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— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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(54) Title: A NOVEL PROCESS FOR PREPARING (2S,3R,4R,5S,6R)-2-[4-CHLORO-3-(4-ETHOXYBENZYL)PHENY 1] -6-(HY DROXY METHYL)TETRAHYDRO-2H-PY RAN-3,4,5-TRIOL AND ITS AMORPHOUS FORM

(57) Abstract: The present invention discloses the process for preparation of (2S,3R,4R,5S,6R)-2-[4- chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol and its amorphous form.

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"A novel process for preparing (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol and its amorphous form"

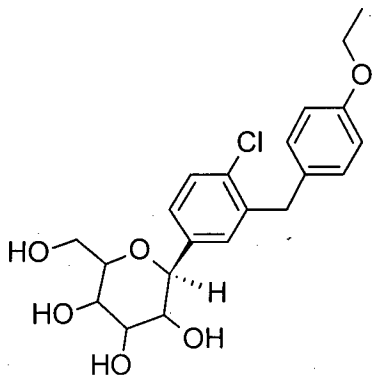
FIELD OF INVENTION:

The present invention relates to an industrially feasible process for preparation of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.

BACKGROUND OF INVENTION:

(2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol is sodium dependent glucose transporter (SGLT) which is currently under investigation for the treatment of type-2 diabetes. (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol is marketed under the tradename Farxiga or Forxiga.

(2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol is also known as D-glucitol, 1,5-anhydro-1-C-[4-chloro-3-[(4ethoxyphenyl)methyl]phenyl]-, (1S). (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol is a white to off-white powder with a molecular formula of $C_{21}H_{25}ClO_6$ and a molecular weight of 408.87



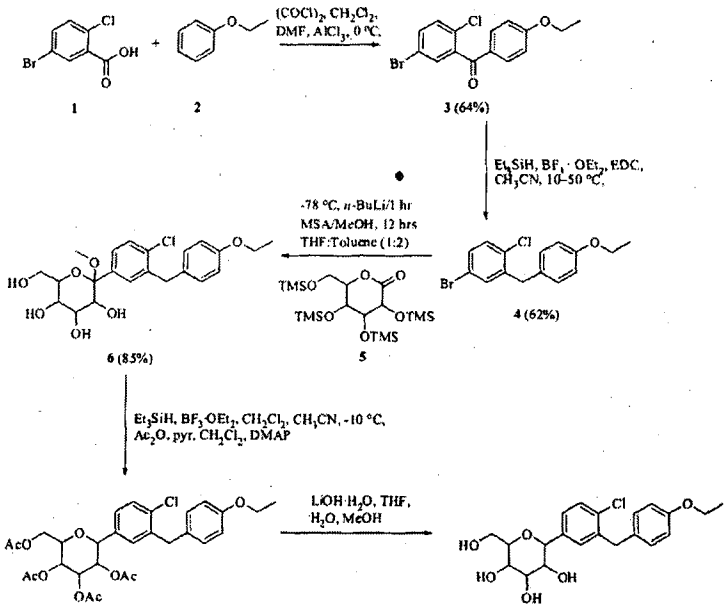
Formula-I

US 6,515,117 B2 discloses (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol and its pharmaceutically acceptable salts. **US 6,515,117 B2** also describes process for preparation of (2S,3R,4R,5S,6R)-2-[4-

chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol which comprises reaction of 5-bromo-2-chloro-4'-ethoxydiphenylmethane with 2,3,4,6-tetra-O-trimethylsilyl-β-D-glucolactone in presence of THF/Toluene, methansulfonic acid to yield o-methylglucoside product which further reacts with Et_3SiH, BF_3Et_2O in presence of MDC and acetonitrile to yield yellow solidified foam which is dissolved in MDC, pyridine and followed by acetylation with acetic anhydride, DMAP to yield tetra acetylated- β-C-glucoside as a white solid which is further deprotected with LiOH H_2O in presence of THF/MeOH/H_2O to get (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.

The drawback of said prior art is having multiple process steps which makes the process very lengthy and tedious. Moreover the process discloses use of hazardous chemicals like pyridine which is not applicable to industry.

Process for preparation of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol is disclosed in **US 7,375,213 B2** and **J.Med.Chem.2008, 51, 1145-1149.** The preparation process is depicted in Scheme-I.



Scheme-1

Prior art US'213 describes reaction of 2-chloro-5-bromo-4'-ethoxy-diphenylmethane with 2,3,4,6-tetra-O-trimethylsilyl-D-gluconolactone, n-BuLi in presence of THF and Heptane. After basification with TEA, the oily residue of methyl-1-C-(2-chloro-4'-

ethoxy-diphenylmethan-3-yl)-α-D-glucopyranose obtained as solid compound after workup. This compound reacts with acetic anhydride in presence of THF, DIPEA and DMAP to get oily residue of methyl-2,3,4,6 tetra-O-acetyl-1-C-(2-chloro-4'-ethoxydiphenylmethan-3-yl)-α-D-glucopyranose which further undergoes reduction reaction in presence of acetonitirle, t riethylsilane, boron trifluoride etherate to yield 2,3,4,6-tetra-O-acetyl-1-C-(2-chloro-4'-ethoxydiphenylmethan-3-yl)-β-D-glucopyranose which is further deprotected by reacting with LiOH monohydrate in presence of THF/MeOH/H_2O to get (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.

