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(72) Inventeurs/Inventors:
WEBER, DIRK, DE;
RENNER, SVENJA, DE;
FIEDLER, TOBIAS, DE;
ORLICH, SIMONE, DE

(73) Propriétaire/Owner:
BOEHRINGER INGELHEIM INTERNATIONAL GMBH, DE

(74) Agent: FETHERSTONHAUGH & CO.

(54) Titre : PROCEDE DE PREPARATION D'UNE FORME CRISTALLINE DE 1-CHLORO-4-(BETA-D-GLUCOPYRANOS-1-YL)-2-[4-((S)-TETRAHYDROFURAN-3-YLOXY)-BENZYL]-BENZENE

(54) Title: METHOD FOR THE PREPARATION OF A CRYSTALLINE FORM OF 1-CHLORO-4-(BETA-D-GLUCOPYRANOS-1-YL)-2-(4-((S)-TETRAHYDROFURAN-3-YLOXY)BENZYL)BENZENE

(57) Abrégé/Abstract:
The invention relates to a method for the preparation for a crystalline form of 1-chloro-4-(B-D-glucopyranos-1-yl)-2-[4-((S)-tetrahydrofuran-3-yloxy)-benzyl]-benzene. In addition the invention relates to a crystalline form obtainable by this method, to a pharmaceutical composition and to the use thereof for preparing medicaments.

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(71) Applicant *(for all designated States except US)*: **BOEHRINGER INGELHEIM INTERNATIONAL GMBH** [DE/DE]; Binger Str. 173, 55216 Ingelheim Am Rhein (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **WEBER, Dirk** [DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Str. 173, 55216 Ingelheim Am Rhein (DE). **RENNER, Svenja** [DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Str. 173, 55216 Ingelheim Am Rhein (DE). **FIEDLER, Tobias** [DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Str. 173, 55216 Ingelheim Am Rhein (DE). **ORLICH, Simone** [DE/DE]; Boehringer Ingelheim GmbH, Corporate Patents, Binger Str. 173, 55216 Ingelheim Am Rhein (DE).

(74) Agents: **HAMMANN, Heinz** et al.; Boehringer Ingelheim GmbH, Corporate Patents, Binger Str. 173, 55216 Ingelheim Am Rhein (DE).

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(54) **Title**: METHOD FOR THE PREPARATION OF A CRYSTALLINE FORM OF 1-CHLORO-4- (BETA-D-GLUCOPYRANOS-1-YL)-2-(4-((S)-TETRAHYDROFURAN-3-YLOXY)BENZYL)BENZENE

(57) **Abstract**: The invention relates to a method for the preparation for a crystalline form of 1-chloro-4-(B-D-glucopyranos-1-yl)-2-[4-((S)-tetrahydrofuran-3-yloxy)-benzyl]-benzene. In addition the invention relates to a crystalline form obtainable by this method, to a pharmaceutical composition and to the use thereof for preparing medicaments.

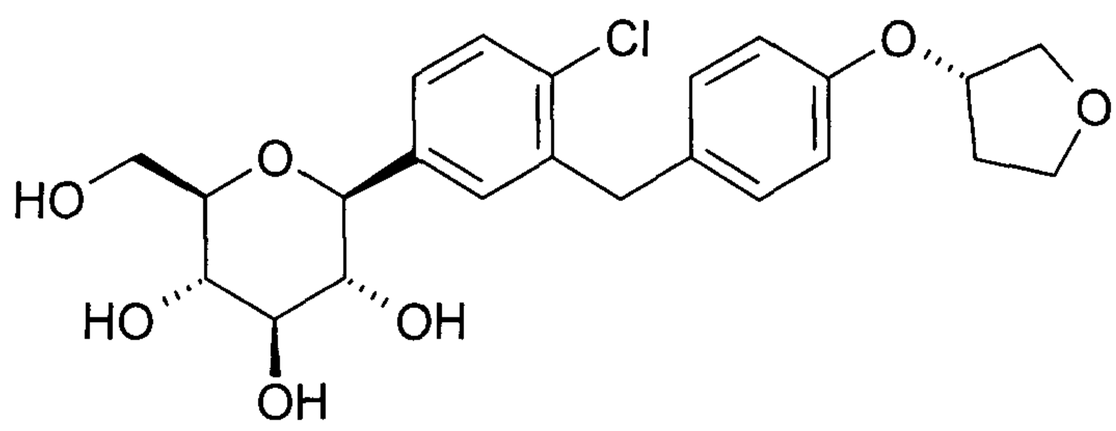
25771-1984

METHOD FOR THE PREPARATION OF A CRYSTALLINE FORM OF 1-CHLORO-4-(BETA-D-GLUCOPYRANOS-1-YL)-2-(4-((S)-TETRAHYDROFURAN-3-YLOXY)BENZYL)BENZENE

The invention relates to a method for the preparation for a crystalline form of 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene. In addition the invention relates to a crystalline form obtainable by such a method and the use of the crystalline form for preparing medicaments.

Background of the invention

The compound 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene (in the following referred to it as "compound A") is described in the international patent application WO 2005/092877 and has the chemical structure according to formula A



A

The compounds described therein have a valuable inhibitory effect on the sodium-dependent glucose cotransporter SGLT, particularly SGLT2.

The international patent application WO 2006/120208 describes various methods of synthesis of SGLT2 inhibitors, inter alia of the compound A.

A crystalline form of the compound A and a method for its preparation are described in the international application WO 2006/117359. As preferred solvents for example methanol, ethanol, isopropanol, ethyl acetate, diethylether, acetone, water and mixtures thereof are described for the crystallization process.

In the synthesis of the compound A, for example according to WO 2006/120208, it is observed that certain impurities may be found in the final substance. Furthermore it is found that crystallization processes as described in the WO 2006/117359

decrease the content of impurities and increase the purity of the compound, but not in a totally satisfactory manner.

It is well known to the one skilled in the art that in the pharmaceutical field highly pure compounds are desired. A very high purity may improve the stability in long-term storage. On the other hand impurities may be attributed to unwanted physico-chemical properties, for example hygroscopicity, or pharmacological side effects.

Aim of the invention

The aim of the present invention is to find an advantageous method for preparing a crystalline form of a compound 1-chloro-4-(ß-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene; in particular a robust method with which the crystalline form may be obtained in a high purity, with a low content of certain impurities, and/or which allows the manufacture of the crystalline form in a commercial scale with a low technical expenditure and a high space/time yield.

Another aim of the present invention is to provide a crystalline form of 1-chloro-4-(ß-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene, in particular in a high purity.

A further aim of the present invention is to provide a pharmaceutical composition comprising the crystalline form.

Another aim of the present invention is to provide a use of the crystalline form.

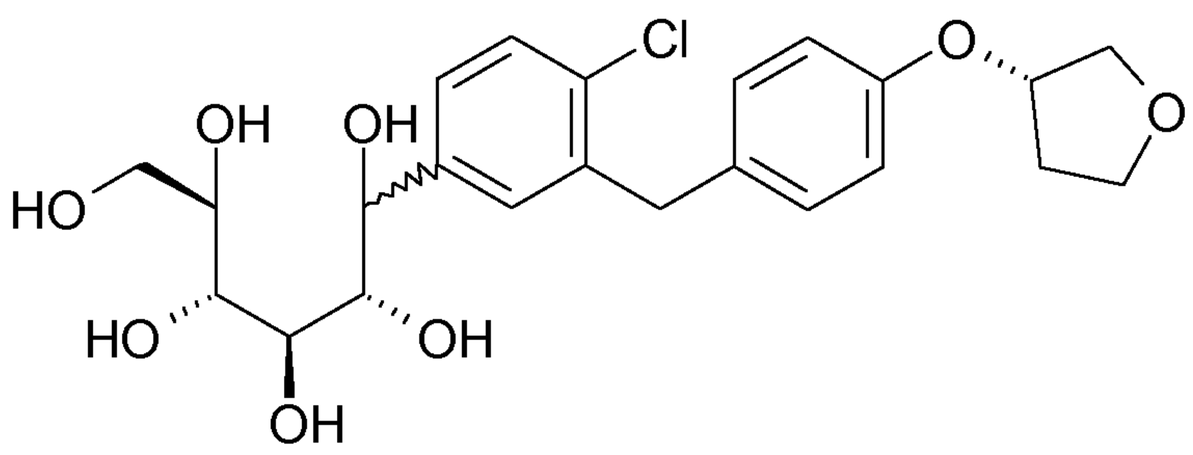
Other aims of the present invention will become apparent to the skilled artisan directly from the foregoing and following description.

