DESCRIPTION

Title of Invention:
METHOD FOR PRODUCING DIPHENYLMETHANE DERIVATIVE

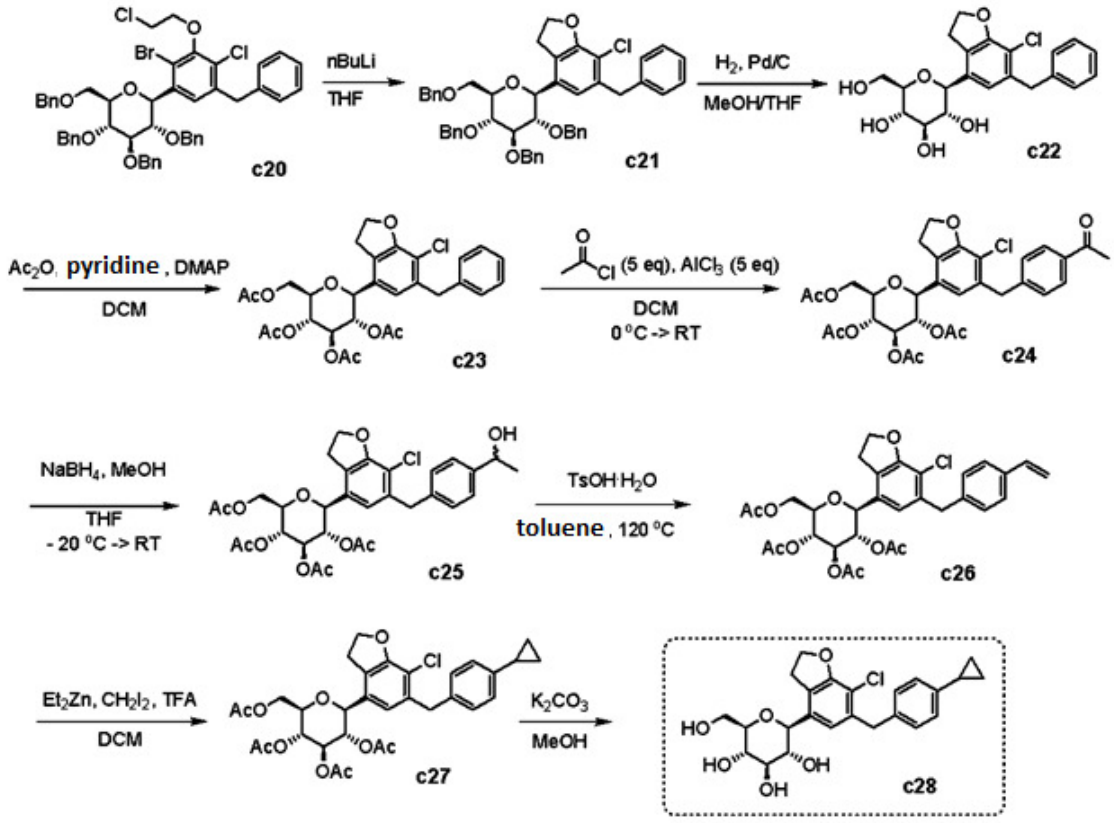
Technical Field

The present disclosure relates generally to a method for producing a diphenylmethane derivative, and more particularly to an improved method for producing a diphenylmethane derivative which is useful as an inhibitor of a sodium-dependent glucose cotransporter (SGLT).

Background Art

The sodium-dependent glucose cotransporter (SGLT) allows transport of Na^+ which goes according to concentration gradient to occur, and at the same time, allows transport of glucose which goes against concentration gradient to occur. Currently, two important SGLT isoforms have been cloned and are known as SGLT1 and SGLT2. SGLT1 is located in the intestines, kidney, and heart, and regulates cardiac glucose transport through expression thereof. Due to being a high-affinity, low-capacity transporter, SGLT1 is responsible for only a portion of renal glucose reabsorption. On the contrary, SGLT2 is a low-affinity, high-capacity transporter which is predominantly located in apical domains of epithelial cells in the early proximal convoluted tubule. In healthy individuals, over 99% of plasma glucose which is filtered in the renal glomeruli is reabsorbed, and less than 1% of total filtered glucose is excreted in the urine. It is estimated that 90% of renal glucose reabsorption is promoted by SGLT2 and the remaining 10% is mediated by SGLT1 in the late proximal straight tubule. Genetic mutation of SGLT2 does not have any particular adverse effects on carbohydrate metabolism. However, increased renal glucose secretion of about 140 g/day is caused depending on mutation. According to human mutation studies, SGLT2 has been a subject of therapeutic studies because it is estimated that SGLT2 is responsible for most renal glucose reabsorption.

