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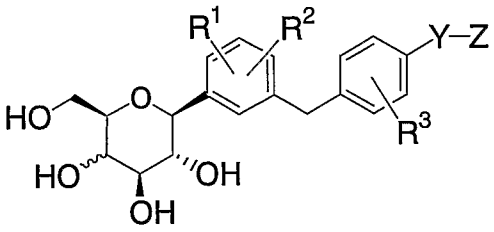
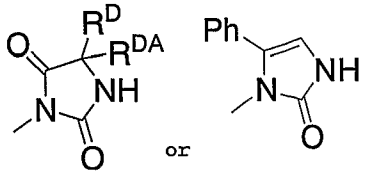
(54) Title: C-PHENYL GLYCITOL COMPOUND



(I)



(57) Abstract: Provided is a novel C-phenyl glycitol compound that may serve as a prophylactic or therapeutic agent for diabetes by inhibiting both SGLT1 activity and SGLT2 activity, thereby exhibiting a glucose absorption suppression action and a urine glucose excretion action. A C-phenyl glycitol compound represented by Formula (I) below or a pharmaceutically acceptable salt thereof or a hydrate thereof wherein R_1 and R_2 are the same or different and represent a hydrogen atom, a hydroxyl group, a C_{1-6} alkyl group, a C_{1-6} alkoxy group or a halogen atom, R_3 is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-6} alkoxy group or a halogen atom, Y is a C_{1-6} alkylene group, -O-(CH_2)n- (n is an integer of 1 to 4) or a C_{2-6} alkenylene group, provided that when Z is NHC(= NH)NH_2 or -NHCON(R^B)R^C, n is not 1, Z is -CONHR^A, -NHC(=NH)NH2 or -NHCON(R^B)R^C, Formula (A) or Formula (B).

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DESCRIPTION

C-PHENYL GLYCITOL COMPOUND

TECHNICAL FIELD

The present invention relates to a C-phenyl glycitol compound having an inhibitory activity for a sodium dependent glucose cotransporter 1 (SGLT1) and a sodium dependent glucose cotransporter 2 (SGLT2).

BACKGROUND ART

When a person suffers from diabetes, the fasting blood glucose level exhibits 126 mg/dL or more. Even though the fasting blood glucose level falls within a normal range, there is a person exhibiting a postprandial blood glucose level as high as 140 to 200 mg/dL. Such a person is diagnosed as impaired glucose tolerance (hereinafter referred to as "IGT"). It has been considered that the risk of a cardiovascular disorder can be reduced by delaying onset of diabetes from IGT, and several supportive findings for this have been obtained. For example, the Da Qing IGT and Diabetes Study carried out in China in 1997 has reported that progression of IGT into Type II diabetes is significantly suppressed by diet and exercise (see Pan XR, et al., Diabets Care, vol 20, p. 534, 1997). As cases where medication is effective, when an α-glucosidase inhibitor, acarbose, which inhibits a hydrolysis of an oligosaccharide to delay glucose absorption from the small intestine, is administered, development of Type II diabetes

from IGT is suppressed and further onset of hypertension is significantly suppressed. This is reported in the document (J.- L. Chiasson, et al., Lancent, vol. 359, p. 2072, 2002).

From the above, to suppress the onset of diabetes, it is important to control IGT by diet therapy, exercise therapy and medication.

Nevertheless, when a person suffers from diabetes, it comes to be necessary to control the blood glucose level at all times. Diabetes is basically treated by diet therapy and exercise therapy; however, when sufficient effect is not obtained by these therapies, medicament must be chosen.

On the small intestine epithelium of a mammal, a sodium dependent glucose cotransporter 1 (SGLT1) is expressed at a high frequency. It is known that SGLT1 serves depending upon sodium and plays a role in active transportation of glucose or galactose in the small intestine. Therefore, if glucose taken from a meal can be suppressed, IGT may be prevented or treated. Based on the concept, a pyrazole derivative inhibiting the activity of SGLT1 has been reported (see International Publication WO2002/098893, 2004/014932, 2004/018491, 2004/019958, 2005/121161 and 2004/050122).

Furthermore, a sodium dependent glucose cotransporter 2 (SGLT2) is expressed at a high frequency in the kidney. Glucose once filtrated by the glomerulus is reabsorbed via SGLT2 (see E. M. Wright, Am. J. Physiol. Renal. Physiol., vol. 280, p. F10, 2001). When an SGLT2 inhibitor is administered to a diabetic rat, glucose excretion into

urine is facilitated, promoting a hypoglycemic action. From this, an SGLT2-specific inhibitor has been considered as a target molecule serving as a therapeutic agent for diabetes (see G. Toggenburger, et al. Biochem. Biophys. Acta., vol. 688, p. 557, 1982). In these circumstances, studies have been conducted on an SGLT2 inhibitor and various types of O-aryl glycoside derivatives have been provided (see EP Patent Application Publication No. 0850948A1 and International Publication WO2001/068660).

Accordingly, if the SGLT1 and SGLT2 activities can be simultaneously inhibited, a novel type of therapeutic agent for diabetes can be provided, which has not only a high postprandial glucose level suppression action ascribed to SGLT1 inhibition but also a progressive hypoglycemic action ascribed to SGLT2 inhibition.

Up to now, a C-phenyl glycoside derivative having a selective inhibitory activity to SGLT2 has been reported (see International Publication WO 2001/027128); however, a C-phenyl glycoside derivative strongly inhibiting both of SGLT1 and SGLT2 has not yet been reported.

DISCLOSURE OF THE INVENTION

An object of the present invention is to provide a C-phenyl glycitol compound, which is expected as a novel-type pharmaceutical for treating diabetes, capable of inhibiting both of SGLT1 and SGLT2 activities, having not only a glucose absorption suppression action from the digestive tract but also a urine glucose excretion action.

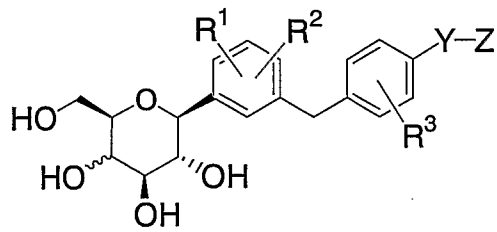
The present inventors conducted intensive studies to

solve the aforementioned object. As a result, they found that a C-phenyl glycitol compound, which is formed by introducing a specific side-chain to an end of an aglycone, has excellent inhibitory actions for SGLT1 and SGLT2 activities. Based on the finding, the present invention was accomplished.

The C-phenyl glycitol compound of the present invention (hereinafter, referred to as "the compound of the invention") will be explained below.

By virtue of the present invention, a novel C-phenyl glycitol compound capable of inhibiting both SGLT1 and SGLT 2 activities can be provided.

First embodiment (1 embodiment) of the present invention is directed to a C-phenyl glycitol compound of the following formula or a pharmaceutically acceptable salt thereof or a hydrate thereof:



(I)

where

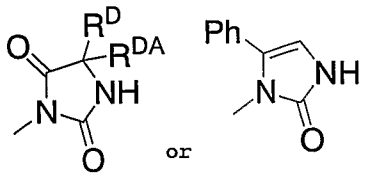
R^1 and R^2 are the same or different and represent a hydrogen atom, a hydroxyl group, a C_{1-6} alkyl group, a C_{1-6} alkoxy group or a halogen atom,

R^3 is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-6} alkoxy group or a halogen atom,

Y is a C_{1-6} alkylene group, -O-(CH_2)n- (n is an integer of

1 to 4) or a C_{2-6} alkenylene group, provided that when Z is $-NHC(=NH)NH_2$ or $-NHCON(R^B)R^C$, n is not 1,

Z is $-CONHR^A$, $-NHC(=NH)NH_2$ or $-NHCON(R^B)R^C$,



where

R^A is

a C_{1-6} alkyl group substituted with 1 to 3 substituents selected from the group consisting of a hydroxyl group, an amino group and a carbamoyl group,

R^B is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl group that may be substituted with 1 to 3 substituents selected from Group A,

(3) a C_{3-12} cycloalkyl group which may be substituted with 1 to 3 substituents selected from a hydroxyl group and a C_{1-6} hydroxyalkyl group,

(4) a 3 to 12-membered heterocycloalkyl group or a 5 to 13-membered heteroaryl group that may be partially saturated, each of which contains one to three ring-constituting atom(s) selected from the group consisting of O, N, S, SO_2, CO and NR^{10} (R^{10} is a hydrogen atom, a C_{1-6} alkyl group, a phenyl-C_{1-6} alkyl group or a C_{2-6} alkoxycarbonyl group), and may be substituted with 1 to 3 subtitituents selected from the group consisting of a hydroxyl group and a C_{1-6} hydroxyalkyl group, or

(5) a C_{6-13} aryl group which may be partially saturated and may be substituted with 1 or 2 substituents selected from a hydroxyl group, and a C_{1-6} alkyl group, a phenyl-C_{1-6} alkyl group and a C_{1-6} alkylsulfonyl group, each of which may be substituted with a hydroxyl group(s)

in which

Group A consists of

a halogen atom, a hydroxyl group, a C_{1-6} alkoxy group which may be substituted with a hydroxyl group(s), a carboxyl group, a C_{2-6} alkoxycarbonyl group, a carbamoyl group, an amino group, a C_{1-6} alkylamino group, a di-C_{1-6} alkylamino group, a C_{2-6} acylamino group, a C_{1-6} alkylthio group which may be substituted with a hydroxyl group(s),

a phenoxy group,

a phenyl group which may be substituted with 1 to 3 substituents selected from Group B (Group B consists of a hydroxyl group, a halogen atom, a C_{1-6} alkoxy group, a C_{1-6} alkyl group which may be substituted with a hydroxyl group(s), a C_{1-6} alkylthio group, a thienyl group, a phenylthio group which may be substituted with a hydroxyl group(s) or a C_{1-6} hydroxyalkyl group(s), and a piperidino group which may be substituted with a hydroxyl group(s) or a C_{1-6} hydroxyalkyl group(s)),

a C_{3-12} cycloalkyl group which may be substituted with 1 to 3 subtitituents selected from the group consisting of a hydroxyl group and a C_{1-6} hydroxyalkyl group,

a 3 to 12-membered heterocycloalkyl group or a 5 to 13-membered heteroaryl group that may be partially saturated,

each of which contains one to three ring-constituting atom(s) selected from the group consisting of O, N, S, SO_2, CO and NR^{10} (R^{10} is a hydrogen atom, a C_{1-6} alkyl group, a phenyl-C_{1-6} alkyl group or a C_{2-6} alkoxycarbonyl group), and may be substituted with 1 to 3 subtitituents selected from the group consisting of a hydroxyl group and a C_{1-6} hydroxyalkyl group, and

$-CONR^{B1}R^{B2}$ wherein R^{B1} and R^{B2} together with the nitrogen atom to which they are attached form a 5 to 6 membered heterocycloalkyl group which may contain as another ring-constituting atom, an oxygen atom, a nitrogen atom or a sulfur atom and may be substituted with 1 or 2 subtitituents selected from the group consisting of a C_{1-6} alkyl group which may be substituted with a hydroxyl group(s), a C_{2-6} alkoxycarbonyl group and a phenylC_{1-6} alkyl group,

R^C is

a hydrogen atom, a C_{1-6} alkyl group which may be substituted with 1 or 2 substituents selected from the group consisiting of a hydroxyl group, a di-C_{1-6} alkylamino group, a C_{2-6} alkoxycarbonyl group and a C_{1-6} alkoxy group, or a C_{3-12} cycloalkyl group which may be substituted with a hydroxyl group(s), and

R^B and R^C together with the nitrogen atom to which they are attached may form a 3 to 12 membered heterocycloalkyl group or a 5 to 13 membered heteroaryl group that may be

partially saturated, each of which may contain 1 or 2 ring-constituting atom selected from O, N, NR^{11}, S, SO_2 and CO and which may be substituted with 1 or 2 subtitituents selected from the group consisting of a hydroxyl group, a C_{2-6} alkoxycarbonyl group, a carbamoyl group, a C_{2-6} acyl(C_{1-6} alkyl)amino group, a di-C_{1-6} alkylaminocarbonyl group, a pyrrolidinyl group, a morpholino group, a pyrrolidin-1-yl-carbonyl group, a C_{1-6} alkyl group that may be substituted with 1 to 3 substituents selected from the group consisiting of a hydroxyl group, a pyrrolidin-1-yl group, a phenyl group and a C_{2-6} alkoxycarbonyl group, and a phenyl group that may be substituted with 1 to 3 substituents selected from the group consisting of a C_{1-6} alkyl group, a C_{1-6} alkoxy group and a halogen atom

where R^{11} is a hydrogen atom, a C_{2-6} acyl group, a phenyl group that may be substituted with a hydroxyl group(s), a pyridyl group, a furylcarbonyl group, an oxolanylcarbonyl group, a C_{2-6} alkoxycarbonyl group or a C_{1-6} alkyl group that may be substituted with 1 or 2 substituents selected from the group consisting of a hydroxyl group, a phenyl group, a di-C_{1-6} alkylamino group, a morpholino group and a pyrrolidin-1-yl-carbonyl group, and

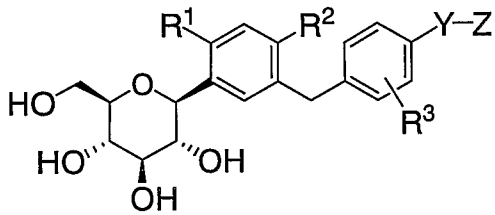
R^D is a hydrogen atom or a C_{1-6} alkyl group which may be substituted with 1 or 2 substituents from the group consisting of a hydroxyl group, a C_{3-12} cycloalkyl group, a phenyl group that may be substituted with a hydroxyl group(s), a pyridyl group, a C_{2-6} alkoxycarbonyl group, an imidazolyl group and a 1-benzylimidazolyl group, and R^{DA} is

a hydrogen atom or a C_{1-6} alkyl group.

BEST MODE FOR CARRYING OUT THE INVENTION

The present invention provide the following other embodiments 2 to 19:

2. The C-phenyl glycitol compound which is a C-phenyl glucitol compound represented by Formula (II) below or a pharmaceutically acceptable salt thereof, or a hydrate thereof,



(II)

where R^1, R^2, R^3, Y and Z are the same as defined in Forumula (I).

3. The C-phenyl glycitol compound or a pharmaceutically acceptable salt thereof, or a hydrate thereof in Formula (II), wherein R^1 is a hydrogen atom, a hydroxyl group, a C_{1-4} alkyl group or a C_{1-4} alkoxy group, and R^2 is a C_{1-4} alkyl group or a halogen atom.

4. The C-phenyl glycitol compound according to the embodiment 2 or 3 or a pharmaceutically acceptable salt thereof, or a hydrate thereof, where R^3 is a hydrogen atom.

5. The C-phenyl glycitol compound or a pharmaceutically acceptable salt thereof, or a hydrate thereof according to embodiment 3 or 4, wherein Y is a C_{1-6} alkylene group or -O-(CH_2)n- (n is an integer of 2 to 4), and Z is -NHCON(R^B)R^C wherein R^B and R^C are as defined in Forumula (I).

6. The C-phenyl glycitol compound or a pharmaceutically acceptable salt thereof, or a hydrate thereof according to embodiment 3 or 4, wherein

Y is a C_{1-6} alkylene group or -O-(CH_2)n- (n is an integer of 2 to 4), and Z is -NHCON(R^B)R^C,

where

R^B is

(1) a C_{1-6} alkyl group which may be substituted with 1 to 3 substituents selected from Group A,

(2) a C_{3-12} cycloalkyl group which may be substituted with 1 to 3 substituents selected from a hydroxyl group and a C_{1-6} hydroxyalkyl group,

(3) a 3 to 12-membered heterocycloalkyl group or a 5 to 13-membered heteroaryl group that may be partially saturated, each of which contains one to three ring-constituting atom(s) selected from the group consisting of O, N, S and NR^{10} (R^{10} is a hydrogen atom, a C_{1-6} alkyl group, a phenyl-C_{1-6} alkyl group or a C_{2-6} alkoxycarbonyl group) and may be substituted with 1 to 3 subtitituents selected from the group consisting of a hydroxyl group and a C_{1-6} hydroxyalkyl group, or

(4) a 6 to 13-membered aryl group which may be partially

saturated and may be substituted with 1 or 2 substituents selected from a hydroxyl group, and a C_{1-6} alkyl group, a phenyl-C_{1-6} alkyl group and a C_{1-6} alkylsulfonyl group, each of which may be substituted with a hydroxyl group(s)

in which

Group A consists of

a halogen atom, a hydroxyl group, a C_{1-6} alkoxy group which may be substituted with a hydroxyl group(s), a C_{2-6} alkoxycarbonyl group, a carbamoyl group, a di-C_{1-6} alkylamino group, a C_{1-6} alkylthio group which may be substituted with a hydroxyl group(s),

a phenoxy group, a thienyl group, benzothienyl group, furyl group,

a phenyl group which may be substituted with 1 to 3 substituents selected from the group consisting of a hydroxyl group, a halogen atom, a C_{1-6} alkoxy group, a C_{1-6} alkyl group which may be substituted with a hydroxyl group(s), a C_{1-6} alkylthio group, a phenylthio group which may be substituted with a hydroxyl group(s) or a C_{1-6} hydroxyalkyl group(s), and a piperidino group which may be substituted with a hydroxyl group(s) or a C_{1-6} hydroxyalkyl group(s),

a C_{3-12} cycloalkyl group which may be substituted with 1 to 3 subtitituents selected from the group consisting of a hydroxyl group and a C_{1-6} hydroxyalkyl group,

a 3 to 12-membered heterocycloalkyl group which contains one to three ring-constituting atom(s) selected from the group consisting of O, N, S and NR^{10} (R^{10} is

a hydrogen atom, a C_{1-6} alkyl group, a phenyl-C_{1-6} alkyl group or a C_{2-6} alkoxycarbonyl group) and
may be substituted with 1 to 3 subtitituents selected from the group consisting of a hydroxyl group and a C_{1-6} hydroxyalkyl group, and
4-C_{1-6} alkylpiperadine-1-ylcarbonyl group,

R^C is a hydrogen atom, and

R^B and R^C together with the nitrogen atom to which they are attached may form a piperidine group which may be substituted with a pyrrolidinyl group or a C_{1-6} alkyl group which is substituted with a diC_{1-6}alkylamino group or a pyrrolidin-1-yl group, or a thiomorpholine group or a decahydroisoquinoline group.

7. The C-phenyl glycitol compound or a pharmaceutically acceptable salt thereof or a hydrate thereof according to any one of embodiments 2 to 4,
wherein
Y is a C_{1-6} alkylene group,
Z is -CONHR^A,
where
R^A is a C_{1-6} alkyl group substituted with 1 to 3 substituents selected from the group consisting of a hydroxyl group and a carbamoyl group.

8. The C-phenyl glycitol compound or a pharmaceutically

acceptable salt thereof or a hydrate thereof according to any one of embodiments 2 to 4, wherein

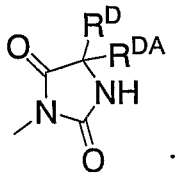
Y is a C_{1-6} alkylene group, and

Z is $-NHC(=NH)NH_2$.

9. The C-phenyl glucitol compound or a pharmaceutically acceptable salt thereof or a hydrate thereof according to any one of embodiments 2 to 4, wherein

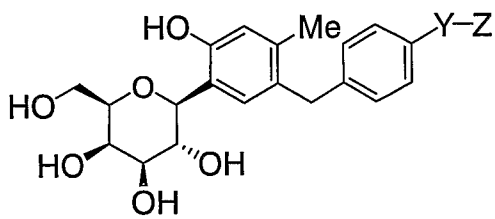
Y is a C_{1-6} alkylene group, and

Z is



R^D is a C_{1-6} alkyl group which is substituted with a C_{3-12} cycloalkyl group or a phenyl group and R^{DA} is a hydrogen atom or a C_{1-6} alkyl group.

10. The C-phenyl glycitol compound according to embodiment 1 which is a C-phenyl galacitol compound represented by Formula (III) below or a pharmaceutically acceptable salt thereof or a hydrate thereof,



(III)

where

Y is

a C_{1-6} alkylene group, and

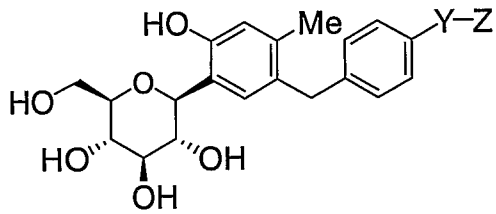
Z is

$-CONHR^A$,

where

R^A is a C_{1-6} alkyl group substituted with 1 to 3 substituents selected from the group consisting of a hydroxyl group and a carbamoyl group.

11. The C-phenyl glycitol compound according to embodiment 1 which is a C-phenyl glucitol compound represented by Formula (IV) below or a pharmaceutically acceptable salt thereof or a hydrate thereof,



(IV)

where

Y is a C_{1-6} alkylene group, and

Z is $-CONHR^{A1}$, $-NHC(=NH)NH_2$ or $-NHCOR^{B1}$,

where

R^{A1} is a C_{1-6} alkyl group substituted with 1 to 3 substituents selected from the group consisting of a hydroxyl group, an amino group and a carbamonyl group, and

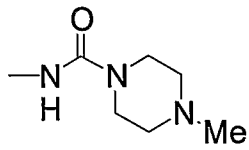
R^{B1} is

a C_{1-6} alkylamino group which may be substituted with 1 to 3 hydroxyl groups or a 4-C_{1-6} alkylpiperazin-1-yl-carbonyl group, or a 4-C_{1-6} alkylpiperazin-1-yl group.

12. The C-phenyl glycitol compound according to embodiment 11 or a pharmaceutically acceptable salt thereof or a hydrate thereof, wherein,

Y is a C_{1-6} alkylene group,

Z is $-CONHR^{A1}$ or $-NHC(=NH)NH_2$, or



where

R^{A1} is a C_{1-6} alkyl group substituted with 1 to 3 substituents selected from the group consisting of a hydroxyl group, an amino group and a carbamonyl group.

13. The C-phenyl glycitol compound according to embodiment 11 or a pharmaceutically acceptable salt thereof or a hydrate thereof, wherein

Y is a C_{1-6} alkylene group, and

Z is $-CONHR^{A1}$

where R^{A1} is a C_{1-6} alkyl group substituted with 1 to 3 substituents selected from the group consisting of a hydroxyl group, an amino group and a carbamonyl group.

14. The C-phenyl glycitol compound according to embodiment 11 or a pharmaceutically acceptable salt thereof or a hydrate thereof, wherein

Y is a C_{1-6} alkylene group, and

Z is $-NHC(=NH)NH_2$.

15. The C-phenyl glycitol compound according to embodiment 11 or a pharmaceutically acceptable salt thereof or a hydrate thereof, wherein

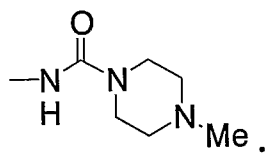
Y is a C_{1-6} alkylene group, and

Z is $-NHCOR^{B1}$ (where R^{B1} is a C_{1-6} alkylamino group substituted with 1 to 3 hydroxyl groups or a 4-C_{1-6} alkylpiperazin-1-yl-carbonyl group, or a 4-C_{1-6} alkylpiperazin-1-yl group).

16. The C-phenyl glycitol compound according to embodiment 11 or a pharmaceutically acceptable salt thereof or a hydrate thereof, wherein

Y is a C_{1-6} alkylene group, and

Z is represented by



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17. A pharmaceutical preparation, which comprises the C-phenyl glycitol compound according to any one of embodiments 1 to 16 or a pharmaceutically acceptable salt thereof or a hydrate thereof as an active ingredient.

18. The pharmaceutical preparation according to embodiment 17, which is an inhibitor of a sodium dependent glucose cotransporter 1 (SGLT1) activity and a sodium dependent glucose cotransporter 2 (SGLT2) activity.

19. The pharmaceutical preparation according to embodiment 17, which is a prophylactic or therapeutic agent for diabetes.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The terms used in the present invention will be defined as follows.

The term of "a C_{1-6} alkyl group" refers to a linear or branched alkyl group having 1 to 6 carbon atoms. Examples thereof may include a methyl group, an ethyl group, an n-propyl group, an isopropyl group, an n-butyl group, an isobutyl group, a tert-butyl group, a sec-butyl group, an n-pentyl group, a tert-pentyl group, an n-hexyl group and an isohexyl group.

The term of "a C_{1-6} alkoxy group" refers to a linear or branched alkoxy group having 1 to 6 carbon atoms. Of them, a C_{1-4} alkoxy group is preferable. Examples of the C_{1-4} alkoxy group may include a methoxy group, an ethoxy group, a propoxy group, an isopropoxy group, an n-butoxy group, an isobutoxy group and a tert-butoxy group.

The term of "a halogen atom" refers to a fluorine atom, a chlorine atom, a bromine atom or an iodine atom.

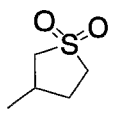
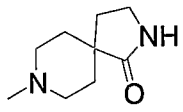
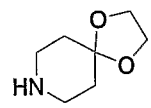
The term of "a C_{1-6} alkylene group" refers to a bivalent group formed by removing a hydrogen atom from a carbon atom of a C_{1-6} alkyl group. Examples of the linear alkylene group may include a methylene group, an ethylene group, a trimethylene group, a tetramethylene group, a pentamethylene group and a hexamethylene group.

The term of "a C_{2-6} alkenylene group" refers to a bivalent group formed by removing a hydrogen atom from a carbon atom of a C_{2-6} alkenyl group. Examples of the linear alkenylene may include a vinylene (ethenylene) group, a propenylene group, a butenylene group, a pentenylene group and a hexenylene group.

The term of "a C_{1-6} alkyl group substituted with 1 to 3 substituents selected from the group consisting of a hydroxyl group, an amino group and a carbamoyl group" refers to a linear or branched C_{1-6} alkyl group in which 1 to 3 hydrogen atom(s) of a C_{1-6} alkyl group is (are) replaced with at least one member selected from the group consisting of a hydroxyl group, an amino group and a carbamoyl group. Examples thereof may include a hydroxymethyl group, a hydroxyethyl group, a 2-hydroxy-1,1-dimethylethyl group, a 1,3-dihydroxy-2-methyl propan-2-yl group, a 1,3-dihydroxy-2-hydroxymethylpropan-2-yl group, a carbamoylmethyl group and a 2-carbamoylethyl group.

The term of "a C_{3-12} cycloalkyl group" refers to a cyclic alkyl group having 3 to 12 carbon atoms and includes monocyclic, dicyclic and spiro-hydrocarbons. Examples of the monocyclic hydrocarbon may include a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl group and a cyclooctyl group. Examples of the dicyclic hydrocarbon may include an adamantyl group, a bicyclo[2.2.1]heptyl group and a bicyclo[2.2.2]heptyl group. Examples of the spiro-hydrocarbon may include a spiro[3.4]octyl group and a spiro[4.5] decanyl group.

The term of "a 3 to 12-membered heterocycloalkyl group which contains one to three ring-constituting atom(s) selected from the group consisting of O, N, NR^{10}, S, SO_2 and CO" refers to the above-defined C_{3-12} cycloalkyl group in which 1 to 3 methylene groups or methine groups are replaced with atom(s) selected from the group consisting of O, N, NR^{10}, S, SO_2 and CO. Examples thereof may include an oxanyl group, a 2-oxooxanyl group, a 1,3-dioxanyl group, a pyrrolidinyl group, a piperidino group, a 2-piperidyl group, a 4-piperidyl group, a piperazinyl group, a morpholino group, a thiomorpholino group, a quinuclidinyl group, a decahydroisoquinolinyl group, a decahydroquinolinyl group,

The term of "a 5 to 13-membered heteroaryl group that may be partially saturated which contains one to three ring-constituting atom(s) selected from group consisting of O, N, NR^{10}, S, SO_2 and CO" refers to a 5 to 13-membered unsaturated monocyclic, dicyclic or tricyclic heterocyclic ring, and may include a furyl group, an imidazolyl group, a thienyl group, a pyridyl group, a benzothienyl group, a 2,3-dihydro-benzofuranyl group, a 2,3-dihydro-1H-benzo[de]isoquinolinyl group, a 2,3-dihydro-1H-indolyl group, a 2,3-dihydro-1H-isoindolyl group and a 2,3,4,9-tetrahydro-1H-b-carbolynyl group.

The term of "a C_{6-13} ary group which may be partially saturated" refers to an unsaturated monocyclic, dicyclic or

tricyclic hydrocarbon ring having 6 to 13 carbon atoms. Examples thereof may include a phenyl group, a naphthyl group, a fluorenyl group, a 1,2,3,4-tetrahydronaphthyl group, an indanyl group.

The term of "a 5 to 6-membered heterocycloalkyl group which R^{B1} and R^{B2} together with the nitrogen atom to which they are attached form and which may contain as another ring-constituting atom, an oxygen atom, a nitrogen atom or a sulfur atom" may include a piperidino group, a piperazino group, a morpholino group, a thiomorpholino group.

The term of "a phenyl C_{1-6} alkyl group" refers to a linear or branched C_{1-6} alkyl group which is substituted with a phenyl group. Examples thereof may include a benzyl group and a phenylethyl group.

The term of "a C_{2-6} alkoxycarbonyl group" has a structure composed of a linear or branched C_{1-5} alkoxy group and a carbonyl group and is preferably a C_{2-5} alkoxycarbonyl group. Examples thereof may include a methoxycarbonyl group, an ethoxycarbonyl group, a propoxycarbonyl group, an isopropoxycarbonyl group, an n-butoxycarbonyl group and a t-butoxycarbonyl group.

The term of "a C_{1-6} alkylthio group" has a structure composed of a linear or branched C_{1-6} alkyl group and a single thio group (-S-) and is preferably a C_{1-4} alkylthio group. Examples of the C_{1-6} alkylthio group include a methylthio group, an ethylthio group and a propylthio group.

The term of "a C_{1-6} alkylamino group" has a structure composed of a linear or branched C_{1-6} alkyl group and an

amino group. Examples thereof may include a methylamino group and an ethylamino group.

The term of "a di-C_{1-6} alkylamino group" has a structure composed of two linear or branched C_{1-6} alkyl groups and an amino group. Examples thereof may include a dimethylamino group and a diethylamino group.

The term of "a C_{2-6} acyl group" refers to a linear or branched aliphatic acyl group which contains 2 to 6 carbon atoms. Examples include an acetyl group, a propionyl group, a pivaloyl group, a butyryl group, an isobutyryl group and a valeryl group.

The term of "a C_{2-6} acylamino group" has a structure composed of a C_{2-6} acyl group and an amino group and is preferably an acetylamino group.

The term of "a C_{2-6} acyl(C_{1-6} alkyl)amino group" has a structure composed of a C_{2-6} acyl group, a C_{1-6} alkyl group and an amino group.

The term of "a di-C_{1-6} alkylaminocarbonyl group" has a structure composed of a di-C_{1-6} alkylamino group and a carbonyl group.

The term of "a C_{1-6} hydroxyalkyl group" refers to a C_{1-6} alkyl group which is substituted with at least one hydroxyl group. Examples include a hydroxymethyl group, a 1-hydroxyethyl group, a 2-hydroxyethyl group, a 3-hydroxypentyl group and a 2-hydroxy-2-methylbutyl group.

The term of "3 to 12 membered heterocycloalkyl group or 5 to 13 membered heteroaryl group which R^B and R^C together with the nitrogen atom to which they are attached

may form and each of which may contain 1 or 2 ring-constituting atom selected from O, N, NR^{11}, S, SO_2 and CO" refers to the 3 to 12 membered heterocycloalkyl group or 5 to 13 membered heteroaryl group as defined above.

The term of "a pharmaceutically acceptable salt" refers to a salt of an alkali metal, an alkaline earth metal, ammonium, alkyl ammonium, or a salt of a mineral acid or an organic acid. Examples thereof may include a sodium salt, a potassium salt, a calcium salt, an ammonium salt, an aluminum salt, a triethylammonium salt, an acetate salt, a propionate salt, a butyrate salt, a formate salt, a trifluoroacetate salt, a maleate salt, a tartrate salt, a citrate salt, a stearate salt, a succinate salt, an ethyl succinate salt, a lactobionate salt, a gluconate salt, a glucoheptonate salt, a benzoate salt, a methanesulfonate salt, an ethanesulfonate salt, a 2-hydroxyethanesulfonate salt, a benzenesulfonate salt, a p-toluenesulfonate salt, a lauryl sulfate salt, a malate salt, an aspartate salt, a glutamate salt, an adipate salt, a salt with cysteine, a salt with N-acetylcysteine, a hydrochloride salt, a hydrobromate salt, a phosphate salt, a sulfate salt, a hydroiodate salt, a nicotinate salt, an oxalate salt, a picrate salt, a thiocyanate salt, an undecanoate salt, a salt with an acrylate polymer and a salt with a carboxyvinyl polymer.

The term of "hydrate" refers to a pharmaceutically acceptable hydrate of the compound of the invention or a salt thereof. The compound of the invention or a salt

thereof absorbs moisture when exposed to the air or recrystallized, with the result that it optionally has hygroscopic water or becomes a hydrate. Such a hydrate may be included in the hydrate in the present invention.

Some compounds of the invention and intermediates thereof thereof which have a chiral center may be present in the form of a diastereomer or an enantiomer. Furthermore, some compounds of the invention and intermediates may be present as a keto-enol tautomer. Moreover, some compounds of the invention and intermediates thereof may be present as a geometric isomer (E, Z form). Therefore, isomers and mixtures thereof mentioned above are all included in the compound of the invention and an intermediate thereof.

In particular, in a compound represented by Formula (I), the steric configuration of the hydroxyl group at the 4-position of the glucose moiety is either an R-form or an S-form, which is indicated by a broken line.

Preferable examples of the compound of the invention will be described below.

In Formula (I), preferable substitution positions of R^1 and R^2 are those as shown in Formula (II).

R^1 is preferably a hydrogen atom, a hydroxyl group, a C_{1-4} alkyl group and a C_{1-4} alkoxy group, more preferably, a hydroxyl group and a C_{1-4} alkoxy group, and further preferably, a hydroxyl group and a methoxy group.

R^2 is preferably a hydroxyl group, a C_{1-6} alkyl group

and a halogen atom, more preferably, a C_{1-4} alkyl group and a halogen atom, and further preferably, a methyl group and a chlorine atom.

In Formula (I) or (II), R^3 is preferably a hydrogen atom, a C_{1-4} alkyl group and a halogen atom, more preferably, a hydrogen atom, a methyl group and a fluorine atom, and most preferably, a hydrogen atom. When R^3 is other than a hydrogen atom, a preferable substitution position is the ortho position relative to the benzyl moiety in Formula (I) or (II).

In Formula (I) or (II), Y may be preferably a C_{1-4} alkylene group, $-O-(CH_2)_2-$ or a C_{2-4} alkenylene group, more preferably, a C_{1-3} alkylene group, or $-O-(CH_2)_2-$, and further preferably, a C_{1-3} alkylene group. When Z is $-NHCON(R^B)R^C$, Y is most preferably $-(CH_2)_2-$.

In Formula (I) or (II) where Z is $-NHCON(R^B)R^C$, R^B and R^C are preferablely the following (i) to (v) embodiments.

(i) R^C is a hydrogen atom and R^B is a C_{1-6} alkyl group that may be substituted with 1, 2 or 3 substituents selected from Group A.

Group A herein is a halogen atom, a hydroxyl group, a C_{1-6} alkoxy group which may be substituted with a hydroxyl group(s), a C_{2-6} alkoxycarbonyl group, a carbamoyl group, a di-C_{1-6} alkylamino group, a C_{2-6} acylamino group, a C_{1-6} alkylthio group which may be substituted with a hydroxyl group(s), a phenoxy group, a furyl group, a thienyl group, a benzothienyl group, a 2,3-dihydro-benzofuranyl group, a phenyl group that may be substituted with 1 to 3

substituents selected from Group B (Group B consists of a hydroxyl group, a halogen atom, a C_{1-6} alkoxy group, a C_{1-6} alkyl group which may be substituted with a hydroxyl group(s), a C_{1-6} alkylthio group, a phenylthio group which may be substituted with a hydroxyl group(s) or a C_{1-6} hydroxyalkyl group(s), and a piperidino group which may be substituted with a hydroxyl group(s) or a C_{1-6} hydroxyalkyl group(s)),

a C_{3-12} cycloalkyl group which may be substituted with 1 to 3 subtitituents selected from the group consisting of a hydroxyl group and a C_{1-6} hydroxyalkyl group,

a 3 to 12-membered heterocycloalkyl group which contains one to three ring-constituting atom(s) selected from the group consisting of O, N, S and NR^{10} (R^{10} is a hydrogen atom, a C_{1-6} alkyl group, a phenyl-C_{1-6} alkyl group or a C_{2-6} alkoxycarbonyl group) and may be substituted with 1 to 3 subtitituents selected from the group consisting of a hydroxyl group and a C_{1-6} hydroxyalkyl group, and

4-C_{1-6} alkylpiperadine-1-ylcarbonyl group.