Object of the invention

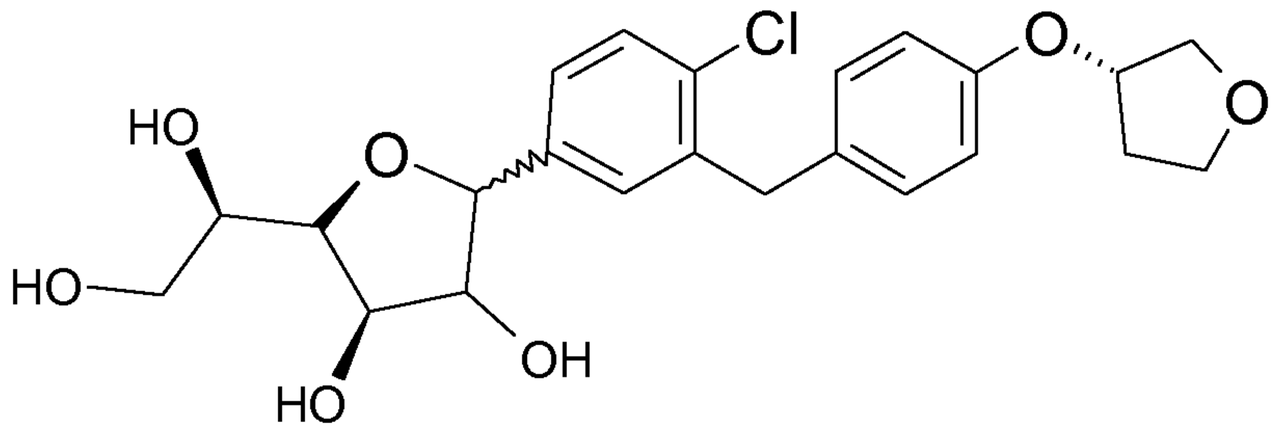
In a first aspect the present invention relates to a method for preparing a crystalline form of a compound 1-chloro-4-(ß-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene comprising the following steps:

(a) dissolving the compound in a mixture of at least two solvents to form a solution wherein the first solvent is selected from the group of solvents consisting of toluene and tetrahydrofuran, and the second solvent is selected from the group of solvents consisting of methanol, ethanol, 1-propanol and 2-propanol, or
the first solvent is ethanol and the second solvent is selected from the group of solvents consisting of ethylacetate, n-propylacetate and methylethylketone;
(b) storing the solution to precipitate the crystalline form of the compound out of solution;
(c) isolating the crystalline form of the compound from the solution.

It is found that with the method according to this invention the crystalline form can be obtained in a high purity and in a high yield, in particular at commercially viable scales. The method shows a low technical expenditure and a high space/time yield. Despite possible variations in the purity of the starting material the method yields the crystalline form in a high purity. In particular the following impurities of the formulas IMP.1 and IMP.2 can be depleted to a high degree:



IMP.1



IMP.2

In another aspect the present invention relates to the crystalline form of a compound 1-chloro-4-(ß-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene obtainable by a process as described hereinbefore and hereinafter.

In another aspect the present invention relates to the crystalline form of a compound 1-chloro-4-(ß-D-glucopyranos-1-yl)-2-[4-((*S*)-tetrahydrofuran-3-yloxy)-benzyl]-benzene having an X-ray powder diffraction pattern that comprises peaks at 18.84, 20.36 and 25.21 degrees 2Θ (±0.1 degrees 2Θ), wherein said X-ray powder diffraction pattern is made using $CuK_{\alpha 1}$ radiation, characterized by a purity above 99 % as measured by HPLC.

In yet another aspect the present invention relates to a pharmaceutical composition comprising the crystalline form as described hereinbefore and hereinafter.

In yet another aspect the present invention relates to a use of the crystalline form as described hereinbefore and hereinafter for preparing a pharmaceutical composition which is suitable for the treatment or prevention of metabolic disorders, in particular of a metabolic disorder selected from the group consisting of type 1 and type 2 diabetes mellitus, complications of diabetes, metabolic acidosis or ketosis, reactive hypoglycaemia, hyperinsulinaemia, glucose metabolic disorder, insulin resistance, metabolic syndrome, dyslipidaemias of different origins, atherosclerosis and related diseases, obesity, high blood pressure, chronic heart failure, oedema and hyperuricaemia.

Further aspects of the present invention become apparent to the one skilled in the art from the following detailed description of the invention and the examples.

Brief Description of the Figures

The Figure 1 shows a background corrected X-ray powder diffractogram of the crystalline form of the compound A.

The Figure 2 shows the thermoanalysis via DSC of the crystalline form of the compound A.

Detailed description of the invention

This crystalline form of the compound A may be identified by means of their characteristic X-ray powder diffraction (XRPD) patterns, in particular as described in the WO 2006/117359.

The crystalline form is characterised by an X-ray powder diffraction pattern that comprises peaks at 18.84, 20.36 and 25.21 degrees 2Θ (±0.1 degrees 2Θ), wherein said X-ray powder diffraction pattern is made using $CuK_{\alpha 1}$ radiation.

In particular said X-ray powder diffraction pattern comprises peaks at 14.69, 18.84, 19.16, 19.50, 20.36 and 25.21 degrees 2Θ (±0.1 degrees 2Θ), wherein said X-ray powder diffraction pattern is made using $CuK_{\alpha 1}$ radiation.

Said X-ray powder diffraction pattern is even more characterised by peaks at 14.69, 17.95, 18.84, 19.16, 19.50, 20.36, 22.71, 23.44, 24.81 and 25.21 degrees 2Θ (±0.1 degrees 2Θ), wherein said X-ray powder diffraction pattern is made using $CuK_{\alpha 1}$ radiation.

More specifically, the crystalline form of the compound A is characterised by an X-ray powder diffraction pattern, made using $CuK_{\alpha 1}$ radiation, which comprises peaks at degrees 2Θ (±0.1 degrees 2Θ) as contained in the Table 1 of WO 2006/117359 or as contained in the Table 1 of the Experiment A of the present application or as shown in the Figure 1 of WO 2006/117359 or as shown in the Figure 1 of the present application.

Furthermore the crystalline form of the compound A is characterised by a melting point of about 151°C ± 5°C (determined via DSC; evaluated as onset-temperature; heating rate 10 K/min).

The X-ray powder diffraction patterns are recorded, within the scope of the present invention, using a STOE - STADI P-diffractometer in transmission mode fitted with a

location-sensitive detector (OED) and a Cu-anode as X-ray source (CuKα1 radiation, λ = 1,54056 Å , 40kV, 40mA).

In order to allow for experimental error, the above described 2Θ values should be considered accurate to ± 0.1 degrees 2Θ, in particular ± 0.05 degrees 2Θ. That is to say, when assessing whether a given sample of crystals of the compound A is the crystalline form in accordance with the invention, a 2 Θ value which is experimentally observed for the sample should be considered identical with a characteristic value described above if it falls within ± 0.1 degrees 2Θ, in particular ± 0.05 degrees 2Θ of the characteristic value.

The melting point is determined by DSC (Differential Scanning Calorimetry) using a DSC 821 (Mettler Toledo).

The present invention relates to a method for preparing a crystalline form of the compound A comprising the following steps:

(a) dissolving the compound A in a mixture of at least two solvents to form a solution wherein the first solvent is selected from the group of solvents consisting of toluene and tetrahydrofuran, and the second solvent is selected from the group of solvents consisting of methanol, ethanol, 1-propanol and 2-propanol, or
the first solvent is ethanol and the second solvent is selected from the group of solvents consisting of ethylacetate, n-propylacetate and methylethylketone;
(b) storing the solution to precipitate the crystalline form of the compound A out of solution;
(c) isolating the crystalline form of the compound A from the solution.

The first solvent is preferably selected from the group of solvents consisting of toluene and tetrahydrofuran.

The second solvent is preferably selected from the group of solvents consisting of methanol, ethanol, 1-propanol and 2-propanol; even more preferably from the group of solvents consisting of ethanol, 1-propanol and 2-propanol.

According to a preferred alternative the first solvent is ethanol and the second solvent is n-propylacetate or ethylacetate.

Examples of mixtures of at least two solvents are toluene/methanol, toluene/ethanol, toluene/1-propanol, toluene/2-propanol, tetrahydrofuran/methanol, tetrahydrofuran/ethanol, tetrahydrofuran/1-propanol, tetrahydrofuran/2-propanol, ethanol/n-propylacetate, ethanol/ethylacetate, ethanol/methylethylketon.

Preferred examples of mixtures of at least two solvents are toluene/ethanol, toluene/1-propanol, toluene/2-propanol, tetrahydrofuran/ethanol, tetrahydrofuran/1-propanol, tetrahydrofuran/2-propanol, ethanol/n-propylacetate, ethanol/ethylacetate.

The weight ratio of the first solvent to the second solvent is preferably in the range from about 1 : 10 to 10 : 1, more preferably from about 1 : 5 to 5 : 1, even more preferably from about 1 : 2 to 2 : 1, most preferably about 1 : 1.

With regard to the preferred examples toluene/ethanol, toluene/1-propanol, toluene/2-propanol, ethanol/n-propylacetate, ethanol/ethylacetate the weight ratio of the first solvent to the second solvent is preferably in the range from about 1 : 5 to 5 : 1, more preferably from about 1 : 2 to 2 : 1, most preferably about 1 : 1.

With regard to the preferred examples tetrahydrofuran/ethanol, tetrahydrofuran/1-propanol, tetrahydrofuran/2-propanol, the weight ratio of the first solvent to the second solvent is preferably in the range from about 1 : 10 to 2 : 1, more preferably from about 1 : 5 to 1 : 1, even more preferably from about 1 : 4 to 1 : 2.