US Laid-open Patent Publication No. 2015/0152075 discloses a compound having a diphenylmethane moiety which has an inhibitory activity on SGLT2, and a method for



However, according to the conventional method for producing the compound c28, a linear synthesis method such as forming a pentagonal ring in an aglycone group after being coupled with a glucose group is employed. In a case of such a linear synthesis, due to a complicated pathway, a low final yield is obtained. Besides, in a case where synthesis of a substituent of the glucose group or a cyclopropylbenzyl group which is bonded to dihydrobenzofuran goes wrong in the middle, or the substituent or cyclopropylbenzyl group is intended to be changed to another, there is inconvenience of having to go through the synthesis thereof again from the beginning. In addition, even for a process of synthesizing a cyclopropyl group of the compound c28, the process is carried out by cyclizing olefin through a Simon-Smith reaction at the end of the synthesis pathway, so that a yield varies greatly depending on a state (purity, anhydrous, or the like) of a reagent (diethyl zinc, solvent) and the like, and a reaction concentration.

In view of the above, the present inventors have discovered that a diphenylmethane derivative can be produced efficiently by a convergent synthesis method in which the respective main groups are separately synthesized and then coupled to each other, rather than the conventional linear synthesis method.

Detailed Description

Aspects of the invention are defined in the independent claims. Some optional features of the invention are defined in the dependent claims. As disclosed herein, it may be possible to provide an improved method for producing a diphenylmethane derivative which is useful as an inhibitor of SGLT.

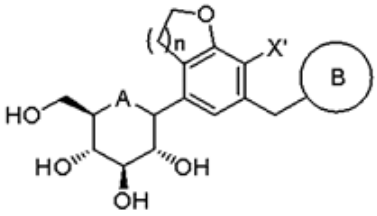
According to an aspect of the present disclosure, there is provided a method for producing a compound of the following Formula 1a, the method comprising the steps of:

(1) reacting a compound of the following Formula 2 with a compound of the following Formula 3 and subjecting the resultant to a cyclization reaction, to obtain a compound of the following Formula 4;

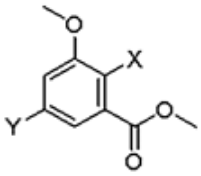
(2) subjecting the compound of Formula 4 to aldehydation or amidation, followed by reacting the resultant with a compound of the following Formula 5 and performing reduction, to obtain a compound of the following Formula 6; and

(3) reacting the compound of Formula 6 with a compound of the following Formula 7, and performing deprotection and reduction,

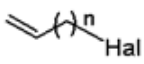
[Formula 1a]



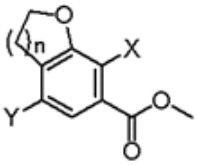
[Formula 2]



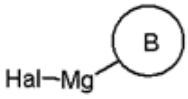
[Formula 3]



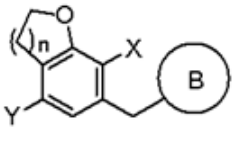
[Formula 4]



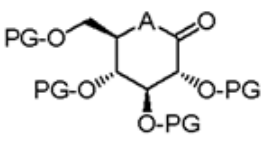
[Formula 5]



[Formula 6]



[Formula 7]



in the formulae,

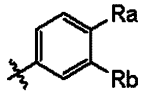
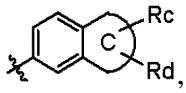
A is oxygen (O) or sulfur (S);

n is 1 or 2;

PG is a protecting group;

X' is halogen or C_{1-7} alkyl;

X, Y, and Hal are each independently halogen;

B is (B-1)  or (B-2) ,

in which Ra, Rb, Rc, and Rd are each independently hydrogen, halogen, hydroxy, mercapto, cyano, nitro, amino, carboxy, oxo, C_{1-7} alkyl, C_{1-7} alkylthio, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{1-7} alkoxy, C_{1-7} alkoxy-C_{1-7} alkyl, C_{2-7} alkenyl-C_{1-7} alkyloxy, C_{2-7} alkynyl-C_{1-7} alkyloxy, C_{3-10} cycloalkyl, C_{3-7} cycloalkylthio, C_{5-10} cycloalkenyl, C_{3-10} cycloalkyloxy, C_{3-10} cycloalkyloxy-C_{1-7} alkoxy, phenyl-C_{1-7} alkyl, C_{1-7} alkylthio-phenyl, phenyl-C_{1-7} alkoxy, mono- or di-C_{1-7} alkylamino, mono- or di-C_{1-7} alkylamino-C_{1-7} alkyl, C_{1-7} alkanoyl, C_{1-7} alkanoylamino, C_{1-7} alkylcarbonyl, C_{1-7} alkoxycarbonyl, carbarmoyl, mono- or di-C_{1-7} alkylcarbamoyl, C_{1-7} alkylsulfonylamino, phenylsulfonylamino, C_{1-7} alkylsulfinyl, C_{6-14} arylsulfanyl, C_{6-14} arylsulfonyl, C_{6-14} aryl, 5- to 13-membered heteroaryl, 5- to 10-membered heterocycloalkyl, 5- to 10-membered heterocycloalkyl-C_{1-7} alkyl, or 5- to 10-membered heterocycloalkyl-C_{1-7} alkoxy;

