxy-benzyl)phenyl)-2-phenylhexahydropyrano[3,2-d] [l,3]dioxine-7,8-diol of formula (VIII), optionally purifying compound of formula (VIII); and



(VIII)

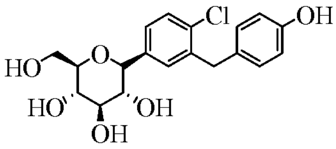
c) deprotecting compound of formula (VIII) to provide dapagliflozin (I).

2. The process of claim 1, wherein the solvent used in step (b) is selected from the group consisting of N,N-dimethylformamide, dimethyl acetamide, dimethyl sulfoxide and mixtures thereof.

3. The process of claim 1, wherein the base used in step (b) is selected from the group consisting of potassium carbonate, sodium carbonate, lithium carbonate, sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, cesium carbonate and mixtures thereof.

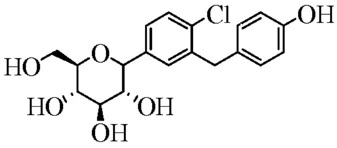
4. The process of claim 1, wherein deprotection of formula (VIII) is carried out in presence of methanol and camphorsulfonic acid.

5. A process for the preparation of formula (VI)



(VI)

comprising the step of purification of formula (IV)



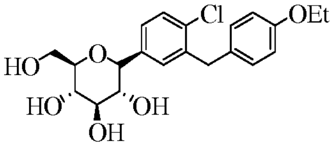
(IV)

in an organic solvent to provide formula (VI).

6. The process of claim 5, wherein organic solvent is selected from the group comprising of ketone, ester and mixtures thereof.

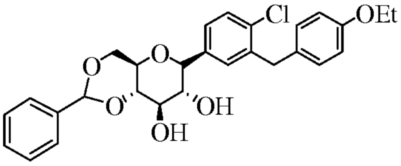
7. The process of claim 6, wherein ketone is selected from the group consisting of acetone, methyl ethyl ketone, methyl isobutyl ketone, diisopropyl ketone, methyl isopropyl ketone and mixtures thereof.

8. A process for the preparation of dapagliflozin (I):



(I)

comprising the step of deprotecting compound of formula (VIII)

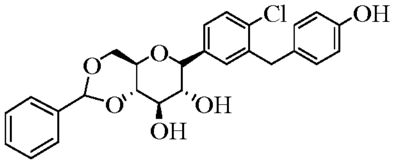


(VIII)

to provide dapagliflozin (I).

9. The process of claim 8, wherein deprotection of formula (VIII) is carried out in presence of methanol and camphorsulfonic acid.

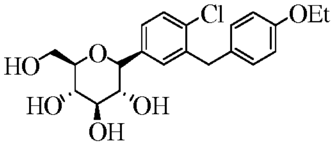
10. A compound of formula (VII), or pharmaceutically acceptable salts, solvates and hydrates thereof;



(VII)

wherein benzaldehyde acetal is substituted or unsubstituted.

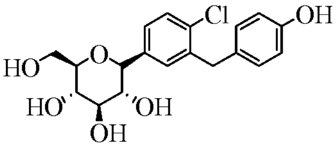
11. A process for the preparation of dapagliflozin (I)



(I)

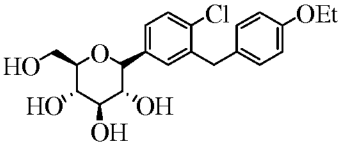
comprising the steps of:

a) reacting compound of formula (VI)



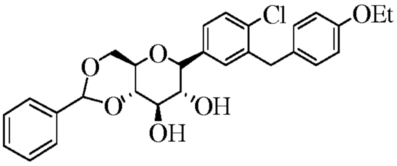
(VI)

with a suitable ethylating agent in presence of suitable solvent and base to provide dapagliflozin (I);



(I)

b) protecting dapagliflozin (I) with substituted or unsubstituted benzaldehyde acetal to provide (4aR,6S,7R,8R,8aS)-6-(4-chloro-3-(4-ethoxybenzyl)phenyl)-2-phenyl-hexahydropyrano[3,2-d] [l,3]dioxine-7,8-diol of formula (VII I), optionally purifying compound of formula (VII I); and



(VIII)

c) deprotecting compound of formula (VI II) to provide dapagliflozin (I).

12. The process of claim 11, wherein the ethylating agent used in step (a) is selected from the group consisting of ethyl iodide, ethyl chloride, ethyl bromide, diethyl sulphate and ethyl para toluenesulfonate.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/070220

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D309/10 C07D493/04
ADD.

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)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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☒ 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 2 October 2017	Date of mailing of the international search report 13/10/2017
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Lauro, Paola

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Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/070220

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US 6 515 117 B2 (SQUIBB BRISTOL MYERS CO [US]) 4 February 2003 (2003-02-04) cited in the application columns 7-8 -----	1-12

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