In the step (a) the compound A may be employed in an amorphous or crystalline form or as a solution, for example obtained in the synthesis of the compound A.

Preferably the solution obtained in the step (a) is a saturated or nearly saturated solution at the given temperature.

The terms "saturated" or "nearly saturated" are related to the starting material of the compound A as used in step (a). For example a solution which is saturated with respect to the starting material of the compound A may be supersaturated with respect to its crystalline form.

The weight ratio of the compound A relative to the mixture of solvents is preferably in the range 1 : 8 to 1 : 2, more preferably 1 : 6 to 1 : 3, even more preferably from 1: 5 to 1:4.

In the step (a) the solution may be heated up to the boiling temperature of the solution or to a temperature in the range from about 60°C to 120°C, for example about 100 °C. The solution obtained in the step (a) may be filtered, for example over charcoal.

At the beginning of the step (b) seeding crystals of the compound A are preferably added to the solution obtained in the step (a), optionally after a filtration step. The amount of the seeding crystals relative to the total amount of the compound A may be in the range from up to about 5 weight-%, more preferably from about 0.001 to 1 weight-%. The seeding crystals may be obtained for example by a process as described in the WO 2006/117359. The seeding crystals are preferably added at a temperature in the range from about 30°C to 80°C, most preferably about 60 to 75°C. Alternatively the crystallization may be induced by methods as known in the art, for example by scratching or rubbing.

In the step (b) the temperature is preferably lowered in order to obtain a high yield of the precipitated crystalline form of the compound A. The temperature may be lowered continously or via a predefined cooling ramp. An example of a cooling ramp is within about 30min to 60±5°C, then within about 90min to 50±5°C, then within about 60min to 40±5°C, then within about 60min to 25±5°C. A preferred final temperature at the end of the step (b) is in the range from about -10°C to 40°C, more preferably from about 0°C to 35°C, most preferably from about 10°C to 30°C.

The duration of the step (b) may be in the range from about 30 min to 48 hours, preferably from about 3 to 6 hours.

The step (b) can be carried out with or without stirring. As known to the one skilled in the art by the period of time and the difference of temperature in step (b) the size, shape and quality of the obtained crystals can be varied.

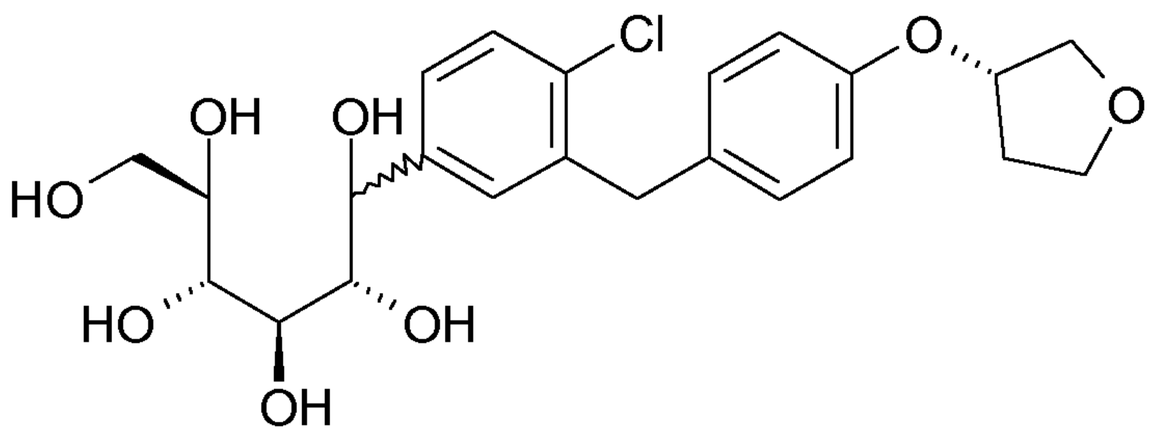
In the step (c) the obtained crystals are isolated, for example via centrifugation or filtration. The obtained crystals are preferably washed with a solvent or a mixture of solvents, wherein the solvent is preferably selected from the group consisting of methanol, ethanol, 1-propanol, 2-propanol or tert.-butylmethylether. The most preferred solvent is ethanol. Preferably remaining solvent(s) are advantageously removed from the crystals in a drying step, preferably at a temperature in the range from about 0°C to 100°C, for example from about 50°C to 80°C. The temperature, the pressure and the duration of this drying step may be chosen in order to lower the content of one or more solvents below a given value. For example the content of toluene in the crystalline form may be chosen to be equal or below 890 ppm, preferably below 500 ppm, even more preferably below 300 ppm. The content of ethanol in the crystalline form may be chosen to be equal or below 5000 ppm, preferably below 2000 ppm, even more preferably below 1000 ppm.

The compound A may be synthesized by methods as specifically and/or generally described or cited in the international application WO 2005/092877. Furthermore the biological properties of the compound A may be investigated as it is described in the international application WO 2005/092877.

The crystalline form in accordance with the invention is preferably employed as drug active substance in substantially pure form, that is to say, essentially free of other crystalline forms of the compound A. Nevertheless, the invention also embraces the crystalline form as herein defined in admixture with another crystalline form or forms. Should the drug active substance be a mixture of crystalline forms, it is preferred that the substance comprises at least 50% of the crystalline form as described herein.

According to another aspect of the present invention the crystalline form of the compound A having an X-ray powder diffraction pattern that comprises peaks at 18.84, 20.36 and 25.21 degrees 2Θ (±0.1 degrees 2Θ), wherein said X-ray powder diffraction pattern is made using $CuK_{\alpha 1}$ radiation is characterized by a purity above 99 % as measured by HPLC. Preferably the purity is above 99.5 %, even more preferably above 99.7 %, most preferably above 99.8 %.

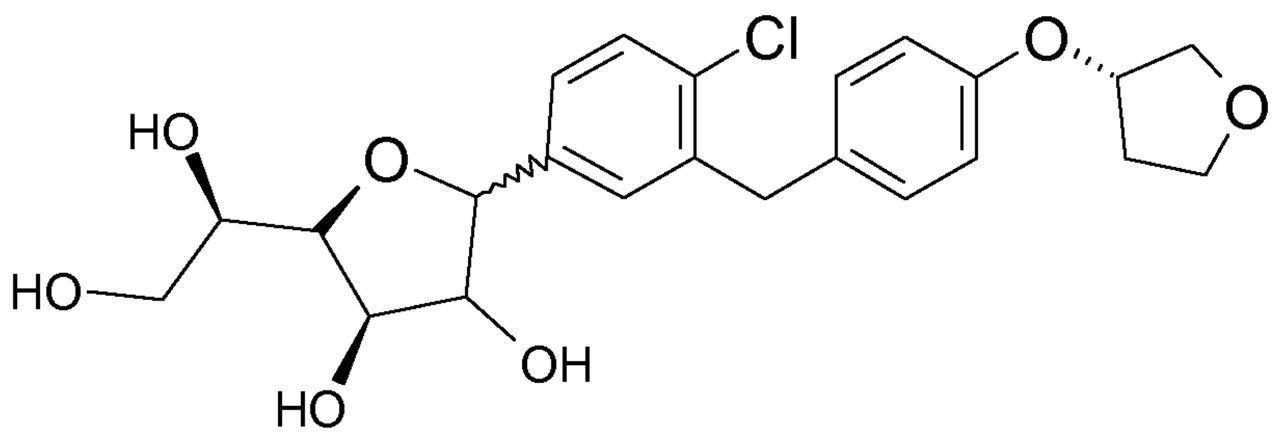
In a preferred embodiment the crystalline form as defined hereinbefore is characterized by a content of the compound of the formula IMP.1



IMP.1

equal or below 1.00 % as measured by HPLC. Preferably the content of the compound of the formula IMP.1 is equal or below 0.15 %, even more preferably equal or below 0.05 % as measured by HPLC.

In another preferred embodiment the crystalline form as defined hereinbefore is characterized by a content of the compound of the formula IMP.2



IMP.2

equal or below 0.15 % as measured by HPLC. Preferably the content of the compound of the formula IMP.2 is equal or below 0.05 % as measured by HPLC.

According to a more preferred embodiment the crystalline form is characterized by a content of the compounds of the formulas IMP.1 and IMP.2 as defined above.

The hereinbefore and hereinafter mentioned purity and impurity may be determined with methods known to the one skilled in the art. Preferably the purity and impurity is measured via HPLC. The purity is preferably determined as 100% minus the sum of all quantified impurities.

Preferably the HPLC device is equipped with a C18 column, in particular a column with a microparticulate C18 packing used for reversed-phase HPLC, for example prepared by chemically bonding a sterically-protected C18 stationary phase (e.g. diisobutyl n-octadecylsilane) to porous silica microspheres (e.g. with a pore size of about 80Å). Advantageous dimensions of the column and microspheres are 4,6 mm (inner dimension) x 50 mm column and 1.8 µm. A UV-detection is preferred, for example at 224 nm.