More preferable examples of Group A include a hydroxyl group, a methoxy group, an ethoxy group, a C_{3-6} cycloalkyl group (a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group), which may be substituted with 1 to 3 subtitituents selected from the group consisting of a hydroxyl group and a C_{1-6} hydroxyalkyl group, a methoxycarbonyl group, a carbamoyl group, a

dimethylamino group, an acetylamino group, a methylthio group, a phenyl group, a 4-hydroxyphenyl group, a 4-methylthiophenyl group, a 3-methoxyphenyl group, a 3,4-dimethoxyphenyl group, a phenoxy group, a 2-(hydroxymethylphenylthio)phenyl group, a thienyl group, a furyl group, a benzothienyl group, a 2,3-dihydro-benzofuranyl group, a 4-methylpiperazin-1-yl carbonyl group, a 1-pyrrolidinyl group, a 1,3-dioxane-2-yl group, a 2-oxyanyl group and a piperidino group.

(ii) R^C is a hydrogen atom and R^B is a C_{3-12} cycloalkyl group that may be substituted with 1, 2 or 3 substituents selected from a hydroxyl group and a C_{1-6} hydroxyalkyl group.

The C_{3-12} cycloalkyl group herein is preferably a cyclopropyl group, a cyclobutyl group, a cyclopentyl group, a cyclohexyl group, a cycloheptyl, a cyclooctyl group, an adamantyl group, a bicyclo[2.2.1]heptyl group, a bicyclo[2.2.2]heptyl group, more preferably, a cyclopentyl group, a cyclohexyl group, a bicyclo[2.2.1]heptyl group or an adamantyl group.

(iii) R^C is a hydrogen atom and R^B is a "3 to 12-membered heterocycloalkyl group or a 5 to 13-membered heteroaryl group that may be partially saturated, each of which contains one to three ring-constituting atom(s) selected from the group consisting of O, N, S and NR^{10} (R^{10} is a hydrogen atom, a C_{1-6} alkyl group, a phenyl-C_{1-6} alkyl group or a C_{2-6} alkoxycarbonyl group)", preferably a

pyrrolidinyl group, a piperidyl group and a quinuclidinyl group, more preferably, a pyrrolidinyl group, a 4-piperidyl group in which a nitrogen atom is substituted with a phenyl C_{1-6} alkyl group or a C_{2-6} alkoxycarbonyl group, and further preferably, a 3-(1-benzyl)pyrrolidinyl group, a 4-(1-benzyl)piperidyl group, or a 4-(1-ethoxycarbonyl)piperidyl group.

(iv) R^C is a hydrogen atom and R^B is a 6 to 13-membered aryl group which may be substituted with 1 or 2 substituents selected from a hydroxyl group, and a C_{1-6} alkyl group, a phenyl-C_{1-6} alkyl group and a C_{1-6} alkylsulfonyl group, each of which may be substituted with a hydroxyl group(s) or a 6 to 13-membered aryl group which is partially saturated which may be substituted with 1 or 2 hydroxyl group(s). Herein the "6 to 13-membered aryl group" includes a phenyl group or a naphthyl group, and the "6 to 13-membered aryl group which is partially saturated" includes a fluorenyl group, a 1,2,3,4-tetrahydro-naphthyl group or an indanyl group.
Of them, a preferable R^B is a phenyl group substituted with a phenyl-C_{1-6} alkyl group, or a fluorenyl group, a 1,2,3,4-tetrahydro-naphthyl group or an indanyl group, each of which which may be substituted with 1 or 2 hydroxyl group(s).

(v) As another preferable example,
R^B and R^C together with the nitrogen atom to which they are

attached form a 3 to 12 membered heterocycloalkyl group which may contain 1 or 2 ring-constituting atom selected from O, N, S and NR^{11} (R^{11} is a C_{1-6} alkyl group that may be substituted with a di-C_{1-6} alkylamino group), and which may be substituted with 1 or 2 substituents selected from a pyrrolidinyl group and a C_{1-6} alkyl group that may be substituted with a substituent selected from the group consisting of a hydroxyl group and a pyrrolidin-1-yl group.

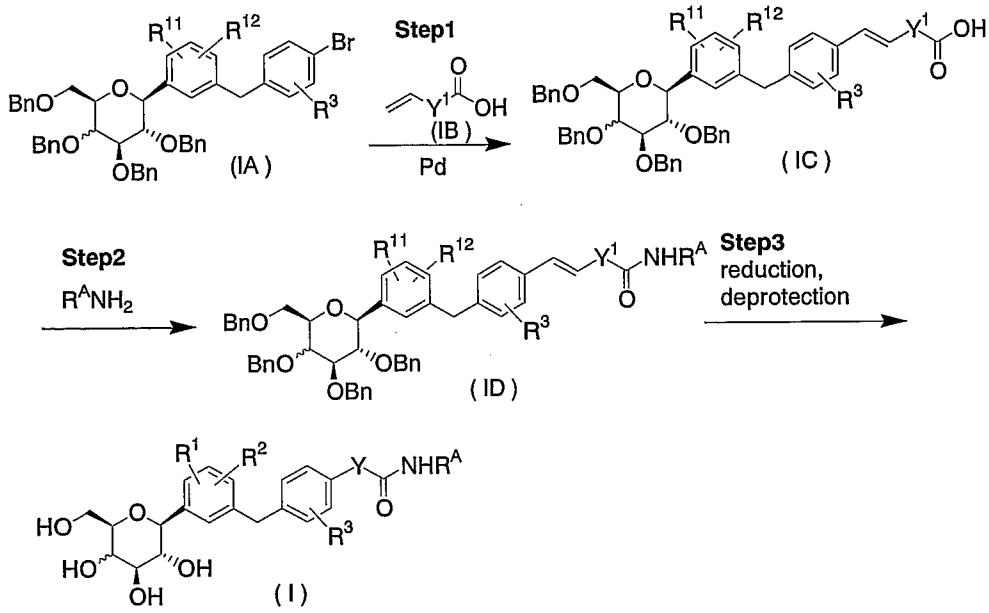
Examples of the (v) embodiment include a piperidino group, a 4-methylpiperidino group, a 2-decahydroisoquinolinyl group, a thiomorpholino group, a 4-[2-(pyrrolidin-1-yl)ethyl]piperidino group, a 4-(pyrrolidin-1-yl)piperidino group, a 3-decahydroquinolinyl group, a 4-[2-(N,N-dimethylamino)ethyl]piperazin-1-yl group and a 3-hydroxymethylpiperidino group.

In Formula (I) or (II) where Z is $-CONHR^A$, R^A is prebefably a C_{1-6} alkyl group substituted with 1 to 3 substituents selected from the group consisiting of a hydroxyl group and a carbamoyl group.

Processes for producing the compound (I) of the invention will be described below.

Production Process 1

The compound (I) of the invention where Y is a C_{2-6} alkylene group or a C_{2-6} alkenylene group and Z is $-CONHR^A$ can be synthesized by the following method.



Note that, in the formula, R^{11} and R^{12} may be the same or different and represent a hydrogen atom, a benzyloxy group, a methoxymethoxy group, a $(C_{1-6}$ alkyl$)_3SiO$-, a C_{1-6} alkyl group, a C_{1-6} alkoxy group or halogen atom, Y^1 represents a single bond or a C_{1-4} alkylene group, and other reference symbols are the same as defined above.

(1) Step 1 (Heck reaction)

A compound (IA) and olefin acetic acid (IB) are allowed to react in the presence of a palladium catalyst, a phosphine ligand and an appropriate base in accordance with the Heck reaction to synthesize a compound (IC). Examples of the palladium catalyst used herein may include palladium acetate, tetrakis(triphenylphosphine)palladium, dibenzylideneacetonepalladium, bis(triphenylphosphine)palladium chloride and palladium-activated carbon. Examples of the phosphine ligand may include triphenylphosphine and tris(2-

methylphenyl)phosphine. Examples of the base include triethylamine, N,N-diisopropylethylamine, potassium carbonate, calcium carbonate, cesium carbonate and potassium t-butoxide. Examples of the solvent to be used in this reaction may include acetonitrile, toluene and tetrahydrofuran. The reaction temperature is from 0°C to a reflux temperature; however, a microwave is optionally used.

(2) Step 2 (Conversion to amide group)

The compound (IC) is subjected to dehydration condensation with an amine (R^ANH_2) to obtain a compound (ID). Preferable examples of the solvent to be used in this reaction include chloroform, dichloromethane and N,N-dimethylformamide. Preferable examples of the dehydration condensation agent include N,N'-dicyclohexylcarbodiimide (DCC), N-ethyl-N'-(3-dimethylaminopropyl) carbodiimide hydrochloride (WSC), 1,1'-carbonyldiimidazole (CDI) and WSC/1-hydroxybenzotriazol monohydrate. The reaction temperature herein is 0°C to 60°C.

(3) Step 3 (Reduction and Deprotection)

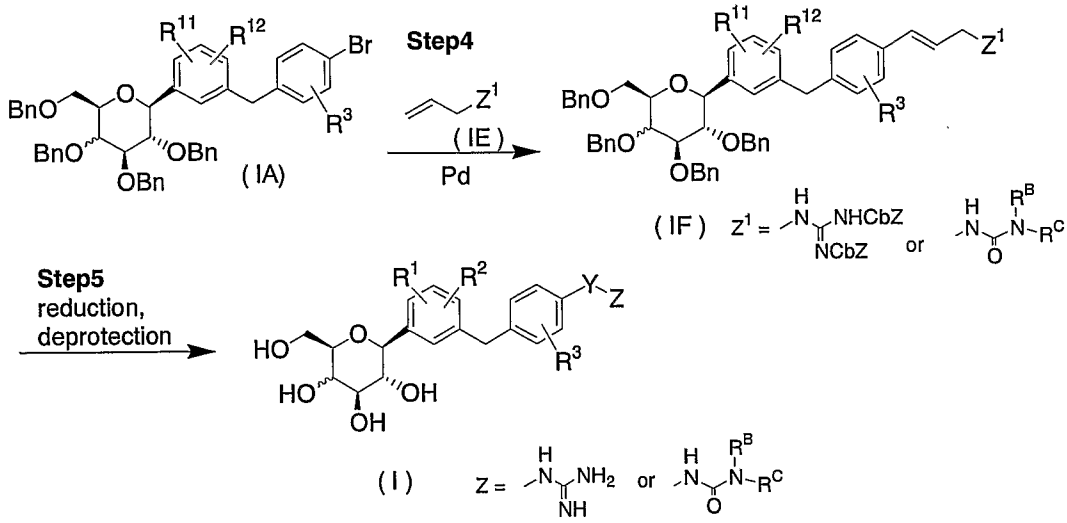
Catalytic hydrogenation of the compound (ID) obtained above is performed by using a catalyst such as palladium activated carbon, palladium hydroxide or a platinum-palladium activated carbon under a hydrogen atmosphere. In this way, reduction of the olefin and debenzylation can be simultaneously performed to obtain the compound (I) of the invention. Of the catalysts mentioned above, palladium activated carbon or palladium hydroxide is preferable. Examples of the solvent to be used in this reaction may

include methanol, ethanol, 2-propanol, ethyl acetate, acetic acid and solvent mixtures thereof. The reaction temperature is from room temperature to a reflux temperature; however, room temperature is preferable.

Alternatively, in the debenzylation, a Lewis acid such as $BF_3 \cdot Et_2O$, BCl_3, $BCl_3 \cdot Me_2S$, BBr_3, $AlCl_3$, CF_3COOH, or TfOH can be used. Examples of the solvent to be used in this reaction may include chloroform, dichloromethane, acetonitrile, diethyl ether, tetrahydrofuran, dimethylsulfide and anisole. Of them, it is preferable to use CF_3COOH, TfOH or ethanedithiol in dimethylsulfide. The reaction temperature is preferably -78°C to 40°C.

Production Process 2

The compound (I) of the invention where Y is a C_{2-6} alkylene group or a C_{2-6} alkenylene group and Z is $-NHC(=NH)NH_2$ or $-NHCON(R^B)R^C$ can be synthesized by the following method. Note that, in the formula, Z^1 represents a guanidino group protected with a benzyloxycarbonyl group or $-NHCON(R^B)R^C$, and other reference symbols are the same as defined above.



(4) Step 4 (Heck reaction)

The Compound (IA) and an allylamine (IE) can be converted into a compound (IF) by the Heck reaction described in Step 1.

(5) Step 5 (Reduction and Deprotection)

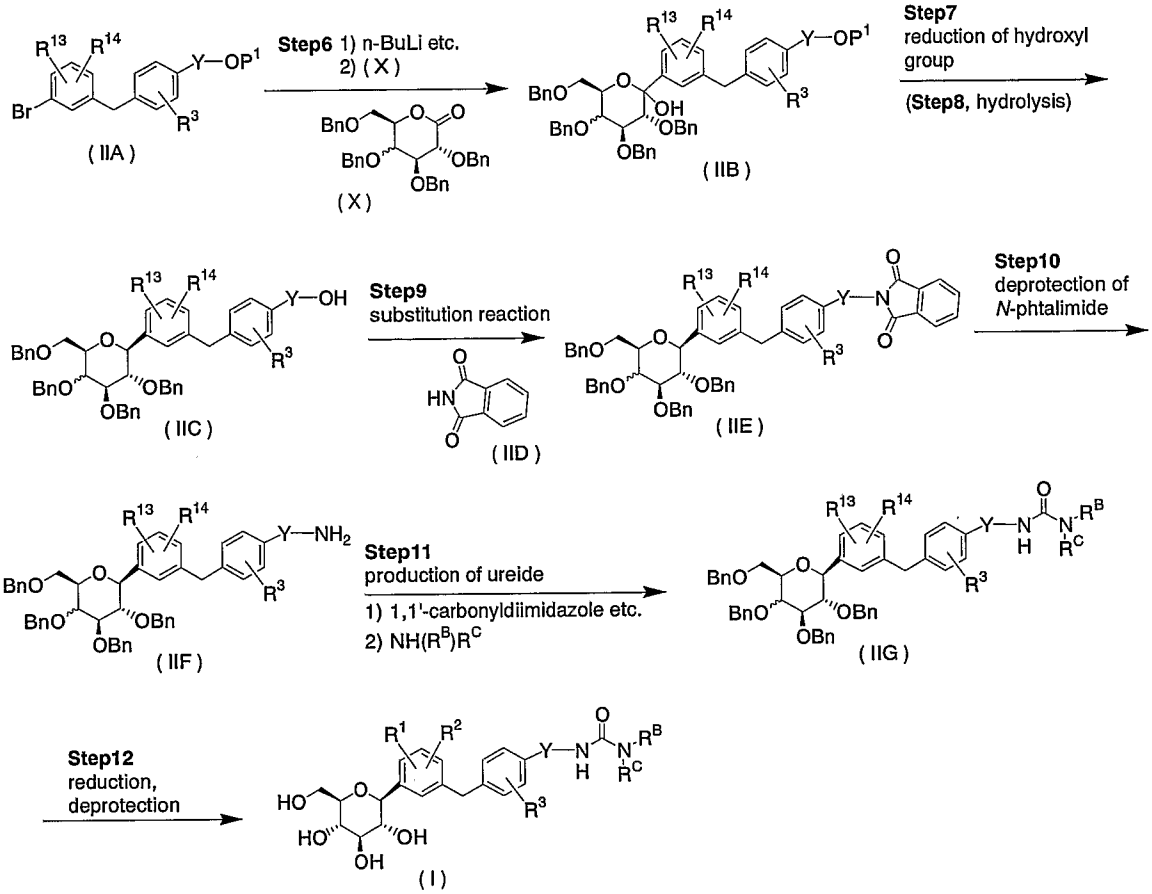
The Compound (IF) obtained above is subjected to deprotection with catalytic hydrogenation or a Lewis acid as described in Step 3 to obtain the compound (I) of the invention where Z is a guanidino group or an ureido group.

Production Process 3

The compound (I) of the invention where Y is a single bond or a C_{1-6} alkylene group and Z is $-NHCON(R^B)R^C$ can be synthesized also by the following method.

Note that, in the formula, R^{13} and R^{14} may be the same or different and represent a hydrogen atom, a benzyloxy group, a C_{1-6} alkyl group, C_{1-6} alkoxy group or a halogen atom, P^1 represents a methoxymethyl group, tetrahydropyranyl group or a $(C_{1-6}$ alkyl$)_3Si-$, and other reference symbols are the same as defined above. The

intermediate (IIB) or the intermediate (IIF) wherein Y is a single bond or a C_{1-6} alkylene group can be also synthesized in the same manner as in Steps 34 to 36 below.



(6) Step 6

An aryllithium reagent can be prepared from an intermediate compound (IIA) (which can be synthesized in accordance with the disclosure of WO06/073197) by use of an organic metal reagent such as n-butyllithium, sec-butyllithium or tert-butyllithium. This is condensed with δ-lactone (X) to obtain a compound (IIB). Examples of the solvent to be used in this reaction may include tetrahydrofuran, diethyl ether and toluene. The reaction temperature is -80°C to room temperature, and

preferably, -78°C to -25°C.

(7) Step 7 (Reduction of hydroxyl group)

The compound (IIB) and Et_3SiH, i-Pr_3SiH, t-$BuMe_2SiH$ or Ph_2SiHCl are allowed to react in the presence of a Lewis acid to reduce a hydroxyl group. Examples of the Lewis acid to be used in this reaction may include $BF_3 \cdot Et_2O$, CF_3COOH, $InCl_3$, $TiCl_4$, TMSOTf, p-toluenesulfonic acid and methanesulfonic acid. Examples of the solvent include chloroform, dichloromethane, toluene, tetrahydrofuran, acetonitrile and solvent mixtures thereof, preferably, a solvent mixture containing acetonitrile such as acetonitrile/chloroform, acetonitrile/dichloromethane, acetonitrile/tetrahydrofuran and acetonitrile/tetrahydrofuran/toluene. The reaction temperature herein is -60°C to 25°C, and preferably, -30°C to 25°C.

In the reaction mentioned above, a protecting group P^1 is optionally removed depending upon the reaction temperature. In this case, a compound (IIC) from which P^1 is removed is optionally obtained.

(8) Step 8 (Hydrolysis)

Following Step 7, a protecting group P^1 can be removed by use of hydrochloric acid, sulfuric acid, p-toluenesulfonic acid monohydrate, pyridinium p-toluenesulfonic acid, hydrogen fluoride pyridine, n-Bu_4NF or the like. Examples of the solvent to be used in this reaction may include methanol, ethanol, 2-propanol, chloroform, dichloromethane, toluene, tetrahydrofuran,

acetonitrile, diisopropyl ether, water and solvent mixtures thereof. When P^1 is a methoxymethyl group, a preferable acid is hydrochloric acid and a preferable solvent is methanol, diisopropyl ether, toluene or tetrahydrofuran, and more preferably, a solvent mixture containing methanol such as methanol/toluene, methanol/diisopropyl ether or methanol/toluene/diisopropyl ether. The reaction temperature differs depending upon the solvent or acid to be used; however, it is 0°C to 100°C, and preferably, 0°C to 80°C.

(9) Step 9 (Substitution reaction)

The compound (IIC) wherer Y is a C_{1-6}alkylene group and a reagent (IID) are condensed in the conditions of the Mitsunobu reaction (Org. Reactions, Vol. 42, p. 335) using an azo reagent and a phosphine to obtain the compound (IIE).

Examples of the phosphine that can be used in the Mitsunobu reaction may include triphenylphosphine, tri-n-butylphosphine, tri-t-butylphosphine, tritolylphosphine and diphenyl-2-pyridylphosphine. Of them, triphenylphosphine and diphenyl-2-pyridyl phosphine are preferable, and triphenylphosphine is more preferable. Examples of the azo reagent include diethyl azodicarboxylate, diisopropyl azodicarboxylate, di-tert-butyl azodicarboxylate, 1,1'-azobis(N,N-dimethylformamide) and 1,1'-(azodicarbonyl)dipiperidine. Of them, diethyl azodicarboxylate and diisopropyl azodicarboxylate are preferable. Examples of the solvent include tetrahydrofuran, dioxane, toluene, methylene chloride,

chloroform, acetonitrile, ethyl acetate, dimethylsulfoxide and N,N-dimethylformamide, and preferably tetrahydrofuran and toluene. The reaction temperature is preferably from -20°C to room temperature.

(10) Step 10 (removing phthalimide)

The compound (IIE) and a hydrazine hydrate or methylhydrazine are allowed to react in an appropriate solvent to obtain an amine (IIF). Preferable examples of the solvent used herein include methanol, ethanol, tetrahydrofuran, water and solvent mixtures thereof. The reaction temperature is from room temperature to 100°C, and preferably from room temperature to 60°C.

The obtained amine (IIF) can be purified by forming a salt with a mineral acid or an organic acid as mentioned above. Examples of the salt preferably used for purification include a hydrochloride, methanesulfonate, ethanesulfonate, 2-hydroxyethanesulfonate, benzenesulfonate and p-toluenesulfonate, and more preferably, benzenesulfonate.

(11) Step 11 (Formation of Urea)

The compound (IIF) can be synthesized with a carbonylation reagent and $NH(R^B)R^C$ to synthesize a compound (IIG). Examples of the carbonylation reagent include 1,1'-carbonyldiimidazole, p-nitrophenylchloroformate and triphosgene. In this reaction, a base such as triethylamine, pyridine or N-methylmorpholine may be preferably used. Examples of the solvent to be used herein include chloroform, dichloromethane, tetrahydrofuran,

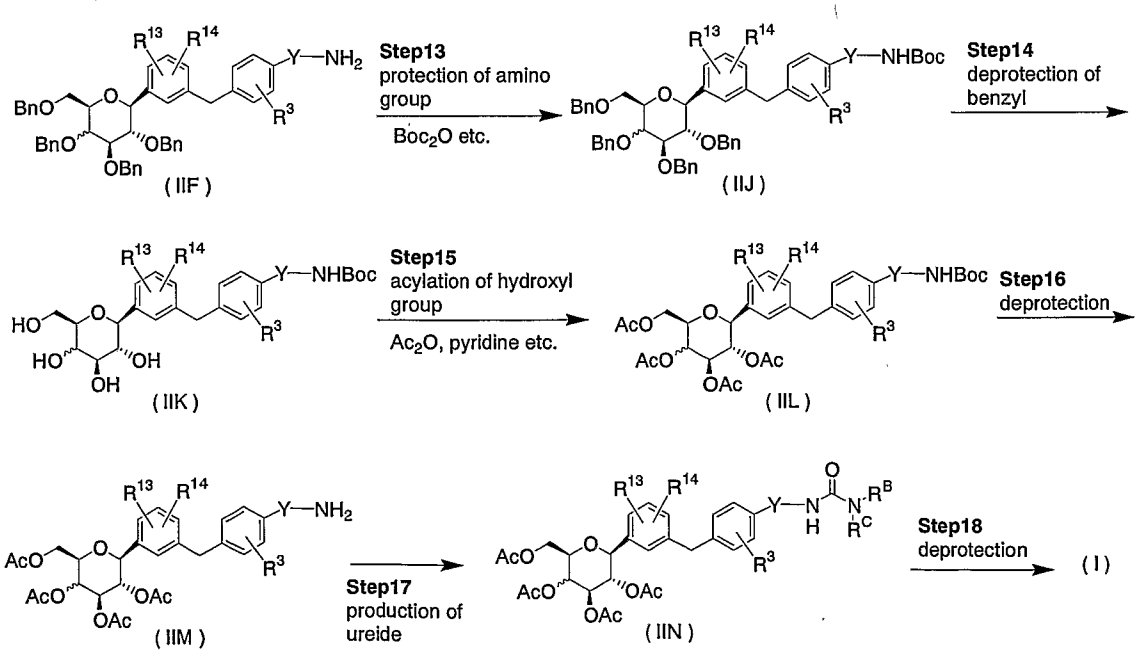
N,N-dimethylformamide and dimethylsulfoxide. A mixture solvent thereof may be used. Preferable examples of the mixture solvent include chloroform/N,N-dimethylformamide, chloroform/dimethylsulfoxide and tetrahydrofuran/N,N-dimethylformamide. The reaction temperature is room temperature to 80°C. When the reaction rate is low, the temperature may be raised.

(12) Step 12 (Deprotection)

The compound (IIG) obtained above is subjected to deprotection with catalytic hydrogenation or a Lewis acid as described in Step 3 to obtain the compound (I) of the invention where Z is an ureido group.

Production Process 4

The compound (I) of the invention where Z is an ureido group can be synthesized after the hydroxyl group of the glucose moiety is protected with an acyl group such as an acetyl group.



(13) Step 13 (Protection of amino group)

The amino group of a compound (IIF) is protected with a protecting group resistant to catalytic hydrogenation, for example, tert-butylcarbonate (Boc) or 9-fluolenylmethylcarbonate (Fmoc). The compound (IIF), $(Boc)_2O$ and Fmoc-Cl are allowed to react in a solvent such as chloroform, dichloromethane, tetrahydrofuran or dioxane in the presence of an appropriate base to obtain a compound (IIJ). Preferable examples of the base include sodium carbonate, sodium hydrogen carbonate, potassium carbonate, potassium hydroxide, sodium hydride, pyridine and triethylamine.

(14) Step 14 (Deprotection of benzyl)

Deprotection of the compound (IIJ) obtained above is performed by catalytic hydrogenation as described in Step 3 to obtain a compound (IIK).

(15) Step 15 (Acylation)

The hydroxyl group of the compound (IIK) is protected by an acyl group such as an acetyl group to obtain a compound (IIL). The compound (IIK), acetic anhydride, pivaloyl chloride, benzoyl chloride etc. are allowed to react in a solvent in the presence of an appropriate base to obtain a compound (IIL). Examples of the solvent to be used in the reaction include chloroform, dichloromethane, dioxane, ethyl acetate, tetrahydrofuran and N,N-dimethylformamide. Preferable examples of the base include triethylamine, collidine and pyridine. As the catalyst, 4-dimethylaminopyridine may be used. The reaction

temperature is preferably 0°C to room temperature.

(16) Step 16 (Deprotection)

From the compound (IIL), the protecting group of the amino group is removed to obtain a compound (IIM). In the case of a Boc group, the compound (IIL) is allowed to react with a hydrochloric acid or trifluoroacetic acid in a solvent such as dichloromethane, chloroform or dioxane or without using a solvent. In the case of an Fmoc group, the compound (IIL) is allowed to react preferably with piperidine or morpholine in N,N-dimethylformamide.

(17) Step 17 (Formation of urea)

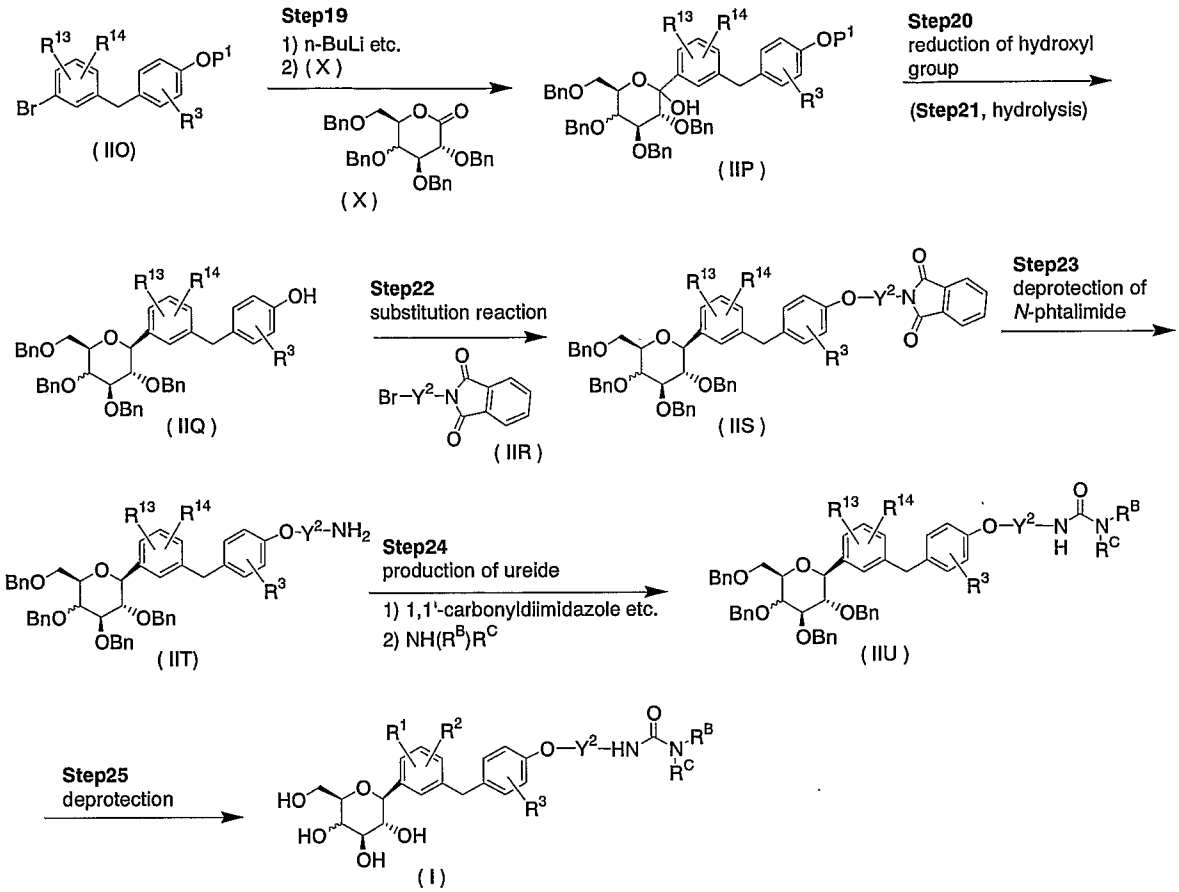
A compound (IIN) can be synthesized from the compound (IIM) in the same process as in Step 11 above.

(18) Step 18 (Deprotection)

The acyl group of the compound (IIN) is removed in basic conditions to obtain the compound (I) of the invention. Examples of the base may include sodium methoxide, sodium hydroxide, lithium hydroxide, potassium carbonate, cesium carbonate and triethylamine. Preferable examples of the solvent include methanol, ethanol, and hydrous methanol.

Production Process 5

The compound (I) of the invention where Y is -O-(CH_2)n- and Z is -NHCON(R^B)R^C can be synthesized by the following method. Note that, in the scheme, Y^2 is a C_{2-4} alkylene group, and other reference symbols are the same as defined above.



(19) Step 19

A compound (IIP) can be prepared in the same manner as in Production process 3, step 6 from a compound (IIO) (which can be synthesized in accordance with the disclosure of WO06/073197) and a compound (X).

(20-21) Step 20 and Step 21

The compound (IIP) is subjected to reduction of a hydroxyl group and removing a protecting group P^1 in the same manner as in Production process 3, steps 7 and 8 to obtain a compound (IIQ).

(22) Step 22

The compound (IIQ) and a reagent (IIR) are allowed to react in the presence of a base to obtain a compound (IIS).

Preferable examples of the base used herein may include sodium carbonate, potassium carbonate, potassium hydroxide, sodium hydride, pyridine, triethylamine. Examples of the solvent to be used in this reaction may include dioxane, acetonitrile, toluene, dimethoxyethane, tetrahydrofuran, N,N-dimethylformamide. The reaction temperature herein is preferably 20°C to 100°C.

(23) Step 23

The compound (IIS) is subjected to removing a phthalimide group in the same manner as in Production process 3, step 10 to obtain a compound (IIT).

(24) Step 24

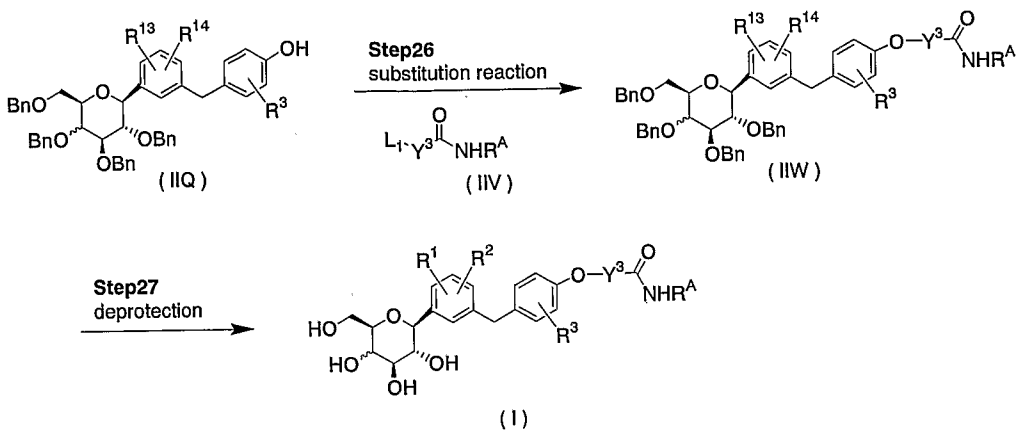
A compound (IIU) can be prepared in the same manner as in Production process 3, step 11 from the compound (IIT).

(25) Step 25

The compound (IIU) is subjected to deprotection in the same manner as in Production process 3, step 12 to obtain the compound (I) of the invention where Y is -O-(CH_2)n-.

Production Process 6

The compound (I) of the invention where Y is -O-(CH_2)n- and Z is $-CONHR^A$ can be synthesized also by the following method. Note that, in the scheme, Y^3 is a C_{1-4} alkylene group, L_1 is a leaving group such as a halogen atom, $MeSO_2O$-, etc. and other reference symbols are the same as defined above.



(IIQ) (IIV) (IIW) (I)

(26) Step 26

The compound (IIQ) and a compound (IIV) are allowed to react in the presence of a base to obtain a compound (IIW). Preferable examples of the base used herein may include sodium hydride, sodium carbonate, potassium carbonate, cesium carbonate, n-butyl lithium. Preferable examples of the solvent to be used in this reaction may include tetrahydrofuran, diethylether, N,N-dimethylformamide, acetone, DMSO. The reaction temperature herein is 0°C to 60°C.

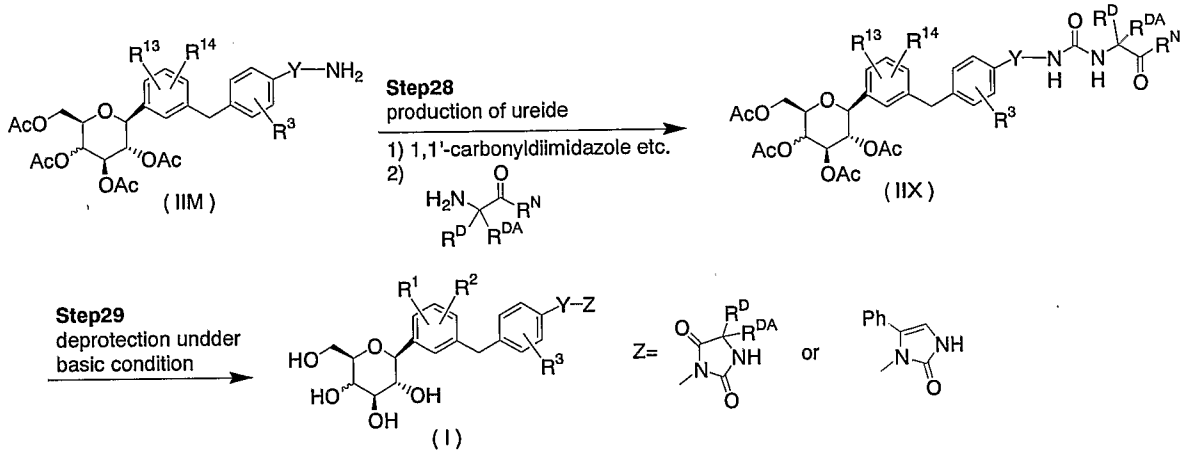
(27) Step 27

The compound (IIW) is subjected to deprotection in the same manner as in Production process 3, step 12 to obtain the compound (I) of the invention where Y is -O-(CH_2)n- and Z is -$CONHR^A$.

Production Process 7

The compound (I) of the invention where Z is a heterocycloalkyl group such as 2,4-dioxoimidazolindinyl can be synthesized by the following method. Note that, in the scheme, R^N is a hydroxyl group, a C_{1-4} alkoxy group or a

phenyl group, and other reference symbols are the same as defined above.



(28) Step 28

The compound (IIM) is condensed with R^AR^BNH, for example, an amine having a carbonyl group at the α-position such as 2-aminoacetophenone or an amino acid in the same manner in Production process 4, step 17 to obtain a compound (IIX).

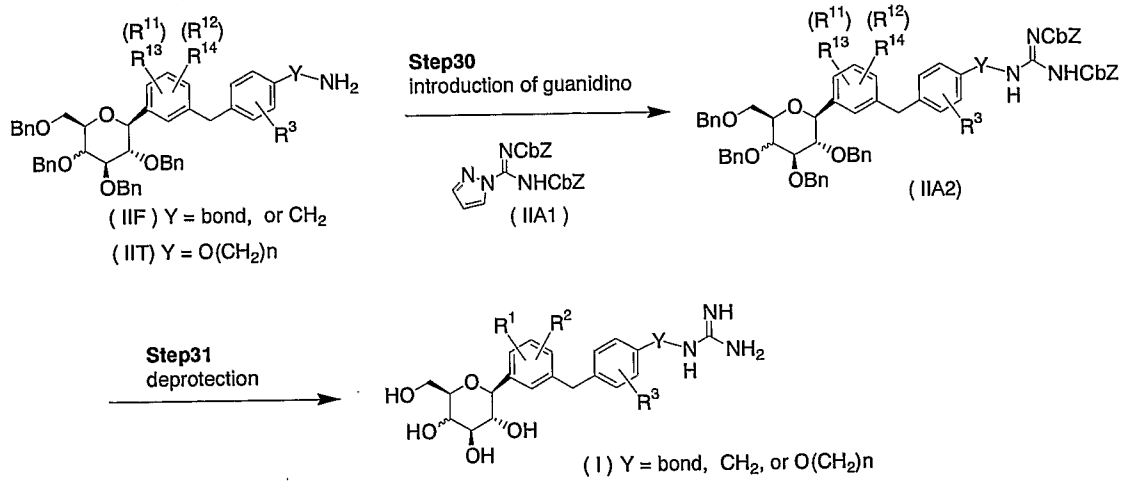
(29) Step 29 (Deprotection under a base condition)

The Compound (IIX) is subjected to deprotection of the acetyl group and at the same time, an intramolecular cyclization of the side chain of the compound (IIX) to obtain the compound (I) of the invention where Z is the above-defined heterocycloalkyl group. The base used herein is preferably sodium methoxide, and the solvent is preferably methanol or ethanol.