The said prior art describes multiple, time consuming process steps which involves getting the intermediate products as oily residue at various stages of the process, which is difficult to purify and handle for further process step. More over the workup involves multiple evaporation of product which may result in decomposition. Another drawback of the process is that the process describes n-BuLi reaction with two pot reaction. It is very difficult to transfer the material from one reactor to second reactor at -78 °C at industrial level with highly moisture sensitive reaction mass. This makes process uneconomical, cumbersome and commercially not viable. Further when practically the said method followed, α-Isomer of the final product is formed in the range of 6-8% along with Des-bromo impurity formed in the range of 7-9 %, which increases after addition of n-butyllithium and kept the mass for overnight reaction. Moreover lactone ring cleavage is also observed in the range of 3-4% after addition of Methanesulphonic Acid/Methanol and maintained overnight for reaction completion, the removal of which is difficult from the final product.

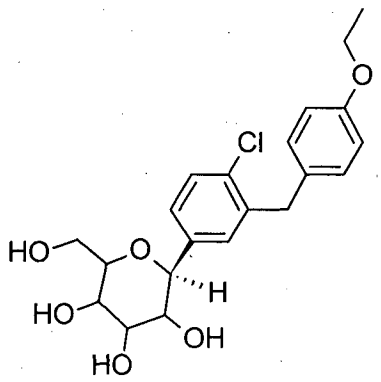
WO 2008002824 A 1 discloses crystalline forms of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol comprising (S)-propylene glycol (PG), (R)-PG, EtOH, ethylene glycol (EG), 1 :2 L-proline, 1 : 1 L-proline, 1 : 1 L-proline hemihydrate, 1 : 1 L-phenylalanine and its preparation process.

In the light of the above drawbacks, it is necessitated to provide economical, robust, safe and commercially viable process for preparing (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.

Accordingly, it is an objective of the present invention to provide a commercially viable process for the preparation of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol, prepared via novel intermediates which gives higher yield and purity and facilitates easy recovery of the final compound. The purification process does not involve any costly technique/equipment, however, carried out with solvents which are industrially feasible. More over the present invention discloses the n-BuLi insitu reaction that makes the present invention cost-effective over the teachings of prior art.

SUMMARY OF THE INVENTION:

The present invention provides the process for preparation of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol**(Formula-I)** and its stable amorphous form.



Formula-I

In one aspect, the present invention describes the silylation process for preparing 3,4,5-Tris-trimethylsilanyloxy-6-trimethylsilanyloxymethyl-tetrahydro-pyran-2-one from 3,4,5-Trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-one which comprises;

(a) Reacting 3,4,5-Trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-one with trimethyl silyl chloride in presence of solvent and organic base at ambient temperature;

(b) Maintaining pH 7-8 by adding sat. sodium bicarbonate; and

(c) Separating organic layer followed by distillation to isolate 3,4,5-Tris-trimethylsilanyloxy-6-trimethylsilanyloxymethyl-tetrahydro-pyran-2-one.

In another aspect, the present invention discloses the process for preparing 2-R^1-2-[4-chloro-3-(4-ethoxy-benzyl)-phenyl]-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol from

3,4,5-Tris-trimethylsilanyloxy-6-trimethylsilanyloxymethyl-tetrahydro-pyran-2-one which comprises;

(a) Reacting 4-(5-bromo-2-chlorobenzyl)phenyl ethyl ether with 3,4,5-Tris-trimethylsilanyloxy-6-trimethylsilanyloxymethyl-tetrahydro-pyran-2-one in presence of mixture of polar aprotic solvent and non-polar solvent, organolithium reagent, alkyl sulfonic acid, monohydric or unsaturated aliphatic alcohol;

(b) Bringing pH from neutral to alkaline;and

(c) Separating organic layer to isolate 2-R^1-2-[4-chloro-3-(4-ethoxy-benzyl)-phenyl]-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol.

In another embodiment, the present invention describes process for preparing (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol by reduction of 2-R^1-2-[4-chloro-3-(4-ethoxy-benzyl)-phenyl]-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol which comprises;

(a) Reacting 2-R^1-2-[4-chloro-3-(4-ethoxy-benzyl)-phenyl]-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol with organosilane in presence of acid, mixture of non-polar solvent and polar aprotic solvent under argon atmosphere;

(b) Quenching with sat. sodium bicarbonate solution; and

(c) Separating layers to isolate (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.

In another embodiment, the instant invention provides process for preparing stable amorphous form of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol from (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol which comprises;

(a) Stirring (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol with non-polar solvent at ambient temperature and

(b) Isolating amorphous form of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.

In another embodiment, the present invention describes the preparation of L-proline complex of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol from (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol which comprises;

(a) Reacting (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol with proline in presence of polar aprotic solvent under argon atmosphere;

(b) Adding non-polar solvent and

(c) Isolating L-proline complex of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.

In another embodiment, the present invention describes the process for preparing amorphous form of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol from L-proline complex of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol which comprises;

(a) Stirring L-proline complex of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol in presence of ethyl acetate;

(b) Adding sat. sodium bicarbonate solution;

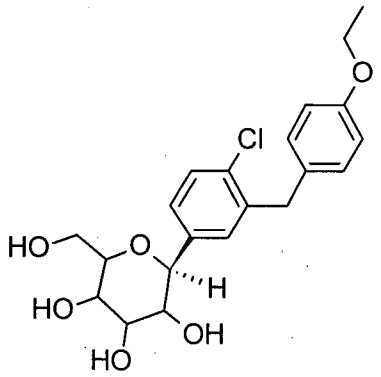
(c) Adding n-Heptane and

(d) Isolating stable amorphous form of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.