Typical parameters for such a HPLC are:

Device:	HPLC with UV-detection		
Column:	C18, 1,8 µm, 50*4,6 mm		
Column temperature:	20 °C		
Gradient:	time (min)	eluent A (%)	eluent B (%)
	0	100	0
	1	70	30
	4	70	30
	8	5	95
	12	5	95
Flow rate:	1,5 mL/min		
Analysis time:	12 min		
Equilibration time:	4 min		
Injection volume:	8 µl		
Detection:	224 nm		

Preferred eluents are:

Eluent A:	water + 0,1% trifluoroacetic acid
Eluent B:	acetonitrile + 0,1% trifluoroacetic acid

A preferred solvent for the samples or as blank solution is a 50/50 (v/v) mixture of acetonitrile/water. Preferably all solvents including water are HPLC grade.

In view of their ability to inhibit the SGLT activity, the crystalline form according to the invention is suitable for the preparation of pharmaceutical compositions for the treatment and/or preventative treatment of all those conditions or diseases which may be affected by the inhibition of the SGLT activity, particularly the SGLT-2 activity. Therefore, the crystalline form is particularly suitable for the preparation of pharmaceutical compositions for prevention or treatment of diseases, particularly metabolic disorders, or conditions such as type 1 and type 2 diabetes mellitus, complications of diabetes (such as e.g. retinopathy, nephropathy or neuropathies, diabetic foot, ulcers, macroangiopathies), metabolic acidosis or ketosis, reactive hypoglycaemia, hyperinsulinaemia, glucose metabolic disorder, insulin resistance, metabolic syndrome, dyslipidaemias of different origins, atherosclerosis and related diseases, obesity, high blood pressure, chronic heart failure, oedema and hyperuricaemia. The crystalline form is also suitable for the preparation of pharmaceutical compositions for preventing beta-cell degeneration such as e.g. apoptosis or necrosis of pancreatic beta cells. The crystalline form is also suitable for the preparation of pharmaceutical compositions for improving or restoring the functionality of pancreatic cells, and also of increasing the number and size of pancreatic beta cells. The crystalline form according to the invention may also be used for the preparation of pharmaceutical compositions usefull as diuretics or antihypertensives and suitable for the prevention and treatment of acute renal failure.

By the administration of the crystalline form according to this invention an abnormal accumulation of fat in the liver may be reduced or inhibited. Therefore according to another aspect of the present invention there is provided a method for preventing, slowing, delaying or treating diseases or conditions attributed to an abnormal accumulation of liver fat in a patient in need thereof characterized in that a pharmaceutical composition according to the present invention is administered. Diseases or conditions which are attributed to an abnormal accumulation of liver fat

are particularly selected from the group consisting of general fatty liver, non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), hyperalimentation-induced fatty liver, diabetic fatty liver, alcoholic-induced fatty liver or toxic fatty liver.

In particular, the crystalline form according to the invention is suitable for the preparation of pharmaceutical compositions for the prevention or treatment of diabetes, particularly type 1 and type 2 diabetes mellitus, and/or diabetic complications.

In addition the crystalline form according to the invention is particularly suitable for the prevention or treatment of overweight, obesity (including class I, class II and/or class III obesity), visceral obesity and/or abdominal obesity.

The dosage required to achieve the corresponding activity for treatment or prevention usually depends on the patient, the nature and gravity of the illness or condition and the method and frequency of administration and is for the patient's doctor to decide. Expediently, the dosage may be from 1 to 100 mg by oral route, in each case administered 1 to 4 times a day. For this purpose, the pharmaceutical compositions according to this invention preferably comprise the crystalline form together with one or more inert conventional carriers and/or diluents. Such pharmaceutical compositions may be formulated as conventional galenic preparations such as plain or coated tablets, capsules, powders, suspensions or suppositories.

The following example of synthesis serves to illustrate a method of preparing the compound A and its crystalline form. It is to be regarded only as a possible method described by way of example, without restricting the invention to its contents.

Determination of the purity or impurity via HPLC:

This method is used for the determination of organic impurities in the compound A. The quantification is carried out via external standard solutions. The reagents (acetonitrile, water, trifluoroacetic acid (TFA)) are use in HPLC grade. The term

"compound A_{XX}" denotes the crystalline form of the compound A as obtained with a method according to this invention.

Mobile Phase

Eluent A: water + 0,1% TFA

Eluent B: acetonitrile + 0,1% TFA

Solutions

Solvent: acetonitrile/water (50/50 (v/v))

Blank solution: solvent

Solution 1

A solution with a concentration of 0,5 mg/ml of the compound IMP.2 is prepared; e.g. 25 mg of the substance are weighed, dissolved in 2 mL of methanol and diluted with solvent to a total volume of 50 mL.

System suitability solution (SST)

A solution with a concentration of 0,5 mg/ml of the compound A_{XX} is prepared, containing approx. 0,5% IMP.2; e.g. 25 mg of the compound A_{XX} are weighed, dissolved in 2 mL of methanol (via ultrasound) and, after addition of 250 µL of solution 1, diluted with solvent to a total volume of 50 mL. Optional, approx. 0,5% of the following possible impurities may be added: IMP.1

Reporting Limit (0,05%)

A solution with 0,05% of the nominal concentration is prepared. Therefore, 50 µl of a stem solution is diluted with solvent to a total volume of 100 mL

Sample Solutions

A solution of the substance to be analyzed is prepared with a concentration of 0,8 mg/mL. Therefore, e.g. 40 mg of the substance are weighed, dissolved in 2 mL of methanol and diluted with solvent to a total volume of 50 mL. This solution is prepared twice.

Stem Solutions

A solution of the compound A_{XX} is prepared with a concentration of 0,8 mg/mL. Therefore, e.g. 40mg of the substance are weighed, dissolved with 2mL of methanol and diluted with solvent to a total volume of 50 mL. This solution is prepared twice.

Reference Solution (0,5%)

A solution of compound A_{XX} with a concentration of 4 µg/ml compared to the nominal weighed sample is prepared. Therefore, e.g. 250 µl of the stem solution are diluted with 50 mL. This solution is prepared twice (once from each stem solution).

Chromatographic Parameters:

Device: HPLC with UV-detection

Column: Zorbax SB-C18, 1,8 µm, 50*4,6 mm, (manufacturer: Agilent)

Column temperature: 20 °C

Gradient:

time (min)	eluent A (%)	eluent B (%)
0	100	0
1	70	30
4	70	30
8	5	95
12	5	95

Flow rate: 1,5 mL/min

Analysis time: 12 min

Equilibration time: 4 min

Injection volume: 8 µl

Detection: 224 nm

Injections:

Solutions	Injections
Blank solution	n ≥1
Reporting limit	1
Reference solution 1	2

Reference solution 2	2
SST	1
Blind solution	n ≥1
Sample 1, Solution 1	2
Sample 1, Solution 2	2
Sample 2, Solution 1	2
Sample 2, Solution 2	2
Further samples	2 each
SST	1

Typical Retention Times:

The order of elution of the peaks in the chromatogram of the SST-solution should correspond to a example chromatogram. The peak assignment is carried out with a example chromatogram or via the relative retention times (RRTs).

Substance	**RT (approx. min)**	**RRT**
IMP.1	3,35	0,84
Compound A_{XX}	3,97	1,00
IMP.2 Isomer 1	4,97	1,25
IMP.2 Isomer 2	5,19	1,31

Evaluation:

The calculation of the content of the impurities is carried out according to the following formula.

$$\%\mathbf{Impurity} = \frac{\overline{\mathbf{PF}_{\mathbf{Sample}}} * \mathbf{V}_{\mathbf{Sample}}}{\overline{\mathbf{EW}_{\mathbf{Sample}}}} * \frac{\overline{\mathbf{EW}_{\mathbf{Stem\ Solution}}} * \mathbf{Potency}_{\mathbf{Reference\ Substance}}}{\overline{\mathbf{PF}_{\mathbf{0,5\%\ Comparison}}} * \mathbf{V}_{\mathbf{Stem\ Solution}} * \mathbf{VF}} * \mathbf{100}$$