Production Process 8

The compound (I) of the invention where Y is a single bond, a methylene group or -O-(CH_2)n- and Z is -NHC(=NH)NH_2

can be synthesized by the following method.



(30) Step 30 (Introduction of a guanidino group)

The compound (IIF) or the compound (IIT) obtained in step 38 or step 23 is reacted with a reagent (IIA1) to obtain a compound (IIA2). Preferable Examples of the solvent to be used in this reaction may include tetrahydrofuran, N,N-dimethylformamide, methanol, ethanol, isopropanol, ethyl acetate, toluene. The reaction temperature herein is from a room temperature to a reflux temperature.

(31) Step 31

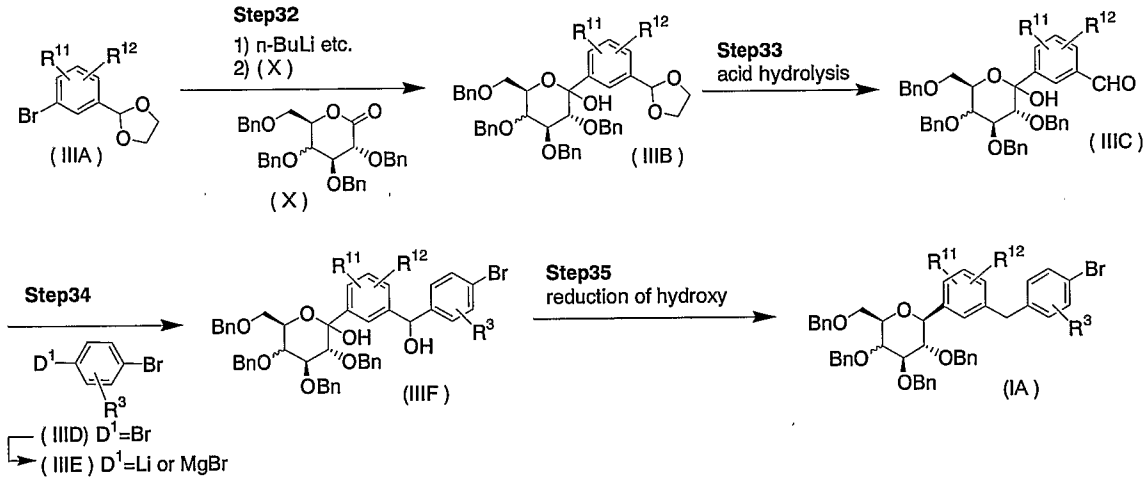
The compound (IIA2) is subjected to deprotection in the same manner as in Production process 3, step 12 to obtain the compound (I) of the invention where Y is a single bond, a methylene group or -O-(CH_2)n- and Z is -NHC(=NH)NH_2.

Production processes of intermediates for producing

the compound (I) will be described below.

Process for producing intermediate (IA)

A process for producing an intermediate (IA) required for production of the compound (I) of the invention will be described below. Note that D^1 represents Li or MgBr. Other reference symbols are the same as defined above.



(32) Step 32

An aryllithium reagent can be prepared from an intermediate compound (IIIA) (which can be synthesized in accordance with the disclosure of WO06/073197) by use of an organic metal reagent such as n-butyllithium, sec-butyllithium or tert-butyllithium. The aryllithium reagent is condensed with δ-lactone (X) to obtain a compound (IIIB). Examples of the solvent to be used in this reaction may include tetrahydrofuran, diethyl ether and toluene. The reaction temperature is -80°C to room temperature, and preferably, -78°C to -25°C.

(33) Step 33 (Acid hydrolysis)

The acetal group of the compound (IIIB) is hydrolyzed by using hydrochloric acid and p-toluenesulfonic acid monohydrate, etc. to produce a compound (IIIC). Preferable examples of the solvent to be used herein include tetrahydrofuran, ethanol, methanol, water and mixtures thereof. The reaction temperature is from 4°C to room temperature, and preferably, room temperature. The reaction time varies depending upon the reaction temperature and it is from 1 hour to 24 hours.

(34) Step 34

A monolithium reagent compound (IIIE) can be produced from a compound (IIID) by use of one equivalent of n-butyllithium, sec-butyllithium or tert-butyllithium to the compound (IIID). Examples of the solvent to be used in this reaction may include tetrahydrofuran, diethyl ether and toluene. The reaction temperature is from -80°C to room temperature, and preferably, -78°C to -25°C. The reaction time is preferably from 5 minutes to 30 minutes. Furthermore, Grignard reagent (IIIE) can be also produced by using one equivalent of metal magnesium. Examples of the solvent to be used in this reaction may include tetrahydrofuran, diethyl ether and diglym. Subsequently, the reagent (IIIE) is added to the intermediate compound (IIIC) to form a compound (IIIF). The reaction temperature is from -80°C to room temperature, and preferably, -78°C to -25°C.

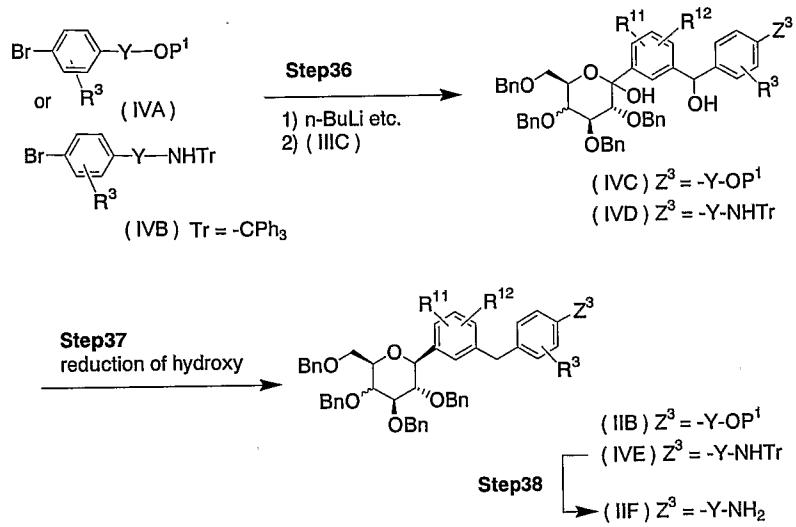
(35) Step 35 (Reduction of hydroxyl group)

The compound (IA) can be synthesized from the compound

(IIIF) in the same manner as in Step 7 above.

Process for producing intermediate (IIB) or (IIF)

The intermediate (IIB) or (IIF) described above can be synthesized in another pathway as shown below



(36) Step 36

A compound (IVC) or (IVD) can be synthesized from a compound (IVA) or (IVB) in the same manner as in Step 34 above.

(37) Step 37 (Reduction of hydroxyl group)

The intermediate (IIB) can be synthesized from the compound (IVC) in the same manner as in Step 7 above. Furthermore, an intermediate (IVE) can be synthesized from the compound (IVD).

(38) Step 38

The compound (IVE) is treated with hydrochloric acid or trifluoroacetic acid in chloroform or dichloromethane to remove a protecting group, trityl (Tr) of the amino group,

with the result that an intermediate (IIF) can be synthesized. The reaction temperature herein is preferably 0°C to room temperature.

The compound of the invention inhibits both activities of SGLT1 and SGLT2 which are involved in a glucose absorption suppression action from the digestive tract and urine glucose excretion action, respectively. Through inhibition of SGLT1, the compound of the invention can treat diabetes and improve IGT to thereby prevent the progression of diabetes. Through inhibition of SGLT2, the compound of the invention can prevent sugar reabsorption and remove excess sugar form the body to thereby treat diabetes. Thus, the compound of the present invention can correct hyperglycemia without the exhaustion of the pancreatic β cells due to glucose toxicity, and improve insulin resistance.

Therefore, the compound of the present invention can be used as an SGLT1 inhibitor and an SGLT2 inhibitor. The present invention provides a pharmaceutical preparation for preventing or treating diseases or conditions which can be ameliorated by inhibition of SGLT1 and SGLT2 activities, e.g. diabetes, diabetes-related diseases, and diabetes complications.

The term "diabetes" used herein include Type 1 diabetes and Type 2 diabetes and other types of diabetes with specific etiology.

Examples of the term "diabetes-related diseases" used

herein may include obesity, hyperinsulinemia, abonormal carbohydrate metabolism, hyperlipidemia, hypercholesterolemia, hypertriglyceridemia, abonormal lipid metabolism, hypertension, congestive heart failure, edema, hyperuricemia and gout.

The term "diabetes complications" used herein can be classified into acute complications and chronic complications.

Examples of the term "acute complications" may include hyperglycemia (e.g., ketoacidosis) and infectious diseases (e.g., skin, soft tissue, biliary tract system, respiratory system and urinary tract infections).

Examples of the term "chronic complications" may include microangiopathy (e.g., nephropathy, retinopathy), arteriosclerosis (e.g., atherosclerosis, myocardial infarction, cerebral infarction, lower limb arterial occlusive disease), neuropathy (e.g., sensory nerves, motor nerves, autonomic nerves), foot gangrene, etc.

Examples of major complications include diabetic retinopathy, diabetic nephropathy and diabetic neuropathy.

The compound of the invention may also be used in combination with any medicinal drug (hereinafter, simply referred to as "a concomitant drug") such as diabetes drugs, diabetic complication drugs, antilipidemic drugs, antihypertensive drugs, anti-obesity drugs, diuretic drugs and antithrombotic drugs, which depends on a different mechanism of action other than inhibition of SGLT1 and SGLT2 activities. When combined with other drugs, the

compound of the present invention can be expected to produce as enhancement of the effect and a reduction of the dose of the compound. In this case, administration time of the compound of the invention and the concomitant drug are not limited. They may be administered to the subject at the same or different times. Furthermore, the compound of the invention and the concomitant drug may be administered as two independent preparations each containing an active ingredient or as a single preparation containing both of them as an active ingredient. The dose of the concomitant drug may be appropriately chosen based on the dosage clinically used. The blend ratio of the compound of the invention to the concomitant drug may be appropriately chosen in consideration of the subject to be administered, administration route, target disease, symptom and combination. For example, when the subject to be administered is a human, the concomitant drug may be used in an amount of 0.01 to 100 parts by mass relative to 1 part by mass of the compound of the invention.

Note that examples of the diabetes durgs may include insulin preparations (e.g., preparations of animal insulin extracted from bovine and swine pancreas; preparations of human insulin genetically synthesized by using *Escherichia coli* or yeast; insulin zinc; protamine insulin zinc, an insulin fragment or a derivative (e.g., INS-1), an oral insulin preparation), an insulin resistivity improver (e.g., pioglitazone or a salt thereof (preferably a hydrochloride), rosiglitazone or a salt thereof (preferably a maleate),

rivoglitazone (CS-011)(R-119702), sipoglitazar (TAK-654), metaglidasen (MBX-102), naveglitazar (LY-519818), MX-6054, balaglitazone (NN-2344), T-131 (AMG131), a PPARγ agonist, a PPARγ antagonist, a PPARγ/α dual agonist, an α-glucocidase inhibitor (e.g., voglibose, acarbose, miglitol, emiglitate), a biguanide agent (e.g., phenformin, metformin, buformin or salts thereof (e.g., a hydrochloride, fumarate, succinate)), an insulin secretagogue (sulfonylurea (e.g., tolbutamide, glibenclamide, gliclazide, chlorpropamide, tolazamide, acetohexamide, glyclopyramide, glimepiride, glipizide, glybuzole), repaglinide, senaglinide, nateglinide, mitiglinide or calcium salt hydrates thereof), a GPR40 agonist, a GPR40 antagonist, a GLP-1 receptor agonist (e.g., GLP-1, GLP-1MR agent, liraglutide (NN-2211), exenatide (AC-2993)(exendin-4), exenatide LAR, BIM-51077, Aib (8, 35) hGLP-1(7, 37)NH2, CJC-1131, AVE0010, GSK-716155), an amylin agonist (e.g., pramlintide), a phosphothyrosinphosphatase inhibitor (e.g., sodium vanadate), a dipeptidylpeptidase IV inhibitor (e.g., compounds described in WO02/038541, NVP-DPP-278, PT-100, P32/98, vildagliptin (LAF-237), P93/01, sitagliptin (MK-431), saxagliptin (BMS-477118), SYR-322, MP-513, T-6666, GRC-8200), a β3 agonist (e.g., AJ-9677, AZ40140), a glyconeogenesis inhibitor (e.g., a glycogen phosphorylase inhibitor, a glucose-6-phosphatase inhibitor, a glucagon antagonist, a fructose-1,6-bisphosphatase inhibitor), an SGLT (sodium-glucose cotransporter) inhibitor (e.g., compounds described in WO04/014931, WO04/089967, WO06/073197, T-1095, sergliflozin (GSK-869682),

GSK-189075, KGT-1251, KGT-1681, KGA-2727, BMS-512148, AVE2268, SAR7226), a 11β-hydroxysteroid dehydrogenase inhibitor (e.g., compounds described in WO06051662, BVT-3498, INCB13739), a GPR119 agonist (e.g., PSN-632408, APD-668), adiponectin or an agonist thereof, an IKK inhibitor (e.g., AS-2868), an AMPK activator, a leptin resistivity improver, a somatostatin receptor agonist, a glucokinase activator (e.g., Ro-28-1675), a pancreatic lipase inhibitor (e.g., orlistat, ATL-962), and a DGAT-1 inhibitor.

Examples of the diabetic complication drugs may include an aldose reductase inhibitor (e.g., tolrestat, epalrestat, zenarestat, zopolrestat, minalrestat, fidarestat, CT-112), a neurotrophy factor and an augmentation drug thereof (e.g., NGF, NT-3, BDNF, a neurotrophin production/secretagogue), a nervous system reactivation promoter (e.g., Y-128), a PKC inhibitor (e.g., ruboxistaurin mesylate; LY-333531), an AGE inhibitor (e.g., ALT946, pimagedine, piratoxathin, N-phenacylthiazolium bromide (ALT766), ALT-711, EXO-226, pyridorin, pyridoxamine), an active oxygen erasing agent (e.g., thioctic acid), a cerebral vasodilating agent (e.g., tiapride, mexiletine), a somatostatin receptor agonist (e.g., BIM 23190) and an apoptosis signal regulating kinase-1(ASK-1) inhibitor.

Examples of the anti-hyperlipidemia drugs may include statin compounds (e.g., pravastatin, simvastatin, lovastatin, atorvastatin, fluvastatin, itavastatin, rosuvastatin, pitavastatin or salts thereof (e.g., sodium

salt, calcium salt)), a squalene synthase inhibitor (e.g., TAK-475), a fibrate compound (e.g., bezafibrate, clofibrate, symfibrate, clinofibrate), an ACAT inhibitor (e.g., avasimibe, eflucimibe), an anion exchange resin (e.g., cholestyramine), probucol, a nicotinic drug (e.g., nicomol, niceritrol), ethyl icosapentate, a vegetable sterol (e.g., soysterol, γ-oryzanol), a CETP inhibitor (e.g., torcetrapib, JTT-705, JTT-302, FM-VP4) and a cholesterol absorption depressant (e.g., ezetimibe).

Examples of the antihypertensive agent may include an angiotensin-converting enzyme inhibitor (e.g., captopril, enalapril, delapril), an angiotensin II antagonist (e.g., candesartan, cilexetil, losartan, eprosartan, valsartan, telmisartan, irbesartan, tasosartan, azilsartan (TAK-536)), a calcium antagonist (e.g., manidipine, nifedipine, amlodipine, efonidipine, nicardipine), a potassium channel opening agent (e.g., levcromakalim, L-27152, A L0 671, NIP-121), and clonidine.

Examples of the anti-obesity drugs may include a central anti-obesity drug (example, dexfenfluramine, fenfluramine, phentermine, sibutramine, amfepramone, dexamphetamine, mazindol, phenylpropanolamine, clobenzorex), an MCH receptor antagonist (e.g., compounds described in WO06/035967, SB-568849; SNAP-7941, T-226296); a neuropeptide Y antagonist (e.g., CP-422935), a cannabinoid receptor antagonist (e.g., rimonabant (SR-141716), SR-147778); a ghrelin antagonist, a 11β-hydroxysteroid dehydrogenase inhibitor (e.g., BVT-3498, INCB13739)), a

pancreatic lipase inhibitor (e.g., orlistat, ATL-962), a DGAT-1 inhibitor, a β3 agonist (e.g., AJ-9677, AZ40140), a peptidergic anorexiant drug (e.g., leptin, CNTF (ciliary body neurotrophy factor)), a cholecystokinin agonist (e.g., lintitript, FPL-15849) and a feeding deterrent (e.g., P-57).

Examples of the diuretic drugs may include a xanthine derivative (e.g., sodium theobromine salicylate, calcium theobromine salicylate), a thiazide preparation (e.g., ethiazide, cyclopenthiazide, trichlormethiazide, hydrochlorothiazide, hydroflumethiazide, bentylhydrochlorothiazide, penflutiazide, polythiazide, methyclothiazide), an anti-aldosterone preparation (e.g., spironolactone, triamteren), a carbonic anhydrase inhibitor (e.g., acetazolamide), a chlorobenzene sulfoneamide preparation (e.g., chlorthalidone, mefruside, indapamide), azosemide, isosorbide, ethacrynic acid, piretanide, bumetanide and furosemide.

Examples of the antithrombotic drugs may include heparin (e.g., heparin sodium, heparin calcium, dalteparin sodium, AVE-5026), warfarin (e.g., warfarin potassium), an anti-thrombin agent (e.g., argatroban, ximelagatran, dabigatran, odiparcil, lepirudin, bivalirudin, desirudin, ART-123, idraparinux, SR-123781, AZD-0837, MCC-977, TGN-255, TGN-167, RWJ-58436, LB-30870, MPC-0920, pegmusirudin, Org-426751), a thrombolytic agent (e.g., urokinase, tisokinase, alteplase, nateplase, monteplase, pamiteplase), a platelet aggregation inhibitor (e.g., ticlepidine hydrochloride, cilostazol, ethyl icosapentate, beraprost sodium,

sarpogrelate hydrochloride), a factor Xa inhibitor (e.g., fondaparinux, BAY-59-7939, DU-176b, YM-150, SR-126517, apixaban, razaxaban, LY-517717, MLN-102, octaparine, otamixaban, EMD-503982, TC-10, CS-3030, AVE-3247, GSK-813893, KFA-1982), a plasma carboxy peptidase B inhibitor (or known as an active-form thrombin-activatable fibrinolysis inhibitor [TAFIa]) such as AZD-9684, EF-6265, MN-462.

The pharmaceutical preparation of the present invention can be administered systemically or topically via oral route or parenteral (e.g., intrarectal, subcutaneous, intramuscular, intravenous, percutaneous) route.

For use as a pharmaceutical preparation, the compound of the present invention may be formulated into any desired dosage form selected from solid compositions, liquid compositions and other compositions, as appropriate for the intended purpose. The pharmaceutical preparation of the present invention can be prepared by blending the compound of the present invention with pharmaceutically acceptable carrier(s). More specifically, the compound of the present invention may be supplemented with commonly used excipients, extenders, binders, disintegrating agents, coating agents, sugar-coating agents, pH regulators, solubilizers, aqueous or non-aqueous solvents and so on, and then formulated using standard techniques into tablets, pills, capsules, granules, powders, solutions, emulsions, suspensions, injections, etc.

Also, the compound of the present invention may be

modified to form an inclusion compound with, e.g., α-, β- or γ-cyclodextrin or methylated cyclodextrin before being formulated.

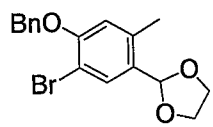
The dose of the compound of present invention will vary depending on the disease or symptom to be treated, body weight, age, gender, and administration route, but it falls 0.1 to 1000 mg/kg weight/day/adult, preferably 0.1 to 200 mg/kg weight/day/adult, and more preferably, 0.1 to 10 mg/kg weight/day/adult. This can be administered once to several times per day.

REFERENCE EXAMPLES

Preparation of intermediates required to prepare the compounds of the present invention will be illustrated below with reference to the following Reference Examples.

Reference Example 1

Preparation of 2-[4-(benzyloxy)-5-bromo-2-methylphenyl]-1,3-dioxolane



(1) Preparation of 1-[4-(benzyloxy)-2-methylphenyl]ethanone

To an N,N-dimethylformamide solution (20 mL) of 4'-hydroxy-2'-methylacetophenone (3.06 g, 20 mmol) were added potassium carbonate (3.66 g, 26.4 mmol), benzyl bromide (2.7 mL, 22.4 mmol), and n-Bu_4NI (0.75 g, 2.03 mmol), and the mixture was stirred for 14 hours at room temperature. To the reaction solution cooled in ice were

added a saturated solution of ammonium chloride, subsequently water and ethyl acetate to separate an organic layer. The organic layer was washed with 20% aqueous solution of sodium thiosulfate and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (hexane:ethyl acetate = 8:1 to 6:1) to obtain the title compound (5.05 g, quant.) as a colorless powder.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.55 (s, 3H) 2.57 (s, 3H) 5.11 (s, 2H) 6.78-6.86 (m, 2H) 7.30-7.47 (m, 5H) 7.75 (dd, *J*=7.93, 1.09 Hz, 1H).

(2) Preparation of 4-(benzyloxy)-5-bromo-2-methylbenzoic acid

To an acetone solution (300 mL) of 1-[4-(benzyloxy)-2-methylphenyl]ethanone (20.9 g, 87.1 mmol) were added an aqueous solution (100 mL) of NaBr (9.86 g, 95.9 mmol), water (200 mL), and Oxone (registered trade mark, oxone-persulfuric acid chloride, from Aldrich) (59.0 g, 95.9 mmol), and the mixture was stirred 2.5 hours at room temperature. To the reaction solution cooled in ice were added an aqueous solution (50 mL) of sodium sulfite (20 g), subsequently water and ethyl acetate to separate an organic layer. The organic layer was washed with 20% aqueous solution of sodium sulfite and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure

to obtain a mixture (27.2 g) of 1-[4-(benzyloxy)-5-bromo-2-methylphenyl]ethanone and 1-[4-(benzyloxy)-3-bromo-2-methylphenyl]ethanone. To the mixture were added a 5% aqueous solution (300 mL, 255 mol) of sodium hypochlorite and an aqueous solution (10 mL) of potassium hydroxide (4.80 g, 85.3 mmol), stirred at 120°C for an hour, cooled to room temperature, and precipitated insoluble matter was filtered. To this insoluble matter was added 2 M hydrochloric acid, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with 2 M hydrochloric acid and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was washed with methanol to obtain the title compound (16.6 g, 59%, 2 steps) as a colorless powder.

1H NMR (300 MHz, DMSO-D6) δ ppm 2.45-2.57 (m, 3H) 5.28 (s, 2H) 7.18 (s, 1H) 7.31-7.54 (m, 5H) 8.03 (s, 1H) 12.83 (brs, 1H).

ESI m/z = 319(M-H), 321(M+2-H).

(3) Preparation of 2-[4-(benzyloxy)-5-bromo-2-methylphenyl]-1,3-dioxolane

To a suspension of 4-(benzyloxy)-5-bromo-2-methylbenzoic acid (16.6 g, 51.7 mmol) in chloroform (80 mL) were added oxalyl chloride (5 mL, 56.9 mmol) and N,N-dimethylformamide (6 drops), and the mixture was stirred for an hour at room temperature. And then the reaction solution was concentrated to obtain 4-(benzyloxy)-5-bromo-2-methylbenzoyl chloride. Then to a chloroform

suspension (60 mL) of N,O-dimethylhydroxylamine hydrochloride (5.55 g, 56.9 mmol) and triethylamine (15 mL, 103 mmol) cooled in ice was added dropwise a chloroform solution (60 mL) of 4-(benzyloxy)-5-bromo-2-methylbenzoyl chloride, and the mixture was stirred for an hour at room temperature. To the reaction solution cooled in ice were added water and chloroform to separate an organic layer. The organic layer was washed with a saturated sodium bicarbonate aqueous solution and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure to obtain 4-(benzyloxy)-5-bromo-N-methoxy-N-methylbenzamide. To a tetrahydrofuran solution (150 mL) of the 4-(benzyloxy)-5-bromo-N-methoxy-N-methylbenzamide was added at -10°C lithium aluminum hydroxide (1.96 g, 51.7 mmol), and the mixture was stirred for an hour at the same temperature. To the reaction solution were added 1 M hydrochloric acid, and then ethyl acetate to separate an organic layer. The organic layer was washed with 1 M hydrochloric acid, a saturated sodium bicarbonate aqueous solution and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure to obtain 4-(benzyloxy)-5-bromo-2-methylbenzaldehyde. To a toluene solution (120 mL) of the 4-(benzyloxy)-5-bromo-2-methylbenzaldehyde were added ethylene glycol (30 mL, 517 mmol) and p-toluenesulfonic acid monohydrate (0.50 g, 2.58 mmol), and heated to reflux for 1.5 hours with a Dean-Stark

apparatus. To the reaction solution was added ethyl acetate to separate an organic layer. The organic layer was washed with water, a saturated sodium bicarbonate aqueous solution and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (hexane:ethyl acetate = 5:1). In addition, the residue was further purified with NH type silica gel column chromatography (chloroform) to obtain the title compound (12.8 g, 71%, 3 steps) as a colorless powder. 1H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.34 (s, 3H) 3.92-4.19 (m, 4H) 5.15 (s, 2H) 5.87 (s, 1H) 6.74 (s, 1H) 7.27-7.51 (m, 5H) 7.72 (s, 1H).

Reference Example 1-2

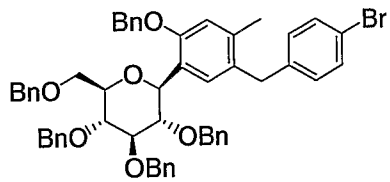
Preparation of 2-[4-(benzyloxy)-5-bromo-2-methylphenyl]-1,3-dioxolane

To a methanol suspension (3.75 mL) of 4-(benzyloxy)-2-methylbenzaldehyde (0.50 g, 2.21 mmol) cooled in ice was added pyridinium hydrobromide perbromide (1.06 g, 3.32 mmol), and the mixture was stirred for 30 minutes. The reaction mixture was stirred for 2.5 hours at room temperature. To the reaction solution were added 20% solution of Na_2SO_3, water and ethyl acetate. An organic layer was extracted with ethyl acetate. To the organic layer was added 1 M hydrochloric acid (20 mL), and the mixture was stirred for 5 minutes. The organic layer was separated, washed with a saturated sodium bicarbonate

aqueous solution and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure to obtain 1.03 g of a residue. To a toluene solution (7.0 mL) of the residue were added ethylene glycol (1.89 mL, 33.9 mmol) and pyridinium p-toluenesulfonate (43 mg, 0.170 mmol), and heated to reflux for 14 hours with a Dean-Stark apparatus. After the reaction solution was cooled, its organic layer was washed with a saturated sodium bicarbonate aqueous solution and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was recrystallized from hexane/ethyl acetate (10:1) to obtain the title compound (748 mg, 63%).

Reference Example 2

Preparation of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-(4-bromobenzyl)-4-methylphenyl]-D-glucitol



(1) Preparation of 2,3,4,6-tetra-O-benzyl-1-C-[2-(benzyloxy)-5-(1,3-dioxolan-2-yl)-4-methylphenyl]-D-glucopyranose

To a tetrahydrofuran solution (36 mL) of 2-[4-(benzyloxy)-5-bromo-2-methylphenyl]-1,3-dioxolane (5.82 g, 16.6 mmol) was added dropwise under nitrogen atmosphere at -78°C a 2.67 M n-butyllithium solution in hexane (6.40 mL,

16.6 mmol), and the mixture was stirred for 30 minutes at the same temperature. Then a tetrahydrofuran solution (18 mL) of 2,3,4,6-tetra-O-benzyl-D-glucono-1,5-lactone (8.16 g, 15.1 mmol) was added dropwise, and the mixture was stirred for 20 minutes at the same temperature. To the reaction solution was added a saturated aqueous solution of ammonium chloride, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of ammonium chloride and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (hexane:ethyl acetate = 3:1 to 2:1) to obtain the title compound (10.7 g, 87%) as a yellow oily compound.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.40 (s, 3H) 3.65-3.86 (m, 3H) 3.89-4.21 (m, 8H) 4.45-4.69 (m, 4H) 4.78-5.03 (m, 5H) 5.91 (s, 1H) 6.71 (s, 1H) 6.97 (dd, *J*=7.31, 2.18 Hz, 2H) 7.10-7.37 (m, 23H) 7.81 (s, 1H).

(2) Preparation of 2,3,4,6-tetra-O-benzyl-1-C-[2-(benzyloxy)-5-formyl-4-methylphenyl]-D-glucopyranose

To a tetrahydrofuran solution (80 mL) of 2,3,4,6-tetra-O-benzyl-1-C-[2-(benzyloxy)-5-(1,3-dioxolan-2-yl)-4-methylphenyl]-D-glucopyranose (10.6 g, 13.0 mmol) cooled in ice was added 6 M hydrochloric acid (80 mL), and the mixture was stirred for 14 hours at room temperature. To the reaction solution was added ice water, and the resulting mixture was extracted with ethyl acetate. The

organic layer was washed with a saturated sodium bicarbonate aqueous solution and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (hexane:ethyl acetate = 2:1) to obtain the title compound (10.2 g, quant.) as a yellow oily compound. 1H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.66 (s, 3H) 3.60-3.72 (m, 2H) 3.74-3.82 (m, 1H) 4.01 (t, *J*=9.09 Hz, 1H) 4.07-4.20 (m, 3H) 4.40-4.61 (m, 5H) 4.71-5.05 (m, 5H) 6.70 (s, 1H) 6.87 (d, *J*=6.68 Hz, 2H) 7.06-7.40 (m, 23H) 8.07 (s, 1H) 10.06 (s, 1H).

(3) Preparation of 2,3,4,6-tetra-O-benzyl-1-C-[2-(benzyloxy)-5-[(4-bromophenyl)(hydroxy)methyl]-4-methylphenyl]-D-glucopyranose

To a tetrahydrofuran solution (80 mL) of 1,4-dibromobenzene (6.20 g, 26.1 mmol) was added dropwise under nitrogen atmosphere at -78°C a 2.67 M n-butyllithium solution in hexane (10.5 mL, 26.1 mmol), and the mixture was stirred for 15 minutes at the same temperature. Then a tetrahydrofuran solution (20 mL) of 2,3,4,6-tetra-O-benzyl-1-C-[2-(benzyloxy)-5-formyl-4-methylphenyl]-D-glucopyranose (10.0 g, 13.0 mmol) was added dropwise, and the mixture was stirred for 30 minutes at the same temperature. To the reaction solution was added a saturated aqueous solution of ammonium chloride, and an organic layer was extracted with ethyl acetate. The organic layer was washed with brine, and dried with anhydrous magnesium sulfate. The drying

agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (hexane:ethyl acetate = 2:1). In addition, the residue was further purified with NH type silica gel column chromatography (hexane:ethyl acetate = 1:1) to obtain the yellow oily title compound (5.50 g, 46%) as a diastereomeric mixture.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.21 (s, 3H) 3.54-3.82 (m, 3H) 3.98-4.23 (m, 4H) 4.36-4.64 (m, 4H) 4.75-5.06 (m, 5H) 5.83-5.86 (m, 1H) 6.71 and 6.73 (each s, 1H) 6.89-7.44 (m, 29H) 7.67 and 7.71 (each s, 1H).

(4) Preparation of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-(4-bromobenzyl)-4-methylphenyl]-D-glucitol

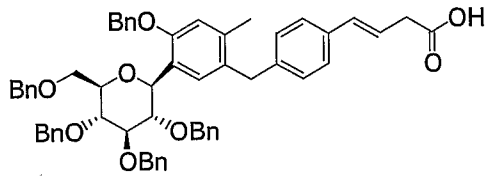
To an acetonitrile solution (60 mL) of 2,3,4,6-tetra-O-benzyl-1-C-[2-(benzyloxy)-5-[(4-bromophenyl)(hydroxy)methyl]-4-methylphenyl]-D-glucopyranose (5.50 g, 5.96 mmol) were added under nitrogen atmosphere at -10°C Et_3SiH (2.90 mL, 17.8 mmol) and $BF_3 \cdot Et_2O$ (1.90 mL, 14.9 mmol), and the mixture was stirred for 15 minutes at the same temperature and the mixture was stirred for 2.5 hours at room temperature. To the reaction solution cooled in ice was added a saturated sodium bicarbonate aqueous solution and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue

was purified with silica gel column chromatography (hexane:ethyl acetate = 15:1 to 10:1) to obtain the title compound (2.70 g, 51%) as a pale yellow oily compound.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.17 (s, 3H) 3.53-3.63 (m, 1H) 3.68-3.91 (m, 7H) 4.00 (d, *J*=11.04 Hz, 1H) 4.39-4.95 (m, 8H) 5.01 (s, 2H) 6.75 (s, 1H) 6.86-6.97 (m, 4H) 7.10-7.35 (m, 24H) 7.36-7.46 (m, 2H).

Reference Example 3

Preparation of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-[4-[(1E)-3-carboxyprop-1-en-1-yl]benzyl]-4-methylphenyl]-D-glucitol



To an acetonitrile solution (8.8 mL) of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-(4-bromobenzyl)-4-methylphenyl]-D-glucitol (780 mg, 0.876 mmol) were added vinyl acetate (184 mg, 2.14 mmol), palladium(II) acetate (20 mg, 0.0890 mmol), tri-O-tolylphosphine (54 mg, 0.177 mmol) and triethylamine (0.64 mL, 4.38 mmol), and reacted at 120°C for 20 minutes with microwave manufactured by Biotage. The reaction solution was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (hexane:ethyl acetate = 5:1, chloroform:methanol = 40:1) to obtain the title compound (681 mg, 87%) as an orange-yellow amorphous compound.

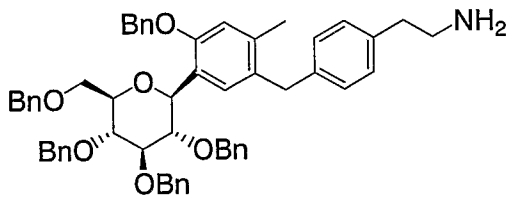
1H NMR (600 MHz, CHLOROFORM-D) δ ppm 2.17 (s, 3H) 3.25 (d,

J=5.50 Hz, 2H) 3.53-3.84 (m, 6H) 3.84-3.95 (m, 2H) 4.00 (d, J=10.55 Hz, 1H) 4.43 (d, J=10.55 Hz, 1H) 4.50 (d, J=11.92 Hz, 1H) 4.57-4.65 (m, 2H) 4.80-4.93 (m, 4H) 4.99 (s, 2H) 6.12-6.22 (m, 1H) 6.42 (d, J=15.59 Hz, 1H) 6.74 (s, 1H) 6.89-7.03 (m, 4H) 7.11-7.47 (m, 26H).

ESI m/z = 893(M-H).

Reference Example 4

Preparation of (1S)-1-[5-[4-(2-aminoethyl)benzyl]-2-(benzyloxy)-4-methylphenyl]-1,5-anhydro-2,3,4,6-tetra-O-benzyl-D-glucitol



(1) Preparation of 2,3,4,6-tetra-O-benzyl-1-C-[2-(benzyloxy)-5-[hydroxy[4-[2-(tritylamino)ethyl]phenyl]methyl]-4-methylphenyl]-D-glucopyranose

To a tetrahydrofuran solution (3 mL) of 2-(4-bromophenyl)-N-tritylethaneamine (0.814 g, 1.84 mmol) was added dropwise under nitrogen atmosphere at -78°C a 2.66 M hexane solution of n-butyllithium (0.69 mL, 1.84 mmol), and the mixture was stirred for 30 minutes at the same temperature. Then a tetrahydrofuran solution (3 mL) of 2,3,4,6-tetra-O-benzyl-1-C-[2-(benzyloxy)-5-formyl-4-methylphenyl]-D-glucopyranose (0.670 g, 0.876 mmol) was added dropwise, and the mixture was stirred for 30 minutes

at the same temperature. To the reaction solution was added water, and the resulting mixture was extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was purified with NH type silica gel column chromatography (chloroform) to obtain the title compound (0.634 g, 64%) as a yellow oily compound.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.12-2.22 (m, 3H) 2.30-2.43 (m, 2H) 2.65-2.76 (m, 2H) 3.64-3.84 (m, 3H) 3.99-4.22 (m, 4H) 4.42-4.65 (m, 5H) 4.75-5.04 (m, 5H) 5.83-5.91 (m, 1H) 6.67-6.72 (m, 1H) 6.88-7.43 (m, 44H).