a ring C is C_{3-10} cycloalkyl, C_{5-10} cycloalkenyl, C_{6-14} aryl, 5- to 13-membered heteroaryl, or 5- to 10-membered heterocycloalkyl;

the alkyl, alkenyl, alkynyl, and alkoxy are each independently unsubstituted, or have one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, amino, mercapto, C_{1-7} alkyl, and C_{2-7} alkynyl;

the cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocycloalkyl are each independently unsubstituted, or have one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, amino, mercapto, C_{1-4} alkyl, and C_{1-4} alkoxy; and

the heteroaryl and heterocycloalkyl each independently contain one or more heteroatoms selected from the group consisting of N, S, and O.

According to another aspect of the present disclosure, there is provided a method for producing a compound of the following Formula 1b, the method comprising the steps of:

(1) reacting a compound of the following Formula 2 with a compound of the following Formula 3 and subjecting the resultant to a cyclization reaction, to obtain a compound of the following Formula 4;

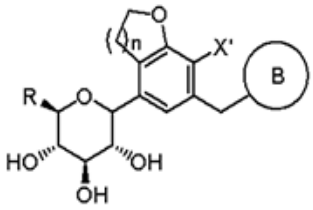
(2) subjecting the compound of Formula 4 to aldehydation or amidation, followed by reacting the resultant with the compound of Formula 5 and performing reduction, to obtain a compound of the following Formula 6;

(3) reacting the compound of Formula 6 with a compound of the following Formula 8 and then performing reduction, to obtain a compound of the following Formula 9;

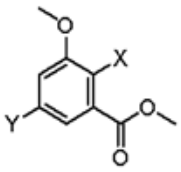
(4) forming a furanose ring of the compound of Formula 9 into a pyranose ring under an acidic condition and then introducing a protecting group thereinto, to obtain a compound of the following Formula 10; and

(5) treating the compound of Formula 10 with thiourea, reacting the resultant with C_{1-7} alkyl halide, and then performing reduction,

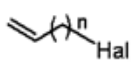
[Formula 1b]



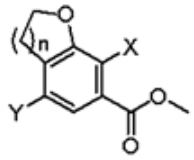
[Formula 2]



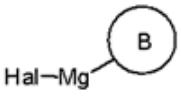
[Formula 3]



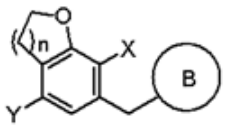
[Formula 4]



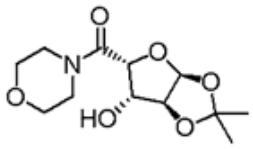
[Formula 5]



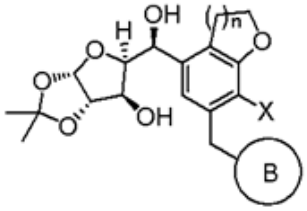
[Formula 6]



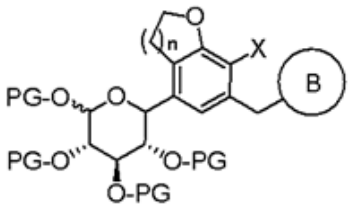
[Formula 8]



[Formula 9]



[Formula 10]



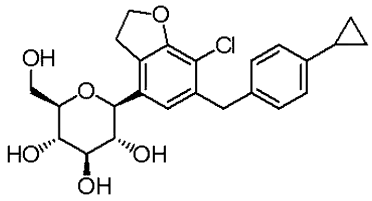
in the formulae,

R is C_{1-7} alkylthio;

B, n, PG, X', X, Y and Hal are as defined above in Formula 1.

According to still another aspect of the present disclosure, there is provided a crystalline form of the compound produced by the above method, specifically a crystalline form of a compound of the following Formula c28.

[Formula c28]



Advantageous Effects

The method for producing a diphenylmethane derivative is carried out by a convergent synthesis method in which main groups are separately synthesized and then coupled to each other. Thus, as compared with the linear synthesis method disclosed in the prior art document, a simple synthesis pathway and a high yield can be achieved, and reproducibility is improved due to the fact that risk factors (such as returning to a first place in the pathway and repeating the synthesis at the time of failure in the middle of the synthesis) which are inherent in the linear synthesis pathway can be reduced.