PF_X: Peak areas

EW_X: weigh-in

Vx: volume to which the dilution is carried out

VF: dilution factor

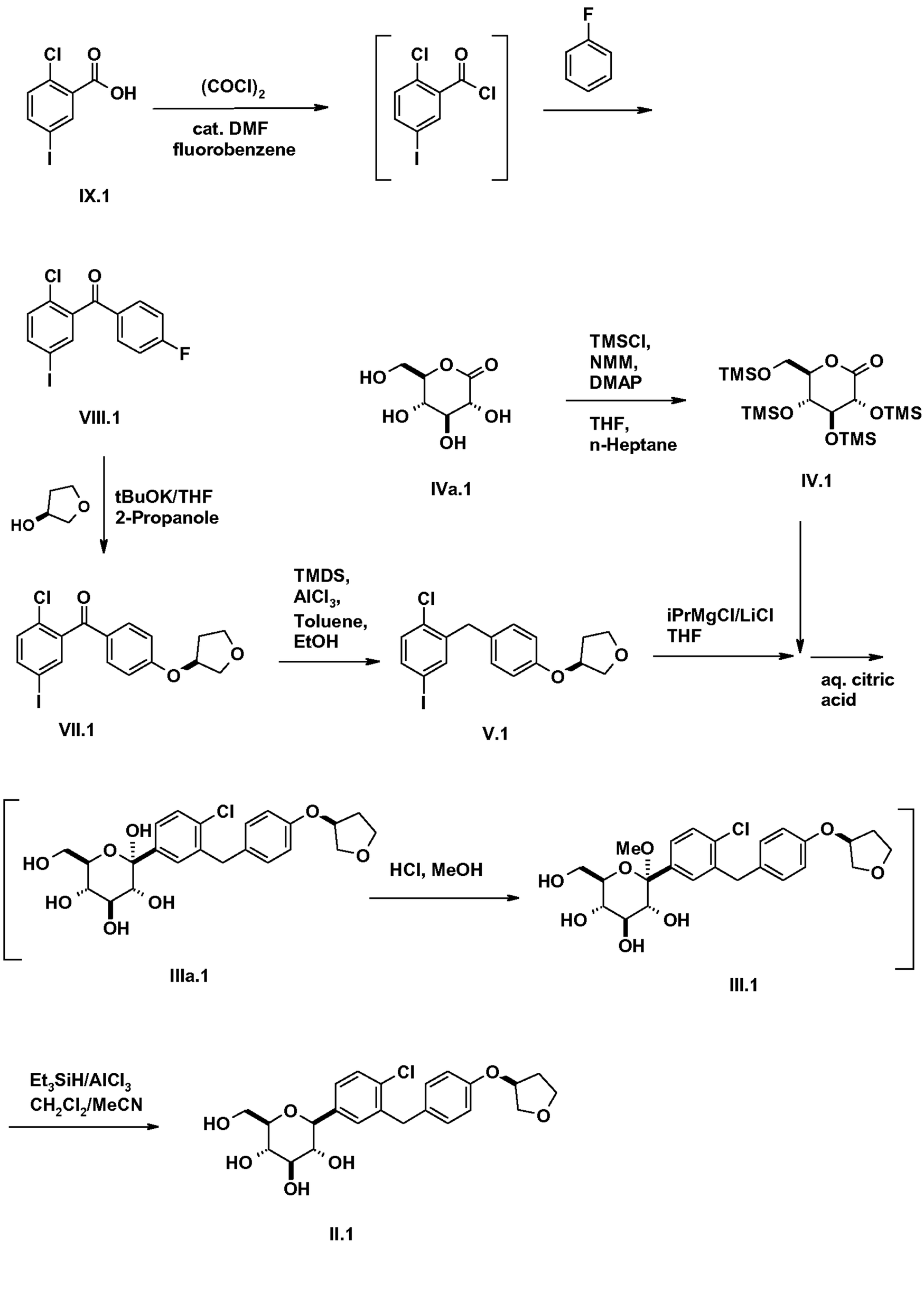
Potency: known potency in % of the compound A_{XX} reference substance

The purity of a sample of the compound A is calculated as 100% minus the sum of all quantified impurities.

Preparation of the compound A:

The terms "room temperature" or "ambient temperature" denote a temperature of about 20°C.

GC	gas chromatography
hrs	hours
i-Pr	iso-propyl
Me	methyl
min	minute(s)
THF	tetrahydrofuran



Example 1: Synthesis of the fluoride VIII.1

Oxalylchloride (176kg; 1386mol; 1,14eq) is added to a mixture of 2-chloro-5-iodo benzoic acid (343kg; 1214mol) (compound IX.1), fluorobenzene (858kg) and N,N-dimethylformamide (2kg) within 3 hours at a temperature in the range from about 25 to 30°C (gas formation). After completion of the addition, the reaction mixture is stirred for additional 2 hours at a temperature of about 25 to 30°C. The solvent

(291kg) is distilled off at a temperature between 40 and 45°C (p=200mbar). Then the reaction solution (911kg) is added to aluminiumchloride $AlCl_3$ (181kg) and fluorobenzene (192kg) at a temperature between about 25 and 30°C within 2 hours. The reaction solution is stirred at the same temperature for about an additional hour. Then the reaction mixture is added to an amount of 570 kg of water within about 2 hours at a temperature between about 20 and 30°C and stirred for an additional hour. After phase separation the organic phase (1200kg) is separated into two halves (600kg each). From the first half of the organic phase solvent (172kg) is distilled off at a temperature of about 40 to 50°C (p=200mbar). Then 2-propanole (640kg) is added. The solution is heated to about 50°C and then filtered through a charcoal cartouche (clear filtration). The cartouche may be exchanged during filtration and washed with a fluorobenzene/2-propanole mixture (1:4; 40kg) after filtration. Solvent (721kg) is distilled off at a temperature of about 40 to 50°C and p=200mbar. Then 2-propanole (240kg) is added at a temperature in the range between about 40 to 50°C. If the content of fluorobenzene is greater than 1% as determined via GC, another 140kg of solvent are distilled off and 2-propanole (140kg) is added. Then the solution is cooled from about 50°C to 40°C within one hour and seeding crystals (50g) are added. The solution is further cooled from about 40°C to 20°C within 2 hours. Water (450kg) is added at about 20°C within 1 hour and the suspension is stirred at about 20°C for an additional hour before the suspension is filtered. The filter cake is washed with 2-propanole/water (1:1; 800kg). The product is dried until a water level of <0.06%w/w is obtained. The second half of the organic phase is processed identically. A total of 410kg (94%yield) of product which has a white to off-white crystalline appearance, is obtained. The identity of the product is determined via infrared spectrometry.

Example 2: Synthesis of the ketone VII.1

To a solution of the fluoride VIII.1 (208kg), tetrahydrofuran (407kg) and (S)-3-hydroxytetrahydrofuran (56kg) is added potassium-*tert*-butanolate solution (20%) in tetrahydrofuran (388kg) within 3 hrs at 16 to 25°C temperature. After completion of the addition, the mixture is stirred for 60min at 20°C temperature. Then the conversion is determined via HPLC analysis. Water (355kg) is added within 20 min at a temperature of 21°C (aqueous quench). The reaction mixture is stirred for 30

min (temperature: 20°C). The stirrer is switched off and the mixture is left stand for 60 min (temperature: 20°C). The phases are separated and solvent is distilled off from the organic phase at 19 to 45°C temperature under reduced pressure. 2-Propanol (703kg) is added to the residue at 40 to 46°C temperature and solvent is distilled off at 41 to 50°C temperature under reduced pressure. 2-Propanol (162kg) is added to the residue at 47°C temperature and solvent is distilled off at 40 to 47°C temperature under reduced pressure. Then the mixture is cooled to 0°C within 1 hr 55 min. The product is collected on a centrifuge, washed with a mixture of 2-propanol (158kg) and subsequently with *tert*.-butylmethylether (88kg) and dried at 19 to 43°C under reduced pressure. 227kg (91,8%) of product are obtained as colourless solid. The identity of the product is determined via infrared spectrometry.

Example 3: Synthesis of the iodide V.1

To a solution of ketone VII.1 (217,4kg) and aluminium chloride ($AlCl_3$; 81,5kg) in toluene (366,8kg) is added 1,1,3,3-tetramethyldisiloxane (TMDS, 82,5kg) within 1 hr 30 min (temperature: 18-26°C). After completion of the addition, the mixture is stirred for additional 1 hr at a temperature of 24°C. Then the conversion is determined via HPLC analysis. Subsequently the reaction mixture is treated with acetone (15,0kg), stirred for 1 hr 5 min at 27°C temperature and the residual TMDS content is analyzed via GC. Then a mixture of water (573kg) and concentrated HCl (34kg) is added to the reaction mixture at a temperature of 20 to 51°C (aqueous quench). The reaction mixture is stirred for 30 min (temperature: 51°C). The stirrer is switched off and the mixture is left stand for 20 min (temperature: 52°C). The phases are separated and solvent is distilled off from the organic phase at 53-73°C temperature under reduced pressure. Toluene (52,8kg) and ethanol (435,7kg) are added to the residue at 61 to 70°C temperature. The reaction mixture is cooled to 36°C temperature and seeding crystals (0,25kg) are added. Stirring is continued at this temperature for 35 min. Then the mixture is cooled to 0 to 5°C and stirred for additional 30 min. The product is collected on a centrifuge, washed with ethanol (157kg) and dried at 15 to 37°C under reduced pressure. 181kg (82,6%) of product are obtained as colourless solid. The identity of the product is determined via the HPLC retention time.

Example 4: Synthesis of the lactone IV.1

A suspension of the D-(+)-gluconic acid-delta-lactone IVa.1 (42,0kg), tetrahydrofuran (277,2kg), 4-methylmorpholine (NMM; 152,4kg) and 4-dimethylaminopyridine (DMAP; 1,44kg) is treated with chlorotrimethylsilane (TMSCl; 130,8kg) within 50 min at 13 to 19°C. After completion of the addition stirring is continued for 1 hr 30 min at 20 to 22°C and the conversion is determined via HPLC analysis. Then n-heptane (216,4kg) is added and the mixture is cooled to 5°C. Water (143kg) is added at 3 to 5°C within 15 min. After completion of the addition the mixture is heated to 15°C and stirred for 15 min. The stirrer is switched off and the mixture is left stand for 15 min. Then the phases are separated and the organic layer is washed in succession two times with water (143kg each). Then solvent is distilled off at 38°C under reduced pressure and n-heptane (130kg) is added to the residue. The resulting solution is filtered and the filter is rinsed with n-heptane (63kg) (filter solution and product solution are combined). Then solvent is distilled off at 39 to 40°C under reduced pressure. The water content of the residue is determined via Karl-Fischer analysis (result: 0,0%). 112,4kg of the product is obtained as an oil (containing residual n-heptane, which explains the yield of >100%). The identity of the product is determined via infrared spectrometry.