The present process gives α-Isomer in the range of 3-5 %., which is removed during purification; further, the Des-bromoimpuirity (2-chloro –4'- ethoxydiphenylmethane) formation is restricted to 3-4 % during purification. Further work up disclosed in present invention is advantageous over the teachings of prior art as the purification process does not involve multiple step workup. The purification process simply carried out with solvents which is commercially feasible. Thus the instant invention provides time saving, cost effective and commercially viable process for preparing (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.

DETAILED DESCRIPTION OF THE INVENTION:

The instant invention provides an efficient, advantageous and economical process for preparing (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol **(Formula-I)** and its amorphous form.



Formula-I

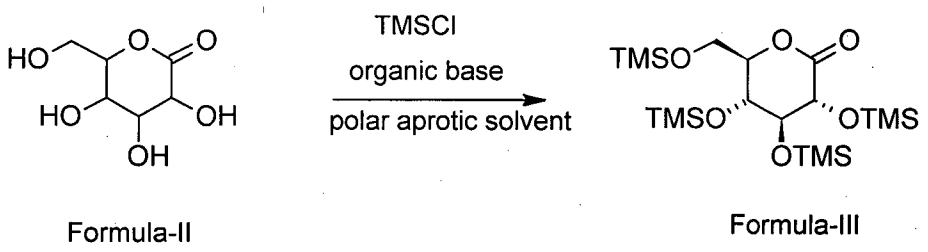
In one embodiment, the present invention describes the silylation process for preparing 3,4,5-Tris-trimethylsilanyloxy-6-trimethylsilanyloxymethyl-tetrahydro-pyran-2-one from 3,4,5-Trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-one which comprises;

(a) Reacting 3,4,5-Trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-one with trimethyl silyl chloride in presence of solvent and organic base at ambient temperature;

(b) Maintaining pH 7-8 by adding sat. sodium bicarbonate;

(c) Separating organic layer followed by distillation to isolate 3,4,5-Tris-trimethylsilanyloxy-6-trimethylsilanyloxymethyl-tetrahydro-pyran-2-one.

The process for preparing 3,4,5-Tris-trimethylsilanyloxy-6-trimethylsilanyloxymethyl-tetrahydro-pyran-2-one depicted in the following reaction **Scheme II.**



Formula-II Formula-III

Scheme-II

The term 'solvent' refers to polar aprotic solvents selected from the group consisting of tetrahydrofuran, ethyl acetate, acetone, dimethylformamide, acetonitrile, dimethyl sulfoxide. The organic base is selected from the group consisting of triethylamine, diisopropyl ethylamine, N-methyl morpholine& N-methyl pyrrolidine.

According to above process, the reaction is carried out at -5 to 0°C.

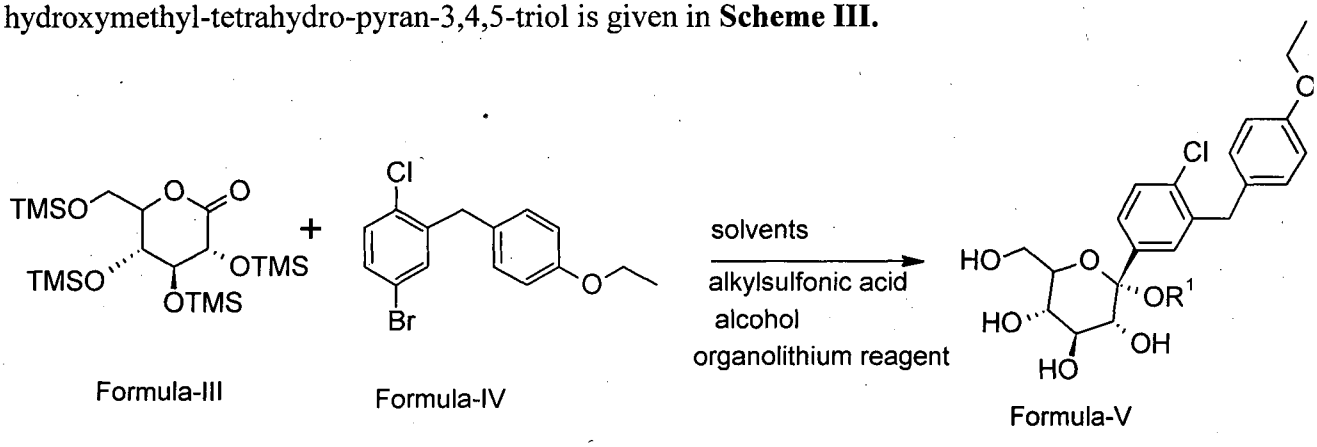
In another embodiment, the instant invention discloses the process for preparing 2-R^1-2-[4-chloro-3-(4-ethoxy-benzyl)-phenyl]-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol from 3,4,5-Tris-trimethylsilanyloxy-6-trimethylsilanyloxymethyl-tetrahydro-pyran-2-one which comprises;

(a) Reacting 4-(5-bromo-2-chlorobenzyl)phenyl ethyl ether with 3,4,5-Tris-trimethylsilanyloxy-6-trimethylsilanyloxymethyl-tetrahydro-pyran-2-one in presence of mixture of polar aprotic solvent and non-polar solvent, organolithium reagent, alkyl sulfonic acid, monohydric or unsaturated aliphatic alcohol;

(b) Bringing pH neutral to alkaline;

(c) Separating organic layer to isolate 2-R^1-2-[4-chloro-3-(4-ethoxy-benzyl)-phenyl]-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol.