In particular, according to the method disclosed in the prior art document, residues of the aglycone group have to be synthesized even after coupling the glucose group with the aglycone group. On the other hand, according to the present disclosure, all residues of the aglycone group can be formed before being coupled with the glucose group. In addition, an aryl group bonded to a terminal group of the aglycone can be easily synthesized, so that various designs of the terminal group are possible.

In addition, a crystalline form of the compound produced by the above method is excellent in physicochemical properties, and thus can be usefully utilized in fields such as production of pharmaceuticals.

Brief Description of Drawings

Figs. 1 and 2 illustrate XRD and DSC spectra of a crystalline form A obtained in Experimental Example 4, respectively.

Figs. 3 and 4 illustrate XRD and DSC spectra of a crystalline form B obtained in Experimental Example 4, respectively.

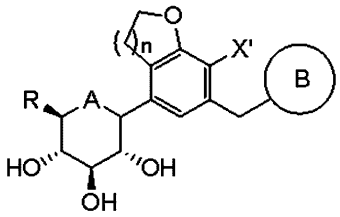
Figs. 5 and 6 illustrate XRD and DSC spectra of a crystalline form C obtained in Experimental Example 4, respectively.

Figs. 7 and 8 illustrate XRD and DSC spectra of a crystalline form D obtained in Experimental Example 4, respectively.

Best Mode for Carrying Out Invention

As disclosed herein, there is a process for producing a compound of Formula 1:

[Formula 1]



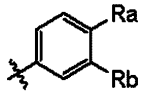
In the formula,

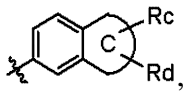
A is oxygen (O) or sulfur (S);

R is hydroxymethyl or C_{1-7} alkylthio;

n is 1 or 2;

X' is halogen (for example, F, Cl, Br, or I) or C_{1-7} alkyl;

B is (B-1) 

or (B-2) 
,

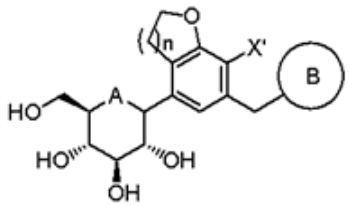
in which Ra, Rb, Rc, and Rd are each independently hydrogen, halogen, hydroxy, mercapto, cyano, nitro, amino, carboxy, oxo, C_{1-7} alkyl, C_{1-7} alkylthio, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{1-7} alkoxy, C_{1-7} alkoxy-C_{1-7} alkyl, C_{2-7} alkenyl-C_{1-7} alkyloxy, C_{2-7} alkynyl-C_{1-7} alkyloxy, C_{3-10} cycloalkyl, C_{3-7} cycloalkylthio, C_{5-10} cycloalkenyl, C_{3-10} cycloalkyloxy, C_{3-10} cycloalkyloxy-C_{1-7} alkoxy, phenyl-C_{1-7} alkyl, C_{1-7} alkylthio-phenyl, phenyl-C_{1-7} alkoxy, mono- or di-C_{1-7} alkylamino, mono- or di-C_{1-7} alkylamino-C_{1-7} alkyl, C_{1-7} alkanoyl, C_{1-7} alkanoylamino, C_{1-7} alkylcarbonyl, C_{1-7} alkoxycarbonyl, carbarmoyl, mono- or di-C_{1-7} alkylcarbamoyl, C_{1-7} alkylsulfonylamino, phenylsulfonylamino, C_{1-7} alkylsulfinyl, C_{6-14} arylsulfanyl, C_{6-14} arylsulfonyl, C_{6-14} aryl, 5- to 13-membered heteroaryl, 5- to 10-membered heterocycloalkyl, 5- to 10-membered heterocycloalkyl-C_{1-7} alkyl, or 5- to 10-membered heterocycloalkyl-C_{1-7} alkoxy;

a ring C is C_{3-10} cycloalkyl, C_{5-10} cycloalkenyl, C_{6-14} aryl, 5- to 13-membered heteroaryl, or 5- to 10-membered heterocycloalkyl;

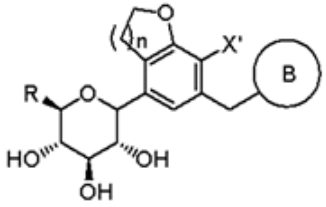
the alkyl, alkenyl, alkynyl, and alkoxy are each independently unsubstituted, or have one or more substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, amino, mercapto, C_{1-7} alkyl, and C_{2-7} alkynyl;

the cycloalkyl, cycloalkenyl, aryl, heteroaryl, and heterocycloalkyl are each independently unsubstituted, or have one or more substituents selected from the group

[Formula 1a]



[Formula 1b]



In the formulae, A, B, R, X', and n are as defined above in Formula 1.