Example 5a: Synthesis of the glucoside II.1

To a solution of the iodide V.1 (267kg) in tetrahydrofuran (429kg) is added Turbogrignard solution (isopropylmagnesium chloride/lithium chloride solution, 14 weight-% iPrMgCl in THF, molar ratio LiCl : iPrMgCl = 0,9 - 1.1 mol/mol) (472kg) at -21 to -15°C temperature within 1 hr 50 min. On completion of the addition the conversion is determined via HPLC analysis. The reaction is regarded as completed when the area of the peak corresponding to the iodide V.1 is smaller than 5,0% of the total area of both peaks, iodide V.1 and the corresponding desiodo compound of iodide V.1. If the reaction is not completed, additional Turbogrignard solution is added until the criterion is met. In this particular case the result is 3,45%. Then the lactone IV.1 (320kg) is added at -25 to -18°C temperature within 1 hr 25 min. The resulting mixture is stirred for further 1 hr 30 min at -13 to -18°C. On completion of the addition the conversion is determined via HPLC analysis (for information). On completion, a solution of citric acid in water (938L; concentration: 10 %-weight) is

added to the reaction mixture of a volume of about 2500L at -13 to 19°C within 1 hr 25 min. The solvent is partially distilled off from the reaction mixture (residual volume: 1816-1905L) at 20 to 30°C under reduced pressure and 2-methyltetrahydrofuran (532kg) is added. Then the stirrer is switched off and the phases are separated at 29°C. After phase separation the pH value of the organic phase is measured with a pH electrode (Mettler Toledo MT HA 405 DPA SC) or alternatively with pH indicator paper (such as pH-Fix 0-14, Macherey and Nagel). The measured pH value is 2 to 3. Then solvent is distilled off from the organic phase at 30 to 33°C under reduced pressure and methanol (1202kg) is added followed by the addition of a solution of 1,25N HCl in methanol (75kg) at 20°C (pH = 0). Full conversion to the acetale III.1 is achieved by subsequent distillation at 20 to 32°C under reduced pressure and addition of methanol (409kg).

Completion of the reaction is obtained when two criteria are fulfilled:

1) The ratio of the sum of the HPLC-area of the alpha-form + beta-form of intermediate III.1 relative to the area of intermediate IIIa.1 is greater or equal to 96,0% : 4,0%.

2) The ratio of the HPLC-area of the alpha-form of intermediate III.1 to the beta-form of III.1 is greater or equal to 97,0% to 3,0%.

In this particular case both criteria are met. Triethylamin (14kg) is added (pH = 7,4) and solvent is distilled off under reduced pressure, acetonitrile (835kg) is added and further distilled under reduced pressure. This procedure is repeated (addition of acetonitrile: 694kg) and methylene chloride (640kg) is added to the resulting mixture to yield a mixture of the acetale III.1 in acetonitrile and methylene chloride. The water content of the mixture is determined via Karl Fischer titration (result: 0,27%). The reaction mixture is then added within 1 hr 40 min at 10 to 19°C to a preformed mixture of $AlCl_3$ (176kg), methylene chloride (474kg), acetonitrile (340kg), and triethylsilane (205kg). The resulting mixture is stirred at 18 to 20°C for 70 min. After completion of the reaction, water (1263L) is added at 20 to 30°C within 1 hr 30 min and the mixture is partially distilled at 30 to 53°C under atmospheric pressure and the phases are separated. Toluene (698kg) is added to the organic phase and solvent is distilled off under reduced pressure at 22 to 33°C. The product is then crystallized by addition of seeding crystals (0,5kg) at 31°C and water (267kg) added after cooling to 20°C. The reaction mixture is cooled to 5°C within 55 min and stirred

at 3 to 5°C for 12 hrs. Finally the product is collected on a centrifuge as colourless, crystalline solid, washed with toluene (348kg) and dried at 22 to 58°C. 211kg (73%) of product are obtained. The identity of the product is determined via the HPLC retention time.

Example 5b: Synthesis of the glucoside II.1

To a solution of the iodide V.1 (30g) in tetrahydrofuran (55mL) is added Turbogrignard solution (isopropylmagnesium chloride/lithium chloride solution, 14 weight-% iPrMgCl in THF, molar ratio LiCl : iPrMgCl = 0,9 - 1.1 mol/mol) (53g) at -14 to -13°C temperature within 35 min. On completion of the addition the conversion is determined via HPLC analysis. The reaction is regarded as completed when the area of the peak corresponding to the iodide V.1 is smaller than 5,0% of the total area of both peaks, iodide V.1 and the corresponding desiodo compound of iodide V.1. If the reaction is not completed, additional Turbogrignard solution is added until the criterion is met. In this particular case the result is 0,35%. Then the lactone IV.1 (36g) is added at -15 to -6°C temperature within 15 min. The resulting mixture is stirred for further 1 hr at -6 to -7°C. On completion, the conversion is determined via HPLC analysis (for information). On completion, a solution of citric acid in water (105mL; concentration: 10 %-weight) is added to the reaction mixture at -15 to 10°C within 30 min.

The solvent is partially distilled off from the reaction mixture (residual volume: 200mL) at 20 to 35°C under reduced pressure and 2-methyltetrahydrofuran (71mL) is added. Then the mixture is stirred for 25min at 30°C. Then the stirrer is switched off and the phases are separated at 30°C. After phase separation the pH value of the organic phase is measured with a pH electrode (Mettler Toledo MT HA 405 DPA SC) or alternatively with pH indicator paper (such as pH-Fix 0-14, Macherey and Nagel). The measured pH value is 3. Then solvent is distilled off from the organic phase at 35°C under reduced pressure and methanol (126mL) is added followed by the addition of a solution of 1,25N HCl in methanol (10,1mL) at 25°C (pH = 1-2). Full conversion to the acetale III.1 is achieved by subsequent distillation at 35°C under reduced pressure and addition of methanol (47mL).

Completion of the reaction is obtained when two criteria are fulfilled:

1) The ratio of the sum of the HPLC-area of the alpha-form + beta-form of intermediate III.1 relative to the area of intermediate IIIa.1 is greater or equal to 96,0% : 4,0%. In this particular case the ratio is 99,6% : 0,43%.

2) The ratio of the HPLC-area of the alpha-form of intermediate III.1 to the beta-form of III.1 is greater or equal to 97,0% to 3,0%. In this particular case the ratio is 98,7% : 1,3%.

Triethylamin (2,1mL) is added (pH = 9) and solvent is distilled off at 35°C under reduced pressure, acetonitrile (120mL) is added and further distilled under reduced pressure at 30 to 35°C. This procedure is repeated (addition of acetonitrile: 102mL) and methylene chloride (55mL) is added to the resulting mixture to yield a mixture of the acetale III.1 in acetonitrile and methylene chloride. The water content of the mixture is determined via Karl Fischer titration (result: 0,04%).

The reaction mixture is then added within 1 hr 5 min at 20°C to a preformed mixture of $AlCl_3$ (19,8g), methylene chloride (49mL), acetonitrile (51mL), and triethylsilane (23g). The resulting mixture is stirred at 20 to 30°C for 60 min. After completion of the reaction, water (156mL) is added at 20°C within 25 min and the mixture is partially distilled at 55°C under atmospheric pressure and the phases are separated at 33°C. The mixture is heated to 43°C and toluene (90mL) is added and solvent is distilled off under reduced pressure at 41 to 43°C. Then acetonitrile (10mL) is added at 41°C and the percentage of acetonitrile is determined via GC measurement. In this particular case, the acetonitrile percentage is 27%-weight. The product is then crystallized by addition of seeding crystals (0,1g) at 44°C and the mixture is further stirred at 44°C for 15min. The mixture is then cooled to 20°C within 60min and water (142mL) is added at 20°C within 30min. The reaction mixture is cooled to 0 to 5°C within 60 min and stirred at 3°C for 16 hrs. Finally the product is collected on a filter as colourless, crystalline solid, washed with toluene (80mL) and dried at 20 to 70°C. 20,4g (62,6%) of product are obtained. The identity of the product is determined via the HPLC retention time.

Preparation of the crystalline form:

Experiment A:

A solution of the compound A (79,0kg) in a mixture of toluene (186,6kg) and ethanol (187,2kg) is heated to reflux until complete dissolution and filtered (hot filtration). The filter is washed with toluene (19,6kg) and the washing solution is combined with the product solution. The product solution is then cooled to 66°C and seeding crystals (0,1kg) are added. The product solution is then cooled to 22°C using a defined cooling ramp: within 30 min to 57°C, then within 90 min to 50°C, then within 60 min to 41°C, then within 60 min to 22°C. Then the suspension is further stirred at 21°C for 1 hr, collected on a centrifuge and washed with ethanol (124,8kg) and dried at about 70°C. 65,5kg (82,9%) of the product is obtained as white crystals with a HPLC purity of 99,9%.