(2) Preparation of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-4-methyl-5-[4-[2-(tritylamino)ethyl]benzyl]phenyl]-D-glucitol

To an acetonitrile solution (6 mL) of 2,3,4,6-tetra-O-benzyl-1-C-[2-(benzyloxy)-5-[hydroxy [4-[2-(tritylamino)ethyl]phenyl]methyl]-4-methylphenyl]-D-glucopyranose (0.638 g, 0.565 mmol) were added under nitrogen atmosphere at 0°C Et_3SiH (0.27 mL, 1.695 mmol) and $BF_3 \cdot Et_2O$ (1.58 mL, 1.24 mmol), and the mixture was stirred for 30 minutes at the same temperature. To the reaction solution cooled in ice was added a saturated sodium bicarbonate aqueous solution and the resulting mixture was extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica

gel column chromatography (hexane:ethyl acetate = 9:1) to obtain the title compound (0.402 g, 59%) as a pale yellow oily compound.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.16 (s, 3H) 2.36 (t, *J*=6.84 Hz, 2H) 2.68 (t, *J*=6.84 Hz, 2H) 3.52-3.65 (m, 1H) 3.67-3.92 (m, 7H) 4.00 (d, *J*=10.88 Hz, 1H) 4.37-4.67 (m, 5H) 4.78-5.06 (m, 5H) 6.73 (s, 1H) 6.83-7.01 (m, 5H) 7.05-7.45 (m, 40H).

(3) Preparation of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[5-[4-(2-aminoethyl)benzyl]-2-(benzyloxy)-4-methylphenyl]-D-glucitol

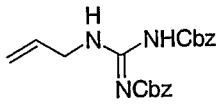
To a chloroform solution of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-4-methyl-5-[4-[2-(tritylamino)ethyl]benzyl]phenyl]-D-glucitol (0.402 g, 0.336 mmol) was added at room temperature trifluoroacetate (0.5 mL), and the mixture was stirred for 3 hours at the same temperature. To the reaction solution was added ethanol and then the solvent was evaporated under reduced pressure. Thus obtained residue was purified with NH type silica gel column chromatography (hexane:ethyl acetate = 4:6, chloroform:methanol = 20:1) to obtain the title compound (0.296 g, quant.) as a colorless oily compound.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.20 (s, 3H) 2.65 (t, *J*=6.84 Hz, 2H) 2.89 (t, *J*=6.84 Hz, 2H) 3.52-3.95 (m, 8H) 4.00 (d, *J*=10.72 Hz, 1H) 4.38-4.67 (m, 5H) 4.81-5.04 (m, 5H) 6.74 (s, 1H) 6.88-7.45 (m, 30H).

Reference Example 5

Preparation of dibenzyl[(Z)-

(allylamino)methylylidene]biscarbamate



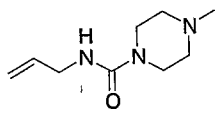
To a tetrahydrofuran solution (4.3 mL) of allylamine (250 mg, 4.38 mmol) was added N,N'-bis-benzyloxy carbonyl-1-guanyl pyrazole (1.98 g, 5.25 mmol), and the mixture was stirred overnight at room temperature. The reaction solution was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (hexane:ethyl acetate = 4:1) to obtain the title compound (1.45 g, 90%) as a colorless powder.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 4.03-4.12 (m, 2H) 5.11-5.28 (m, 6H) 5.81-5.96 (m, 1H) 7.23-7.43 (m, 10H) 8.35-8.45 (m, 1H) 11.76 (s, 1H).

ESI m/z = 368(M+H).

Reference Example 6

Preparation of N-allyl-4-methyl-piperazine-1-carboxyamide



To a chloroform solution (70 mL) of allylamine (400 mg, 7.00 mmol) were added triethylamine (1.31 mL, 9.45 mmol) and 4-nitrophenyl chloroformate (1.62 g, 8.06 mmol), and the mixture was stirred overnight at room temperature. To this reaction solution was added 1-methylpiperazine (771 mg, 7.70 mmol), and the mixture was stirred overnight at room temperature. The reaction solution was evaporated under

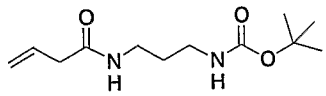
reduced pressure. To thus obtained residue was added ethyl acetate, and precipitated insoluble matter was filtered off. The filtrate was concentrated, and thus obtained residue was purified with NH type silica gel column chromatography (hexane:ethyl acetate = 5:1, ethyl acetate), and silica gel column chromatography (ethyl acetate, chloroform:methanol = 20:1 to 5:1) to obtain the title compound (1.38 g, quant.) as a colorless powder.

1H NMR (300 MHz, DMSO-D_6) δ ppm 2.16 (s, 3H) 2.18-2.26 (m, 4H) 3.23-3.31 (m, 4H) 3.59-3.68 (m, 2H) 4.95-5.12 (m, 2H) 5.72-5.87 (m, 1H) 6.63 (t, *J*=5.44 Hz, 1H).

ESI m/z = 206(M+Na).

Reference Example 7

Preparation of tert-butyl[3-(buta-3-enoylamino) propyl]carbamate



To a chloroform solution (58 mL) of vinyl acetate (500 mg, 5.81 mmol) were added tert-butyl N-(3-aminopropyl)carbamate (2.02 g, 11.6 mmol), 1-hydroxybenzotriazole (0.86 g, 6.39 mmol) and WSC (1.56 g, 8.13 mmol), and the mixture was stirred overnight at room temperature. To the reaction solution was added water and an organic layer was extracted with chloroform. The organic layer was washed with a saturated aqueous solution of ammonium chloride and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and

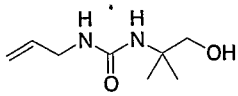
the solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (hexane:ethyl acetate = 1:1, ethyl acetate) to obtain the title compound (1.32 g, 94%) as a colorless powder.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 1.44 (s, 9H) 1.52-1.71 (m, 2H) 3.01 (d, *J*=6.99 Hz, 2H) 3.09-3.23 (m, 2H) 3.30 (q, *J*=6.37 Hz, 2H) 4.89 (s, 1H) 5.14-5.31 (m, 2H) 5.83-6.06 (m, 1H) 6.21 (s, 1H).

ESI m/z = 265(M+Na).

Reference Example 8

Preparation of N-allyl-N'-(2-hydroxy-1,1-dimethylethyl) urea



To a chloroform solution (60 mL) of allylamine (1.5 g, 26.3 mmol) were added triethylamine (4.9 mL, 35.5 mmol) and at 4°C 4-nitrophenyl chloroformate (6.09 g, 30.2 mmol), and the mixture was stirred for an hour. To this reaction solution was added at the same temperature a chloroform solution (3 mL) of 2-amino-2-methylpropanol (2.58 g, 28.9 mmol), and the mixture was stirred overnight at room temperature. The reaction solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (ethyl acetate) to obtain the title compound (4.0 g, 88%) as a yellow oily compound.

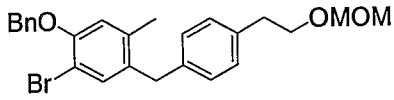
1H NMR (300 MHz, CHLOROFORM-D) δ ppm 1.26 (s, 6H) 3.55 (s, 2H) 3.71-3.80 (m, 2H) 4.85-5.08 (m, 2H) 5.08-5.24 (m, 2H)

5.77-5.91 (m, 1H).

ESI m/z = 195 (M+Na).

Reference Example 9

Preparation of 1-benzyloxy-2-bromo-5-methyl-4-[4-[2-(methoxymethoxy)ethyl]benzyl]benzene



To a tetrahydrofuran solution (1 L) of 1-bromo-4-[2-(methoxymethoxy)ethyl]benzene (50.2 g, 0.205 mol) was added dropwise under nitrogen atmosphere at -78°C a 2.6 M n-butyllithium solution in hexane (78.8 mL, 0.205 mol), and the mixture was stirred for 15 minutes at the same temperature. Then a tetrahydrofuran solution (150 mL) of 4-benzyloxy-5-bromo-2-methyl benzaldehyde (56.9 g, 0.195 mol) was added dropwise over an hour, and the mixture was stirred for 30 minutes at the same temperature. To the reaction solution was added a saturated aqueous solution of ammonium chloride, and an organic layer was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of ammonium chloride and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure to obtain [4-(benzyloxy)-5-bromo-2-methylphenyl] [4-[2-(methoxymethoxy)ethyl]phenyl]methanol.

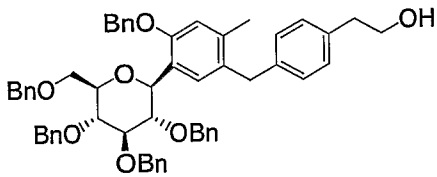
Then to a chloroform solution (1 L) of [4-(benzyloxy)-5-bromo-2-methylphenyl] [4-[2-(methoxymethoxy)ethyl]phenyl]methanol (102 g) cooled in ice were added Et_3SiH (46.7 mL, 0.293 mol) and $BF_3 \cdot Et_2O$ (29.7 mL,

0.243 mol), and the mixture was stirred for 15 minutes at the same temperature. To the reaction solution cooled in ice was added a saturated sodium bicarbonate aqueous solution and warmed to room temperature. The resulting mixture was extracted with ethyl acetate, washed with brine, and then the organic layer was dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was purified with NH type silica gel column chromatography (hexane:ethyl acetate = 19:1 to 9:1) to obtain the title compound (60 g, 68%) as a pale yellow oily compound.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.16 (s, 3H) 2.87 (t, *J*=6.99 Hz, 2H) 3.28 (s, 3H) 3.75 (t, *J*=6.99 Hz, 2H) 3.85 (s, 2H) 4.61 (s, 2H) 5.12 (s, 2H) 6.77 (s, 1H) 7.03 (d, *J*=8.08 Hz, 2H) 7.15 (d, 2H) 7.26 (d, *J*=3.57 Hz, 1H) 7.30-7.45 (m, 3H) 7.47 (d, 2H).

Reference Example 10

Preparation of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-[4-(2-hydroxyethyl)benzyl]-4-methylphenyl]-D-glucitol



To a tetrahydrofuran solution (150 mL) of 1-benzyloxy-2-bromo-5-methyl-5-[4-[2-(methoxymethoxy)ethyl]benzyl]benzene (13.0 g, 28.5 mmol) was added dropwise under nitrogen atmosphere at -78°C a

2.6 M n-butyllithium solution in hexane (11.0 mL, 28.5 mmol), and the mixture was stirred for 15 minutes at the same temperature. Then a tetrahydrofuran solution (30 mL) of 2,3,4,6-tetra-O-benzyl-D-glucono-1,5-lactone (14.0 g, 26.0 mmol) was added dropwise, and the mixture was stirred for 15 minutes at the same temperature. To the reaction solution was added a saturated aqueous solution of ammonium chloride, and an organic layer was extracted with toluene. The organic layer was washed with a saturated aqueous solution of ammonium chloride and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure to obtain 26.0 g of a residue.

The residue was dissolved in acetonitrile (70 mL) and tetrahydrofuran (70 mL). To this solution cooled in ice were added Et_3SiH (2.90 mL, 17.8 mmol) and $BF_3 \cdot Et_2O$ (1.90 mL, 14.9 mmol), and the mixture was stirred for an hour at the same temperature. To the reaction solution cooled in ice was added a saturated sodium bicarbonate aqueous solution, and warmed to room temperature. To this solution was added water (70 mL) and an organic layer was extracted with toluene. And then the organic layer was washed with brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure to obtain 27.0 g of a residue.

The residue was dissolved in isopropyl ether (140 mL). Then to this solution were added 2-propanol (140 mL) and 6 M hydrochloric acid (140 mL), and the reaction mixture was

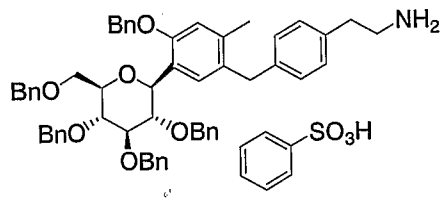
stirred at 80°C for 2 hours. After the mixture was cooled to room temperature, to the mixture was added water (70 mL). An organic layer was extracted with toluene. And then the organic layer was washed with a saturated sodium bicarbonate aqueous solution and brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (hexane:ethyl acetate = 9:1 to 7:3) to obtain the title compound (12.0 g, 54%) as a pale yellow oily compound.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.20 (s, 3H) 2.78 (t, *J*=6.53 Hz, 2H) 3.54-3.64 (m, 1H) 3.68-3.88 (m, 8H) 3.93 (br. s., 2H) 4.00 (d, *J*=10.72 Hz, 1H) 4.42 (d, *J*=10.72 Hz, 1H) 4.50 (d, 1H) 4.56-4.66 (m, 2H) 4.81-4.95 (m, 3H) 5.00 (s, 2H) 6.75 (s, 1H) 6.92 (d, *J*=7.77 Hz, 2H) 7.02 (s, 4H) 7.10-7.35 (m, 22H) 7.36-7.44 (m, 2H).

ESI m/z = 873 ($M+NH_4$).

Reference Example 11

Preparation of (1S)-1-[5-[4-(2-aminoethyl)benzyl]-2-(benzyloxy)-4-methylphenyl]-1,5-anhydro-2,3,4,6-tetra-O-benzyl-D-glucitol benzenesulfonic acid



To a tetrahydrofuran solution (140 mL) of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-[4-(2-hydroxyethyl)benzyl]-4-methylphenyl]-D-glucitol (12.0 g, 14.0 mmol), triphenyl phosphine (5.51 g, 21.0 mmol), and

phthalimide (2.27 g, 15.4 mmol) was added a 40% diisopropyl azodicarboxylate solution (11.1 mL, 21.0 mmol) in toluene under nitrogen atmosphere at 0°C over 3 minutes. This reaction solution was stirred at room temperature for 30 minutes, and then methanol (70 mL) was added thereto. Then hydrazine monohydrate (6.79 mL, 140 mmol) was added, and the reaction mixture was stirred at 60°C for 3 hours. After the mixture was cooled to room temperature, a 2 M sodium hydroxide aqueous solution (100 mL) was added thereto, and an organic layer was extracted with toluene. The organic layer was washed with a 2 M sodium hydroxide aqueous solution (100 mL) and brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to obtain 22.7 g of a residue.

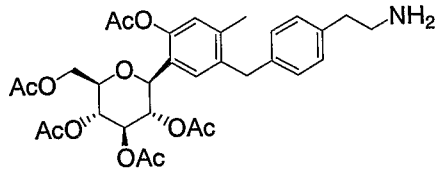
The residue was dissolved in methanol (140 mL), a methanol solution (50 mL) of benzenesulfonic acid monohydrate (2.51 g, 14.0 mmol) was added thereto, and the mixture was stirred for 15 minutes at room temperature. This mixture was evaporated under reduced pressure to obtain an amorphous compound. To thus obtained amorphous compound were added 2-propanol (230 mL) and methanol (90 mL), and the mixture was heated to reflux to dissolve a residue. This mixture was cooled to room temperature and left for 15 hours. Thus obtained crystal was filtered to obtain the colorless title compound (9.89 g, 70%).

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.12 (s, 3H) 2.72-2.85 (m, 2H) 2.89-3.05 (m, 2H) 3.54-3.63 (m, 1H) 3.68-3.89 (m, 8H) 3.99 (d, *J*=10.57 Hz, 1H) 4.39-4.53 (m, 2H) 4.56-4.65 (m,

2H) 4.82-4.94 (m, 3H) 4.98 (s, 2H) 6.72 (s, 1H) 6.79-6.85 (m, 2H) 6.87-6.96 (m, 4H) 7.06-7.44 (m, 25H) 7.75-7.90 (m, 4H).

Reference Example 12

Preparation of (1S)-1-[5-[4-(2-aminoethyl)benzyl]-2-acetoxy-4-methylphenyl]-1,5-anhydro-2,3,4,6-tetra-O-acetyl-D-glucitol



(1) Preparation of (1S)-1-[5-[4-(2-tert-butoxycarbonylaminoethyl)benzyl]-2-acetoxy-4-methylphenyl]-1,5-anhydro-2,3,4,6-tetra-O-acetyl-D-glucitol

To a chloroform solution (100 mL) of (1S)-1-[5-[4-(2-aminoethyl)benzyl]-2-(benzyloxy)-4-methylphenyl]-1,5-anhydro-2,3,4,6-tetra-O-benzyl-D-glucitol benzenesulfonic acid (10.7 g, 10.6 mmol) cooled in ice were added under nitrogen atmosphere triethylamine (2.22 mL, 15.9 mmol) and di-tert-butyl-dicarbonate (2.78 g, 12.7 mmol), and the mixture was stirred for 30 minutes at the same temperature. To the reaction solution was added water, and the mixture was warmed to room temperature. Then the resulting mixture was extracted with ethyl acetate. The organic layer was washed with 1 M hydrochloric acid and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure to obtain 11.8 g of a residue.

The residue was dissolved in ethyl acetate (50 mL) and

methanol (100 mL). And 20% palladium hydroxide (2.50 g) was added thereto, and the mixture was stirred under hydrogen atmosphere at room temperature for 2.5 hours. The reaction solution was filtered through celite, and the solvent was evaporated under reduced pressure to obtain a residue.

This residue was dissolved in pyridine (100 mL). To this solution were added under nitrogen atmosphere acetic anhydride (6.01 mL, 63.6 mmol) and N,N-dimethylaminopyridine, and the mixture was stirred overnight at room temperature. After that, acetic anhydride (4.00 mL, 42.4 mmol) was further added thereto, and the mixture was stirred for 2 hours at the same temperature. To the reaction solution was added water, and an organic layer was extracted with ethyl acetate. The organic layer was washed with 3 M hydrochloric acid, a saturated sodium bicarbonate aqueous solution and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure to obtain a residue. Thus obtained residue was dissolved by adding ethyl acetate thereto, and hexane was added thereto to obtain a crystal. Thus obtained crystal was filtered to obtain the title compound (5.58 g, 74%) as a colorless powder.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 1.43 (s, 9H) 1.77 (s, 3H) 2.00 (s, 3H) 2.04 (s, 3H) 2.07 (s, 3H) 2.19 (s, 3H) 2.35 (s, 3H) 2.75 (t, *J*=6.92 Hz, 2H) 3.28-3.42 (m, 2H) 3.75-3.83 (m, 1H) 3.92 (s, 2H) 4.08 (dd, *J*=12.43, 2.18 Hz,

1H) 4.30 (dd, *J*=12.36, 4.74 Hz, 1H) 4.54 (t, 1H) 5.14-5.23 (m, 1H) 5.25-5.37 (m, 2H) 6.87 (s, 1H) 7.02 (d, 2H) 7.10 (d, 2H) 7.16 (s, 1H).

ESI m/z = 731 ($M+NH_4$).

(2) Preparation of (1S)-1-[5-[4-(2-aminoethyl)benzyl]-2-acetoxy-4-methylphenyl]-1,5-anhydro-2,3,4,6-tetra-O-acetyl-D-glucitol

To a chloroform solution (80 mL) of (1S)-1-[5-[4-(2-tert-butoxycarbonylaminoethyl)benzyl]-2-acetoxy-4-methylphenyl]-1,5-anhydro-2,3,4,6-tetra-O-acetyl-D-glucitol was added trifluoroacetate (23 mL), and the mixture was stirred for 1.5 hours at room temperature. The solvent was evaporated under reduced pressure to obtain a residue. Thus obtained residue was diluted with chloroform, and washed with a saturated sodium bicarbonate aqueous solution and brine. This solution was dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure to obtain the title compound (4.67 g, quant.) as a colorless powder.

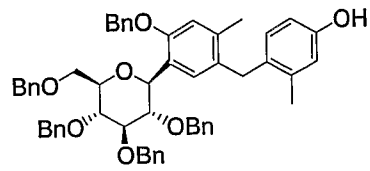
1H NMR (300 MHz, CHLOROFORM-D) δ ppm 1.77 (s, 3H) 2.00 (s, 3H) 2.04 (s, 3H) 2.07 (s, 3H) 2.19 (s, 3H) 2.35 (s, 3H) 2.67 (t, 2H) 2.85-3.07 (m, 2H) 3.75-3.84 (m, 1H) 3.92 (s, 2H) 4.08 (dd, *J*=12.36, 2.10 Hz, 1H) 4.30 (dd, *J*=12.36, 4.59 Hz, 1H) 4.53 (t, 1H) 5.13-5.23 (m, 1H) 5.24-5.36 (m, 2H) 6.86 (s, 1H) 7.02 (d, 2H) 7.11 (d, 2H) 7.17 (s, 1H).

ESI m/z = 614 (M+H).

Reference Example 13

Preparation of (1S)-1,5-anhydro-2,3,4,6-tetra-O-

benzyl-1-[2-(benzyloxy)-5-(4-hydroxy-2-methylbenzyl)-4-methylphenyl]-D-glucitol



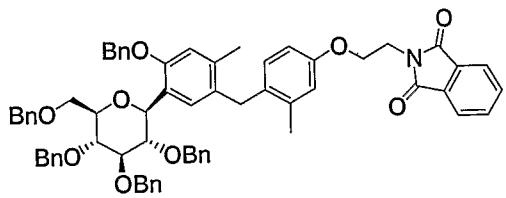
To a tetrahydrofuran solution (15 mL) of 1-bromo-4-methoxymethoxy-2-methyl benzene (0.80 g, 3.46 mmol) was added dropwise under nitrogen atmosphere at -60°C a 2.6 M hexane solution of n-butyllithium (1.33 mL, 3.46 mmol), and the mixture was stirred for 15 minutes at the same temperature. Then a tetrahydrofuran solution (6 mL) of 2,3,4,6-tetra-O-benzyl-1-C-[2-(benzyloxy)-5-formyl-4-methylphenyl]-D-glucopyranose (1.10 g, 1.44 mmol) was added dropwise, and the mixture was stirred for 15 minutes at the same temperature. To the reaction solution was added a saturated aqueous solution of ammonium chloride, and warmed to room temperature. And then the resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure to obtain 1.7 g of an oily matter.

Then the oily matter was dissolved in acetonitrile (10 mL) and chloroform (10 mL). To this solution were added at 4°C Et_3SiH (0.92 mL, 5.76 mmol) and $BF_3 \cdot Et_2O$ (0.46 mL, 3.60 mmol). The reaction solution was stirred for 30 minutes at the same temperature, and the mixture was stirred for 30 minutes at room temperature. To the reaction solution was

added a saturated sodium bicarbonate aqueous solution. And the volatiles were evaporated under reduced pressure, and the residue was extracted with ethyl acetate. The organic layer was washed with brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (hexane:ethyl acetate = 3:1) to obtain the title compound (420 mg, 35%) as a pale yellow oily compound. 1H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.17 (s, 3H) 2.22 (s, 3H) 3.49-3.59 (m, 1H) 3.63-3.84 (m, 6H) 3.97 (d, *J*=11.04 Hz, 1H) 4.31-4.50 (m, 3H) 4.52-4.68 (m, 3H) 4.79-4.92 (m, 4H) 5.02 (s, 2H) 6.37 (dd, *J*=8.32, 2.41 Hz, 1H) 6.55 (d, *J*=2.49 Hz, 1H) 6.66 (d, *J*=8.24 Hz, 1H) 6.78 (s, 1H) 6.88-6.97 (m, *J*=5.21, 4.43 Hz, 2H) 7.01 (s, 1H) 7.10-7.50 (m, 23H).
ESI m/z = 858 ($M+NH_4$), 839 (M-H).

Reference Example 14

Preparation of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-[4-[2-(1,3-dioxo-1,3-dihydro-2H-isoindole-2-yl)ethoxy]-2-methylbenzyl]-4-methylphenyl]-D-glucitol



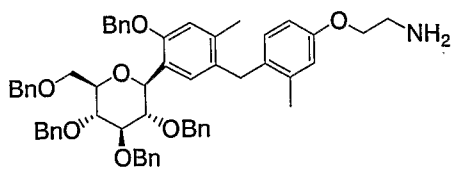
To a N,N-dimethylformamide solution (5.0 mL) of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-(4-hydroxy-2-methylbenzyl)-4-methylphenyl]-D-glucitol (340 mg, 0.40 mmol) and N-(2-bromoethyl) phthalimide (1.02 g, 4.0

mmol) were added potassium carbonate (553 mg, 4.0 mmol) and n-Bu_4NI (14 mg, 0.038 mmol). The reaction mixture was stirred at 80°C for 3.5 hours. After the mixture was cooled to room temperature, water was added thereto, and an organic layer was extracted with ethyl acetate. The organic layer was washed with brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure to obtain a residue. Thus obtained residue was purified with silica gel column chromatography (hexane:ethyl acetate = 3:1) to obtain the title compound (60 mg, 15%) as a pale yellow oily compound.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.17 (s, 3H) 2.18 (s, 3H) 3.49-3.60 (m, 1H) 3.63-3.85 (m, 6H) 3.89-4.19 (m, 5H) 4.34-4.52 (m, 3H) 4.53-4.65 (m, 3H) 4.75-4.93 (m, 3H) 5.01 (s, 2H) 6.44 (dd, *J*=8.55, 2.64 Hz, 1H) 6.60-6.71 (m, 2H) 6.77 (s, 1H) 6.88-6.97 (m, 2H) 7.05 (s, 1H) 7.13-7.45 (m, 23H) 7.66-7.72 (m, 2H) 7.80-7.88 (m, 2H).

Reference Example 15

Preparation of (1S)-1-[5-[4-(2-aminoethoxy)-2-methylbenzyl]-2-(benzyloxy)-4-methylphenyl]-1,5-anhydro-2,3,4,6-tetra-O-benzyl-D-glucitol



To a tetrahydrofuran (0.8 mL) and methanol (0.2 mL) solution of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-[4-[2-(1,3-dioxo-1,3-dihydro-2H-isoindole-2-

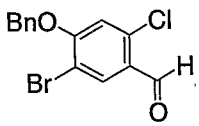
yl)ethoxy]-2-methylbenzyl]-4-methylphenyl]-D-glucitol (60 mg, 0.059 mmol) was added hydrazine monohydrate (30 mg, 0.59 mmol), and the reaction mixture was stirred at 65°C for an hour. After the mixture was cooled to room temperature, a 2 M aqueous solution of sodium hydroxide was added thereto, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to obtain the title compound quantitatively.

1H NMR (300 MHz, CHLOROFORM-D) δ .ppm 2.21 (s, 3H) 2.22 (s, 3H) 3.03 (t, *J*=4.74 Hz, 2H) 3.50-3.62 (m, 1H) 3.65-3.83 (m, 6H) 3.88 (t, *J*=4.74 Hz, 2H) 3.98 (d, *J*=10.88 Hz, 1H) 4.34-4.51 (m, 3H) 4.55-4.65 (m, 3H) 4.77-4.93 (m, 3H) 5.02 (s, 2H) 6.43-6.51 (m, 1H) 6.66-6.72 (m, 2H) 6.78 (s, 1H) 6.91-6.98 (m, 2H) 7.06 (s, 1H) 7.11-7.45 (m, 23H).

In addition, the compound (I) in which R^3 represents a methoxy group or a fluorine atom can be synthesized by using 1-bromo-2-methoxy-4-methoxymethoxy benzene or 1-bromo-2-fluoro-4-methoxymethoxy benzene as a starting material according to the method as with Reference Examples 13 to 15.

Reference Example 16

Preparation of 4-(benzyloxy)-5-bromo-2-chlorobenzaldehyde



To a chloroform solution (300 mL) of 2-chloro-4-

hydroxy benzonitrile (14.0 g, 91.2 mmol) was added dropwise under nitrogen atmosphere at -50°C a 0.95 M diisobutyl aluminum hydride solution in hexane (307 mL, 291 mmol), and the mixture was stirred for 1.5 hours at the same temperature. The temperature of the solution is increased to room temperature, and the mixture was stirred further for 3 hours. Subsequently, the reaction solution was cooled in ice, and methanol was added dropwise thereto. To the reaction solution was added 3 M hydrochloric acid, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with a saturated sodium bicarbonate aqueous solution and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure to obtain 7.25 g of a residue.

The residue was dissolved in methanol (140 mL). To this solution cooled in ice under nitrogen atmosphere was added pyridine hydrobromide perbromide (16.3 g, 50.9 mmol), and the mixture was stirred for 4 hours. To the reaction solution was added a 20% solution of Na_2SO_3 , and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with 3 M hydrochloric acid, a saturated sodium bicarbonate aqueous solution and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (hexane:ethyl acetate = 3:1) to obtain 6.17 g of a colorless powder.

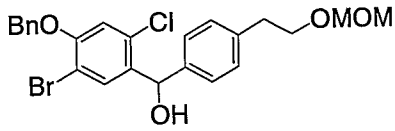
This powder was dissolved in acetone (260 mL). To this solution were added under nitrogen atmosphere benzyl bromide (3.45 mL, 28.8 mmol) and potassium carbonate (4.70 g, 34.1 mmol), and the mixture was stirred at 50°C for 4.5 hours. The reaction solution was cooled to room temperature, and then filtered through celite. The solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (hexane:ethyl acetate = 10:1) to obtain the title compound (2.02 g, 6.9%) as a colorless powder.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 5.23 (s, 2H) 6.97 (s, 1H) 7.32-7.50 (m, 5H) 8.15 (s, 1H) 10.27 (s, 1H).

ESI m/z = 325 (M+H).

Reference Example 17

Preparation of [4-(benzyloxy)-5-bromo-2-chlorophenyl][4-[2-(methoxymethoxy)ethyl]phenyl]methanol



To a tetrahydrofuran solution (6 mL) of 1-bromo-4-[2-(methoxymethoxy)ethyl]benzene (1.52 g, 6.20 mmol) was added dropwise under nitrogen atmosphere at -78°C a 2.6 M hexane solution of n-butyllithium (2.38 mL, 6.20 mmol), and the mixture was stirred for 10 minutes at the same temperature. Then a tetrahydrofuran solution (6 mL) of 4-(benzyloxy)-5-bromo-2-chlorobenzaldehyde (2.02 g, 6.20 mmol) was added dropwise over 10 minutes, and the mixture was stirred for 30 minutes at the same temperature. To the reaction solution was added a saturated aqueous solution of ammonium

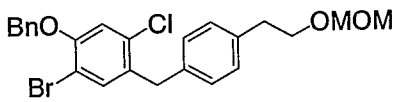
chloride, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of ammonium chloride and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (hexane:ethyl acetate = 10:1) to obtain the title compound (750 mg, 25%) as a colorless oily compound.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.24 (d, *J*=3.57 Hz, 1H) 2.89 (t, *J*=6.92 Hz, 2H) 3.27 (s, 3H) 3.75 (t, *J*=6.84 Hz, 2H) 4.60 (s, 2H) 5.12 (s, 2H) 6.09 (d, *J*=3.57 Hz, 1H) 6.91 (s, 1H) 7.15-7.51 (m, 9H) 7.80 (s, 1H).

ESI m/z = 508 ($M+NH_4$).

Reference Example 18

Preparation of 1-(benzyloxy)-2-bromo-5-chloro-4-[4-[2-(methoxymethoxy)ethyl]benzyl]benzene



To a chloroform solution (8 mL) of [4-(benzyloxy)-5-bromo-2-chlorophenyl][4-[2-(methoxymethoxy)ethyl]phenyl]methanol (750 mg, 1.53 mmol) cooled in ice were added Et_3SiH (367 μL, 2.30 mmol) and $BF_3 \cdot Et_2O$ (232 μL, 1.83 mmol), and the mixture was stirred for an hour at the same temperature. To this solution cooled in ice was added a saturated sodium bicarbonate aqueous solution, and warmed to room temperature. An organic layer was extracted with ethyl acetate, washed with

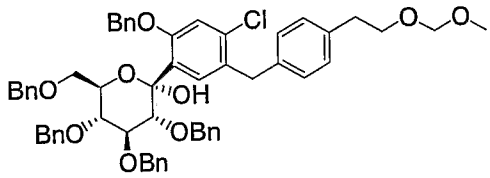
brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (hexane:ethyl acetate = 4:1) to obtain the title compound (290 mg, 40%) as a colorless oily compound.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.88 (t, *J*=7.15 Hz, 2H) 3.28 (s, 3H) 3.75 (t, *J*=6.99 Hz, 2H) 3.97 (s, 2H) 4.61 (s, 2H) 5.12 (s, 2H) 6.96 (s, 1H) 7.10 (d, 2H) 7.17 (d, 2H) 7.28-7.50 (m, 6H).

ESI m/z = 492 ($M+NH_4$).

Reference Example 19

Preparation of 2,3,4,6-tetra-O-benzyl-1-C-[2-(benzyloxy)-4-chloro-5-[4-[2-(methoxymethoxy)ethyl]benzyl]phenyl]-D-glucopyranose



To a tetrahydrofuran solution (3 mL) of 1-(benzyloxy)-2-bromo-5-chloro-4-[4-[2-(methoxymethoxy)ethyl]benzyl]benzene (290 mg, 0.609 mmol) was added dropwise under nitrogen atmosphere at -78 °C a 2.6 M hexane solution of n-butyllithium (234 μL, 0.609 mmol), and the mixture was stirred for 5 minutes at the same temperature. Then a tetrahydrofuran solution (3 mL) of 2,3,4,6-tetra-O-benzyl-D-glucono-1,5-lactone (328 mg, 0.609 mmol) was added dropwise, and the mixture was stirred for an hour at the same temperature. To the reaction

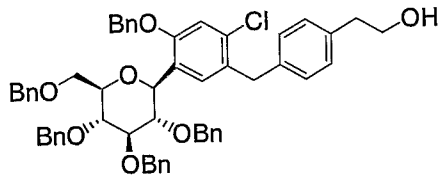
solution was added a saturated aqueous solution of ammonium chloride, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with a saturated aqueous solution of ammonium chloride and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (hexane:ethyl acetate = 3:1) to obtain the title compound (124 mg, 22%) as a colorless oily compound.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.85 (t, *J*=6.99 Hz, 2H) 3.28 (s, 3H) 3.60 (s, 5H) 3.94-4.02 (m, 3H) 4.04-4.15 (m, 3H) 4.43-4.61 (m, 6H) 4.71-4.97 (m, 5H) 6.89 (s, 3H) 7.37 (s, 27H) 7.50 (s, 1H).

ESI m/z = 952 ($M+NH_4$).

Reference Example 20

Preparation of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-4-chloro-5-[4-(2-hydroxyethyl)benzyl]phenyl]-D-glucitol



To an acetonitrile (0.5 mL) and tetrahydrofuran (0.5 mL) solution of 2,3,4,6-tetra-O-benzyl-1-C-[2-(benzyloxy)-4-chloro-5-[4-[2-(methoxymethoxy)ethyl]benzyl]phenyl]-D-glucopyranose (124 mg, 0.133 mmol) cooled in ice were added Et_3SiH (63.6 μL, 0.400 mmol) and $BF_3 \cdot Et_2O$ (40.4 μL, 0.320 mmol), and the mixture was stirred for 1.5 hours at the

same temperature and the mixture was stirred for 4.5 hours at room temperature. To the reaction solution cooled in ice was added a saturated sodium bicarbonate aqueous solution and an organic layer was extracted with ethyl acetate. The organic layer was washed with brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure to obtain 119 mg of a residue.

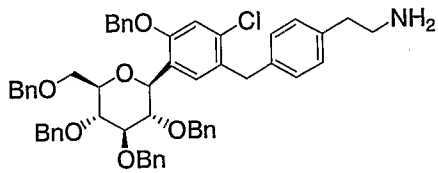
The residue was dissolved in isopropyl ether (0.7 mL). Then to this solution were added 2-propanol (0.7 mL) and 6 M hydrochloric acid (0.7 mL), and the reaction mixture was stirred at 80°C for 3 hours. After the mixture was cooled to room temperature, to the mixture was added water, and the resulting mixture was extracted with ethyl acetate. And then the organic layer was washed with a saturated sodium bicarbonate aqueous solution and brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (hexane:ethyl acetate = 7:3) to obtain the title compound (79.1 mg, 68%) as a colorless oily compound.

1H NMR (600 MHz, CHLOROFORM-D) δ ppm 2.77 (t, *J*=6.42 Hz, 2H) 3.52-3.60 (m, 1H) 3.64-3.82 (m, 7H) 3.92-3.99 (m, 3H) 4.03 (d, 1H) 4.41-4.51 (m, 2H) 4.54-4.64 (m, 2H) 4.82-4.89 (m, 3H) 4.91-4.97 (m, 2H) 6.86 (d, *J*=7.34 Hz, 2H) 6.90 (s, 1H) 7.02-7.06 (m, 2H) 7.06-7.10 (m, 2H) 7.13 (t, *J*=7.34 Hz, 2H) 7.15-7.20 (m, 3H) 7.20-7.33 (m, 17H) 7.36 (d, *J*=7.79 Hz, 2H).

ESI m/z = 892 ($M+NH_4$).