The reaction scheme for preparing 2-R^1-2-[4-chloro-3-(4-ethoxy-benzyl)-phenyl]-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol is given in **Scheme III.**



Formula-III Formula-IV Formula-V

where R^1= allyl, prop-2-ynyl,isopropyl

Scheme-III

In the above said process, the polar aprotic solvent is selected from the group consisting of tetrahydrofuran, ethyl acetate, acetone, dimethylformamide, acetonitrile, dimethyl sulfoxide. The non-polar solvent is selected from the group consisting of Toluene, Hexane, 1,4-Dioxane, Chloroform, Diethyl ether, Dichloromethane.

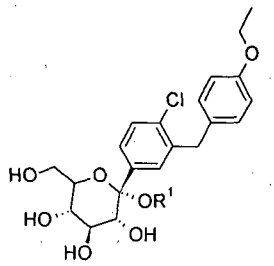
According to above process the reaction temperature is -70 to -80 °C.

The term 'organolithium reagent' refers to alkyllithium reagents selected from the group consisting of n-butyl lithium, methyl lithium, t-butyl lithium. The term alkyl sulfonic acid refers to methane sulfonic acid. The unsaturated aliphatic alcohol is selected from the group consisting of allyl alcohol, isopropyl alcohol or propargyl alcohol.

The present process gives α- Isomer in the range of 3-4 %., which is removed during purification, Des-bromoimpuirity (2-chloro –4'- ethoxydiphenylmethane) formation is restricted to 3-5 %during purification.

In above process R^1 is allyl, prop-2ynyl.

The main advantage of above said process is deprotection step which undergoes insitu simultaneously. Therefore additional and multiple steps/ work up can be avoided which results in economical, time saving and safe process. Accordingly, the invention encompasses the compound 2-R^1-2-[4-chloro-3-(4-ethoxy-benzyl)-phenyl]-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol of formula V.



wherein, R^1 is allyl, prop-2ynyl.

Formula-V

Therefore, the invention encompasses the novel intermediate compounds of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol, viz.,

(a) 2-Allyloxy-2-[4-chloro-3-(4-ethoxy-benzyl)-phenyl]-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol
(b) 2-[4-Chloro-3-(4-ethoxy-benzyl)-phenyl]-6-hydroxymethyl-2-prop-2-ynyloxy-tetrahydro-pyran-3,4,5-triol.

The novel intermediates are having better leaving groups- allyl, propargyl as compare to hydroxyl, alkyl which increases reaction rate and gives higher yield with reduced reaction time.

In another embodiment the instant invention discloses process for preparing des-bromo (4-(5-2-chlorobenzyl) phenyl ethyl ether) impurity which comprises;

(a) Reacting 4-(5-bromo-2-chlorobenzyl) phenyl ethyl ether with alkyllithium in presence of mixture of polar aprotic solvent and non-polar solvent;
(b) Adding ammonium chloride solution and
(c) Isolating 2-chloro –4'- ethoxydiphenylmethane.

The alkyl lithiums is selected from the group consisting of n-butyl lithium, methyl lithium, t-butyl lithium. The polar aprotic solvent is selected from the group consisting of tetrahydrofuran, ethyl acetate, acetone, dimethylformamide, acetonitrile, dimethyl sulfoxide. The non-polar solvent is selected from the group consisting of Toluene, Hexane, 1,4-Dioxane, Chloroform, Diethyl ether, Dichloromethane. According to above process the reaction temperature is -70 to -80°C.

The main object is achieved by removing the des-bromo impurity during the purification of 2-2-R^1-2-[4-chloro-3-(4-ethoxy-benzyl)-phenyl]-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol, without involving any special techniques, that makes the process less cumbersome and cost-effective.

In another embodiment the present invention describes process for preparing (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol by reduction of 2-R^1-2-[4-chloro-3-(4-ethoxy-benzyl)-phenyl]-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol which comprises;

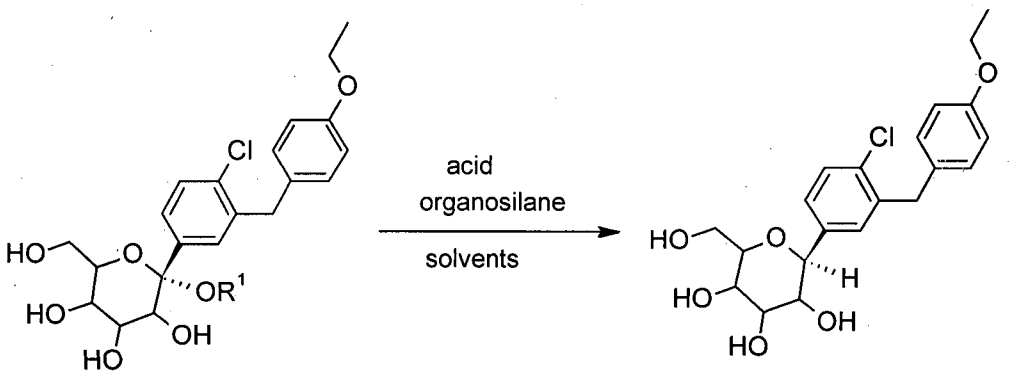
(a) Reacting 2-R^1-2-[4-chloro-3-(4-ethoxy-benzyl)-phenyl]-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol with organosilane in presence of acid, mixture of non-polar solvent and polar aprotic solvent under argon atmosphere;

(b) Quenching with sat. sodium bicarbonate solution;

(c) Separating layers and

(d) Isolating (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.

The reaction scheme for said process is given in Scheme-IV.