Via differential scanning calorimetry (DSC) as described hereinbefore, a melting point of 151°C is determined (Figure 2).

Via X-ray powder diffraction as described hereinbefore, using $CuK_{\alpha 1}$ radiation, the crystalline form is characterised and a pattern as shown in the Figure 1 is obtained. The intensity shown in the Figure 1 is given in units of cps (counts per second) and is background corrected.

In addition the crystalline form is characterised by the following lattice parameters: orthorhombic symmetry, space group $P2_12_12_1$ with the cell parameters, a=5.70(1) Å, b=9.25(2) Å, c=39.83(1) Å, and cell volume=2101(1) Å3 which can be obtained by indexing of the X-ray powder diagram to be measured at room temperature using $CuK_{\alpha 1}$ radiation, which comprises peaks at degrees 2Θ (±0.1 degrees 2Θ) as contained in Table 1. In the Table 1 above the values "2Θ [°]" denote the angle of diffraction in degrees and the values "d [Å]" denote the specified distances in Å between the lattice planes. Furthermore the h, k, l indices are provided and the difference between the experimental and the calculated d-values in Å.

Table 1: Indexed* X-ray powder diffraction pattern of the crystalline form (only peaks up to 30° in 2 Θ are listed):

2 Θ [°]	**d-value [Å]**	**Intensity I/I_0 [%]**	Indexing			$d_{exp-calc}$ **[Å]**
			h	k	l	
4.43	19.93	10	0	0	2	-0.003
8.86	9.97	3	0	0	4	-0.010
9.82	9.00	3	0	1	1	0.014
11.63	7.60	2	0	1	3	-0.020
13.32	6.64	22	0	0	6	-0.001
14.66	6.04	36	0	1	5	-0.005
15.69	5.64	50	1	0	1	-0.001
16.16	5.48	16	1	0	2	-0.006
17.92	4.95	71	1	0	4	-0.001
18.30	4.84	24	0	1	7	0.011
18.40	4.82	26	1	1	1	-0.002
18.81	4.71	100	1	1	2	0.000
19.13	4.64	67	1	0	5	0.000
19.46	4.56	31	1	1	3	-0.002
20.34	4.36	67	1	1	4	-0.005
20.52	4.33	25	1	0	6	-0.003
21.15	4.20	7	0	2	4	-0.006
21.43	4.14	13	1	1	5	0.003
22.06	4.03	35	1	0	7	0.002
22.68	3.92	30	1	1	6	0.001

23.42	3.80	20	0	2	6	0.006
23.71	3.75	8	1	0	8	0.003
24.08	3.69	5	1	1	7	0.003
24.31	3.66	9	0	1	10	0.007
24.77	3.59	14	1	2	0	0.007
25.18	3.53	30	1	2	2	0.004
25.62	3.47	29	1	1	8	0.007
26.36	3.38	3	1	2	4	0.003
26.84	3.32	16	0	0	12	0.003
27.24	3.27	16	1	1	9	-0.010
27.87	3.20	2	0	2	9	0.001
28.22	3.16	2	1	2	6	-0.002
28.98	3.08	5	1	1	10	0.001
29.39	3.04	15	1	2	7	0.010
29.55	3.02	3	0	2	10	-0.016

* For indexing the lattice parameters from single crystal analysis are used as starting values.

Refined cell parameters from XRPD-pattern:

all peaks (35) up to 30° Θ indexed

symmetry: orthorhombic

space group: $P2_12_12_1$

a = 5.70(1) Å

b = 9.25(2) Å

c = 39.83(1) Å

α = ß = γ = 90°

V = 2101(1) $Å^3$

Figure of merit: 118

Experiment B:

In the following experiment it is investigated how the method according to this invention is able to deplete an impurity of the formula IMP.1 as described hereinbefore.

The compound of the formula IMP.1 is added to the crystalline form of the compound A as obtained according to the Experiment A such that the amounts according to the Table 2 are obtained. For example in order to obtain the 0.5 weight-% mixture 6.96g of the crystalline form of the compound A as obtained according to the Experiment A and 0.04 g the compound IMP.1 are combined.

Thereafter half of this mixture of compounds is recrystallized according to the procedure of the Experiment A on a laboratory scale. The crystalline form of compound A is obtained as a white crystalline material. The content of the compound of the formula IMP.1 is analyzed via HPLC.

The other half of this mixture of compounds is recrystallized using a mixture of methanol and water according to the following procedure:
About 7 g of a mixture of the crystalline form of the compound A as obtained according to the Experiment A and the compound IMP.1 is added to a mixture of methanol (7,1g) and water (7,3g) and is heated to 60°C until complete dissolution. The clear solution is stirred for 15 min. Then water (11,9g) is added to the solution and after completion of the addition the solution is cooled to 57°C and seeding crystals are added. The solution is then further stirred at 57°C for 30 min. The product solution is then cooled to 25°C within 2 hrs and 20 min. Then the suspension is further stirred at 25°C for 15 min, collected on a filter and washed with a mixture of methanol (1,66g) and water (9,5g) and dried at about 45°C. 6,5g (93,1%) of the product is obtained as white crystals.

The compound A is obtained as a white crystalline material. The content of the compound of the formula IMP.1 is analyzed via HPLC.

Table 2

Amount of the impurity IMP.1 in the compound A		
Before recrystallization (weight-%)	After recrystallization using toluene/ ethanol (HPLC-%)	After recrystallization using methanol/ water (HPLC-%)
0.5 %	0.07 %	0.07 %
1.0 %	0.06 %	0.12 %
1.5 %	0.07 %	0.85 %
2.0 %	0.09 %	0.67 %
3.0 %	0.14 %	1.68 %
5.0 %	0.34 %	3.05 %

It is observed that using a crystallization process with a mixture of toluene and ethanol a better depletion of the impurity IMP.1 can be obtained than with a process using a methanol/ water mixture.

Experiment C:

In the following experiment it is investigated how the method according to this invention is able to deplete an impurity of the formula IMP.2 as described hereinbefore.

Different samples of raw material of the compound A, for example as obtained from a not optimized lab-scale procedure according to Example 5a or 5b, are analyzed via HPLC with respect to their content of IPM.2.

Thereafter each sample is recrystallized according to the procedure of the Experiment A on a laboratory scale using a mixture of toluene and ethanol to obtain the crystalline form of compound A. The content of IPM.2 and the overall purity of the crystalline form of compound A is analyzed via HPLC.

Table 3

Content of IMP.2 before recrystallization (HPLC-%)	Content of IMP.2 after recrystallization (HPLC-%)	Overall purity after recrystallization using toluene / ethanol (HPLC-%)	Yield
0.89 %	0.05 %	99.95 %	90.1 %
1.26 %	0.14 %	99.86 %	89.3 %
1.75 %	0.13 %	99.82 %	87.1 %
2.75 %	0.17 %	99.72 %	86.1 %
3.94 %	0.29 %	99.61 %	79.1 %
7.30 %	0.51 %	99.21 %	73.3 %

Experiment D:

In the following experiment it is investigated how the method according to this invention is able to purify raw material of the compound A.

Different samples of raw material of the compound A, for example as obtained from a not optimized lab-scale procedure according to Example 5a or 5b, are analyzed via HPLC with respect to their purity.

Thereafter each sample is recrystallized according to the procedure of the Experiment A on a laboratory scale using a mixture of toluene and ethanol to obtain the crystalline form of compound A. The overall purity of the crystalline form of compound A is analyzed via HPLC.

The other half of each sample is recrystallized using a mixture of methanol and water according to the procedure as described in the Experiment B.

The purities of the samples of the raw material and the crystallized material are given in the Table 4.

Table 4

Purity before recrystallization (HPLC-%)	Purity after recrystallization using toluene/ ethanol (HPLC-%)	Purity after recrystallization using methanol/ water (HPLC-%)
96.17 %	99.82 %	98.25 %
96.74 %	99.84 %	99.64 %
97.09 %	99.80 %	99.26 %
97.43 %	99.81 %	99.54 %
95.60 %	99.75 %	98.63 %

It is observed that using a crystallization process with a mixture of toluene and ethanol a higher purity of the compound A can be obtained than with a process using a methanol/ water mixture.

Experiment E:

In the following experiment the influence of the solvent mixture and ratio on the purity and yield of the recrystallization procedure according to Experiment A is investigated.

Therefore, a sample of the of raw material of the compound A, for example as obtained according to Example 5a or 5b, is analyzed via HPLC with respect to its purity and the result is found to be 95.16%. Then, this sample is recrystallized according to the procedure of Experiment A on a laboratory scale (compound A: 35 g; sum of first and second solvent: 162 g) with the modification that the two solvents ethanol and toluene are replaced against the given solvent mixtures in Table 5 to obtain the crystalline form of compound A. The overall purity of the crystalline form of compound A is analyzed via HPLC.