Reference Example 21

Preparation of (1S)-1-[5-[4-(2-aminoethyl)benzyl]-2-(benzyloxy)-4-chlorophenyl]-1,5-anhydro-2,3,4,6-tetra-O-benzyl-D-glucitol



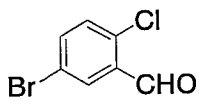
To a tetrahydrofuran solution (2.0 mL) of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-4-chloro-5-[4-(2-hydroxyethyl)benzyl]phenyl]-D-glucitol (79.0 mg, 0.090 mmol), triphenyl phosphine (53.1 mg, 0.203 mmol), and phthalimide (23.9 mg, 0.162 mmol) cooled in ice was added a 40% diisopropyl azodicarboxylate solution in toluene (386 μL, 0.203 mmol) under nitrogen atmosphere. After the reaction solution was stirred at room temperature for 1.5 hours, methanol (1 mL) was added thereto. Then hydrazine monohydrate (43.7 μL, 0.90 mmol) was added, and the reaction mixture was stirred at 60°C for 3 hours. After the mixture was cooled to room temperature, a 2 M sodium hydroxide aqueous solution was added thereto, and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (chloroform:methanol = 9:1) to obtain the title compound (39.2 mg, 50%) as a colorless oily compound.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.68 (t, 2H) 2.83-2.96 (m, 2H) 3.52-3.61 (m, 1H) 3.62-3.86 (m, 5H) 3.99 (t, *J*=10.57 Hz, 3H) 4.41-4.67 (m, 5H) 4.81-4.92 (m, 3H) 4.95 (s, 2H) 6.88 (d, *J*=5.60 Hz, 3H) 6.97-7.43 (m, 28H).

ESI m/z = 874 (M+H).

Reference Example 22

Preparation of 5-bromo-2-chlorobenzaldehyde



To a suspension of 5-bromo-2-chlorobenzoic acid (18.5 g, 78.5 mmol)in chloroform (157 mL) was added N,N-dimethylformamide (0.5 mL), and oxalylchloride (8.1 mL, 94.2 mmol) was added dropwise thereto at room temperature. This reaction solution was stirred for 30 minutes, and then concentrated under reduced pressure. Thus obtained residue was dissolved in chloroform(157 mL), and added dropwise at 0°C to a suspension of N,O-dimethylhydroxylamine hydrochloride (9.19 g, 94.2 mmol) and triethylamine (26.3 mL, 188 mmol) in chloroform. This reaction solution was stirred for 30 minutes at the same temperature, and then washed with water, a saturated sodium bicarbonate aqueous solution and brine. And an organic layer was dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure to obtain 24.0 g of a residue.

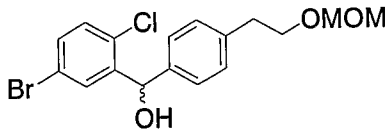
Thus obtained residue was dissolved in tetrahydrofuran (157 mL), and lithium aluminum hydroxide (1.19 g, 29.0 mmol) was gradually added thereto at 0°C. After this

reaction solution was cooled to 0°C, 2 M hydrochloric acid was gradually added thereto, and the mixture was stirred at room temperature for 30 minutes. The organic layer was washed with a saturated sodium bicarbonate aqueous solution and then brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was recrystallized from a mixed solution of ethyl acetate:hexane (1:9) to obtain the title compound (11.3 g, 65%) as colorless crystals.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 7.35 (d, J=8.47 Hz, 1H) 7.65 (dd, *J*=8.47, 2.56 Hz, 1H) 8.04 (d, *J*=2.56 Hz, 1H) 10.41 (s, 1H).

Reference Example 23

Preparation of (5-bromo-2-chlorophenyl) [4-[2-(methoxymethoxy)ethyl]phenyl]methanol



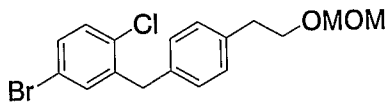
By conducting a method as with Reference Example 17 in which 5-bromo-2-chlorobenzaldehyde was used instead of 4-(benzyloxy)-5-bromo-2-chlorobenzaldehyde, the title compound (4.55 g, 63%) was obtained as a colorless oily compound.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.89 (t, *J*=6.99 Hz, 2H) 3.26 (s, 3H) 3.74 (t, *J*=6.99 Hz, 2H) 4.59 (s, 2H) 6.11 (s, 1H) 7.13-7.39 (m, 6H) 7.82-7.84 (m, 1H).

Reference Example 24

Preparation of 5-bromo-2-chloro-4-[4-[2-

(methoxymethoxy)ethyl]benzyl]benzene



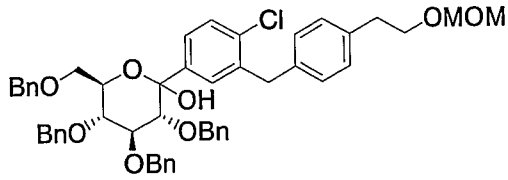
To a chloroform solution (1.4 mL) of (5-bromo-2-chlorophenyl) [4-[2-(methoxymethoxy)ethyl]phenyl]methanol (0.265 g, 0.687 mmol) was added triethylamine (105 μL, 0.756 mmol). And methanesulfonylchloride (58.5 μL, 0.756 mmol) was added dropwise thereto at 0°C and the mixture was stirred for 2 hours at the same temperature. To the reaction solution was added water, and the resulting mixture was extracted twice with ethyl acetate. The organic layer was washed with brine, and the organic layer was dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure to obtain a residue.

To a chloroform solution (3.4 mL) of thus obtained residue and Et_3SiH (165 μL, 1.03 mmol) was added $BF_3 \cdot Et_2O$ (104 μL, 0.824 mmol) at 0°C, and the mixture was stirred for an hour at the same temperature. This reaction solution was washed with a saturated sodium bicarbonate aqueous solution (twice) and then brine, and the organic layer was dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (hexane:ethyl acetate = 9:1) to obtain a pale yellow crude product (41 mg).

ESI m/z = 386 ($M+NH_4$).

Reference Example 25

Preparation of 2,3,4,6-tetra-O-benzyl-1-C-[4-chloro-3-[4-[2-(methoxymethoxy)ethyl]benzyl]phenyl]-D-glucopyranose

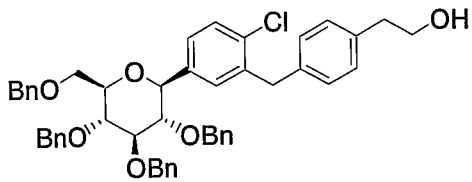


A crude product of the title compound (1.07 g) was obtained as a colorless oily matter according to the method as with Reference Example 19 in which 5-bromo-2-chloro-4-[4-[2-(methoxymethoxy)ethyl]benzyl]benzene was used instead of 1-(benzyloxy)-2-bromo-5-chloro-4-[4-[2-(methoxymethoxy)ethyl]benzyl]benzene.

ESI m/z = 846 ($M+NH_4$).

Reference Example 26

Preparation of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[4-chloro-3-[4-(2-hydroxyethyl)benzyl]phenyl]-D-glucitol

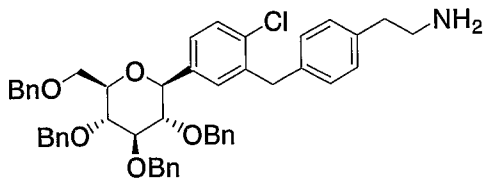


A crude product of the title compound (0.262 g) was obtained as a colorless oily matter according to the method as with Reference Example 20 in which 2,3,4,6-tetra-O-benzyl-1-C-[4-chloro-3-[4-[2-(methoxymethoxy)ethyl]benzyl]phenyl]-D-glucopyranose was used instead of 2,3,4,6-tetra-O-benzyl-1-C-[2-(benzyloxy)-4-chloro-5-[4-[2-(methoxymethoxy)ethyl]benzyl]phenyl]-D-glucopyranose

ESI m/z = 786 ($M+NH_4$).

Reference Example 27

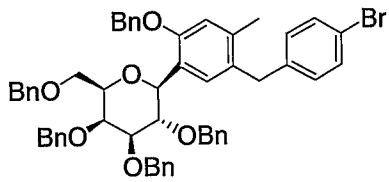
Preparation of (1S)-1-[3-[4-(2-aminoethyl)benzyl]-4-chlorophenyl]-1,5-anhydro-2,3,4,6-tetra-O-benzyl-D-glucitol



A crude product of the title compound (0.230 g) was obtained as a pale yellow oily matter according to the method as with Reference Example 21 in which (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[4-chloro-3-[4-(2-hydroxyethyl)benzyl]phenyl]-D-glucitol was used instead of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-4-chloro-5-[4-(2-hydroxyethyl)benzyl]phenyl]-D-glucitol.

Reference Example 28

Preparation of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-(4-bromobenzyl)-4-methylphenyl]-D-galactitol



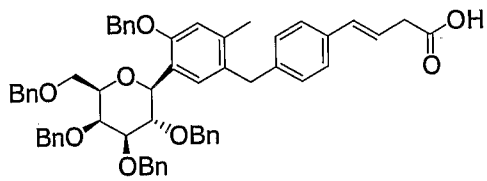
The title compound was synthesized according to the method as with Reference Example 2 in which 2,3,4,6-tetra-O-benzyl-D-galactono-1,5-lactone was used instead of 2,3,4,6-tetra-O-benzyl-D-glucono-1,5-lactone.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.12 (s, 3H) 3.32-3.81

(m, 4H) 3.86 (s, 2H) 4.07 (t, *J*=10.72 Hz, 3H) 4.32-4.47 (m, 2H) 4.49-4.80 (m, 5H) 4.93-5.07 (m, 3H) 6.72 (s, 1H) 6.80-7.01 (m, 4H) 7.06-7.46 (m, 26H). ESI m/z = 911 (M+Na). 913(M+2+Na).

Reference Example 29

Preparation of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-(2-(benzyloxy)-5-[4-[(1E)-3-carboxyprop-1-en-1-yl]benzyl]-4-methylphenyl)-D-galactitol



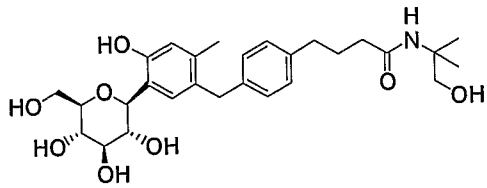
The title compound (377 mg, 41%) was obtained as a pale yellow amorphous compound from (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-(4-bromobenzyl)-4-methylphenyl]-D-galactitol (918 mg, 1.03 mmol) according to the method as with Reference Example 3.

EXAMPLES

The compounds of the present invention will be further described in more detail in the following examples and test examples, which are not intended to limit the scope of the invention.

Example 1

Preparation of (1S)-1,5-anhydro-1-[2-hydroxy-5-[4-[4-[(2-hydroxy-1,1-dimethylethyl)amino]-4-oxobutyl]benzyl]-4-methylphenyl)-D-glucitol



(1) Preparation of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-[4-[(1E)-4-[(2-hydroxy-1,1-dimethylethyl)amino]-4-oxobut-1-en-1-yl]benzyl]-4-methylphenyl]-D-glucitol

To a chloroform solution (2.2 mL) of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-[4-[(1E)-3-carboxyprop-1-en-1-yl]benzyl]-4-methylphenyl]-D-glucitol (200 mg, 0.223 mmol) were added 2-amino-2-methyl-1-propanol (40 mg, 0.446 mmol), 1-hydroxy benzotriazole (33 mg, 0.245 mmol) and WSC (60 mg, 0.312 mmol), and the mixture was stirred overnight at room temperature. To the reaction solution was added water, and the resulting mixture was extracted with chloroform. The organic layer was washed with brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (hexane:ethyl acetate = 5:1 to 1:2) to obtain the title compound (120 mg, 56%) as an orange-yellow oily compound. 1H NMR (300 MHz, CHLOROFORM-D) δ ppm 1.26 (s, 6H) 2.19 (s, 3H) 3.11 (d, *J*=7.46 Hz, 2H) 3.54-3.63 (m, 3H) 3.67-3.85 (m, 5H) 3.89-4.05 (m, 3H) 4.40-4.68 (m, 4H) 4.81-4.95 (m, 3H) 5.00 (s, 2H) 5.60 (s, 1H) 6.08-6.21 (m, 1H) 6.45 (d, *J*=15.54 Hz, 1H) 6.75 (s, 1H) 6.89-6.97 (m, 2H) 7.03 (d, *J*=7.93 Hz, 2H) 7.11-7.45 (m, 26H).

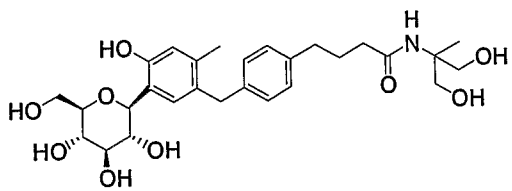
ESI m/z = 988.5(M+Na).

(2) Preparation of (1S)-1,5-anhydro-1-[2-hydroxy-5-[4-[4-[(2-hydroxy-1,1-dimethylethyl)amino]-4-oxobutyl]benzyl]-4-methylphenyl]-D-glucitol

To a methanol solution (1.2 mL) of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-[4-[(1E)-4-[(2-hydroxy-1,1-dimethylethyl)amino]-4-oxobut-1-en-1-yl]benzyl]-4-methylphenyl]-D-glucitol (120 mg, 0.124 mmol) was added 10% palladium-activated carbon (22 mg), and the mixture was stirred overnight under a hydrogen atmosphere at room temperature. The reaction solution was filtered through celite, and evaporated under reduced pressure to obtain a residue. Thus obtained residue was purified with silica gel column chromatography (chloroform:methanol = 20:1 to 5:1) to obtain the title compound (58 mg, 90%) as a colorless powder. NMR data and MS data of the compound are shown in Table 1.

Example 2

Preparation of (1S)-1,5-anhydro-1-[2-hydroxy-5-[4-[4-[[2-hydroxy-1-(hydroxymethyl)-1-methylethyl]amino]-4-oxobutyl]benzyl]-4-methylphenyl]-D-glucitol



(1)Preparation of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-[4-[(1E)-4-[[2-hydroxy-1-(hydroxymethyl)-1-methylethyl]amino]-4-oxobut-1-en-1-yl]benzyl]-4-methylphenyl]-D-glucitol

The title compound (91 mg, 44%) was obtained as a colorless oily compound according to the method as with Example 1 (1) in which 2-amino-2-methyl-1,3-propanediol was used instead of 2-amino-2-methyl-1-propanol.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 1.19 (s, 3H) 2.20 (s, 3H) 3.15 (d, *J*=6.06 Hz, 2H) 3.49-3.83 (m, 10H) 3.87-4.04 (m, 3H) 4.37-4.67 (m, 4H) 4.80-4.94 (m, 3H) 5.00 (s, 2H) 6.00-6.23 (m, 2H) 6.40-6.52 (m, 1H) 6.75 (s, 1H) 6.93 (dd, *J*=7.38, 1.94 Hz, 2H) 7.03 (d, *J*=8.24 Hz, 2H) 7.11-7.35 (m, 24H) 7.35-7.46 (m, 2H).

ESI m/z = 1004.5(M+Na).

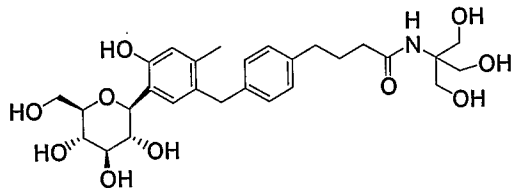
(2) Preparation of (1S)-1,5-anhydro-1-[2-hydroxy-5-[4-[4-[[2-hydroxy-1-(hydroxymethyl)-1-methylethyl]amino]-4-oxobutyl]benzyl]-4-methylphenyl]-D-glucitol

To a methanol solution (1 mL) of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-[4-[(1E)-4-[[2-hydroxy-1-(hydroxymethyl)-1-methylethyl]amino]-4-oxobut-1-en-1-yl]benzyl]-4-methylphenyl]-D-glucitol (91 mg, 0.0926 mmol) was added 10% palladium-activated carbon (16 mg), and the mixture was stirred overnight under a hydrogen atmosphere at room temperature. The reaction solution was filtered through celite, and evaporated under reduced pressure to obtain a residue. Thus obtained residue was dissolved in methanol (1 mL). And 20% palladium hydroxide (91 mg) was added thereto, and the mixture was stirred under hydrogen atmosphere at room temperature for 2 days. The reaction solution was filtered through celite, and evaporated under reduced pressure to obtain a residue.

Thus obtained residue was purified with silica gel column chromatography (chloroform:methanol = 5:1) to obtain the title compound (32 mg, 65%) as a colorless powder. NMR data and MS data of the compound are shown in Table 1.

Example 3

Preparation of (1S)-1,5-anhydro-1-[2-hydroxy-5-[4-[4-[[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]amino]-4-oxobutyl]benzyl]-4-methylphenyl]-D-glucitol



(1) Preparation of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-[4-[(1E)-4-[[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]amino]-4-oxobut-1-en-1-yl]benzyl]-4-methylphenyl]-D-glucitol

The title compound (151 mg, 55%) was obtained as a pale yellow powder according to the method as with Example 1 (1) in which tris(hydroxymethyl)aminomethane was used instead of 2-amino-2-methyl-1-propanol.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.22 (s, 3H) 3.18 (dd, *J*=7.15, 1.09 Hz, 2H) 3.43-3.81 (m, 12H) 3.87-4.02 (m, 3H) 4.36-4.67 (m, 4H) 4.80-4.93 (m, 3H) 5.00 (s, 2H) 6.10-6.22 (m, 1H) 6.47 (d, *J*=15.85 Hz, 1H) 6.68 (s, 1H) 6.75 (s, 1H) 6.93 (d, *J*=5.91 Hz, 2H) 7.03 (d, *J*=8.08 Hz, 2H) 7.10-7.35 (m, 24H) 7.36-7.44 (m, 2H).

ESI m/z = 998.5(M+H).

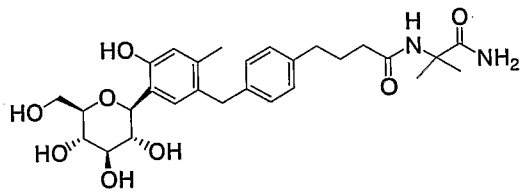
(2) Preparation of (1S)-1,5-anhydro-1-[2-hydroxy-5-[4-[4-[[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]amino]-4-

oxobutyl]benzyl]-4-methylphenyl]-D-glucitol

The title compound (60 mg, 76%) was obtained as a colorless powder according to the method as with Example 2 (2). NMR data and MS data of the compound are shown in Table 1.

Example 4

Preparation of (1S)-1-[5-[4-[4-[(2-amino-1,1-dimethyl-2-oxoethyl)amino]-4-oxobutyl]benzyl]-2-hydroxy-4-methylphenyl]-1,5-anhydro-D-glucitol



(1) Preparation of (1S)-1-[5-[4-[(1E)-4-[(2-amino-1,1-dimethyl-2-oxoethyl)amino]-4-oxobut-1-en-1-yl]benzyl]-2-(benzyloxy)-4-methylphenyl]-1,5-anhydro-2,3,4,6-tetra-O-benzyl-D-glucitol

The title compound (75 mg, 42%) was obtained as a pale yellow powder according to the method as with Example 1 (1) in which 2-amino-2-methylpropionamide was used instead of 2-amino-2-methyl-1-propanol.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 1.55 (s, 3H) 1.57 (s, 3H) 2.19 (s, 3H) 3.12 (dd, *J*=7.38, 1.17 Hz, 2H) 3.53-3.87 (m, 6H) 3.89-4.05 (m, 3H) 4.39-4.54 (m, 2H) 4.57-4.66 (m, 2H) 4.81-4.94 (m, 3H) 5.00 (s, 2H) 6.08-6.23 (m, 2H) 6.46 (d, *J*=16.01 Hz, 1H) 6.75 (s, 1H) 6.93 (dd, *J*=7.07, 1.79 Hz, 2H) 7.03 (d, *J*=8.24 Hz, 2H) 7.10-7.35 (m, 24H) 7.36-7.45 (m, 2H).

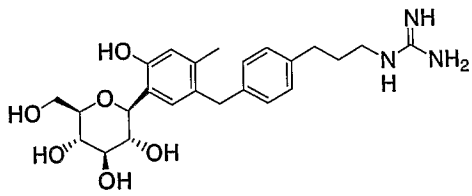
ESI m/z = 1001.5(M+Na).

(2) Preparation of (1S)-1-[5-[4-[4-[(2-amino-1,1-dimethyl-2-oxoethyl)amino]-4-oxobutyl]benzyl]-2-hydroxy-4-methylphenyl]-1,5-anhydro-D-glucitol

To a methanol solution (1 mL) of (1S)-1-[5-(4-[(1E)-4-[(2-amino-1,1-dimethyl-2-oxoethyl)amino]-4-oxobut-1-en-1-yl]benzyl)-2-(benzyloxy)-4-methylphenyl]-1,5-anhydro-2,3,4,6-tetra-O-benzyl-D-glucitol (75 mg, 0.0765 mmol) was added 20% palladium hydroxide (15 mg), and the mixture was stirred overnight under a hydrogen atmosphere at room temperature. The reaction solution was filtered through celite, and evaporated under reduced pressure to obtain a residue. Thus obtained residue was purified with silica gel column chromatography (chloroform:methanol = 5:1, ethyl acetate:ethanol:water = 20:2:1) to obtain the title compound (32 mg, 79%) as a colorless powder. NMR data and MS data of the compound are shown in Table 1.

Example 5

Preparation of (1S)-1-[5-[4-[3-[[amino(imino)methyl]amino]propyl]benzyl]-2-hydroxy-4-methylphenyl]-1,5-anhydro-D-glucitol



(1) Preparation of (1S)-1-[5-[4-[(1E)-3-[[benzyloxy carbonyl amino(benzyloxycarbonylimino)methyl]amino]prop-1-en-1-yl]benzyl]-2-(benzyloxy)-4-methylphenyl]-1,5-anhydro-2,3,4,6-tetra-O-benzyl-D-glucitol

To an acetonitrile solution (3 mL) of (1S)-1,5-

anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-(4-bromobenzyl)-4-methylphenyl]-D-glucitol (271 mg, 0.305 mmol) were added dibenzyl[(Z)-(allylamino)methylylidene]biscarbamate (335 mg, 0.914 mmol), palladium(II) acetate (18 mg, 0.0791 mmol), tri-O-tolylphosphine (61 mg, 0.201 mmol) and triethylamine (154 mg, 1.52 mmol), and reacted at 120°C for 20 minutes with microwave manufactured by Biotage. The reaction solution was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (hexane:ethyl acetate = 5:1) to obtain the title compound (163 mg, 46%) as a pale yellow amorphous compound.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.18 (s, 3H) 3.53-3.86 (m, 6H) 3.91 (s, 1H) 4.00 (d, *J*=11.04 Hz, 1H) 4.19 (t, *J*=5.75 Hz, 2H) 4.38-4.55 (m, 2H) 4.57-4.67 (m, 2H) 4.80-4.95 (m, 3H) 5.00 (s, 2H) 5.10-5.20 (m, 4H) 6.03-6.16 (m, 1H) 6.41-6.52 (m, 1H) 6.75 (s, 1H) 6.92 (dd, *J*=7.31, 1.71 Hz, 2H) 7.01 (d, *J*=8.08 Hz, 2H) 7.07-7.44 (m, 37H) 8.38-8.45 (m, 1H) 11.77 (s, 1H)

ESI m/z = 1176(M+H).

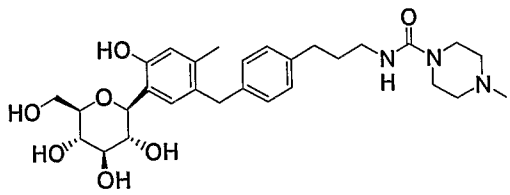
(2) Preparation of (1S)-1-[5-[4-[3-[[amino(imino)methyl]amino]propyl]benzyl]-2-hydroxy-4-methylphenyl]-1,5-anhydro-D-glucitol

To a methanol (2.6 mL)-ethyl acetate (1.3 mL) mixture solution of (1S)-1-[5-[4-[(1E)-3-[[benzyloxy carbonyl amino(benzyloxycarbonylimino)methyl]amino]prop-1-en-1-yl]benzyl]-2-(benzyloxy)-4-methylphenyl]-1,5-anhydro-2,3,4,6-tetra-O-benzyl-D-glucitol (154 mg, 0.131 mmol) was

added 20% palladium hydroxide (160 mg), and the mixture was stirred under a hydrogen atmosphere at room temperature overnight. The reaction solution was filtered through celite, and evaporated under reduced pressure to obtain a residue. Thus obtained residue was dissolved in methanol (1.5 mL). And 20% palladium hydroxide (63 mg) was added thereto, and the mixture was stirred under a hydrogen atmosphere at room temperature for 2 days. The reaction solution was filtered through celite, and evaporated under reduced pressure to obtain a residue. Thus obtained residue was purified with silica gel column chromatography (ethyl acetate:ethanol:water = 10:2:1 then 5:2:1, and then ethanol:water = 10:1) to obtain the title compound (38 mg, 63%) as a colorless powder. NMR data and MS data of the compound are shown in Table 1.

Example 6

Preparation of (1S)-1,5-anhydro-1-[2-hydroxy-4-methyl-5-[4-[3-[[(4-methylpiperazin-1-yl)carbonyl]amino]propyl]benzyl]phenyl]-D-glucitol



(1) Preparation of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-4-methyl-5-[4-[(1E)-3-[[(4-methylpiperazin-1-yl)carbonyl]amino]prop-1-en-1-yl]benzyl]phenyl]-D-glucitol

The title compound (180 mg, 54%) was obtained as a

pale yellow oily compound according to the method as with Example 5 (1) in which N-allyl-4-methylpiperazine-1-carboxyamide was used instead of dibenzyl[(Z)-(allylamino)methylylidene]biscarbamate.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.18 (s, 3H) 2.23-2.64 (m, 5H) 3.31-3.86 (m, 11H) 3.91 (s, 2H) 3.95-4.07 (m, 2H) 4.36-4.55 (m, 3H) 4.55-4.66 (m, 2H) 4.77-4.95 (m, 4H) 5.00 (s, 2H) 6.05-6.23 (m, 1H) 6.38-6.50 (m, 1H) 6.74 (s, 1H) 6.92 (dd, *J*=8.24, 1.24 Hz, 2H) 7.03 (t, *J*=6.99 Hz, 2H) 7.08-7.36 (m, 25H) 7.37-7.46 (m, 2H).

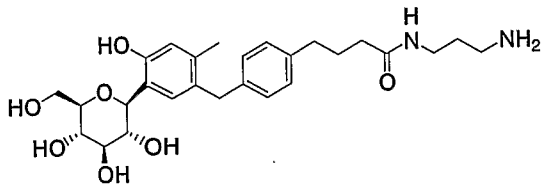
ESI m/z = 992(M+H).

(2) Preparation of (1S)-1,5-anhydro-1-[2-hydroxy-4-methyl-5-[4-[3-[[(4-methylpiperazin-1-yl)carbonyl]amino]propyl]benzyl]phenyl]-D-glucitol

The title compound (51 mg, 53%) was obtained as a colorless powder according to the method as with Example 5 (2). NMR data and MS data of the compound are shown in Table 1.

Example 7

Preparation of (1S)-1-[5-[4-[4-[(3-aminopropyl)amino]-4-oxobutyl benzyl] 2-hydroxy-4-methylphenyl]-1,5-anhydro-D-glucitol



(1) Preparation of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-[4-[(1E)-4-[[3-[(tert-

butoxycarbonyl)amino]propyl]amino]-4-oxobut-1-en-1-yl]benzyl]-4-methylphenyl)-D-glucitol

The title compound (200 mg, 56%) was obtained as a colorless oily compound according to the method as with Example 5 (1) in which tert-butyl[3-(buta-3-enoylamino)propyl]carbamate was used instead of dibenzyl[(Z)-(allylamino)methylylidene]biscarbamate.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 1.40 (s, 9H) 1.49-1.67 (m, 2H) 2.18 (s, 3H) 3.05-3.20 (m, 4H) 3.29 (q, *J*=6.32 Hz, 2H) 3.50-3.85 (m, 6H) 3.91 (s, 2H) 4.00 (d, *J*=10.72 Hz, 1H) 4.37-4.56 (m, 2H) 4.56-4.67 (m, 2H) 4.78-4.95 (m, 4H) 5.00 (s, 2H) 6.10-6.37 (m, 2H) 6.46 (d, *J*=15.70 Hz, 1H) 6.74 (s, 1H) 6.88-6.96 (m, 2H) 7.02 (d, *J*=8.24 Hz, 2H) 7.10-7.33 (m, 25H) 7.37-7.44 (m, 2H).

ESI m/z = 1073(M+Na).

(2) Preparation of (1S)-1-[5-[4-[(1E)-4-[(3-aminopropyl)amino]-4-oxobutyl-1-ene-1-yl]benzyl]-2-(benzyloxy)-4-methylphenyl]-1,5-anhydro-2,3,4,6-tetra-O-benzyl-D-glucitol

To an ethyl acetate solution (2 mL) of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-[4-[(1E)-4-[[3-[(tert-butoxycarbonyl)amino]propyl]amino]-4-oxobut-1-en-1-yl]benzyl]-4-methylphenyl]-D-glucitol (200 mg, 0.190 mmol), which was cooled in ice, was added a 4 M hydrochloric acid/ethyl acetate solution, and the mixture was stirred at room temperature for 2 days. To the reaction solution were added ethyl acetate and a saturated sodium bicarbonate aqueous solution to separate an organic

layer. The organic layer was washed with water and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (chloroform:methanol = 5:1, and then ethyl acetate:ethanol:water = 5:2:1) to obtain the title compound (54 mg, 30%) as a pale yellow oily compound.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 1.83-1.98 (m, 2H) 2.17 (s, 3H) 2.87-3.03 (m, 2H) 3.03-3.20 (m, 2H) 3.26-3.40 (m, 2H) 3.51-3.83 (m, 6H) 3.89 (s, 2H) 4.00 (d, *J*=10.57 Hz, 1H) 4.38-4.54 (m, 2H) 4.54-4.66 (m, 2H) 4.80-4.94 (m, 3H) 4.99 (s, 2H) 6.06-6.22 (m, 1H) 6.37-6.62 (m, 2H) 6.74 (s, 1H) 6.91 (dd, *J*=6.92, 1.63 Hz, 2H) 7.01 (d, *J*=8.08 Hz, 2H) 7.07-7.35 (m, 25H) 7.35-7.47 (m, 4H).

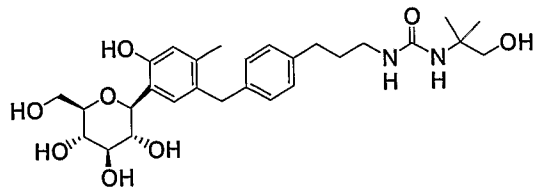
ESI m/z = 951(M+H).

(3) Preparation of (1S)-1-[5-[4-[4-[(3-aminopropyl)amino]-4-oxobutyl]benzyl]-2-hydroxy-4-methylphenyl]-1,5-anhydro-D-glucitol

The title compound (1 mg, 3.5%) was obtained as a colorless amorphous compound according to the method as with Example 5 (2). NMR data and MS data of the compound are shown in Table 1.

Example 8

Preparation of (1S)-1,5-anhydro-1-[5-[4-[3-[[(2-hydroxy-1,1-dimethylethyl)aminocarbonyl]amino]propyl]benzyl]-2-hydroxy-4-methylphenyl)-D-glucitol



(1) Preparation of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[5-[4-[(1E)-3-[[(2-hydroxy-1,1-dimethylethyl)aminocarbonyl]amino]prop-1-en-1-yl]benzyl]-2-(benzyloxy)-4-methylphenyl)-D-glucitol

To an acetonitrile solution (5.4 mL) of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-(4-bromobenzyl)-4-methylphenyl]-D-glucitol (0.48 g, 0.539 mmol) were added N-allyl-N'-(2-hydroxy-1,1-dimethylethyl) urea (223 mg, 1.29 mmol), palladium(II) acetate (24 mg, 0.108 mmol), tri-O-tolylphosphine (66 mg, 0.216 mmol) and triethylamine (273 mg, 2.69 mmol), and the mixture was stirred at 120°C for 20 minutes with microwave manufactured by Biotage. The reaction solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (chloroform and then chloroform:methanol = 50:1) to obtain the title compound (210 mg, 40%) as a pale yellow amorphous compound.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 1.26 (s, 6H) 2.19 (s, 3H) 3.45-4.13 (m, 13H) 4.31-4.69 (m, 6H) 4.77-5.06 (m, 5H) 5.98-6.18 (m, 1H) 6.44 (d, *J*=15.85 Hz, 1H) 6.74 (s, 1H) 6.86-7.48 (m, 31H)

ESI m/z = 982 (M+H).

(2) Preparation of (1S)-1-[2-(acetoxy)-5-[4-[3-[[[[2-(acetoxy)-1,1-dimethylethyl]amino]carbonyl]amino]propyl]benzyl]-4-

methylphenyl]-1,5-anhydro-2,3,4,6-tetra-O-acetyl-D-glucitol

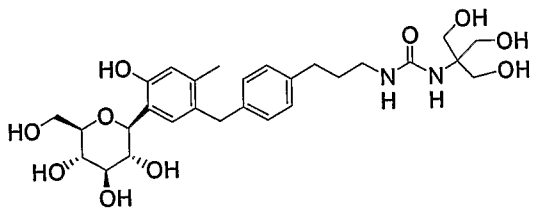
To an ethanol solution (3 mL) of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[5-[4-[(1E)-3-[[(2-hydroxy-1,1-dimethylethyl)aminocarbonyl]amino]prop-1-en-1-yl]benzyl]-2-(benzyloxy)-4-methylphenyl]-D-glucitol (210 mg, 0.214 mmol) was added 20% palladium hydroxide (210 mg), and the mixture was stirred overnight under a hydrogen atmosphere at room temperature. The reaction solution was filtered through celite, and the solvent was evaporated under reduced pressure to obtain a residue. Thus obtained residue was purified with silica gel column chromatography (chloroform:methanol = 5:1) to obtain a colorless powder substance (83 mg). To a pyridine solution (1 mL) of this substance was added acetic anhydride (0.25 mL), and the mixture was stirred overnight at room temperature. To this reaction solution was added a saturated sodium bicarbonate aqueous solution and an organic layer was extracted with ethyl acetate. The organic layer was washed with brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (hexane:ethyl acetate = 2:3 to 1:2) to obtain the title compound (70 mg) as a colorless amorphous compound.

(3) Preparation of (1S)-1,5-anhydro-1-[5-[4-[3-[[(2-hydroxy-1,1-dimethylethyl)aminocarbonyl]amino]propyl]benzyl]-2-hydroxy-4-methylphenyl]-D-glucitol

To a methanol solution (1 mL) of (1S)-1-[2-(acetoxy)-5-[4-[3-[[[[2-(acetoxy)-1,1-dimethylethyl)amino]carbonyl]amino]propyl]benzyl]-4-methylphenyl]-1,5-anhydro-2,3,4,6-tetra-O-acetyl-D-glucitol (70 mg) was added sodium methoxide (a 1 M methanol solution, 0.5 mL, 0.5 mmol), and the mixture was stirred for an hour at room temperature. To this reaction solution was added dry ice, and the solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (chloroform:methanol = 5:1) to obtain the title compound (35 mg, 31%, 3 steps) as a colorless oily compound. NMR data and MS data of the compound are shown in Table 1.

Example 9

Preparation of (1S)-1,5-anhydro-1-[5-[4-[3-[[[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]aminocarbonyl]amino]propyl]benzyl]-2-hydroxy-4-methylphenyl]-D-glucitol



(1) Preparation of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[5-[4-[(1E)-3-[[[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]aminocarbonyl]amino]prop-1-en-1-yl]benzyl]-2-(benzyloxy)-4-methylphenyl]-D-glucitol

The title compound (322 mg) was obtained as a pale yellow amorphous compound according to the method as with

Example 8 (1) in which N-allyl-N'-[2-hydroxy-1,1-bis(hydroxymethyl)ethyl] urea was used instead of N-allyl-N'-(2-hydroxy-1,1-dimethylethyl) urea.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.19 (s, 3H) 3.48-4.06 (m, 17H) 4.34-5.08 (m, 11H) 5.98-6.11 (m, 1H) 6.44 (d, *J*=16.32 Hz, 1H) 6.74 (s, 1H) 6.84-7.46 (m, 31H).

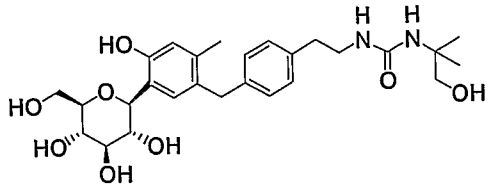
ESI/APCl m/z=1014(M+H).

(2) Preparation of (1S)-1,5-anhydro-1-[5-[4-[2-[[[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]aminocarbonyl]amino]propyl]benzyl]-2-hydroxy-4-methylphenyl]-D-glucitol

The title compound (60 mg) was obtained as a colorless powder according to the method as with Example 8 (2) in which (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[5-[4-[(1E)-3-[[[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]aminocarbonyl]amino]prop-1-en-1-yl]benzyl]-2-(benzyloxy)-4-methylphenyl)-D-glucitol was used instead of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[5-[4-[(1E)-3-[[(2-hydroxy-1,1-dimethylethyl)aminocarbonyl]amino]prop-1-en-1-yl]benzyl]-2-(benzyloxy)-4-methylphenyl)-D-glucitol. NMR data and MS data of the compound are shown in Table 1.