According to a preferred example of the compound of Formula 1a, A may be oxygen; n may be 1; X' may be halogen; and B may be phenyl which is unsubstituted or substituted with one or two substituents selected from the group consisting of halogen, hydroxy, cyano, nitro, amino, mercapto, C_{1-7} alkyl, C_{3-10} cycloalkyl, and C_{1-7} alkoxy.

In addition, the compounds of Formulae 1a and 1b may be compounds in which the glucose is in an α-form, a β-form, or a racemic form thereof.

Preferably, the compounds of Formulae 1a and 1b may be compounds in which the glucose is in a β-form.

Method for producing compound of Formula 1a (Formula 1 in which R = hydroxymethyl)

According to an aspect of the present disclosure, there is provided a method for producing the compound of Formula 1a (Formula 1 in which R = hydroxymethyl), the method comprising the following steps of:

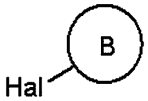
(1) reacting a compound of the following Formula 2 with a compound of the following Formula 3 and subjecting the resultant to a cyclization reaction, to obtain a compound of the following Formula 4;

(2) subjecting the compound of Formula 4 to aldehydation or amidation, followed by reacting the resultant with the compound of Formula 5 and performing reduction, to obtain a compound of the following Formula 6; and

(3) reacting the compound of Formula 6 with a compound of the following Formula 7, and performing deprotection and reduction.

following Formula 5a can be reacted with metal magnesium (Mg) to produce the compound of Formula 5.

[Formula 5a]



In the formula, B is as defined above in Formula 1 and Hal is halogen.

As described above, according to the present disclosure, the group B of the final compound (compound of Formula 1a) can be easily introduced in advance according to a method of producing a Grignard reagent before coupling of the aglycone group with the glucose group, which not only allows various derivatization but also allows a final yield to be improved.

On the other hand, according to the prior art document (US Laid-open Patent Publication No. 2015/0152075 A1), in order to complete the group B of the final compound, after being coupled with the glucose group, a complicated synthesis process is required at the end of the synthesis pathway, and thus there is a problem that a reaction yield and a reaction reproducibility vary greatly due to a long process.

Step (3)

In the step (3), the compound of Formula 6 is reacted with the compound of Formula 7, and then deprotection and reduction are performed.

A reaction of the compound of Formula 6 with the compound of Formula 7 may be carried out in the presence of n-butyllithium, sec-butyllithium, t-butyllithium, i-propylmagnesium chloride (i-PrMgCl), or the like.

The compound of Formula 6 can be reacted with the compound of Formula 7 to obtain a compound of the following Formula 7a:

[Formula 7a]

In addition, the compound of Formula 7d may be used in the next step through purification after synthesis thereof. For example, (i) after being synthesized, the compound of Formula 7d may be caused to form an azeotropic mixture with an organic solvent such as toluene, and the residue obtained by repeating a concentration process to remove residual moisture may be used in the next step, or (ii) after being synthesized, the compound of Formula 7d may be subjected to crystallization, and the solid content obtained by removing residual moisture through vacuum drying may be used in the next step.

Alkylation step

In addition, according to the present disclosure, it is possible to further include an alkylation reaction after the step (3), and as a result, X' in the Formula 1 may be C_{1-7} alkyl.

For example, the product after the step (4) may be reacted with methylboronic acid to obtain the compound of Formula 1a in which X' is substituted with methyl.

Crystallization step

The compound of Formula 1a may be produced in a crystalline form, an amorphous form, or a mixture thereof. However, the compound of Formula 1a in a crystalline form is preferred from the viewpoint of being excellent in stability and non-hygroscopicity and thus of having physicochemical properties which facilitate formulation.

Therefore, the method may further comprise crystallizing the compound of Formula 1a after the step (3). The crystallization may be performed using various solvents, and thus various crystalline forms can be obtained.

As an example, the solvent used for the crystallization may be selected from toluene; ethyl acetate; dichloromethane; acetone; acetonitrile; a mixture of 2-propanol, tetrahydrofuran, and dichloromethane; and a mixture of tetrahydrofuran and n-hexane, and as a result, a crystalline form A can be produced.

As another example, the solvent used for the crystallization may be selected from a mixture of methanol and distilled water; a mixture of methanol and n-hexane; and a mixture of methanol, dichloromethane, and n-hexane, and as a result, a crystalline form B can be produced.

As still another example, the solvent used for the crystallization may be selected from a mixture of ethanol, distilled water, and n-hexane; and a mixture of tetrahydrofuran and toluene, and as a result, a crystalline form C can be produced.

As yet another example, the solvent used for the crystallization may be a mixture of ethanol and n-hexane, and as a result, a crystalline form D can be produced.