Table 5

Solvent system (ratio weight : weight)	Overall purity after recrystallization (HPLC-%)	Yield
Ethanol / Toluene = 1 : 1	99.72 %	80.8 %
1-Propanol / Toluene = 1 : 1	99.80 %	82.2 %
2-Propanol / Toluene = 1 : 1	99.72 %	72.0 %
Methanol / Toluene = 1 : 4	99.69 %	54.6 %
Ethanol / Tetrahydrofuran = 4 : 1	99.62 %	82.9 %
2-Propanol / Tetrahydrofuran = 2 : 1	99.67 %	67.9 %
Ethanol / n-Propylacetate = 1 : 1	99.68 %	79.1 %
Ethanol / Methylethylketone = 1 : 1	99.61 %	67.1 %
Ethanol / Ethylacetate = 1 : 1	99.70 %	78.4 %

Experiment F:

In the following experiment it is investigated how the method according to this invention is able to purify raw material of the compound A in comparison to a procedure using a mixture of ethanol and water (see for example the experiment "Variant 2" in WO 2006/117359).

A sample of raw material of the compound A, for example as obtained from a not optimized lab-scale procedure according to Example 5a or 5b, is analyzed via HPLC with respect to their purity.

Thereafter the sample is recrystallized according to the procedure of the Experiment A on a laboratory scale using a mixture of toluene and ethanol to obtain the crystalline form of compound A. The overall purity of the crystalline form of compound A is analyzed via HPLC.

The other half of the sample is recrystallized using a mixture of ethanol and water according to the following procedure:

40g of compound A are dissolved in 200mL of water/ethanol mixture (2:3 volume ratio) upon heating up to about 50 °C. 320mL of water are added at a temperature

range of 45 to 50 °C and the solution is allowed to cool to about 20 °C in 1 to 3 hrs. After 16 hrs the crystalline form is isolated as beige crystals by filtration. The product is dried at elevated temperature (40 to 50 °C) for about 4 to 6 hrs.

The purities of the samples of the raw material and the crystallized material are given in the Table 6.

Table 6

Purity before recrystallization (HPLC-%)	Purity after recrystallization using toluene/ ethanol (HPLC-%)	Purity after recrystallization using ethanol/ water (HPLC-%)
96.14 %	99.74 %	97.4 %

It is observed that using a crystallization process with a mixture of toluene and ethanol a higher purity of the compound A can be obtained than with a process using an ethanol / water mixture.

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CLAIMS:

1. A method for preparing a crystalline form of a compound 1-chloro-4-(β-D-glucopyranos-1-yl)-2-[4-((S)-tetrahydrofuran-3-yloxy)-benzyl]-benzene comprising the following steps:

(a) dissolving the compound in a mixture of at least two solvents to form a solution wherein the first solvent is selected from the group of solvents consisting of toluene and tetrahydrofuran, and the second solvent is selected from the group of solvents consisting of methanol, ethanol, 1-propanol and 2-propanol, or

the first solvent is ethanol and the second solvent is selected from the group of solvents consisting of ethylacetate, n-propylacetate and methylethylketone;

(b) storing the solution to precipitate the crystalline form of the compound out of solution;

(c) isolating the crystalline form of the compound from the solution.

2. A method according to claim 1 wherein the first solvent is toluene or tetrahydrofuran.

3. A method according to claim 2 wherein the second solvent is ethanol, 1-propanol or 2-propanol.

4. A method according to claim 1 wherein the mixture of at least two solvents is selected from the group of combinations consisting of toluene/ethanol, toluene/1-propanol, toluene/2-propanol, tetrahydrofuran/ethanol, tetrahydrofuran/1-propanol, tetrahydrofuran/2-propanol, ethanol/n-propylacetate and ethanol/ethylacetate.

5. A method according to claim 1 wherein the first solvent is toluene.

6. A method according to claim 1 wherein the mixture of at least two solvents is selected from the group of combinations consisting of toluene/ethanol, toluene/1-propanol and toluene/2-propanol.

7. A method according to claim 6 wherein the mixture of at least two solvents is the combination consisting of toluene/ethanol.

8. A method according to claim 6 or 7 wherein the weight ratio of the first solvent to the second solvent is in the range from about 1:5 to 5:1,

9. A method according to claim 6 or 7 wherein the weight ratio of the first solvent to the second solvent is in the range from about 1:2 to 2:1.

10. A method according to claim 1 wherein the mixture of at least two solvents is selected from the group of combinations consisting of tetrahydrofuran/ethanol, tetrahydrofuran/1-propanol and tetrahydrofuran/2-propanol.

11. A method according to claim 10 wherein the weight ratio of the first solvent to the second solvent is in the range from about 1:10 to 2:1.

12. A method according to claim 10 wherein the weight ratio of the first solvent to the second solvent is in the range from about 1:5 to 1:1.

13. A method according to claim 10 wherein the weight ratio of the first solvent to the second solvent is in the range from about 1:4 to 1:2.

14. A method according to claim 1 wherein the crystalline form is characterized by an X-ray powder diffraction pattern that comprises peaks at 18.84, 20.36 and 25.21 degrees 2Θ (±0.1 degrees 2Θ), wherein said X-ray powder diffraction pattern is made using $CuK_{\alpha 1}$ radiation.

15. A method according to claim 14 wherein the X-ray powder diffraction pattern further comprises peaks at 14.69, 19.16 and 19.50 degrees 2Θ (±0.1 degrees 2Θ), wherein said X-ray powder diffraction pattern is made using $CuK_{\alpha 1}$ radiation.

Figure 1: X-ray powder diffraction pattern of the crystalline form (background corrected)

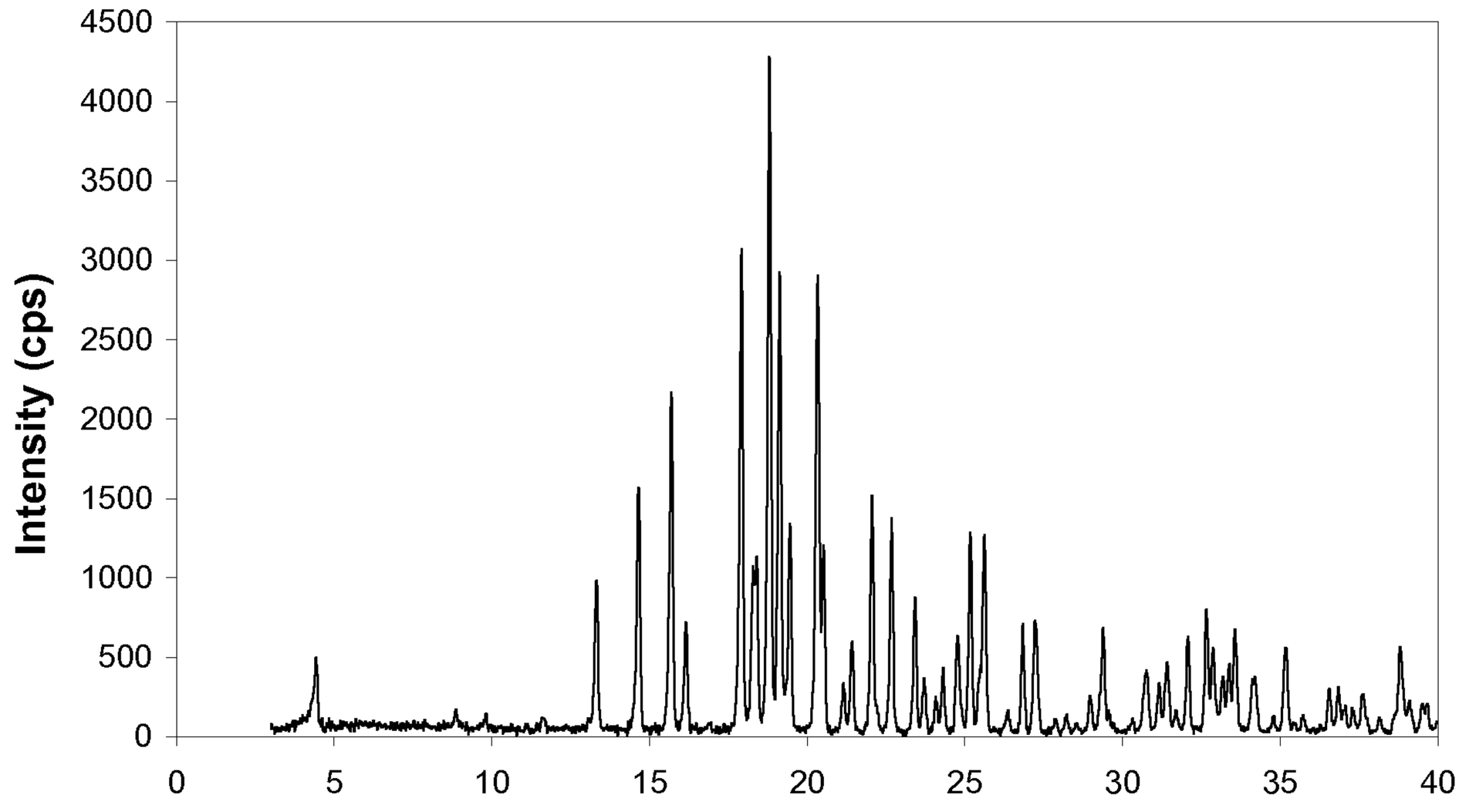

Figure 2: DSC diagram of the crystalline form