Example 10

Preparation of (1S)-1,5-anhydro-1-[5-[4-[2-[[(2-hydroxy-1,1-dimethylethyl)aminocarbonyl]amino]ethyl]benzyl]-2-hydroxy-4-methylphenyl]-D-glucitol



(1) Preparation of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-[4-[2-[[[(2-hydroxy-1,1-dimethylethyl)amino]carbonyl]amino]ethyl]benzyl]-4-methylphenyl)-D-glucitol

To a chloroform solution (3 mL) of 4-nitrophenyl chloroformate (0.177 g, 0.879 mmol) and pyridine (0.071 mL, 0.88 mmol), which was cooled in ice, was added dropwise a chloroform solution (3 mL) of (1S)-1-[5-[4-(2-aminoethyl)benzyl]-2-(benzyloxy)-4-methylphenyl]-1,5-anhydro-2,3,4,6-tetra-O-benzyl-D-glucitol (0.250 g, 0.293 mmol), and the mixture was stirred for 20 minutes at room temperature. After that, a chloroform solution (3 mL) of 2-amino-2-methyl-1-propanol (0.209 g, 2.344 mmol) and dimethyl sulfoxide (3 mL) were added thereto, and the mixture was stirred overnight at the same temperature. To the reaction solution was added water, and an organic layer was extracted with ethyl acetate. The organic layer was washed with water and brine (3 times), and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure to obtain a residue. Thus obtained residue was purified with NH type silica gel column chromatography (chloroform) to obtain the title compound (0.184 g, 65%) as a pale yellow oily compound.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 1.18 (s, 6H) 2.21 (s,

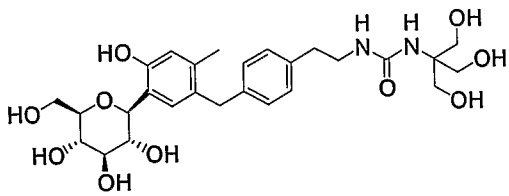
3H) 2.68 (t, *J*=6.68 Hz, 2H) 3.21-3.37 (m, 2H) 3.45-3.94 (m, 10H) 4.00 (d, *J*=10.88 Hz, 1H) 4.37-4.65 (m, 5H) 4.81-5.03 (m, 5H) 6.75 (s, 1H) 6.87-7.05 (m, 7H) 7.07-7.44 (m, 23H).

(2) Preparation of (1S)-1,5-anhydro-1-[5-[4-[2-[[(2-hydroxy-1,1-dimethylethyl)aminocarbonyl]amino]ethyl]benzyl]-2-hydroxy-4-methylphenyl]-D-glucitol

To a methanol solution (4 mL) of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-[4-[2-[[[(2-hydroxy-1,1-dimethylethyl)amino]carbonyl]amino]ethyl]benzyl]-4-methylphenyl]-D-glucitol (0.184 mg, 0.190 mmol) was added 20% palladium hydroxide (0.180 g), and the mixture was stirred under a hydrogen atmosphere at room temperature overnight. The reaction solution was filtered through celite and evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (chloroform:methanol = 17:3) to obtain the title compound (57 mg, 58%) as a colorless powder. NMR data and MS data of the compound are shown in Table 1.

Example 11

Preparation of (1S)-1,5-anhydro-1-[5-[4-[2-[[[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]aminocarbonyl]amino]ethyl]benzyl]-2-hydroxy-4-methylphenyl]-D-glucitol



(1) Preparation of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-[4-[2-[[[[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]amino]carbonyl]amino]ethyl]benzyl]-4-methylphenyl]-D-glucitol

The title compound (251 mg) was obtained as a pale yellow amorphous compound according to the method as with Example 10 (1) in which tris(hydroxymethyl)aminomethane was used instead of 2-amino-2-methyl-1-propanol.

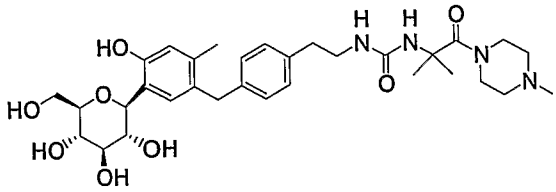
1H NMR (300 MHz, CHLOROFORM-D) δ ppm 2.22 (s, 3H) 2.68 (t, *J*=6.61 Hz, 2H) 3.24-3.35 (m, 2H) 3.41-3.99 (m, 14H) 4.00 (d, *J*=10.88 Hz, 1H) 4.38-4.70 (m, 5H) 4.79-5.03 (m, 5H) 5.27 (s, 1H) 6.76 (s, 1H) 6.87-7.44 (m, 30H).

(2) Preparation of (1S)-1,5-anhydro-1-[5-[4-[2-[[[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]aminocarbonyl]amino]ethyl]benzyl]-2-hydroxy-4-methylphenyl]-D-glucitol

The title compound (85 mg) was obtained as a colorless powder according to the method as with Example 10 (2) in which (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-[4-[2-[[[[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]amino]carbonyl]amino]ethyl]benzyl]-4-methylphenyl]-D-glucitol was used instead of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-[4-[2-[[[(2-hydroxy-1,1-dimethylethyl)amino]carbonyl]amino]ethyl]benzyl]-4-methylphenyl)-D-glucitol. NMR data and MS data of the compound are shown in Table 1.

Example 12

Preparation of (1S)-1,5-anhydro-1-[5-[4-[2-[[[1-[1-(4-methylpiperazin-1-yl)carbonyl]-1-(methyl)ethyl]aminocarbonyl]amino]ethyl]benzyl]-2-hydroxy-4-methylphenyl]-D-glucitol



(1) Preparation of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-[4-[2-[[[[1-[1-(4-methylpiperazin-1-yl)carbonyl]-1-(methyl)ethyl]amino]carbonyl]amino]ethyl]benzyl]-4-methylphenyl]-D-glucitol

The title compound (326 mg) was obtained as a pale yellow amorphous compound according to the method as with Example 10 (1) in which 2-methyl-1-(4-methylpiperazin-1-yl)-1-oxopropane-2-amine was used instead of 2-amino-2-methyl-1-propanol.

1H NMR (300 MHz, CHLOROFORM-D) δ ppm 1.41 (s, 6H) 2.20 (s, 3H) 2.26 (s, 3H) 2.31-2.37 (m, 4H) 2.70 (t, *J*=6.84 Hz, 2H) 3.29-3.41 (m, 2H) 3.50-3.94 (m, 12H) 4.00 (d, *J*=10.88 Hz, 1H) 4.37-4.67 (m, 5H) 4.81-5.02 (m, 5H) 6.75 (s, 1H) 6.88-7.44 (m, 30H).

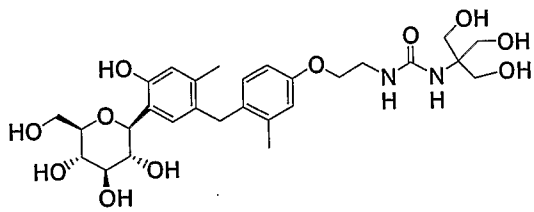
(2) Preparation of (1S)-1,5-anhydro-1-[5-[4-[2-[[[1-[1-(4-methylpiperazin-1-yl)carbonyl]-1-(methyl)ethyl]aminocarbonyl]amino]ethyl]benzyl]-2-hydroxy-4-methylphenyl]-D-glucitol

The title compound (35 mg) was obtained as a colorless powder according to the method as with Example 10 (2) in

which (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-[4-[2-[[[[1-[1-(4-methylpiperazin-1-yl)carbonyl]-1-(methyl)ethyl]amino]carbonyl]amino]ethyl)benzyl]-4-methylphenyl]-D-glucitol was used instead of (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-[4-[2-[[[(2-hydroxy-1,1-dimethylethyl)amino]carbonyl]amino]ethyl]benzyl]-4-methylphenyl]-D-glucitol. NMR data and MS data of the compound are shown in Table 1.

Example 13

Preparation of (1S)-1,5-anhydro-1-[5-[4-[2-[[[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]aminocarbonyl]amino]ethoxy]-2-methylbenzyl]-2-hydroxy-4-methylphenyl]-D-glucitol



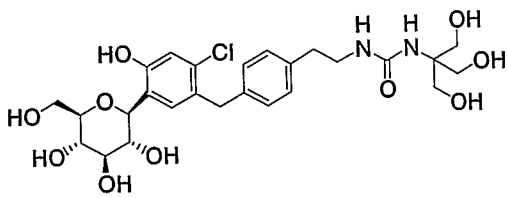
To a chloroform solution (0.5 mL) of 1,1'-carbonyldiimidazole (14 mg, 0.089 mmol) were added a chloroform solution (1.5 mL) of (1S)-1-[5-[4-(2-aminoethoxy)-2-methyl benzyl]-2-(benzyloxy)-4-methylphenyl]-1,5-anhydro-2,3,4,6-tetra-O-benzyl-D-glucitol (52 mg, 0.059 mmol) and N-methyl morpholine (9 mg), and the mixture was stirred for 15 minutes at room temperature. After that, to this reaction solution were added tris(hydroxymethyl)aminomethane (21 mg, 0.177 mmol) and

N,N-dimethylformamide (2 mL), and this reaction mixture was stirred at 60°C for 1.5 hours. After the reaction mixture was cooled to room temperature, ethyl acetate was added thereto. And the mixture was washed with water, 1 M hydrochloric acid, and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure to obtain 60 mg of a residue.

Thus obtained residue was dissolved in methanol (1 mL). And 20% palladium hydroxide (15 mg) was added thereto, and the mixture was stirred under a hydrogen atmosphere at room temperature for 2 hours. The reaction solution was filtered through celite, and evaporated under reduced pressure to obtain a residue. Thus obtained residue was purified with silica gel column chromatography (ethyl acetate:ethanol:water = 10:2:1) to obtain the title compound (30 mg, 86%) as a colorless powder. NMR data and MS data of the compound are shown in Table 1.

Example 14

Preparation of (1S)-1,5-anhydro-1-[4-chloro-5-[4-[2-[[[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]aminocarbonyl]amino]ethyl]benzyl]-2-hydroxyphenyl]-D-glucitol



To a chloroform solution (1 mL) of 1,1'-carbonyldiimidazole (10.8 mg, 0.0669 mmol) were added a

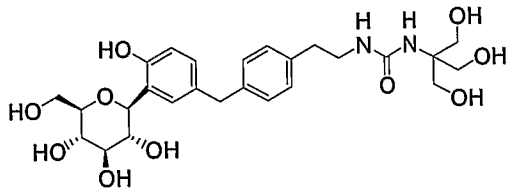
chloroform solution (1 mL) of (1S)-1-[5-[4-(2-aminoethyl)benzyl]-2-(benzyloxy)-4-chlorophenyl]-1,5-anhydro-2,3,4,6-tetra-O-benzyl-D-glucitol (39.0 mg, 0.0446 mmol) and N-methyl morpholine (7.36 μL), and the mixture was stirred for 10 minutes at room temperature. After that, to this reaction solution were added tris(hydroxymethyl)aminomethane (16.2 mg, 0.134 mmol) and N,N-dimethylformamide (1 mL), and this reaction mixture was stirred at 60°C for 2 hours. After the reaction mixture was cooled to room temperature, ethyl acetate was added thereto. And the mixture was washed with water, 1 M hydrochloric acid, and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure to obtain 41.2 mg of a residue.

Thus obtained residue (22.3 mg, 0.022 mmol) was dissolved in chloroform (250 μL) and ethanethiol (250 μL). And to this solution cooled in ice was added $BF_3 \cdot Et_2O$ (50 μL), and the mixture was stirred at the same temperature for 2 hours. The solvent was evaporated and thus obtained residue was purified with silica gel column chromatography (ethyl acetate:ethanol:water = 10:2:1 and then methanol) to obtain the title compound (10.8 mg, 86%) as a colorless amorphous compound. NMR data and MS data of the compound are shown in Table 1.

Example 15

Preparation of (1S)-1,5-anhydro-1-[5-[4-[2-[[[2-hydroxy-1,1-

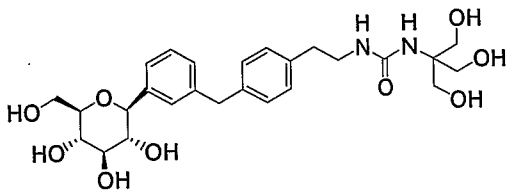
bis(hydroxymethyl)ethyl]aminocarbonyl]amino]ethyl]benzyl]-2-hydroxyphenyl]-D-glucitol



The title compound (8.5 mg, 93%) was obtained as a colorless oily compound according to the method as with Example 13 in which (1S)-1-[5-[4-(2-aminoethyl)benzyl]-2-(benzyloxy)-4-chlorophenyl]-1,5-anhydro-2,3,4,6-tetra-O-benzyl-D-glucitol was used instead of (1S)-1-[5-[4-(2-aminoethoxy)-2-methyl benzyl]-2-(benzyloxy)-4-methylphenyl]-1,5-anhydro-2,3,4,6-tetra-O-benzyl-D-glucitol. NMR data and MS data of the compound are shown in Table 1.

Example 16

Preparation of (1S)-1,5-anhydro-1-[3-[4-[2-[[[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]aminocarbonyl]amino]ethyl]benzyl]phenyl]-D-glucitol

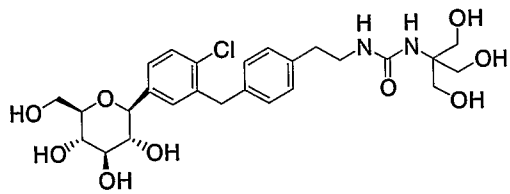


A crude product of the title compound was obtained according to the method as with Example 13 in which (1S)-1-[3-[4-(2-aminoethyl)benzyl]-4-chlorophenyl]-1,5-anhydro-2,3,4,6-tetra-O-benzyl-D-glucitol was used instead of (1S)-1-[5-[4-(2-aminoethoxy)-2-methyl benzyl]-2-(benzyloxy)-4-methylphenyl]-1,5-anhydro-2,3,4,6-tetra-O-benzyl-D-glucitol. After that, the crude product was purified with HPLC

(0.025% acetic acid aqueous solution:acetonitrile = 3:1, YMC-Pack ODS-AM 150 x 10 mm I.D., 5.0 mL/min., λ = 210 nM) to obtain the title compound (13 mg, 15%) as a colorless amorphous compound. NMR data and MS data of the compound are shown in Table 1.

Example 17

Preparation of (1S)-1,5-anhydro-1-[4-chloro-3-[4-[2-[[[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]aminocarbonyl]amino]ethyl]benzyl]phenyl]-D-glucitol

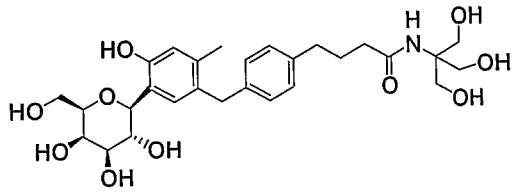


A crude product of the title compound was obtained according to the method as with Example 14 in which (1S)-1-[3-[4-(2-aminoethyl)benzyl]-4-chlorophenyl]-1,5-anhydro-2,3,4,6-tetra-O-benzyl-D-glucitol was used instead of (1S)-1-[5-[4-(2-aminoethyl)benzyl]-2-(benzyloxy)-4-chlorophenyl]-1,5-anhydro-2,3,4,6-tetra-O-benzyl-D-glucitol. After that, the crude product was purified with HPLC (0.025% acetic acid aqueous solution:acetonitrile = 7:3, Waters Sunfire Prep C, 150 x 19 mm I.D., 8.0 mL/min., λ = 210 nM) to obtain the title compound (12 mg, 17%) as a colorless amorphous compound.

NMR data and MS data of the compound are shown in Table 1.

Example 18

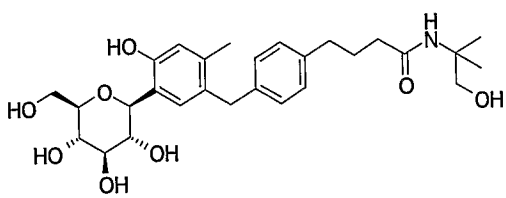
Preparation of (1S)-1,5-anhydro-1-[2-hydroxy-5-[4-[4-[[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]amino]-4-oxobutyl]benzyl]-4-methylphenyl]-D-galactitol

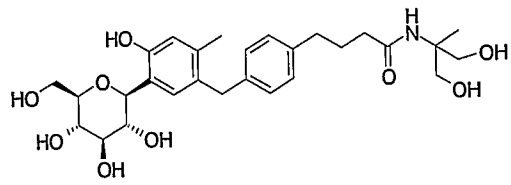
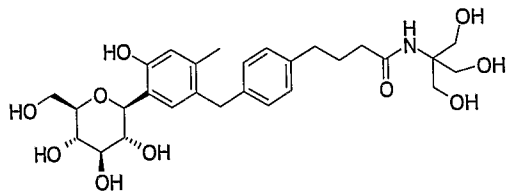
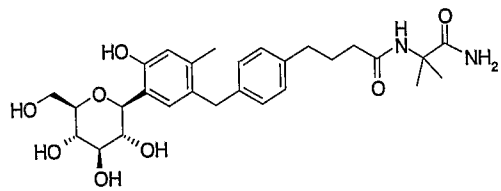
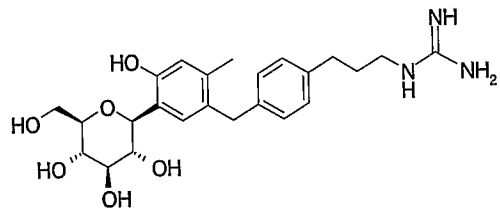
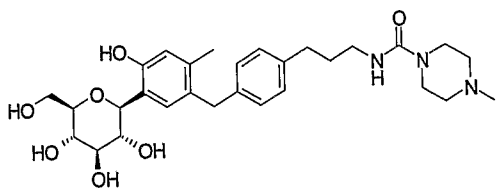


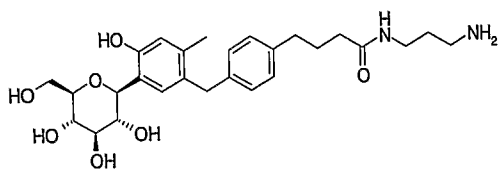
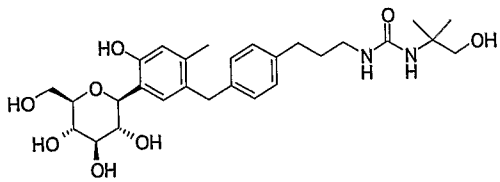
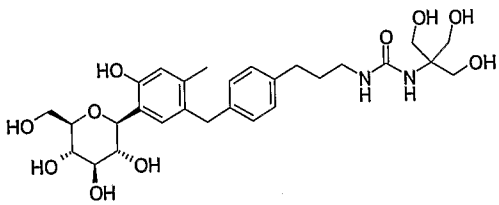
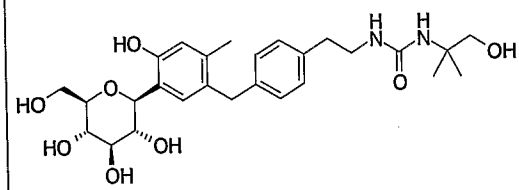
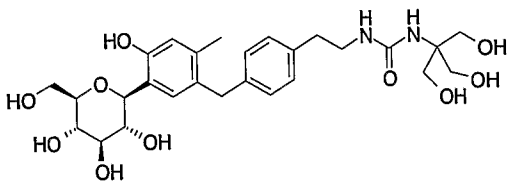
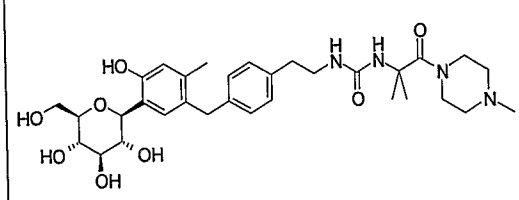
The title compound (37 mg, 47%) was obtained as a colorless powder from (1S)-1,5-anhydro-2,3,4,6-tetra-O-benzyl-1-[2-(benzyloxy)-5-[4-[(1E)-3-carboxyprop-1-en-1-yl]benzyl]-4-methylphenyl]-D-galactitol (199 mg, 0.222 mmol) according to the method as with Example 3. NMR data and MS data of the compound are shown in Table 1.

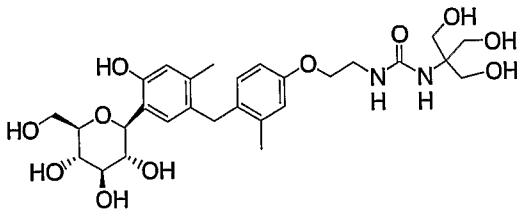
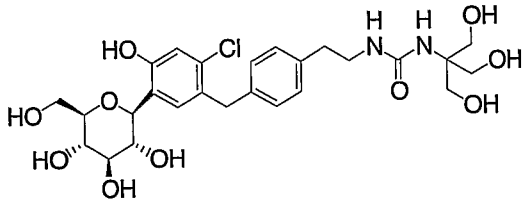
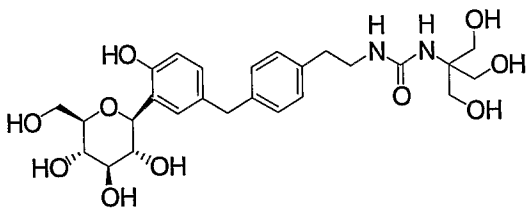
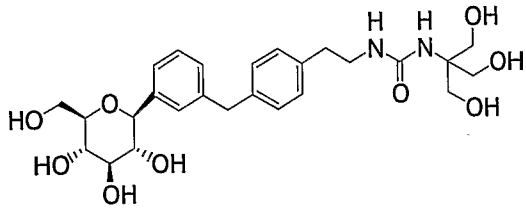
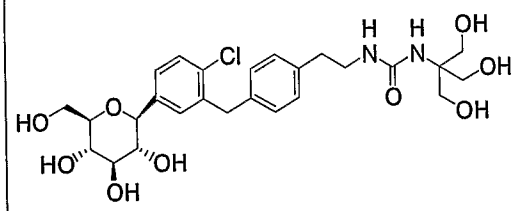
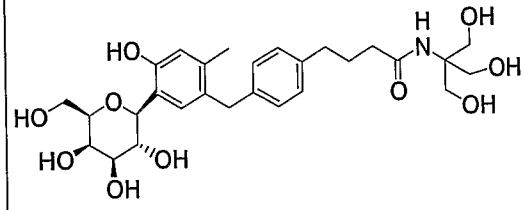
Furthermore, compounds 19 to 36 were also synthesized from corresponding materials in accordance with Reference Examples and Examples.

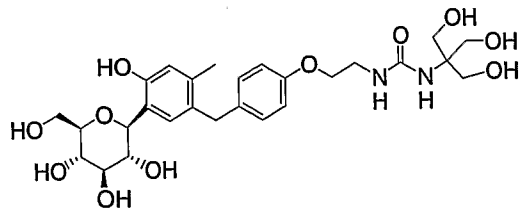
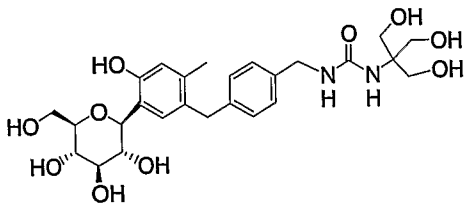
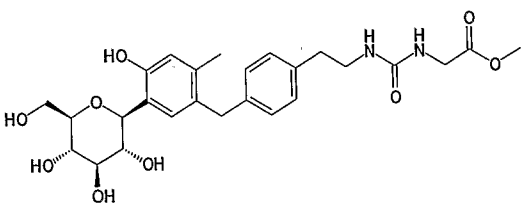
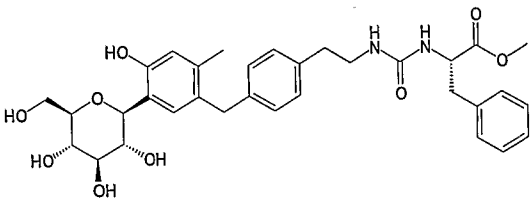
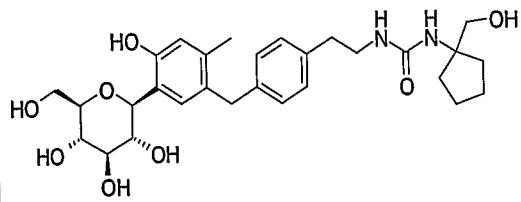
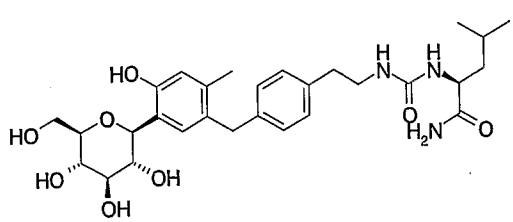
[Table 1]

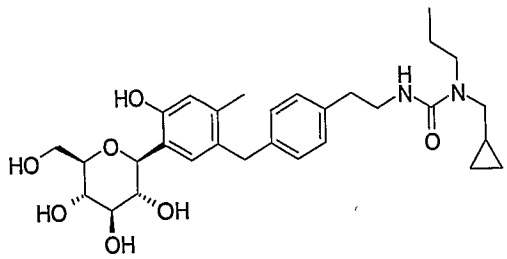
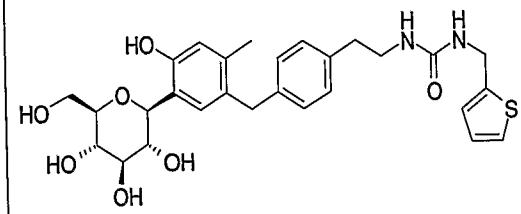
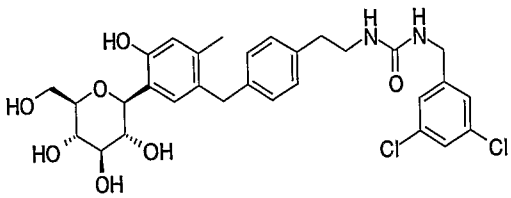
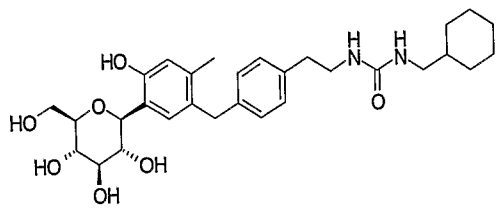
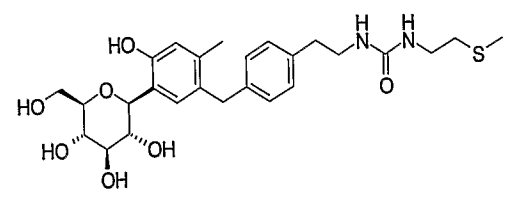
Compound No	structure	NMR (solvent, methanol -d_4), MS
1		1H NMR (600 MHz) δ ppm 1.25 (s, 6 H) 1.81 - 1.89 (m, 2 H) 2.09 (s, 3 H) 2.12 - 2.18 (m, 2 H) 2.54 - 2.59 (m, 2 H) 3.38 - 3.50 (m, 3 H) 3.53 - 3.57 (m, 3 H) 3.70 (dd, *J*=12.15, 5.27 Hz, 1 H) 3.84 - 3.89 (m, 3 H) 4.51 (d, *J*=9.63 Hz, 1 H) 6.63 (s, 1 H) 6.99 - 7.08 (m, 4 H) 7.12 (s, 1 H). ESI m/z = 518(M+H).

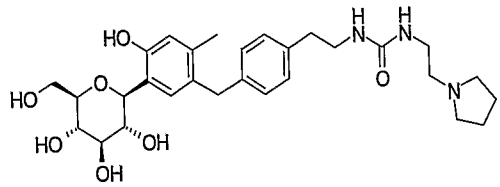
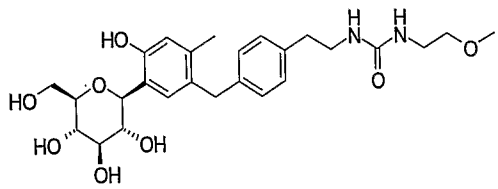
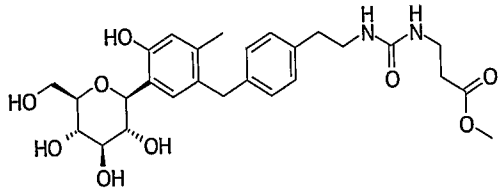
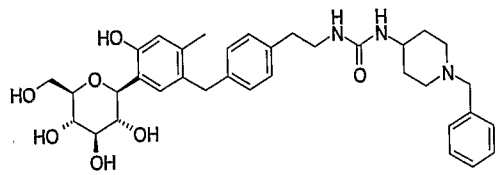
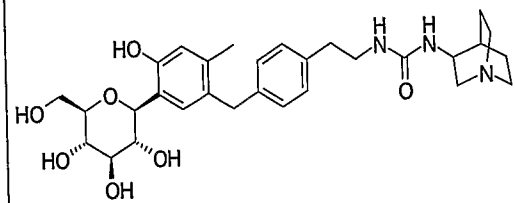
2		1H NMR (600 MHz) δ ppm 1.22 (s, 3 H) 1.80 - 1.91 (m, 2 H) 2.09 (s, 3 H) 2.15 - 2.23 (m, 2 H) 2.58 (t, *J*=7.57 Hz, 2 H) 3.37 - 3.50 (m, 3 H) 3.51 - 3.73 (m, 6 H) 3.83 - 3.90 (m, 3 H) 4.51 (d, *J*=9.63 Hz, 1 H) 6.63 (s, 1 H) 6.99 - 7.09 (m, 4 H) 7.12 (s, 1 H). ESI m/z = 556(M+Na).
3		1H NMR (600 MHz) δ ppm 1.84 - 1.93 (m, 2 H) 2.10 (s, 3 H) 2.21 - 2.27 (m, 2 H) 2.59 (t, *J*=7.57 Hz, 2 H) 3.37 - 3.44 (m, 2 H) 3.48 (t, *J*=8.48 Hz, 1 H) 3.53 - 3.59 (m, 1 H) 3.70 (s, 7 H) 3.83 - 3.90 (m, 3 H) 4.51 (d, *J*=9.63 Hz, 1 H) 6.63 (s, 1 H) 6.99 - 7.10 (m, 4 H) 7.11 (s, 1 H). ESI m/z = 572(M+Na).
4		1H NMR (600 MHz) δ ppm 1.44 (s, 6 H) 1.82 - 1.90 (m, 2 H) 2.09 (s, 3 H) 2.19 (t, *J*=7.57 Hz, 2 H) 2.57 (t, *J*=7.57 Hz, 2 H) 3.37 - 3.52 (m, 2 H) 3.56 (t, *J*=9.17 Hz, 2 H) 3.70 (dd, *J*=11.92, 5.04 Hz, 1 H) 3.82 - 3.90 (m, 3 H) 4.51 (d, *J*=9.63 Hz, 1 H) 6.63 (s, 1 H) 6.98 - 7.08 (m, 4 H) 7.11 (s, 1 H). ESI m/z = 553(M+Na).
5		1H NMR (600 MHz) δ ppm 1.82 - 1.91 (m, 2 H) 2.10 (s, 3 H) 2.61 - 2.67 (m, 2 H) 3.15 (t, *J*=7.11 Hz, 2 H) 3.37 - 3.44 (m, 2 H) 3.48 (t, *J*=8.71 Hz, 1 H) 3.55 (t, *J*=9.17 Hz, 1 H) 3.70 (dd, *J*=11.92, 5.04 Hz, 1 H) 3.83 - 3.91 (m, 3 H) 4.51 (d, *J*=9.63 Hz, 1 H) 6.63 (s, 1 H) 7.01 - 7.13 (m, 5 H). ESI m/z = 460(M+H).
6		1H NMR (600 MHz) δ ppm 1.74 - 1.82 (m, 2 H) 2.10 (s, 3 H) 2.29 (s, 3 H) 2.37 - 2.42 (m, 4 H) 2.54 - 2.60 (m, 2 H) 3.15 (t, *J*=7.11 Hz, 2 H) 3.33 - 3.44 (m, 6H) 3.48 (t, *J*=8.94 Hz, 1 H) 3.53 - 3.58 (m, 1 H) 3.70 (dd, *J*=12.15, 5.27 Hz, 1 H) 3.83 - 3.89 (m, 3 H) 4.51 (d, *J*=9.63 Hz, 1 H) 6.63 (s, 1 H) 6.99 - 7.09 (m, 4 H) 7.12 (s, 1 H). ESI m/z = 544(M+H).

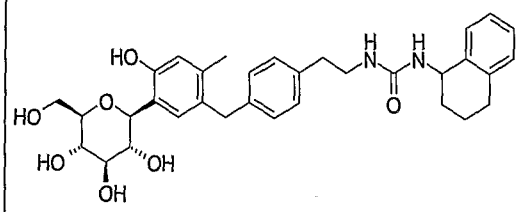
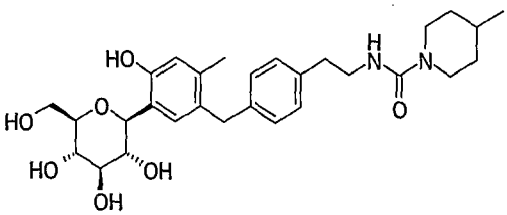
7		1H NMR (600 MHz) δ ppm 1.77 - 1.84 (m, 2 H) 1.85 - 1.93 (m, 2 H) 2.10 (s, 3 H) 2.17 - 2.23 (m, 2 H) 2.58 (t, *J*=7.57 Hz, 2 H) 2.87 - 2.91 (m, 2 H) 3.24 (t, *J*=6.65 Hz, 2 H) 3.37 - 3.51 (m, 3 H) 3.53 - 3.58 (m, 1 H) 3.70 (dd, *J*=12.15, 5.27 Hz, 1 H) 3.84 - 3.88 (m, 3 H) 4.51 (d, *J*=9.63 Hz, 1 H) 6.63 (s, 1 H) 7.01 - 7.08 (m, 4 H) 7.11 (s, 1 H). ESI m/z = 503(M+H).
8		1H NMR (600 MHz) δ ppm 1.23 (s, 6 H) 1.68 - 1.76 (m, 2 H) 2.09 (s, 3 H) 2.54 - 2.60 (m, 2 H) 3.05 (t, *J*=6.88 Hz, 2 H) 3.37 - 3.44 (m, 2 H) 3.45 - 3.58 (m, 4 H) 3.70 (dd, *J*=11.92, 5.04 Hz, 1 H) 3.83 - 3.90 (m, 3 H) 4.51 (d, *J*=9.63 Hz, 1 H) 6.63 (s, 1 H) 6.98 - 7.03 (m, 2 H) 7.03 - 7.08 (m, 2 H) 7.12 (s, 1 H). ESI m/z = 533 (M+H), 531 (M-H).
9		1H NMR (600 MHz) δ ppm 1.70 - 1.77 (m, 2 H) 2.09 (s, 3 H) 2.54 - 2.62 (m, 2 H) 3.07 (t, *J*=6.88 Hz, 2 H) 3.36 - 3.60 (m, 5 H) 3.61 - 3.73 (m, 6 H) 3.82 - 3.91 (m, 3 H) 4.51 (d, *J*=9.63 Hz, 1 H) 6.63 (s, 1 H) 6.99 - 7.08 (m, 4 H) 7.08 - 7.15 (m, 1 H). ESI m/z=587(M+Na).
10		1H NMR (300 MHz) δ ppm 1.25 (s, 6 H) 2.13 (s, 3 H) 2.72 (t, *J*=7.07 Hz, 2 H) 3.25 - 3.37 (m, 3 H) 3.38 - 3.80 (m, 6 H) 3.86 - 3.96 (m, 3 H) 4.56 (d, *J*=9.33 Hz, 1 H) 6.68 (s, 1 H) 7.03 - 7.19 (m, 5 H). ESI m/z = 519 (M+H), 541 (M+Na)
11		1H NMR (600 MHz) δ ppm 2.09 (s, 3 H) 2.68 (t, *J*=7.34 Hz, 2 H) 3.24 - 3.32 (m, 3 H) 3.36 - 3.66 (m, 9 H) 3.68 - 3.74 (m, 1 H) 3.81 - 3.90 (m, 3 H) 4.52 (d, *J*=9.63 Hz, 1 H) 6.64 (s, 1 H) 7.00 - 7.14 (m, 5 H). ESI m/z = 552 (M+H), 574 (M+Na)
12		1H NMR (600 MHz) δ ppm 1.39 (s, 6 H) 2.10 (s, 3 H) 2.23 (s, 3 H) 2.70 (t, *J*=7.11 Hz, 2 H) 3.26 - 3.91 (m, 18 H) 4.52 (d, *J*=9.63 Hz, 1 H) 6.63 (s, 1 H) 7.02 - 7.14 (m, 5 H). ESI m/z = 616 (M+H), 637 (M+Na).