Formula-V Formula-I

where R^1 = allyl, prop-2-ynyl

Scheme-IV

According to above said process the term 'organosilane' refers to alkylsilane or polyalkylsilane is selected from the group consisting of trimethylsilane, triethylsilane, tetramethylsilane, dimethylsilane. The non-polar solvent is selected from the group consisting of Dichloromethane, Toluene, Hexane, 1,4-Dioxane, Chloroform, Diethyl ether and the polar aprotic solvent is selected from the group consisting of acetonitrile, tetrahydrofuran, ethyl acetate, acetone, dimethylformamide, dimethyl sulfoxide. The acid for the above said process is selected from the group consisting of borontrifluoride in diethylether, trifluoroacetic acid, methanesulfonic acid.

The above reaction is carried out at -40 to 55 °C.

In above process R^1 is allyl, prop-2ynyl.

In one another embodiment the instant invention provides process for preparing stable amorphous form of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol from (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol which comprises;

(a) Stirring (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol with non-polar solvent at ambient temperature and

(b) Isolating stable amorphous form of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.

The non-polar solvent for said process is selected from the group consisting of n-Heptane, Dichloromethane, Toluene, Hexane, 1,4-Dioxane, Chloroform, Diethyl ether. The ambient temperature is 25-30 °C.

The other object of the present invention is to get stable amorphous form of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol which is achieved without using any special technique which makes the process simple, cost- effective and time saving.

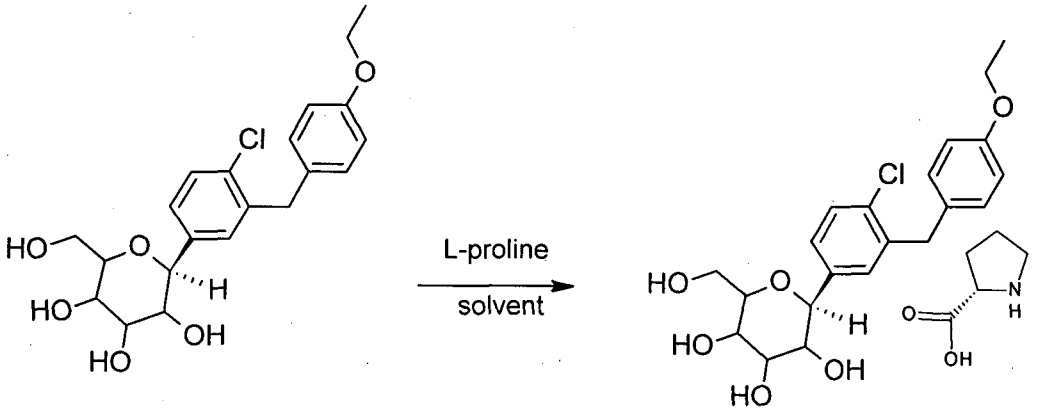
In another embodiment the present invention describes the preparation of L-proline complex of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol from (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol which comprises;

(a) Reacting (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol with L-proline in presence of polar aprotic solvent under argon atmosphere;

(b) Adding non-polar solvent and

(c) Isolating L-proline complex of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.

The reaction scheme for said process is given in Scheme-V.



Scheme-V

The polar aprotic solvent for above said process is selected from the group consisting of ethyl acetate, acetone, acetonitrile, tetrahydrofuran, dimethylformamide,. dimethyl sulfoxide and the non-polar solvent is selected from the group consisting of n-Heptane, Dichloromethane, Toluene, Hexane, 1,4-Dioxane, Chloroform, Diethyl ether. The temperature for the above said process is 60-65 °C.

In another embodiment the present invention describes the process for preparing amorphous form of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol from L-proline complex of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol which comprises;

(a) Stirring L-proline complex of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol in presence of ethyl acetate;
(b) Adding sat. sodium bicarbonate solution;
(c) Adding n-Heptane and
(d) Isolating stable amorphous form of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol

The following examples, which include preferred embodiments, will serve to illustrate the practice of this invention, it being understood that the particulars shown are by way of example and for purpose of illustrative discussion of preferred embodiments of the invention.

Examples:

Example-1: Preparation of 3,4,5-Tris-trimethylsilanyloxy-6-trimethylsilanyloxymethyl-tetrahydro-pyran-2-one

To 750 cc of dry THF added 1.12 mole 3,4,5-Trihydroxy-6-hydroxymethyl-tetrahydro-pyran-2-one at ambient temperature and stirred for 20 min. To the reaction mass added 9.0 mole N-Methyl morpholine and stirred for another 30.0 min at ambient temperature. Reaction mass was cooled to -5 °C to 0 °C and stirred for 30.0 min. Added 18.0 mole Trimethyl sillyl chloride at the temp -5 °C to 0 °C and stirred for 30.0 min. Temperature was raised to 25 °C to 30 °C and maintained for 18-20hrs. After reaction complies by GC, the reaction mass was cooled to -5 deg to 0 deg. Added Sat.Sodium bicarbonate solution to obtain the pH 7-8 and stirred for 1 hr at 0 °C. Added 500 cc toluene and stirred for 1hr. Reaction mass was settled down for 30.0 min and layers were separated. To the Aqueous layer added 250 cc of toluene and stirred for 30.0 min. Layers separated and both the organic layers mixed and back washed with sat.brine solution. Organic layer was distilled under reduced pressure at a temperature of about 40 – 48 deg. Unload the oily mass .