As a preferred example, the solvent used for the crystallization may be selected from the group consisting of toluene, ethyl acetate, dichloromethane, a mixture of tetrahydrofuran and dichloromethane, and a mixture of tetrahydrofuran and n-hexane.

Method for producing compound of Formula 1b (Formula 1 in which R = alkylthio and A = oxygen)

According to another aspect of the present disclosure, there is provided a method for producing the compound of Formula 1b (Formula 1 in which R = C_{1-7} alkylthio and A = oxygen), the method comprising the following steps of:

(1) reacting a compound of the following Formula 2 with a compound of the following Formula 3 and subjecting the resultant to a cyclization reaction, to obtain a compound of the following Formula 4;

(2) subjecting the compound of Formula 4 to aldehydation or amidation, followed by reacting the resultant with the compound of Formula 5 and performing reduction, to obtain a compound of the following Formula 6;

(3) reacting the compound of Formula 6 with a compound of the following Formula 8 and then performing reduction, to obtain a compound of the following Formula 9;

(4) forming a furanose ring of the compound of Formula 9 into a pyranose ring under an acidic condition and then introducing a protecting group thereinto, to obtain a compound of the following Formula 10; and

(5) treating the compound of Formula 10 with thiourea, reacting the resultant with C_{1-7} alkyl halide, and then performing reduction.

Crystaline form

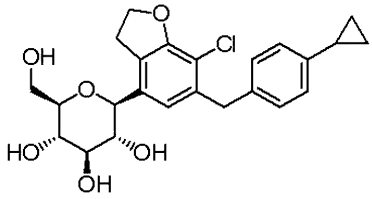
According to still another aspect of the present disclosure, there is provided a crystalline form of the compound produced according to the above-described production method.

As an example, the present disclosure provides a crystalline form of the compound of Formula 1a.

As a specific example, the present disclosure provides a crystalline form of the compound of Formula 1a in which A is O, B is cyclopropylphenyl, n is 1, and X' is Cl, and which is in a β-form.

That is, the present disclosure provides a crystalline form of a compound of the following Formula c28.

[Formula c28]



The compound of Formula c28 can be produced by the above-described production method of Formula 1a.

According to the present disclosure, it is possible that the compound of Formula c28 is in various crystalline forms, and the respective crystalline forms will be described in detail below.

In the following, the term "about" may mean to be within 5% and preferably within 2%, of a predetermined value or range. For example, "about 10%" may mean 9.5% to 10.5%, and preferably 9.8% to 10.2%. As another example, "about 100°C" may mean 95°C to 105°C, and preferably 98°C to 102°C.

First, the present disclosure provides a crystalline form A of the compound of Formula c28. The crystalline form A has an XRD spectrum which includes peaks at

diffraction angles (2θ) of 6.2°±0.2°, 7.2°±0.2°, 8.8°±0.2°, 17.6°±0.2°, 19.0°±0.2°, 22.5°±0.2°, and 25.1°±0.2° in a case of being irradiated using a Cu-Kα light source. These peaks may be peaks with a relative intensity (I/I_o) being about 5% or higher and preferably about 10% or higher.

The XRD spectrum of the crystalline form A may further include peaks at diffraction angles (2θ) of 15.4°±0.2°, 18.6°±0.2°, 21.6°±0.2°, and 23.8°±0.2°.

In addition, the crystalline form may have an endothermic peak in which a starting point is about 157°C and the lowest point is about 159°C, at DSC (10°C/minute).

In addition, the present disclosure provides a crystalline form B of the compound of Formula c28. The crystalline form B has an XRD spectrum which includes peaks at diffraction angles (2θ) of 7.0°±0.2°, 14.9°±0.2°, 17.7°±0.2°, 18.8°±0.2°, 20.6°±0.2°, 21.8°±0.2°, and 23.5°±0.2° in a case of being irradiated using a Cu-Kα light source. These peaks may be peaks with a relative intensity (I/I_o) being about 5% or higher and preferably about 10% or higher.

The XRD spectrum of the crystalline form B may further include peaks at diffraction angles (2θ) of 5.6°±0.2°, 9.4°±0.2°, and 11.0°±0.2°.

In addition, the crystalline form may have an endothermic peak in which a starting point is about 79°C and the lowest point is about 88°C, and an endothermic peak in which a starting point is about 103°C and the lowest point is about 111°C, at DSC (10°C/minute).

In addition, the present disclosure provides a crystalline form C of the compound of Formula c28. The crystalline form C has an XRD spectrum which includes peaks at diffraction angles (2θ) of 5.6°±0.2°, 7.3°±0.2°, 15.7°±0.2°, 17.2°±0.2°, 18.9°±0.2°, 21.2°±0.2°, and 21.9°±0.2° in a case of being irradiated using a Cu-Kα light source. These peaks may be peaks with a relative intensity (I/I_o) being about 5% or higher and preferably about 10% or higher.