13		1H NMR (300 MHz) δ ppm 2.12 (s, 3 H) 2.25 (s, 3 H) 3.34 - 3.57 (m, 6 H) 3.66 (s, 6 H) 3.67 - 3.71 (m, 1 H) 3.77 (s, 2 H) 3.79 - 3.89 (m, 1 H) 3.96 (t, *J*=5.28 Hz, 2 H) 4.45 (d, *J*=9.48 Hz, 1 H) 6.58 - 6.65 (m, 1 H) 6.67 (s, 1 H) 6.69 - 6.81 (m, 2 H) 6.90 (s, 1 H). ESI m/z = 581 (M+H), 603 (M+Na).
14		1H NMR (600 MHz) δ ppm 2.69 (t, *J*=7.11 Hz, 2 H) 3.24 - 3.28 (m, 2 H) 3.34 - 3.41 (m, 2 H) 3.42 - 3.50 (m, 2 H) 3.60 (s, 6 H) 3.67 (dd, *J*=12.15, 5.27 Hz, 1 H) 3.83 (dd, *J*=11.92, 1.83 Hz, 1 H) 3.89 - 4.01 (m, 2 H) 4.51 (d, *J*=9.17 Hz, 1 H) 6.81 (s, 1 H) 7.08 (s, 4 H) 7.24 (s, 1 H). ESI m/z = 571 (M+H), 593 (M+Na).
15		1H NMR (600 MHz) δ ppm 2.69 (t, *J*=7.11 Hz, 2 H) 3.24 - 3.28 (m, 2 H) 3.34 - 3.43 (m, 2 H) 3.46 (t, *J*=8.48 Hz, 1 H) 3.52 (t, *J*=9.17 Hz, 1 H) 3.60 (s, 6 H) 3.68 (dd, *J*=11.92, 5.04 Hz, 1 H) 3.77 - 3.89 (m, 3 H) 4.52 (d, *J*=9.63 Hz, 1 H) 6.70 (d, *J*=8.25 Hz, 1 H) 6.92 (dd, *J*=8.25, 1.83 Hz, 1 H) 7.09 (s, 4 H) 7.18 (d, *J*=2.29 Hz, 1 H). ESI m/z = 537 (M+H), 559 (M+Na).
16		1H NMR (300 MHz) δ ppm 2.71 (t, *J*=7.07 Hz, 2 H) 3.25 - 3.49 (m, 6 H) 3.62 (s, 6 H) 3.64 - 3.73 (m, 1 H) 3.84 - 3.95 (m, 3 H) 4.09 (d, *J*=9.17 Hz, 1 H) 7.08 - 7.17 (m, 5 H) 7.21 - 7.31 (m, 3 H). ESI m/z = 521 ($M+NH_4$).
17		1H NMR (300 MHz) δ ppm 2.71 (t, *J*=7.07 Hz, 2 H) 3.21 - 3.48 (m, 6 H) 3.61 (s, 6 H) 3.64 - 3.73 (m, *J*=11.97, 5.13 Hz, 1 H) 3.83 - 3.91 (m, 1 H) 3.99 - 4.14 (m, 3 H) 7.12 (s, 4 H) 7.24 - 7.38 (m, 3 H). ESI m/z = 555 (M+H), 577 (M+Na).
18		1H NMR (600 MHz) δ ppm 1.85 - 1.95 (m, 2 H) 2.10 (s, 3 H) 2.38 (t, *J*=7.34 Hz, 2 H) 2.60 (t, *J*=7.34 Hz, 2 H) 3.56 - 3.61 (m, 6 H) 3.61 - 3.68 (m, 1 H) 3.68 - 3.74 (m, 1 H) 3.74 - 3.80 (m, 1 H) 3.85 - 3.91 (m, 2 H) 3.96 (d, *J*=3.21 Hz, 1 H) 4.14 (s, 2 H) 4.42 (d, *J*=9.63 Hz, 1 H) 6.63 (s, 1 H) 7.00 - 7.09 (m, 4 H) 7.13 - 7.20 (m, 1 H). ESI m/z = 550 (M+H), 548 ($M-H^-$).

19		1H NMR (300 MHz) δ ppm 2.09 (s, 3 H) 3.37 - 3.51 (m, 6 H) 3.52 - 3.60 (m, 1 H) 3.65 (s, 6 H) 3.68 - 3.76 (m, 1 H) 3.80 - 3.91 (m, 3 H) 3.95 (t, *J*=5.13 Hz, 2 H) 4.51 (d, *J*=9.33 Hz, 1 H) 6.63 (s, 1 H) 6.80 (d, *J*=8.24 Hz, 2 H) 7.01 (d, *J*=8.24 Hz, 2 H) 7.10 (s, 1 H)
20		1H NMR (300 MHz) δ ppm 2.08 (s, 3 H) 3.38 - 3.61 (m, 4 H) 3.65 (s, 6 H) 3.67 - 3.73 (m, 1 H) 3.81 - 3.94 (m, 3 H) 4.22 (s, 2 H) 4.51 (d, *J*=9.48 Hz, 1 H) 6.63 (s, 1 H) 7.03 - 7.09 (m, 2 H) 7.11 - 7.19 (m, 3 H). ESI m/z = 537 (M+H).
21		1H NMR (300 MHz) δ ppm 2.10 (s, 3 H) 2.72 (t, *J*=7.07 Hz, 2 H) 3.29 - 3.37 (m, 2 H) 3.38 - 3.46 (m, 3 H) 3.49 (t, 1 H) 3.56 (t, *J*=8.32 Hz, 1 H) 3.70 (s, 3 H) 3.81 - 3.91 (m, 5 H) 4.51 (d, *J*=9.64 Hz, 1 H) 6.63 (s, 1 H) 7.00 - 7.15 (m, 5 H). ESI m/z = 541 (M+Na).
22		1H NMR (300 MHz) δ ppm 2.09 (s, 3 H) 2.66 (t, *J*=7.31 Hz, 2 H) 2.93 (dd, 1 H) 3.06 (dd, 1 H) 3.21 - 3.28 (m, 2 H) 3.39 - 3.45 (m, 2 H) 3.47 (t, 1 H) 3.57 (t, *J*=8.86 Hz, 1 H) 3.62 - 3.75 (m, 4 H) 3.87 (t, *J*=5.44 Hz, 3 H) 4.47 - 4.59 (m, 2 H) 6.63 (s, 1 H) 6.98 - 7.08 (m, 4 H) 7.10 - 7.19 (m, 3 H) 7.18 - 7.30 (m, 3 H). ESI m/z = 631 (M+Na).
23		1H NMR (600 MHz) δ ppm 1.54 - 1.77 (m, 8 H) 2.07 (s, 3 H) 2.67 (t, *J*=7.11 Hz, 2 H) 3.24 - 3.27 (m, 2 H) 3.36 - 3.42 (m, 2 H) 3.46 (t, *J*=8.71 Hz, 1 H) 3.53 (d, *J*=9.63 Hz, 1 H) 3.56 (s, 2 H) 3.68 (dd, *J*=11.92, 5.50 Hz, 1 H) 3.81 - 3.87 (m, 3 H) 4.50 (d, *J*=9.63 Hz, 1 H) 6.61 (s, 1 H) 7.02 (d, 2 H) 7.06 (d, 2 H) 7.10 (s, 1 H). ESI m/z = 567 (M+Na). 543 (M-H).
24		1H NMR (600 MHz, METHANOL-d_3) δ ppm 0.87 - 0.96 (m, 6 H) 1.40 - 1.55 (m, 2 H) 1.61 - 1.70 (m, 1 H) 2.08 (s, 3 H) 2.69 (t, *J*=7.11 Hz, 2 H) 3.30 - 3.34 (m, 2 H) 3.35 - 3.42 (m, 2 H) 3.46 (t, *J*=8.25 Hz, 1 H) 3.54 (t, *J*=9.17 Hz, 1 H) 3.68 (dd, *J*=11.92, 5.04 Hz, 1 H) 3.80 - 3.87 (m, 3 H) 4.18 (dd, *J*=10.32, 4.81 Hz, 1 H) 4.50 (d, *J*=9.63 Hz, 1 H) 6.61 (s, 1 H) 6.97 - 7.11 (m, 5 H). ESI m/z = 582 (M+Na). 558 (M-H).

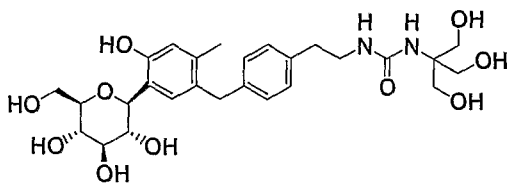
25		1H NMR (600 MHz, METHANOL-d_3) δ ppm 0.16 (q, 2 H) 0.44 (q, J=5.96 Hz, 2 H) 0.83 (t, J=7.34 Hz, 3 H) 0.86 - 0.96 (m, 1 H) 1.45 - 1.54 (m, 2 H) 2.06 (s, 3 H) 2.72 (t, J=7.34 Hz, 2 H) 3.08 (d, J=6.42 Hz, 2 H) 3.17 (t, 2 H) 3.32 (m, 2 H) 3.36 - 3.43 (m, 2 H) 3.46 (t, J=8.71 Hz, 1 H) 3.54 (t, 1 H) 3.69 (dd, J=11.92, 5.04 Hz, 1 H) 3.81 - 3.87 (m, 3 H) 4.50 (d, J=9.63 Hz, 1 H) 6.60 (s, 1 H) 7.01 (d, J=8.25 Hz, 2 H) 7.06 (d, 2 H) 7.11 (s, 1 H). ESI m/z = 565 (M+Na). 541 (M-H).
26		1H NMR (600 MHz) δ ppm 2.07 (s, 3 H) 2.69 (t, J=7.11 Hz, 2 H) 3.29 - 3.33 (m, 2 H) 3.36 - 3.42 (m, 2 H) 3.46 (t, J=8.71 Hz, 1 H) 3.54 (t, J=9.40 Hz, 1 H) 3.68 (dd, J=11.92, 5.50 Hz, 1 H) 3.81 - 3.87 (m, 3 H) 4.42 (s, 2 H) 4.49 (d, J=9.63 Hz, 1 H) 6.61 (s, 1 H) 6.87 - 6.91 (m, 2 H) 7.01 (d, 2 H) 7.05 (d, 2 H) 7.10 (s, 1 H) 7.22 (dd, J=4.36, 2.06 Hz, 1 H). ESI m/z = 565 (M+Na). 541 (M-H).
27		1H NMR (600 MHz) δ ppm 2.07 (s, 3 H) 2.70 (t, J=6.88 Hz, 2 H) 3.30 - 3.34 (m, 2 H) 3.36 - 3.42 (m, 2 H) 3.46 (t, J=8.71 Hz, 1 H) 3.53 (t, 1 H) 3.68 (dd, J=11.92, 5.04 Hz, 1 H) 3.81 - 3.88 (m, 3 H) 4.23 (s, 2 H) 4.49 (d, J=9.63 Hz, 1 H) 6.61 (s, 1 H) 7.02 (d, 2 H) 7.06 (d, 2 H) 7.10 (s, 1 H) 7.21 (d, 2 H) 7.27 (d, 1 H). ESI m/z = 605 (M+H). 603 (M-H).
28		1H NMR (600 MHz) δ ppm 0.82 - 0.96 (m, 2 H) 1.13 - 1.30 (m, 3 H) 1.31 - 1.42 (m, 1 H) 1.60 - 1.77 (m, 5 H) 2.07 (s, 3 H) 2.68 (t, J=7.11 Hz, 2 H) 2.89 (d, J=6.88 Hz, 2 H) 3.23 - 3.32 (m, 2 H) 3.35 - 3.41 (m, 2 H) 3.46 (t, J=8.71 Hz, 1 H) 3.54 (t, J=9.17 Hz, 1 H) 3.68 (dd, J=11.92, 5.04 Hz, 1 H) 3.80 - 3.87 (m, 3 H) 4.49 (d, J=9.63 Hz, 1 H) 6.61 (s, 1 H) 7.01 (d, 2 H) 7.06 (d, 2 H) 7.10 (s, 1 H). ESI m/z = 543 (M+H). 541 (M-H).
29		1H NMR (600 MHz) δ ppm 2.03 - 2.11 (m, 6 H) 2.52 (t, J=6.88 Hz, 2 H) 2.69 (t, J=7.11 Hz, 2 H) 3.24 - 3.27 (m, 2 H) 3.28 - 3.31 (m, 2 H) 3.35 - 3.42 (m, 2 H) 3.47 (t, 1 H) 3.53 (t, 1 H) 3.68 (dd, J=11.92, 5.04 Hz, 1 H) 3.81 - 3.87 (m, 3 H) 4.50 (d, J=9.63 Hz, 1 H) 6.61 (s, 1 H) 7.01 (d, 2 H) 7.06 (d, 2 H) 7.10 (s, 1 H). ESI m/z = 543 (M+Na). 519 (M-H).

30		1H NMR (600 MHz) δ ppm 1.77 (ddd, *J*=6.76, 3.32, 3.21 Hz, 4 H) 2.08 (s, 3 H) 2.51 - 2.57 (m, 6 H) 2.69 (t, *J*=7.11 Hz, 2 H) 3.22 (t, *J*=6.65 Hz, 2 H) 3.29 - 3.33 (m, 2 H) 3.35 - 3.42 (m, 2 H) 3.46 (t, *J*=8.71 Hz, 1 H) 3.53 (t, *J*=9.17 Hz, 1 H) 3.68 (dd, *J*=12.15, 5.27 Hz, 1 H) 3.82 - 3.87 (m, 3 H) 4.49 (d, *J*=9.63 Hz, 1 H) 6.61 (s, 1 H) 7.02 (d, 2 H) 7.06 (d, 2 H) 7.09 (s, 1 H). ESI m/z = 544 (M+H). 542 (M-H).
31		1H NMR (600 MHz) δ ppm 2.08 (s, 3 H) 2.68 (t, *J*=7.11 Hz, 2 H) 3.23 (t, *J*=5.50 Hz, 2 H) 3.24 - 3.33 (m, 5 H) 3.35 - 3.43 (m, 4 H) 3.46 (t, *J*=8.71 Hz, 1 H) 3.54 (t, *J*=9.17 Hz, 1 H) 3.68 (dd, 1 H) 3.80 - 3.88 (m, 3 H) 4.49 (d, *J*=9.63 Hz, 1 H) 6.61 (s, 1 H) 7.02 (d, 2 H) 7.06 (d, 2 H) 7.10 (s, 1 H). ESI m/z = 527 (M+Na). 503 (M-H).
32		1H NMR (600 MHz) δ ppm 2.07 (s, 3 H) 2.45 (t, *J*=6.42 Hz, 2 H) 2.67 (t, *J*=7.11 Hz, 2 H) 3.21 (t, *J*=6.88 Hz, 2 H) 3.30 - 3.35 (m, 2 H) 3.35 - 3.42 (m, 2 H) 3.46 (t, 1 H) 3.54 (dd, 1 H) 3.64 (s, 3 H) 3.68 (dd, *J*=11.92, 5.04 Hz, 1 H) 3.80 - 3.90 (m, 3 H) 4.49 (d, *J*=9.63 Hz, 1 H) 6.61 (s, 1 H) 7.01 (d, 2 H) 7.05 (d, 2 H) 7.10 (s, 1 H). ESI m/z = 555 (M+Na). 531 (M-H).
33		1H NMR (600 MHz) δ ppm 1.37 - 1.50 (m, 2 H) 1.80 - 1.89 (m, 2 H) 2.08 (s, 3 H) 2.31 (br. s., 2 H) 2.67 (t, *J*=6.88 Hz, 2 H) 2.88 (br. s., 2 H) 3.25 - 3.34 (m, 2 H) 3.35 - 3.43 (m, 2 H) 3.43 - 3.52 (m, 2 H) 3.54 (t, 1 H) 3.59 - 3.71 (m, 3 H) 3.79 - 3.87 (m, 3 H) 4.49 (d, *J*=9.63 Hz, 1 H) 6.61 (s, 1 H) 7.01 (d, 2 H) 7.05 (d, 2 H) 7.10 (s, 1 H) 7.25 - 7.37 (m, 5 H). ESI m/z = 620 (M+H). 618 (M-H).
34		1H NMR (600 MHz) δ ppm 1.40 - 1.80 (m, 4 H) 2.08 (s, 3 H) 2.35 - 2.42 (m, 1 H) 2.66 - 2.82 (m, 5 H) 3.14 - 3.21 (m, 1 H) 3.29 - 3.35 (m, 4 H) 3.35 - 3.43 (m, 2 H) 3.46 (t, *J*=8.94 Hz, 1 H) 3.53 (t, 1 H) 3.66 - 3.71 (m, 2 H) 3.81 - 3.88 (m, 3 H) 4.49 (d, *J*=9.63 Hz, 1 H) 6.61 (s, 1 H) 7.02 (d, 2 H) 7.06 (d, 2 H) 7.11 (s, 1 H). ESI m/z = 556 (M+H). 554 (M-H).

35		1H NMR (600 MHz) δ ppm 1.72 (m, 1 H) 1.73 - 1.80 (m, 1 H) 1.80 - 1.88 (m, 1 H) 1.90 - 1.97 (m, 1 H) 2.07 (s, 3 H) 2.65 - 2.81 (m, 4 H) 3.24 - 3.27 (m, 2 H) 3.31 - 3.42 (m, 3 H) 3.46 (t, *J*=8.71 Hz, 1 H) 3.54 (t, *J*=9.17 Hz, 1 H) 3.68 (dd, *J*=11.92, 5.04 Hz, 1 H) 3.80 - 3.87 (m, 3 H) 4.49 (d, *J*=9.63 Hz, 1 H) 6.60 (s, 1 H) 7.02 (d, *J*=8.25 Hz, 3 H) 7.05 - 7.12 (m, 6 H). ESI m/z = 599 (M+Na). 575 (M-H).
36		1H NMR (600 MHz) δ ppm 0.91 (d, *J*=6.42 Hz, 3 H) 0.96 - 1.05 (m, 2 H) 1.47 - 1.56 (m, 1 H) 1.58 (d, *J*=15.13 Hz, 2 H) 2.06 (s, 3 H) 2.65 - 2.73 (m, 4 H) 3.27 - 3.31 (m, 2 H) 3.35 - 3.43 (m, 2 H) 3.46 (t, *J*=8.71 Hz, 1 H) 3.54 (t, *J*=9.40 Hz, 1 H) 3.68 (dd, *J*=11.92, 5.50 Hz, 1 H) 3.81 - 3.86 (m, 3 H) 3.89 (d, *J*=12.84 Hz, 2 H) 4.50 (d, *J*=9.63 Hz, 1 H) 6.60 (s, 1 H) 7.00 (d, 2 H) 7.05 (d, 2 H) 7.10 (s, 1 H). ESI m/z = 551 (M+Na). 527 (M-H).

Example 11-1 (another preparation method of the compound of Example 11)

Preparation of (1S)-1,5-anhydro-1-[5-[4-[2-[[[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]aminocarbonyl]amino]ethyl]benzyl]-2-hydroxy-4-methylphenyl]-D-glucitol



(1) Preparation of (1S)-1,5-anhydro-2,3,4,6-tetra-O-acetyl-1-[2-acetoxy-5-[4-[2-[[[[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]amino]carbonyl]amino]ethyl]benzyl]-4-methylphenyl]-D-glucitol

To a chloroform solution (300 μL) of 1,1'-carbonyldiimidazole (7.30 mg, 0.045 mmol) were added a

chloroform solution (150 μL) of (1S)-1-[5-[4-(2-aminoethyl)benzyl]-2-acetoxy-4-methylphenyl]-1,5-anhydro-2,3,4,6-tetra-O-acetyl-D-glucitol (18.4 mg, 0.030 mmol) and N-methyl morpholine (4.95 μL, 0.045 mmol), and the mixture was stirred for 30 minutes at room temperature. After that, to this reaction solution were added tris(hydroxymethyl)aminomethane (10.9 mg, 0.09 mmol) and N,N-dimethylformamide (150 μL), and this reaction mixture was stirred at 60°C overnight. After the reaction mixture was cooled to room temperature, ethyl acetate was added thereto. And the mixture was washed with water, 1 M hydrochloric acid, and brine, and dried with anhydrous magnesium sulfate. The drying agent was filtered off, and the solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (chloroform:methanol = 95:5) to obtain the title compound (7.9 mg, 35%) as a colorless amorphous compound.

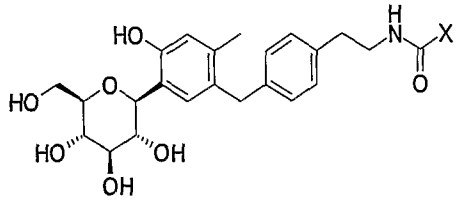
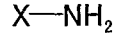
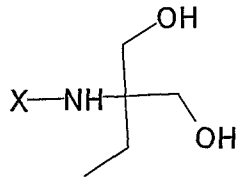
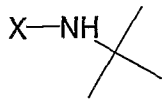
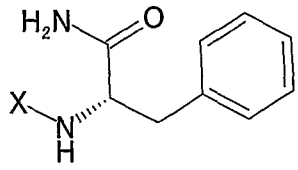
(2) Preparation of (1S)-1,5-anhydro-1-[5-[4-[2-[[[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]aminocarbonyl]amino]ethyl]benzyl]-2-hydroxy-4-methylphenyl]-D-glucitol

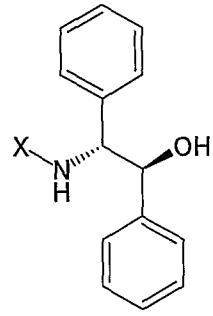
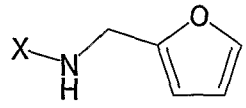
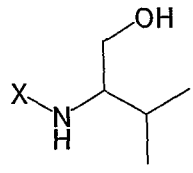
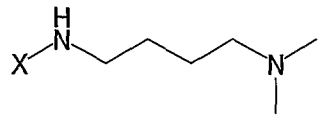
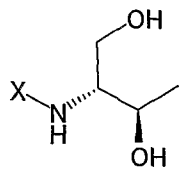
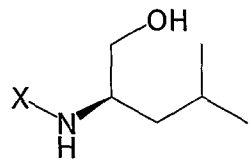
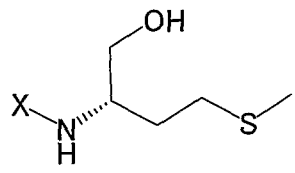
To a methanol solution (600 μL) of (1S)-1,5-anhydro-2,3,4,6-tetra-O-acetyl-1-[2-acetoxy-5-[4-[2-[[[[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]amino]carbonyl]amino]ethyl]benzyl]-4-methylphenyl]-D-glucitol (7.9 mg, 0.0104 mmol) was added a 2.5 wt. % methanol solution of sodium methoxide (34 μL,

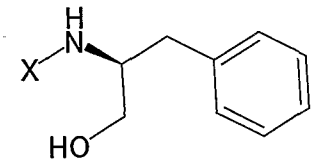
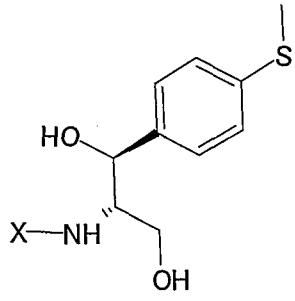
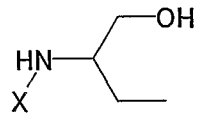
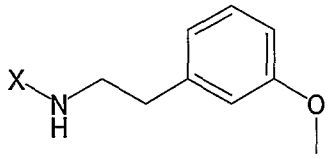
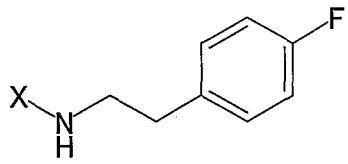
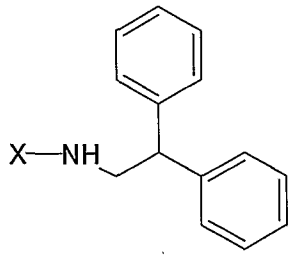
0.015 mmol) , and the mixture was stirred for an hour at room temperature. The solvent was evaporated under reduced pressure. Thus obtained residue was purified with silica gel column chromatography (methanol) to obtain the title compound (3.0 mg, 52%) as a colorless amorphous compound.

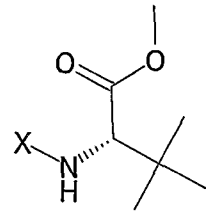
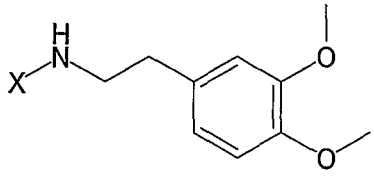
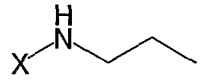
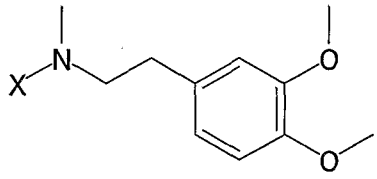
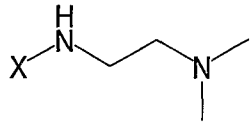
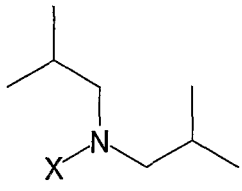
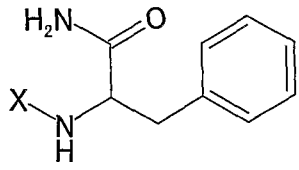
Compounds 37 to 188 were synthesized by using corresponding amines in accordance with the method as with Example 11-1.

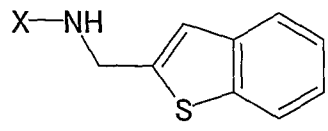
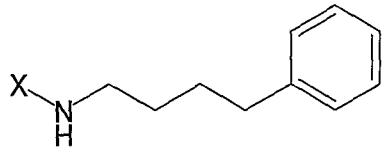
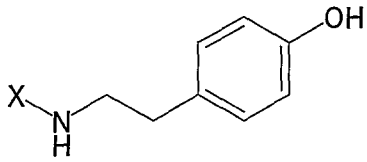
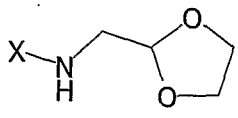
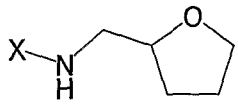
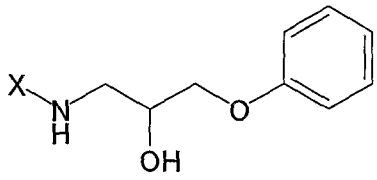
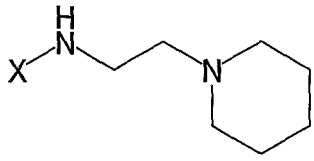
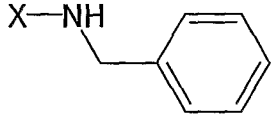
[Table 2]

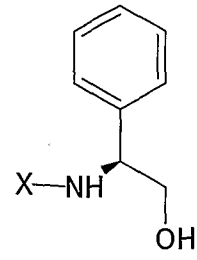
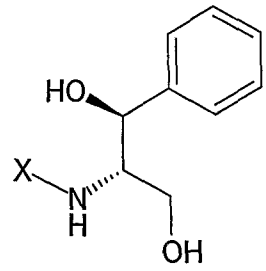
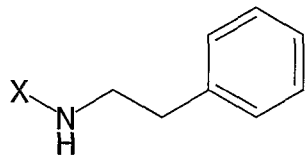
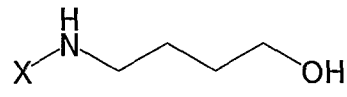
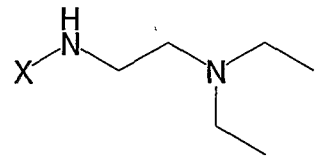
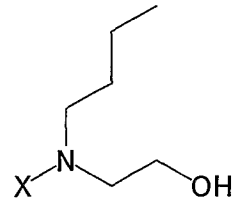
compound No.		formula	Exact MS	MS (M+H) or (M+Na)	MS (M-H)	ionization
37		C23H30N2O7	446.21	484	460	ESI
38		C28H40N2O9	548.27	571	547	ESI
39		C27H38N2O7	502.27	525	501	ESI
40		C32H39N3O8	593.27	616	592	ESI

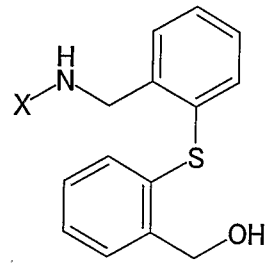
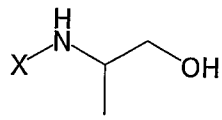
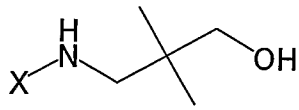
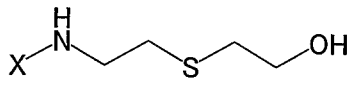
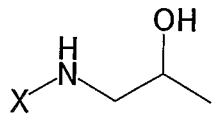
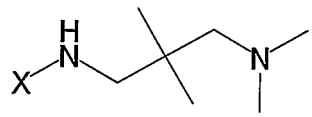
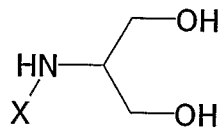
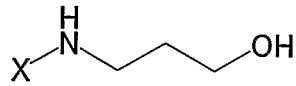
41		C37H42N2O8	642.29	665	641	ESI
42		C28H34N2O8	526.23	527	525	ESI
43		C28H40N2O8	532.28	555	531	ESI
44		C29H43N3O7	545.31	546	544	ESI
45		C27H38N2O9	534.26	557	533	ESI
46		C29H42N2O8	546.29	569	545	ESI
47		C28H40N2O8S	564.25	587	563	ESI

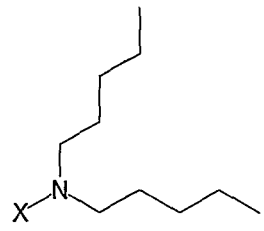
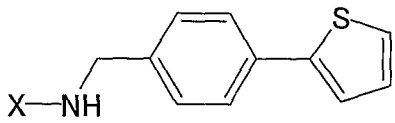
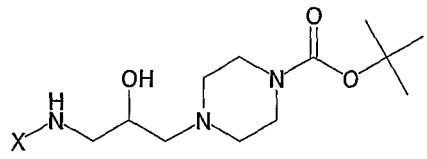
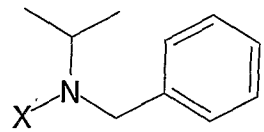
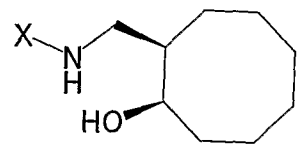
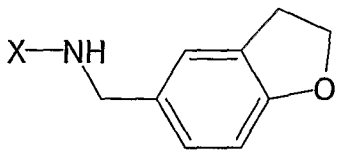
48		C32H40N2O8	580.28	603	579	ESI
49		C33H42N2O9S	642.26	665	641	ESI
50		C27H38N2O8	518.26	541	517	ESI
51		C32H40N2O8	580.28	603	579	ESI
52		C31H37FN2O7	568.26	591	567	ESI
53		C37H42N2O7	626.3	649	625	ESI

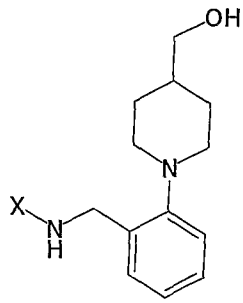
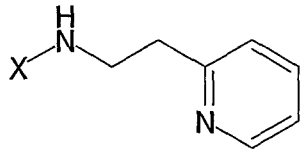
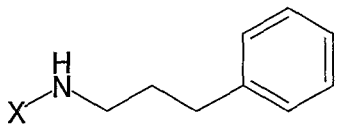
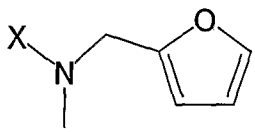
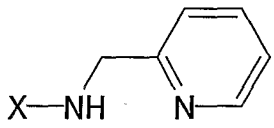
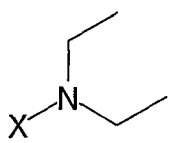
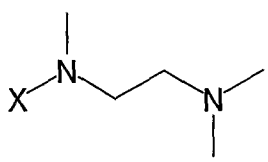
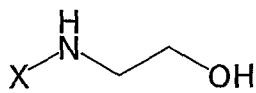
54		C30H42N2O9	574.29	597	573	ESI
55		C33H42N2O9	610.29	633	609	ESI
56		C26H36N2O7	488.25	511	487	ESI
57		C34H44N2O9	624.3	625	623	ESI
58		C27H39N3O7	517.28	518	516	ESI
59		C31H46N2O7	558.33	581	557	ESI
60		C32H39N3O8	593.27	616	ND	ESI

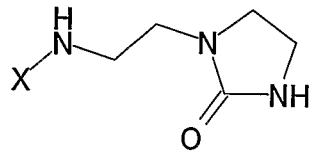
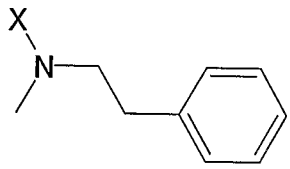
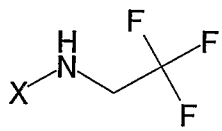
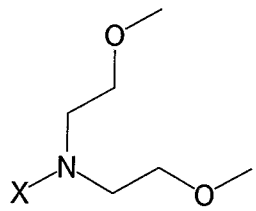
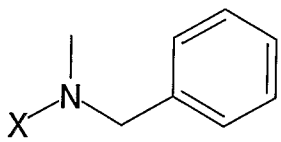
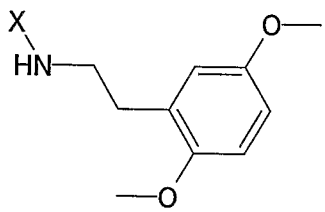
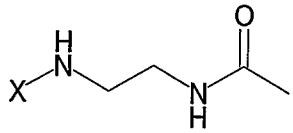
61		C32H36N2O7S	592.22	615	591	ESI
62		C33H42N2O7	578.3	601	577	ESI
63		C31H38N2O8	566.26	589	565	ESI
64		C27H36N2O9	532.24	555	531	ESI
65		C28H38N2O8	530.26	553	529	ESI
66		C32H40N2O9	596.27	619	595	ESI
67		C30H43N3O7	557.31	558	556	ESI
68		C30H36N2O7	536.25	559	535	ESI

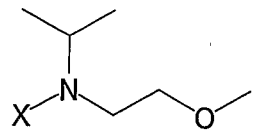
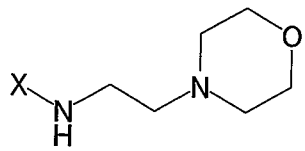
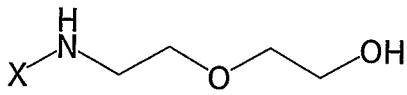
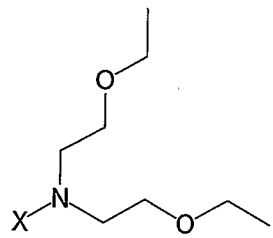
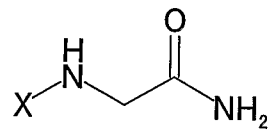
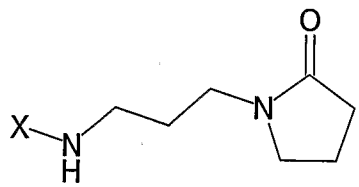
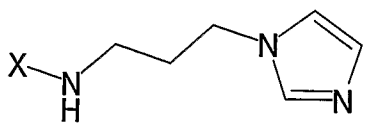
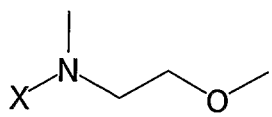
69		C31H38N2O8	566.26	589	565	ESI
70		C32H40N2O9	596.27	619	595	ESI
71		C31H38N2O7	550.27	551	549	ESI
72		C27H38N2O8	518.26	541	517	ESI
73		C29H43N3O7	545.31	546	544	ESI
74		C29H42N2O8	546.29	569	545	ESI

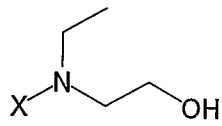
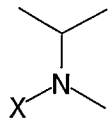
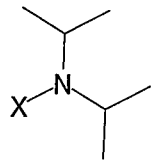
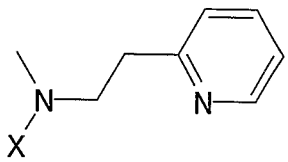
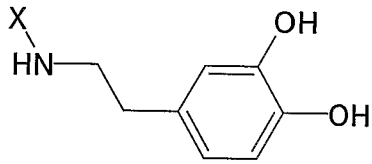
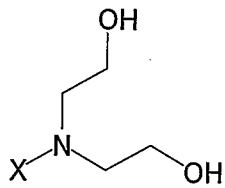
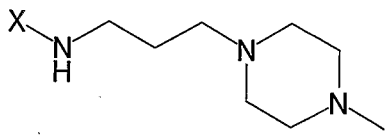
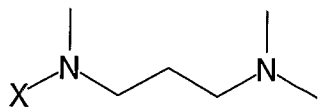
75		C37H42N2O8S	674.27	676	673	APCI
76		C26H36N2O8	504.25	527	503	ESI
77		C28H40N2O8	532.28	555	531	ESI
78		C27H38N2O8S	550.23	573	549	ESI
79		C26H36N2O8	504.25	527	503	ESI
80		C30H45N3O7	559.33	560	558	ESI
81		C26H36N2O9	520.24	543	519	ESI
82		C26H36N2O8	504.25	527	503	ESI