Purity: 92-96 %

Example-2: Preparation of 2-Allyloxy-2-[4-chloro-3-(4-ethoxy-benzyl)-phenyl]-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol

To the mixture of 10 cc THF and 10 cc Toluene added 0.138 mole 4-(5-bromo-2-chlorobenzyl)phenyl ethyl ether at ambient temperature and stirred for 15 min. Cooled to -70 to -80°C in dry ice /acetone bath and stirred for 15 min. Added a solution of 0.014 mole n-Butyl lithium (1.9M in hexanes) at -70 to -80°C. and stirred for 1hr. Added solution of 3, 4, 5-Tris-trimethylsilanyloxy-6-trimethylsilanyloxymethyl-tetrahydro-pyran-2-one in 5 cc of Toluene at -70 to -80°C and stirred for 2 to 3hrs. After the compliance of the reaction, reaction mass was quenched with Methane sulphonic acid and Allyl alcohol mixture at -70 to -80°C. Temperature was raised to ambient temperature and stirred overnight. Reaction mass was quenched with 30 cc sat.sodiumbicarbonate solution to bring the pH neutral to alkaline and stirred for 30.0 min. Layers separated and aqueous layer was extracted with 10 cc of Toluene. Organic layer was combined and washed with 30cc water and 50 cc sat. brine solution. Organic layer was distilled under reduced pressure to recover toluene. Solid compound was dissolved in 50cc of toluene and quenched in n-Hexane to obtain 83 % the compound as crystalline solid.

HPLC purity: 88 – 91 %

IR data:

Anomeric C-O stretching: 1242 cm^{-1}

Allylic C- O stretching: 1177 cm^{-1}

Allylic C- H stretching: 3010 – 3120 cm^{-1}

Aromatic C- Cl stretching: 820 cm^{-1}

Lactones O – H stretching: 3240 – 3380 cm^{-1}

Lactones C – O stretching: 1045 – 1092 cm^{-1}

Aromatic C=C stretching: 1510 , 1548 , 1603 , 1703 cm^{-1}

Alkane C – H stretching: 2877,2866, 2956, 2958, 2962 cm^{-1}

Aromatic C – H stretching: 3050 - 3090 cm^{-1}

Dip-Mass
(M+Na) 487.19 m/z
(M+K) 503.17 m/z

Example 3: Preparation of 2-prop-2ynyl-2-[4-Chloro-3-(4-ethoxy-benzyl)-phenyl]-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol

To the mixture of 10 cc THF and 10 cc Toluene added 0.138 mole 4-(5-bromo-2-chlorobenzyl)phenyl ethyl ether at ambient temperature and stirred for 15 min. Cooled to -70 to -80°C in dry ice /acetone bath and stirred for 15 min. Added a solution of 0.014 mole n-Butyl lithium (1.9M in hexanes) at -70 to -80°C. and stirred for 1hr. Added solution of 3, 4, 5-Tris-trimethylsilanyloxy-6-trimethylsilanyloxymethyl-tetrahydro-pyran-2-one in 5 cc of Toluene at -70 to -80°C and stirred for 2 to 3hrs. After the compliance of the reaction, the reaction mass was quenched with Methane sulphonic acid and propargyl alcohol mixture at -70 to -80°C. Temperature was raised to ambient temperature and stirred overnight. Reaction mass was quenched with 30 cc sat.sodiumbicarbonate solution to bring the pH neutral to alkaline. Reaction mass stirred for 30.0 min. Layers separated and aqueous layer was extracted with 10 cc of Toluene. Organic layer were combined and washed with 30cc water and 50 cc sat. brine solution. Organic layer was distilled under reduced pressure to recover toluene. Solid compound dissolved in 50cc of toluene and quenched in n-Hexane to obtain 75 - 80 % the compound as crystalline solid.

HPLC purity: 88 – 93 %

IR data:

Anomeric C-O stretching: 1242 cm^{-1}

Propargyl —C≡≡≡CH stretching: 2125 cm^{-1}

Propargyl C- H stretching : 3010 – 3120 cm^{-1}

Aromatic C- Cl stretching: 820 cm^{-1}

Lactones O – H stretching: 3240 – 3380 cm^{-1}

Lactones C – O stretching: 1045 – 1092 cm^{-1}

Aromatic C=C stretching: 1510 , 1548 , 1603 , 1703 cm^{-1}

Alkane C – H stretching: 2877, 2866,2956,2958,2962 cm^{-1}

Aromatic C – H stretching: 3050 - 3090 cm^{-1}

Dip-Mass

(M+Na) 485.25 m/z

(M+K) 501.25 m/z

Example-4: Preparation of 2-[4-Chloro-3-(4-ethoxy-benzyl)-phenyl]-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol

To the mixture of 20 cc (1:1 MDC + ACN) added 0.11 mole 2-Allyloxy-2-[4-chloro-3-(4-ethoxy-benzyl)-phenyl]-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol under argon atmosphere, and stirred the reaction mass for 30.0 min. Cooled the reaction mass to -40 to -55°C in a dry ice/acetone bath under argon atmosphere. Charged 3 mole Triethylsilane at -40 to -55°C and stirred the reaction mass for 30.0 min at -50 to -55°C. Slowly added Borontrifloride in diethyl ether solution at -40 to -55°C and stirred the reaction mass for 2 hrs. Quenched the reaction mass with 50 cc sat. sodium bicarbonate solution at -40 to -55°C . and stirred the reaction mass for 30.0 min. Slowly raised the temperature to 25 to 30°C. Settled down the reaction mass and separated the layers, extracted the aqueous layer with 100 cc of MDC. Combined the organic layer and wash with 500 cc water. Washed the organic layer with 500 cc of sat. Brine solution. Distilled out the MDC under reduced pressure below 40°C. to get 85 %the light yellow solid.