The XRD spectrum of the crystalline form C may further include peaks at diffraction angles (2θ) of 19.9°±0.2° and 23.1°±0.2°.

In addition, the crystalline form may have an endothermic peak in which a starting point is about 157°C and the lowest point is about 159°C, at DSC (10°C/minute).

In addition, the present disclosure provides a crystalline form D of the compound of Formula c28. The crystalline form D has an XRD spectrum which includes peaks at diffraction angles (2θ) of 5.5°±0.2°, 7.2°±0.2°, 15.3°±0.2°, 17.2°±0.2°, 17.6°±0.2°, 18.9°±0.2°, and 21.1°±0.2° in a case of being irradiated using a Cu-K_α light source. These peaks may be peaks with a relative intensity (I/I_o) being about 5% or higher.

The XRD spectrum of the crystalline form D may further include peaks at diffraction angles (2θ) of 20.0°±0.2°, 22.5°±0.2°, and 25.1°±0.2°.

In addition, the crystalline form may have an endothermic peak in which a starting point is about 157°C and the lowest point is about 160°C, at DSC (10°C/minute).

Such crystalline forms of the compound of Formula c28 are excellent in physicochemical properties (for example, hygroscopicity and chemical stability), and thus can be easily handled in various fields (for example, production of pharmaceuticals).

Mode for Carrying Out Invention

Hereinafter, the present invention will be described in more detail with reference to examples. However, the following examples are intended to merely illustrate the present invention, and the scope of the present invention is not limited to these examples.

The meanings of abbreviations indicated in the following examples are as follows.

- AcOH: Acetic acid
- ACN: Acetonitrile
- Ac_2O: Acetic anhydride
- $BF_3.OEt_2$: Boron trifluoride etherate
- DIPEA: N,N-Diisopropylethylamine
- DCM: Dichloromethane
- DMAP: 4-Dimethylaminopyridine
- DMF: N,N-Dimethylformamide
- EtOAc: Ethyl acetate
- EtOH: ethanol
- Et_3SiH: Triethylsilane
- HBTU: 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate

(3) A reaction solvent, an amount added of $NaBH_4$, and an amount added of Lewis acid were adjusted as shown in Table 7 below, and a reaction was performed. As a result, the reaction did not proceed in a case where only THF was used or THF/i-PrOH was used, as a reaction solvent. On the other hand, in a case where THF/ethanol was used as a reaction solvent, a good yield of 95% or higher was obtained even by using only $NaBH_4$ without Lewis acid.

[Table 7]

Test no.	Reactant	$NaBH_4$ (eq)	Lewis acid	Reaction result (weight ratio) (stating material:product:by-product1)
1	THF	2.0	-	100: - : -
2	Ethanol/water (4:1)	2.0	$CaCl_2$ (1.0 eq)	- :60:40
3	THF/methanol (1:1)	3.0	$CaCl_2$ (1.5 eq)	70:30: -
4	THF/ethanol (1:1)	2.4	$CaCl_2$ (1.2 eq)	- :100: -
5	THF/ethanol (1:1)	3.0	$CaCl_2$ (1.5 eq)	- :100: -
6	THF/ethanol (2:1)	3.0	-	- :100: -
7	THF/isopropanol (1:1)	3.0	$CaCl_2$ (1.5 eq)	100: - : -

Experimental Example 4: Production and analysis of crystalline form

From a compound produced according to the disclosed method, specifically, crude (2S,3R,4R,5S,6R)-2-(7-chloro-6-(4-cyclopropylbenzyl)-2,3-dihydrobenzofuran-4-yl)-6-(hydroxymethyl)tetrahydro-2H-pyran-3,4,5-triol (Compound **c28**) which had been obtained according to the steps 1 to 14 in Example 1, crystals were produced through a crystallization process in various solvents and analyzed.

For an XRD spectrum, powder X-ray diffraction was measured using an X-ray diffractometer by irradiation with a Cu-$K\alpha$ radiation (wavelength, λ = 1.54056 Å) according to an ordinary method.

For differential scanning calorimetry (DSC), measurement was performed at a rate of +1°C/min using a differential scanning calorimeter.

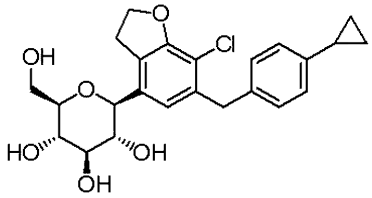
(1) Production of crystal using toluene solvent

Crystallization using toluene is similar to that described in a later portion of a procedure of the step 14 in Example 1. Specifically, a toluene (8-fold with respect to a weight of **c28**) solution of the crude compound **c28** was dissolved by being heated at 40°C for 30 minutes, and then cooled to room temperature. After the suspension was formed at

CLAIMS

1. A crystalline form of a compound of the following Formula c28

[Formula c28]



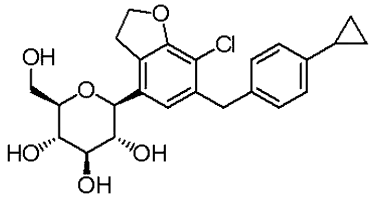
wherein the crystalline form has an X-ray diffraction (XRD) spectrum which includes peaks at diffraction angles (2θ) of 6.2°±0.2°, 7.2°±0.2°, 8.8°±0.2°, 17.6°±0.2°, 19.0°±0.2°, 22.5°±0.2°, and 25.1°±0.2° in a case of being irradiated using a Cu-Kα light source.

2. A crystalline form as claimed in claim 1 wherein the XRD spectrum further includes peaks at diffraction angles (2θ) of 15.4°±0.2°, 18.6°±0.2°, 21.6°±0.2°, and 23.8°±0.2°.

3. A crystalline form as claimed in claim 1 or 2 wherein the crystalline form has an endothermic peak in which a starting point is 157°C and the lowest point is 159°C, at differential scanning calorimetry (DSC) (10°C/minute).

4. A crystalline form of a compound of the following Formula c28.

[Formula c28]



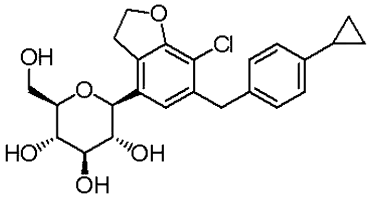
wherein the crystalline form has an X-ray diffraction (XRD) spectrum which includes peaks at diffraction angles (2θ) of 7.0°±0.2°, 14.9°±0.2°, 17.7°±0.2°, 18.8°±0.2°, 20.6°±0.2°, 21.8°±0.2°, and 23.5°±0.2° in a case of being irradiated using a Cu-Kα light source.

5. A crystalline form as claimed in claim 4 wherein the XRD spectrum further includes peaks at diffraction angles (2θ) of 5.6°±0.2°, 9.4°±0.2°, and 11.0°±0.2°.

6. A crystalline form as claimed in claim 4 or 5 wherein the crystalline form has a starting point is 79°C and the lowest point is 88°C, and an endothermic peak in which a starting point is 103°C and the lowest point is 111°C, at differential scanning calorimetry (DSC) (10°C/minute).

7. A crystalline form of a compound of the following Formula c28.

[Formula c28]



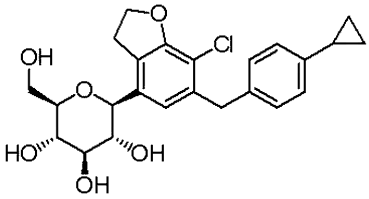
wherein the crystalline form has an X-ray diffraction (XRD) spectrum which includes peaks at diffraction angles (2θ) of 5.6°±0.2°, 7.3°±0.2°, 15.7°±0.2°, 17.2°±0.2°, 18.9°±0.2°, 21.2°±0.2°, and 21.9°±0.2° in a case of being irradiated using a Cu-Kα light source.

8. A crystalline form as claimed in claim 1 wherein the XRD spectrum further includes peaks at diffraction angles (2θ) of 19.9°±0.2° and 23.1°±0.2°.

9. A crystalline form as claimed in claim 7 or 8 wherein the crystalline form has a starting point is 157°C and the lowest point is 159°C, at differential scanning calorimetry (DSC) (10°C/minute).

10. A crystalline form of a compound of the following Formula c28.

[Formula c28]



wherein the crystalline form has an X-ray diffraction (XRD) spectrum which includes peaks at diffraction angles (2θ) of 5.5°±0.2°, 7.2°±0.2°, 15.3°±0.2°, 17.2°±0.2°, 17.6°±0.2°, 18.9°±0.2°, and 21.1°±0.2° in a case of being irradiated using a Cu-Kα light source.

11. A crystalline form as claimed in claim 1 wherein the XRD spectrum further includes peaks at diffraction angles (2θ) of 20.0°±0.2°, 22.5°±0.2°, and 25.1°±0.2°.

12. A crystalline form as claimed in claim 10 or 11 wherein the crystalline form has a starting point is 157°C and the lowest point is 160°C, at differential scanning calorimetry (DSC) (10°C/minute).

13. A crystalline form as claimed in claim 1 for use in the treatment of diabetes.

14. A crystalline form as claimed in claim 4 for use in the treatment of diabetes.

15. A crystalline form as claimed in claim 7 for use in the treatment of diabetes.

16. A crystalline form as claimed in claim 10 for use in the treatment of diabetes.