HPLC purity: 92-95 %

Example 5: Preparation of 2-[4-Chloro-3-(4-ethoxy-benzyl)-phenyl]-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol

To the mixture of 20 cc (1:1 MDC + ACN) added 0.11 mole 2-prop-2-ynyl-2-[4-Chloro-3-(4-ethoxy-benzyl)-phenyl]-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol under argon

atmosphere. Stirred the reaction mass for 30.0 min. Cooled the reaction mass to -40 to -55°C in a dry ice/acetone bath under argon atmosphere. Charged 3 mole Triethylsilane at -40 to -55°C and stirred the reaction mass for 30.0 min at -50 to -55°C. Slowly added Borontrifloride in diethyl ether solution at -40 to -55°C and stirred the reaction mass for 2 hrs. Quenched the reaction mass with 50 cc sat. sodium bicarbonate solution at -40 to -55°C and Stirred the reaction mass for 30.0 min. Slowly raised the temperature to 25 to 30°C. Settled down the reaction mass and separated the layers, extracted the aqueous layer with 100 cc of MDC. Combined the organic layer and washed with 500 cc water. Washed the organic layer with 500 cc of sat. Brine solution. Distilled out the MDC under reduced pressure below 40°C. to get 85%the light yellow solid.

HPLC purity: 90%

Example 6: Preparation of amorphous form of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol

To the solid obtained from example 4 charged 500cc of n-heptane and stirred for ½hrs at ambient temperature. Heated the reaction mass to 55-60°C and stirred it for 2-3 hrs.; cooled to room temperature and maintained for 4-5 hrs. Filtered the solid and washed the cake with 100 cc n-heptane. Dried at 40-45°C under vacuum to get 85% amorphous form of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.

HPLC purity: 91-93%

Example 7: Preparation of amorphous form of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol

To the solid obtained from example 5 charged 500cc of n-heptane and stirred for ½ hrs at ambient temperature. Heated the reaction mass to 55-60°C and stirred it for 2-3 hrs., cooled to room temperature and maintained for 4-5 hrs. Filtered the solid and washed the cake with 100 cc n-heptane. Dried at 40-45°C under vacuum to get 85-88% amorphous form of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.

HPLC purity: 89-91%

Example 8: Preparation of L-proline – (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol co crystal

To the 10 cc of Ethyl acetate charged 1.0 mole (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol under argon atmosphere at ambient temperature and stirred for 30.0 min to get clear solution. Slowly heated the reaction mass to 60 – 65°C and stirred for 1 hr. Slowly added L-proline at 60 – 65°C and maintained for 1 hr. Slowly added 15 cc n-Heptane to the reaction mass at 60 – 65°C and stirred the mass for 2.5 hrs. Cooled the mass to ambient temperature for 3-4 hrs and maintained for 5 hrs. Filtered the mass under argon atmosphere. Washed the cake with 10 cc n-Heptane. Dried the cake at 50-55°C under reduced pressure to get 92% titled compound.

HPLC purity: 99%

Example 9: Preparation of L-proline – (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triolco crystal

To the 10 cc of acetone charged 1.0 mole (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol under argon atmosphere at ambient temperature and stirred for 30.0 min to get clear solution. Slowly heated the reaction mass to 60 – 65°C and stirred for 1 hr. Slowly added proline at 60 – 65°C and maintained for 1 hr. Slowly added 15 cc n-Heptane to the reaction mass at 60 – 65°C and stirred the mass for 2.5 hrs. Cooled the mass to ambient temperature for 3-4 hrs and maintained for 5 hrs. Filtered the mass under argon atmosphere. Washed the cake with 10 cc n-Heptane. Dried the cake at 50-55°C under reduced pressure to get 93-95% titled compound.

HPLC purity: 98-99%

Example 10: Preparation of amorphous form of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol

To the 15 cc ethyl acetate added (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol at ambient temperature and stirred for 30.0 min. Slowly added 5- 8 cc sat. sodium bicarbonate solution at ambient temperature and stirred for 1.5 hr to get the clear solution. Settled down and separated layers. Extracted the aqueous layer with 25 cc ethyl acetate.

Combined the organic layers and washed the ethyl acetate layer with 50 cc sat. Sodium chloride solution. Distilled out ethyl acetate under reduced pressure at 40 – 45°C to get fluffy solid. Charged 50 cc n-Heptane and stirred for 5 hrs to get 70-78% the title compound as Amorphous soild.

HPLC purity: 99.8-99.95 %

Example 11: Preparation of 2-chloro –4'- ethoxydiphenylmethane (impurity)

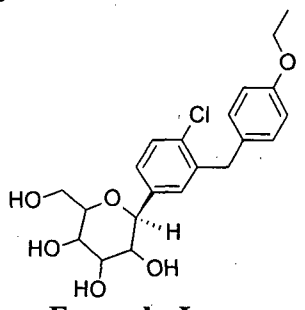
To the 20 cc THF and 20 cc Toluene added 0.25 mole 2-chloro-5-bromo-4'-ethoxydiphenylmethane under argon atmosphere. Cooled the reaction mass to - 78^0 C. Slowly added n-Butyl lithium (1.9 M in hexane) at – 78^0 C and stirred for 30 min. Slowly added 20 % Ammonium chloride solution to the reaction mass. Brought the reaction mass to ambient temperature and stirred for 30 min. Settled and separated layers. Extracted the aqueous layer with 50 cc toluene. Washed the combined organic layer with 500 cc brine solution. Distilled out the toluene and charged heptanes, stirred for 2 – 3 hrs at ambient temperature. Filtered the product and dried the product at 45 – 50^0C under reduced pressure to get 93 % titled compound.

Mass: (m+1) 247 m/z found 247.11

HPLC purity: 96.33 %

We claim,

1. A process for preparing (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol(**Formula-I**) comprising



Formula-I

(a) Reacting 4-(5-bromo-2-chlorobenzyl)phenyl ethyl ether with 3,4,5-Tris-trimethylsilanyloxy-6-trimethylsilanyloxymethyl-tetrahydro-pyran-2-one in presence of mixture of polar aprotic solvent and non-polar solvent, organolithium reagent, alkyl sulfonic acid, monohydric or unsaturated aliphatic alcohol;

(b) Bringing pH neutral to alkaline to isolate 2-R^1-2-[4-chloro-3-(4-ethoxy-benzyl)-phenyl]-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol;

(c) Reacting 2-R^1-2-[4-chloro-3-(4-ethoxy-benzyl)-phenyl]-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol with organosilane in presence of acid, mixture of non-polar solvent and polar aprotic solvent under argon atmosphere and

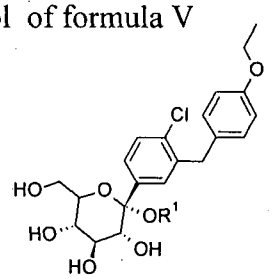
(d) Quenching with sat. sodium bicarbonate solution to isolate (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.

2. The process according to claim 1, wherein the polar aprotic solvent is selected from the group consisting of acetonitrile, tetrahydrofuran, ethyl acetate, acetone, dimethylformamide and dimethyl sulfoxide.
3. The process according to claim 1, wherein the non-polar solvent is selected from the group consisting of Dichloromethane, Toluene, Hexane, 1,4-Dioxane, Chloroform, Diethyl ether and n-Heptane.
4. The process according to claim 1, wherein the R^1 is allyl or prop-2ynyl.
5. The process according to claim 1, wherein the organolithium reagent is alkyllithium reagents selected from the group consisting of n-butyl lithium, methyl lithium and t-butyl lithium.

6. The process according to claim 1, wherein the alkyl sulfonic acid is methane sulfonic acid.
7. The process according to claim 1, wherein the unsaturated aliphatic alcohol is selected from the group consisting of allyl alcohol or propargyl alcohol.
8. The process according to claim 1, wherein the acid is selected from the group consisting of borontrifloride in diethylether, trifluoroacetic acid and methanesulfonic acid.
9. The process according to claim 1, wherein the organosilane is alkylsilane or polyalkylsilane selected from the group consisting of trimethylsilane, triethylsilane, tetramethylsilane and dimethylsilane.
10. The process according to claim 1, wherein the reaction temperature for step (a) and (e) is -70 to -80 °C and -40 to -55 °C respectively.
11. A process for preparing amorphous form of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol comprising
    (a) Stirring (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol with non-polar solvent at ambient temperature and
    (b) Isolating stable amorphous form of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.
12. The process according to claim 11, wherein the non-polar solvent is n-heptane.
13. A process for preparing L-prolin complex of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol comprising
    (a) Reacting (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol with L-proline in presence of polar aprotic solvent under argon atmosphere;
    (b) Adding non-polar solvent and
    (c) Isolating L-proline complex of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol.
14. The process according to claim 13, wherein the polar aprotic solvent is ethyl acetate and non-polar solvent is n-Heptane.

15. The process according to any of the preceding claims, wherein the purity of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol and L-prolin complex of (2S,3R,4R,5S,6R)-2-[4-chloro-3-(4-ethoxybenzyl)phenyl]-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol is 99.8-99.9 % and 98-99% respectively.

16. The compound, 2-R^1-2-[4-chloro-3-(4-ethoxy-benzyl)-phenyl]-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol of formula V



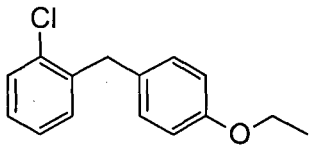
Formula-V.

17. The compound according to claim 16 is selected from the group consisting of

(a) 2-Allyloxy-2-[4-chloro-3-(4-ethoxy-benzyl)-phenyl]-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol and

(b) 2-prop-2ynyl-2-[4-Chloro-3-(4-ethoxy-benzyl)-phenyl]-6-hydroxymethyl-tetrahydro-pyran-3,4,5-triol.

18. A process for preparing des-bromo impurity, (2-chloro –4'-ethoxydiphenylmethane) (formula-VI) which comprises;



Formula-VI

(a) Reacting 2-chloro-5-bromo-4'-ethoxydiphenylmethane with alkyllithium in presence of mixture of polar aprotic solvent and non-polar solvent;

(b) Adding ammonium chloride solution and

(c) Isolating 2-chloro –4'- ethoxydiphenylmethane.

19. The process according to claim 18, wherein the alkyllithium reagent is selected from the group consisting of n-butyl lithium, methyl lithium and t-butyl lithium.

20. The process according to claim 18, wherein the non-polar solvent is selected from the group consisting of Dichloromethane, Toluene, Hexane, 1,4-dioxane, Chloroform, Diethyl ether and n-Heptane.

21. The process according to claim 18, wherein the polar aprotic solvent is selected from the group consisting of acetonitrile, tetrahydrofuran, ethyl acetate, acetone, dimethylformamide and dimethylsulfoxide.
22. The process according to claim 18, wherein the reaction temperature is -70 to -80 °C.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2015/000334

A. CLASSIFICATION OF SUBJECT MATTER
C07D309/00 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, C07H and A61K

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)

IPO INTERNAL, PATSEER

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US2004138439 A1 DESHPANDE PRASHANT P [US] et al 15-07-2004 (15 JULY 2004) cited in application Example 17, para.[0039], [0130]	1-10, 16-22
X	WO2013064909 A2 HENSCHKE, Julian Paul; (AU) et al 10-05-2013 (10 MAY 2013) Example 1, para.[0065] to [0066]	11-12
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