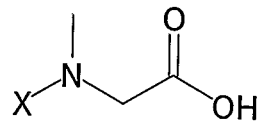
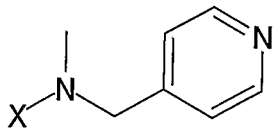
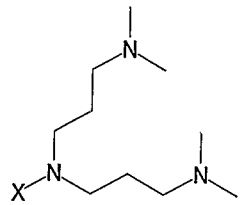
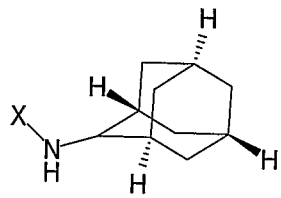
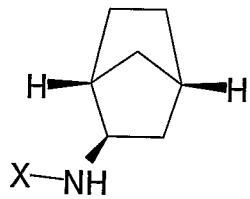
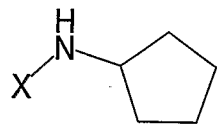
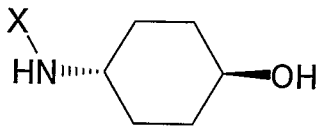
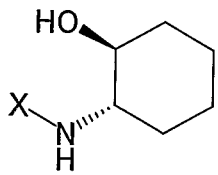
83		C33H50N2O7	586.36	609	585	ESI
84		C34H38N2O7S	618.24	641	617	ESI
85		C35H52N4O10	688.37	689	687	ESI
86		C33H42N2O7	578.3	601	577	ESI
87		C32H46N2O8	586.33	587	585	ESI
88		C32H38N2O8	578.26	579	577	ESI

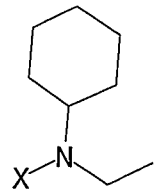
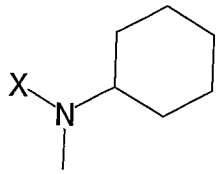
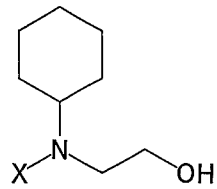
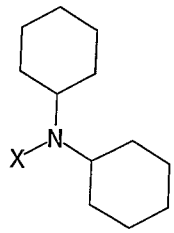
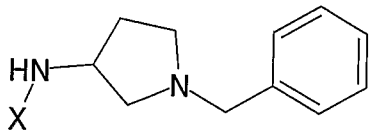
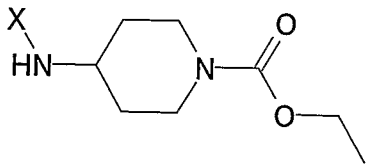
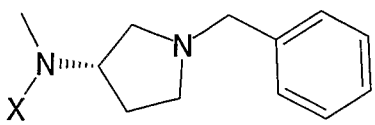
89		C36H47N3O8	649.34	672	648	ESI
90		C30H37N3O7	551.26	574	550	ESI
91		C32H40N2O7	564.28	565	563	ESI
92		C29H36N2O8	540.25	563	539	ESI
93		C29H35N3O7	537.25	560	536	ESI
94		C27H38N2O7	502.27	503	501	ESI
95		C28H41N3O7	531.29	532	530	ESI
96		C25H34N2O8	490.23	513	489	ESI

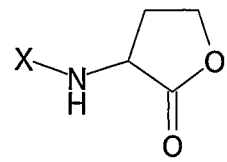
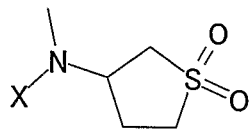
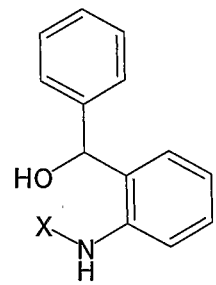
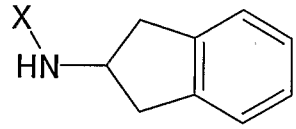
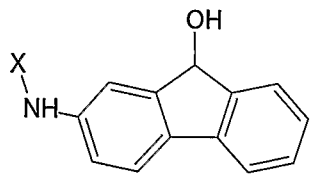
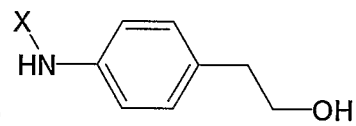
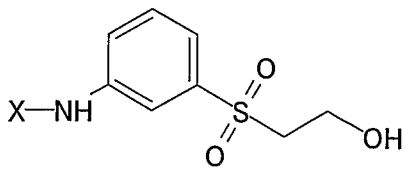
97		C28H38N4O8	558.27	559	557	ESI
98		C32H40N2O7	564.28	587	563	ESI
99		C25H31F3N2O7	528.21	551	527	ESI
100		C29H42N2O9	562.29	563	561	ESI
101		C31H38N2O7	550.27	551	549	ESI
102		C33H42N2O9	610.29	633	609	ESI
103		C27H37N3O8	531.26	554	530	ESI

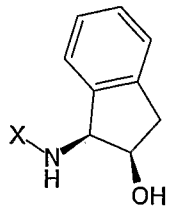
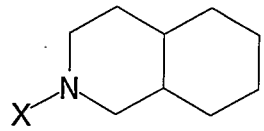
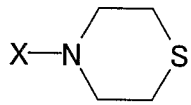
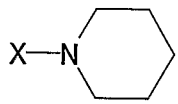
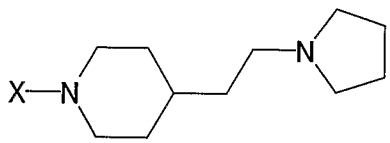
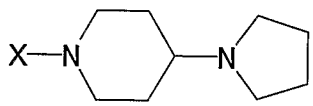
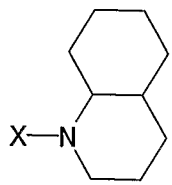
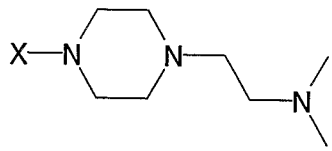
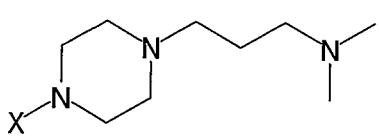
104		C29H42N2O8	546.29	569	545	ESI
105		C29H41N3O8	559.29	582	558	ESI
106		C27H38N2O9	534.26	557	533	ESI
107		C31H46N2O9	590.32	613	589	ESI
108		C25H33N3O8	503.23	504	502	ESI
109		C30H41N3O8	571.29	594	570	ESI
110		C29H38N4O7	554.27	577	553	ESI
111		C27H38N2O8	518.26	541	517	ESI

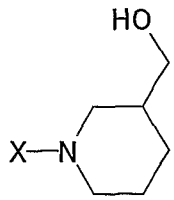
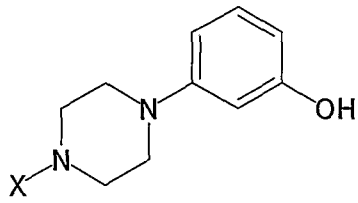
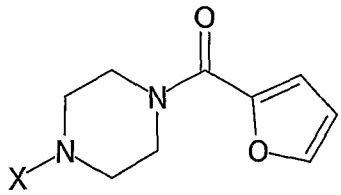
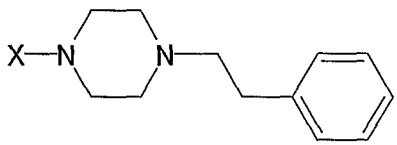
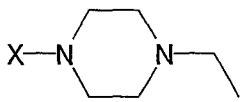
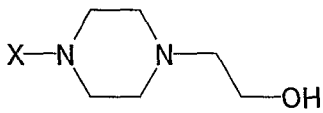
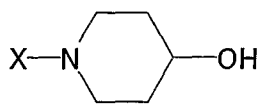
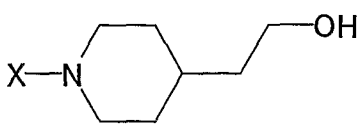
112		C27H38N2O8	518.26	541	517	ESI
113		C27H38N2O7	502.27	525	501	ESI
114		C29H42N2O7	530.3	531	529	ESI
115		C31H39N3O7	565.28	588	564	ESI
116		C31H38N2O9	582.26	ND	581	ESI
117		C27H38N2O9	534.26	557	533	ESI
118		C31H46N4O7	586.34	587	ND	ESI
119		C29H43N3O7	545.31	547	544	ESI

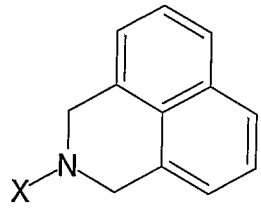
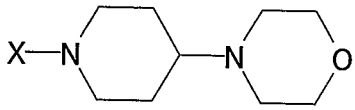
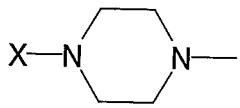
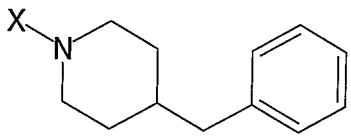
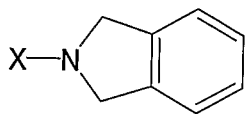
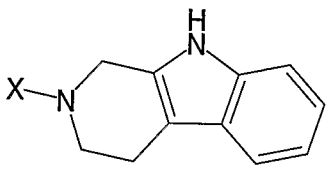
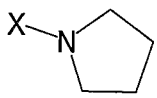
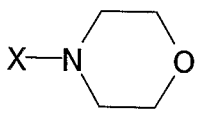
120		C26H34N2O9	518.23	ND	517	ESI
121		C30H37N3O7	551.26	574	550	ESI
122		C33H52N4O7	616.38	617	615	ESI
123		C33H44N2O7	580.31	581	579	ESI
124		C30H40N2O7	540.28	563	539	ESI
125		C28H38N2O7	514.27	537	513	ESI
126		C29H40N2O8	544.28	567	543	ESI
127		C29H40N2O8	544.28	567	543	ESI

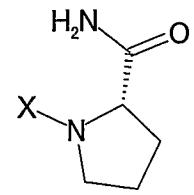
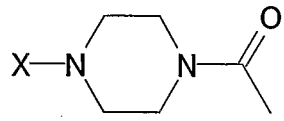
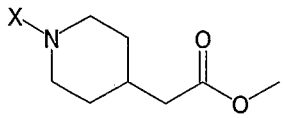
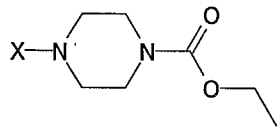
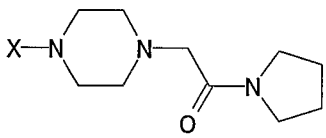
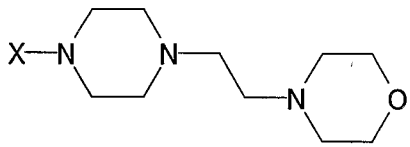
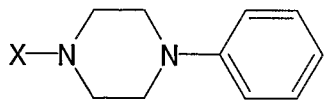
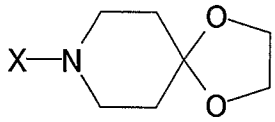
128		C31H44N2O7	556.31	579	555	ESI
129		C30H42N2O7	542.3	565	541	ESI
130		C31H44N2O8	572.31	595	571	ESI
131		C35H50N2O7	610.36	633	609	ESI
132		C34H43N3O7	605.31	606	604	ESI
133		C31H43N3O9	601.3	624	600	ESI
134		C35H45N3O7	619.33	620	618	ESI

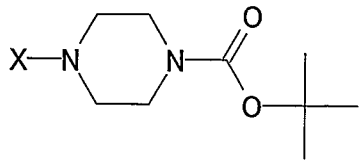
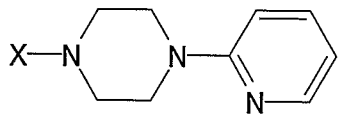
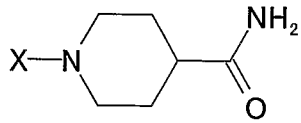
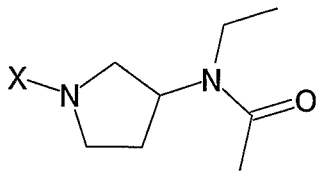
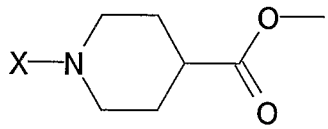
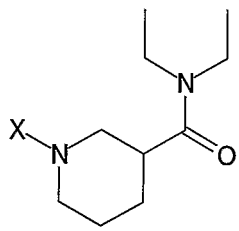
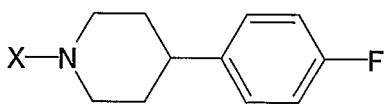
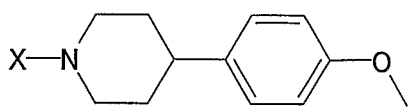
135		C27H34N2O9	530.23	553	529	ESI
136		C28H38N2O9S	578.23	601	577	ESI
137		C36H40N2O8	628.28	651	627	ESI
138		C32H38N2O7	562.27	563	561	ESI
139		C36H38N2O8	626.26	649	625	ESI
140		C31H38N2O8	566.26	589	565	ESI
141		C31H38N2O10S	630.22	653	629	ESI

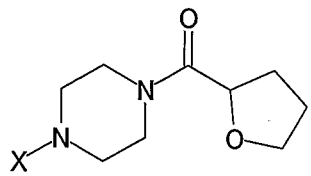
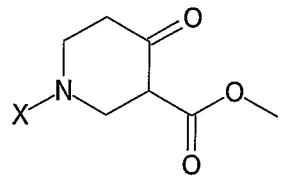
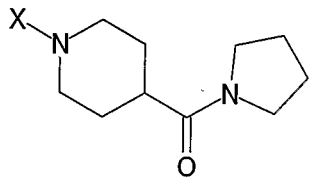
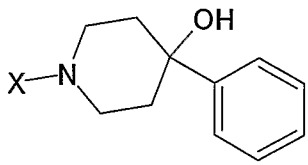
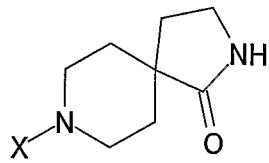
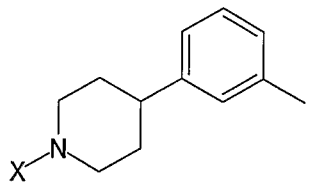
142		C32H38N2O8	578.26	601	577	ESI
143		C32H44N2O7	568.31	591	567	ESI
144		C27H36N2O7S	532.22	555	531	ESI
145		C28H38N2O7	514.27	537	513	ESI
146		C34H49N3O7	611.36	613	610	ESI
147		C32H45N3O7	583.33	585	582	ESI
148		C32H44N2O7	568.31	591	567	ESI
149		C31H46N4O7	586.34	587	585	ESI
150		C32H48N4O7	600.35	601	599	ESI

151		C29H40N2O8	544.28	567	543	ESI
152		C33H41N3O8	607.29	630	606	ESI
153		C32H39N3O9	609.27	632	608	ESI
154		C35H45N3O7	619.33	642	618	ESI
155		C29H41N3O7	543.29	566	542	ESI
156		C29H41N3O8	559.29	560	558	ESI
157		C28H38N2O8	530.26	553	529	ESI
158		C30H42N2O8	558.29	581	557	ESI

159		C35H38N2O7	598.27	621	597	ESI
160		C32H45N3O8	599.32	622	598	ESI
161		C28H39N3O7	529.28	552	528	ESI
162		C35H44N2O7	604.31	627	603	ESI
163		C31H36N2O7	548.25	571	547	ESI
164		C34H39N3O7	601.28	624	600	ESI
165		C27H36N2O7	500.25	523	499	ESI
166		C27H36N2O8	516.25	539	515	ESI

167		C28H37N3O8	543.26	566	542	ESI
168		C29H39N3O8	557.27	580	556	ESI
169		C31H42N2O9	586.29	609	585	ESI
170		C30H41N3O9	587.28	610	586	ESI
171		C33H46N4O8	626.33	649	625	ESI
172		C33H48N4O8	628.35	651	627	ESI
173		C33H41N3O7	591.29	614	590	ESI
174		C30H40N2O9	572.27	595	571	ESI

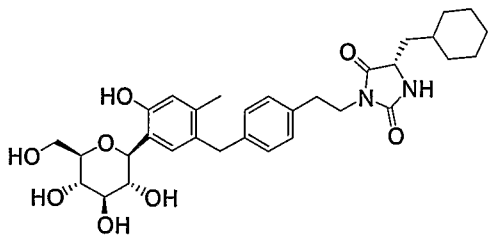
175		C32H45N3O9	615.32	638	614	ESI
176		C32H40N4O7	592.29	593	591	ESI
177		C29H39N3O8	557.27	580	556	ESI
178		C31H43N3O8	585.3	608	584	ESI
179		C30H40N2O9	572.27	595	571	ESI
180		C33H47N3O8	613.34	636	612	ESI
181		C34H41FN2O7	608.29	631	607	ESI
182		C35H44N2O8	620.31	643	619	ESI

183		C32H43N3O9	613.3	636	612	ESI
184		C30H38N2O10	586.25	ND	585	ESI
185		C33H45N3O8	611.32	634	610	ESI
186		C34H42N2O8	606.29	629	605	ESI
187		C31H41N3O8	583.29	606	582	ESI
188		C35H44N2O7	604.31	627	603	ESI

Furthermore, the compound (III) in which R^B represents an an alkyl group substituted with an amino group can be synthesized by using ethylenediamine or N-methyl-1,3-propanediamine in accordance with the method as with Example 11-1.

Example 19

Preparation of (1S)-1,5-anhydro-1-[5-[4-[2-[(4S)-4-(cyclohexylmethyl)-2,5-dioxo imidazolidine-1-yl] ethyl]benzyl]-2-hydroxy-4-methylphenyl]-D-glucitol



The title compound (5 mg, 29%) was obtained as a colorless oily compound according to the method as with Example 11-1 in which 3-cyclohexyl-L-alanine methyl ester hydrochloride was used instead of tris(hydroxymethyl)aminomethane.

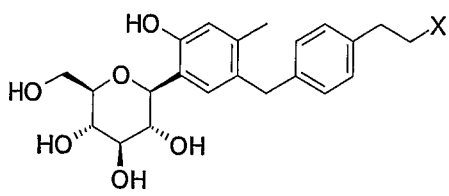
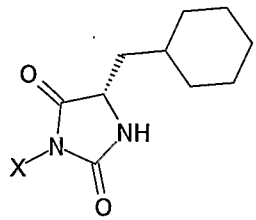
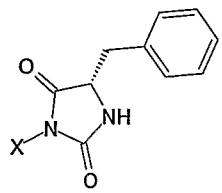
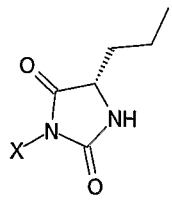
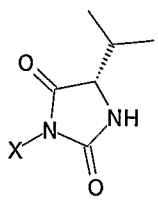
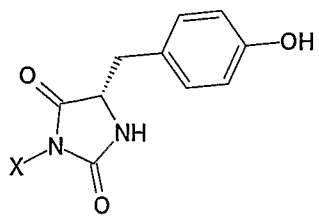
1H NMR (600 MHz, METHANOL-D_4) δ ppm 0.81-1.00 (m, 2H) 1.31 (br. s., 3H) 1.38-1.47 (m, 1H) 1.48-1.55 (m, 1H) 1.56-1.78 (m, 4H) 2.05 (s, 3H) 2.83 (t, *J*=7.34 Hz, 2H) 3.28-3.33 (m, 2H) 3.35-3.43 (m, 2H) 3.46 (t, *J*=8.71 Hz, 1H) 3.54 (t, *J*=9.17 Hz, 1H) 3.57-3.71 (m, 3H) 3.81-3.88 (m, 3H) 3.96 (dd, *J*=9.40, 4.36 Hz, 1H) 4.50 (d, *J*=10.09 Hz, 1H) 6.60 (s, 1H) 7.00 (d, 2H) 7.04 (d, 2H) 7.08 (d, *J*=5.96 Hz, 1H).

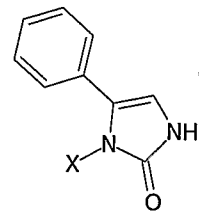
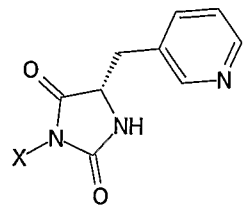
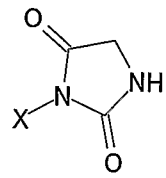
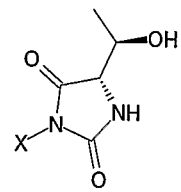
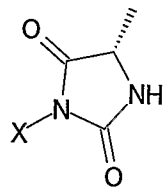
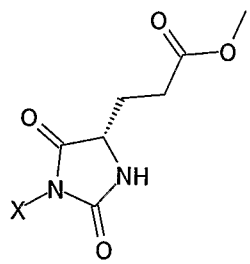
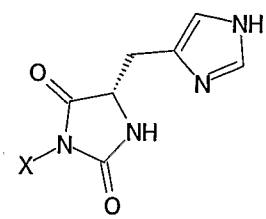
ESI m/z=605(M+Na). 581(M-H).

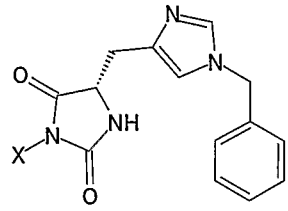
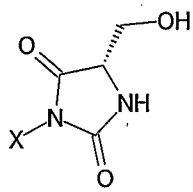
Compounds 190 to 202 were synthesized by using corresponding amino acids in accordance with the method as

with Example 19.

[Table 3]

Compound No.		formula	Exact MS	MS (M+H) or (M+Na)	MS (M-H)	ionization
189		C32H42N2O8	582.29	605	581	ESI
190		C32H36N2O8	576.25	599	575	ESI
191		C28H36N2O8	528.25	551	527	ESI
192		C28H36N2O8	528.25	551	527	ESI
193		C32H36N2O9	592.24	615	591	ESI

194		C31H34N2O7	546.24	569	545	ESI
195		C31H35N3O8	577.24	600	576	ESI
196		C25H30N2O8	486.2	509	485	ESI
197		C27H34N2O9	530.23	553	529	ESI
198		C26H32N2O8	500.22	523	499	ESI
199		C29H36N2O10	572.24	595	571	ESI
200		C29H34N4O8	566.24	589	565	ESI

201		C36H40N4O8	656.28	679	655	ESI
202		C26H32N2O9	516.21	539	515	ESI

Formulation Example

[Table 4]

Formulation of tablet containing 100 mg of drug:	
Content in single tablet:	
Drug	108.35 mg
Lactose - monohydrate	38.65 mg
Crystalline cellulose	22.00 mg
Calcium carboxymethylcellulose	20.00 mg
Hydroxypropylcellulose	10.00 mg
Magnesium stearate	1.00 mg
	200.00 mg

Preparation Method

The drug (the compound of the present invention) is mixed with lactose monohydrate, crystalline cellulose, calcium carboxymethylcellulose, and hydroxypropylcellulose. This mixture is pulverized with a pulverizer. The pulverized mixture is mixed with a mixer-granulator for 1 minute, and then granulated with water for 4 to 8 minutes. Thus obtained granulated products are dried at 70°C for 40 minutes. The dry granulated powder is sifted with a 500 μm sieve. The sifted dry granulated powder and magnesium

stearate are mixed with a V-type mixer at 30 rpm for 3 minutes. Thus obtained granule for making tablets is subjected to compression molding with a rotary tablet machine to make tablets.

[Table 5]

Weight of Tablets:	200 mg
Tablet size:	8 mm, round

Test Example 1

(1) Cloning of Human SGLT1 and SGLT2 and Introduction thereof into Expression Vector

An SGLT1 sequence (NM_000343) was reverse-transcripted from human small intestinal mRNA, then amplified, and then introduced into pCMV-tag5A from Stratagene Corporation. An SGLT2 sequence (NM_003041) was prepared from human nephric mRNA as with the above method, and then introduced into pcDNA3.1+hygro from Invitrogen Corporation. Each cloned sequence was confirmed to be identical with the reported sequence.

(2) Preparation of CHO-k1 Cells Stably Expressing Human SGLT1 and Human SGLT2

The human SGLT1 and human SGLT2 expression vectors were transfected into CHO-k1 cells by using Lipofectamine 2000 from Invitrogen Corporation. The SGLT expression cells were incubated in the presence of Geneticin (SGLT1) or Hygromycin B (SGLT2) at a 500 μg/mL concentration to select resistant strains, and specific activity of sugar uptake was obtained as an indicator by the following system.

(3) Inhibition Test of Sodium-dependent Sugar Uptake in Cells

Cells stably expressing human SGLT1 and human SGLT2 were used for the inhibition test of sodium-dependent glucose uptake.

The cells were incubated in a pretreatment buffer A (200 μL for SGLT1, and 2 mL for SGLT2) for 20 minutes. The pretreatment buffer was removed and an uptake buffer B (75 μL for SGLT1, and 200 μL for SGLT2) containing a test compound was added to conduct an uptake reaction at 37°C for 30 minutes (SGLT1) or an hour (SGLT2). After the reaction, the cells were washed with a washing buffer C twice (200 μL for SGLT1, and 2 mL for SGLT2), and then dissolved in a 0.2 M solution of NaOH (75 μL for SGLT1, and 400 μL for SGLT2). After a liquid scintilater was added thereto and mixed sufficiently, radioactivity was measured with microBETA (SGLT1) or a liquid scintillation counter from Beckman Coulter, Inc (SGLT2). As a control group, an uptake buffer containing no test compound was prepared. In addition, as the basic uptake buffer, an uptake buffer B containing choline chloride instead of NaCl was prepared.

·A pretreatment buffer A: 140 mM choline chloride, 2 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES/5 mM Tris, pH 7.4.

·An uptake buffer B : 1 mM of methyl α-D-glucopyranoside containing [^{14}C]methyl α-D-glucopyranoside, 140 mM NaCl, 2 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES/5 mM Tris, pH 7.4.

·A washing buffer C: 10 mM methyl α-D-glucopyranoside,

140 mM choline chloride, 2 mM KCl, 1 mM $CaCl_2$, 1 mM $MgCl_2$, 10 mM HEPES/5 mM Tris, pH 7.4.

In order to obtain IC_{50} values, test compounds having adequate 6 concentrations were used and the test compound concentrations (IC_{50} values) at which sugar uptake is inhibited by 50% in comparison with the amount of sugar uptake (100%) of the control group were calculated. Test results are shown in Table 6.

[Table 6]

compound No	SGLT1 (nM)	SGLT2 (nM)
1	11	17
2	32	18
3	35	65
4	51	31
8	65	29
9	175	29
10	51	23
11	59	34
12	113	48
14	49	21
17	79	25
19	302	101
20	382	164
21	75	34
22	37	12
23	19	19
24	37	25
25	64	20
26	52	15
27	54	15
28	64	18
29	75	17
30	111	13
31	148	39
32	245	44
33	12	11
34	49	10
35	83	34
36	94	34

In addition, the sugar uptake inhibition rates at 100 nM concentration of the test compound in comparison with the control group are shown in Table 7.

[Table 7]

compound No.	SGLT1 % inhibition at 100nM	SGLT2 % inhibition at 100nM
38	89	83
39	80	83
40	79	89
41	78	86
42	78	87
43	77	86
45	75	80
46	74	91
47	73	89
48	73	87
49	73	81
50	71	77
51	71	84
52	71	84
53	70	74
54	79	73
55	69	69
56	68	77
57	68	51
59	67	86
60	66	91
61	65	95
62	65	79
63	63	81
64	62	76
65	62	76
66	62	83
67	61	82
68	60	83
69	60	83
70	59	83
71	59	86
123	78	87
124	71	79
125	68	90
132	90	90
137	71	79
138	65	84
143	66	80

Test Example 2

Confirmation Study of Inhibitory Effect on Elevation of Blood Glucose Level in Streptozotocin Diabetic Model Rats

(1) Preparation of Diabetic Model Rats

7-week-old SD/IGS rats (from CHARLES RIVER LABORATORIES JAPAN, INC., male) were fasted for about 16 hours. Then to these rats under etherization were administered 50 mg/kg of streptozotocin (STZ) via the tail vein to prepare diabetic model rats. Similarly, to rats under etherization were administered 1 mL/kg physiological saline containing 1.25 mmol/L of citric acid via tail veins to prepare normal control rats. One week (8 weeks old) after administration of STZ or 1.25 mmol/L citric acid physiological saline, the rats were subjected to oral glucose tolerance test.

(2) Oral Glucose Tolerance Test

After the rats were fasted for about 16 hours, the medicament (1 mg/kg) suspended in a 0.5% carboxymethyl cellulose (CMC) aqueous solution was orally administered to a medicament treated group, and only a 0.5% aqueous solution of CMC was orally administered to a control group. At 5 minutes after the administration, a glucose solution (2 g/kg) was orally administered to each rat, and blood was collected at 5 points in total: before the administration (0 time), after 0.25, 0.5, 1 and 2 hours after the oral administration.

The blood was collected from the orbital sinus venosus of each rat under etherization with a heparin-coated blood

collection tube and centrifuged, and then blood plasma was separated. The concentration of glucose in the blood plasma was determined with Glucose CII Test Wako from Wako Pure Chemical Industries, Ltd. As for the intensity of inhibitory effect on elevation of blood glucose level, area under the blood glucose level curve (AUC) was calculated by the trapezoidal rule based on the blood glucose levels of the medicament treated group from 0 time to 1 hour time. And a basal value is subtracted from AUC to describe the intensity as area under the blood glucose level increment (ΔAUC) and describe the intensity as a decrease rate from the ΔAUC of the control group. The results are shown in Table 8.

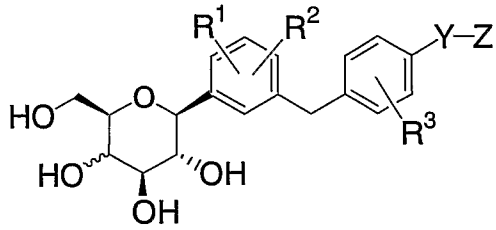
[Table 8]

compound No	STZ rats-OGTT(2g/kg)
	%inhibition ΔAUC0-1h(mgh/dL) @1mg/kg
1	41.7
2	51.6
3	63.9
4	51.0
8	45.1
11	69.3
9	50.1
10	67.8
12	48.8

By virtue of the present invention, it is expected to provide a preventive or therapeutic agent for diabetes comprising, as an active ingredient, a C-phenyl glycitol compound having not only a glucose absorption suppression action from the digestive tract but also a urine glucose excretion action by inhibiting a sodium dependent glucose cotransporter 1 (SGLT1) expressing on the epithelium of the small intestine and a sodium dependent glucose cotransporter 2 (SGLT2) expressing in the kidney.

CLAIMS

1. A C-phenyl glycitol compound represented by Formula (I) below or a pharmaceutically acceptable salt thereof, or a hydrate thereof



(I)

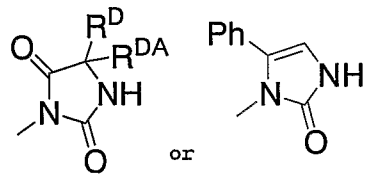
where

R^1 and R^2 are the same or different and represent a hydrogen atom, a hydroxyl group, a C_{1-6} alkyl group, a C_{1-6} alkoxy group or a halogen atom,

R^3 is a hydrogen atom, a C_{1-6} alkyl group, a C_{1-6} alkoxy group or a halogen atom,

Y is a C_{1-6} alkylene group, -O-(CH_2)n- (n is an integer of 1 to 4) or a C_{2-6} alkenylene group, provided that when Z is -$NHC(=NH)NH_2$ or -$NHCON(R^B)R^C$, n is not 1,

Z is -$CONHR^A$, -$NHC(=NH)NH_2$ or -$NHCON(R^B)R^C$,



where

R^A is

a C_{1-6} alkyl group substituted with 1 to 3 substituents selected from the group consisting of a hydroxyl group, an

amino group and a carbamoyl group,

R^B is

(1) a hydrogen atom,

(2) a C_{1-6} alkyl group that may be substituted with 1 to 3 substituents selected from Group A,

(3) a C_{3-12} cycloalkyl group which may be substituted with 1 to 3 substituents selected from a hydroxyl group and a C_{1-6} hydroxyalkyl group,

(4) a 3 to 12-membered heterocycloalkyl group or a 5 to 13-membered heteroaryl group that may be partially saturated, each of which contains one to three ring-constituting atom(s) selected from the group consisting of O, N, S, SO_2, CO and NR^{10} (R^{10} is a hydrogen atom, a C_{1-6} alkyl group, a phenyl-C_{1-6} alkyl group or a C_{2-6} alkoxycarbonyl group), and may be substituted with 1 to 3 subtitituents selected from the group consisting of a hydroxyl group and a C_{1-6} hydroxyalkyl group, or

(5) a C_{6-13} aryl group which may be partially saturated and may be substituted with 1 or 2 substituents selected from a hydroxyl group, and a C_{1-6} alkyl group, a phenyl-C_{1-6} alkyl group and a C_{1-6} alkylsulfonyl group, each of which may be substituted with a hydroxyl group(s)

in which

Group A consists of

a halogen atom, a hydroxyl group, a C_{1-6} alkoxy group which may be substituted with a hydroxyl group(s), a carboxyl group, a C_{2-6} alkoxycarbonyl group, a carbamoyl group, an amino group, a C_{1-6} alkylamino group, a di-C_{1-6} alkylamino

group, a C_{2-6} acylamino group, a C_{1-6} alkylthio group which may be substituted with a hydroxyl group(s),
a phenoxy group,
a phenyl group which may be substituted with 1 to 3 substituents selected from Group B (Group B consists of a hydroxyl group, a halogen atom, a C_{1-6} alkoxy group, a C_{1-6} alkyl group which may be substituted with a hydroxyl group(s), a C_{1-6} alkylthio group, a thienyl group, a phenylthio group which may be substituted with a hydroxyl group(s) or a C_{1-6} hydroxyalkyl group(s), and a piperidino group which may be substituted with a hydroxyl group(s) or a C_{1-6} hydroxyalkyl group(s)),
a C_{3-12} cycloalkyl group which may be substituted with 1 to 3 subtitituents selected from the group consisting of a hydroxyl group and a C_{1-6} hydroxyalkyl group,
a 3 to 12-membered heterocycloalkyl group or a 5 to 13-membered heteroaryl group that may be partially saturated, each of which contains one to three ring-constituting atom(s) selected from the group consisting of O, N, S, SO_2, CO and NR^{10} (R^{10} is a hydrogen atom, a C_{1-6} alkyl group, a phenyl-C_{1-6} alkyl group or a C_{2-6} alkoxycarbonyl group), and may be substituted with 1 to 3 subtitituents selected from the group consisting of a hydroxyl group and a C_{1-6} hydroxyalkyl group, and
$-CONR^{B1}R^{B2}$ wherein R^{B1} and R^{B2} together with the nitrogen atom to which they are attached form a 5 to 6 membered heterocycloalkyl group which may contain as another ring-constituting atom, an oxygen atom, a nitrogen atom or a

sulfur atom and may be substituted with 1 or 2 subtitituents selected from the group consisting of a C_{1-6} alkyl group which may be substituted with a hydroxyl group(s), a C_{2-6} alkoxycarbonyl group and a phenylC_{1-6} alkyl group,

R^C is
a hydrogen atom, a C_{1-6} alkyl group which may be substituted with 1 or 2 substituents selected from the group consisiting of a hydroxyl group, a di-C_{1-6} alkylamino group, a C_{2-6} alkoxycarbonyl group and a C_{1-6} alkoxy group, or a C_{3-12} cycloalkyl group which may be substituted with a hydroxyl group(s), and

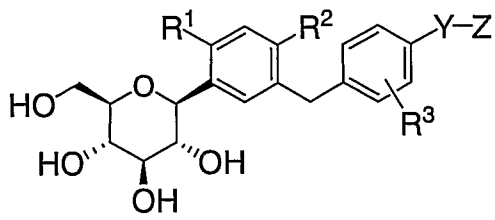
R^B and R^C together with the nitrogen atom to which they are attached may form a 3 to 12 membered heterocycloalkyl group or a 5 to 13 membered heteroaryl group that may be partially saturated, each of which may contain 1 or 2 ring-constituting atom selected from O, N, NR^{11}, S, SO_2 and CO and which may be substituted with 1 or 2 subtitituents selected from the group consisting of a hydroxyl group, a C_{2-6} alkoxycarbonyl group, a carbamoyl group, a C_{2-6} acyl(C_{1-6} alkyl)amino group, a di-C_{1-6} alkylaminocarbonyl group, a pyrrolidinyl group, a morpholino group, a pyrrolidin-1-yl-carbonyl group, a C_{1-6} alkyl group that may be substituted with 1 to 3 substituents selected from the group consisiting of a hydroxyl group, a pyrrolidin-1-yl group, a phenyl group and a C_{2-6} alkoxycarbonyl group, and a phenyl

group that may be substituted with 1 to 3 substituents selected from the group consisting of a C_{1-6} alkyl group, a C_{1-6} alkoxy group and a halogen atom

where R^{11} is a hydrogen atom, a C_{2-6} acyl group, a phenyl group that may be substituted with a hydroxyl group(s), a pyridyl group, a furylcarbonyl group, an oxolanylcarbonyl group, a C_{2-6} alkoxycarbonyl group or a C_{1-6} alkyl group that may be substituted with 1 or 2 substituents selected from the group consisting of a hydroxyl group, a phenyl group, a di-C_{1-6} alkylamino group, a morpholino group and a pyrrolidin-1-yl-carbonyl group, and

R^D is a hydrogen atom or a C_{1-6} alkyl group which may be substituted with 1 or 2 substituents from the group consisting of a hydroxyl group, a C_{3-12} cycloalkyl group, a phenyl group that may be substituted with a hydroxyl group(s), a pyridyl group, a C_{2-6} alkoxycarbonyl group, an imidazolyl group and a 1-benzylimidazolyl group, and R^{DA} is a hydrogen atom or a C_{1-6} alkyl group.

2. The C-phenyl glycitol compound according to claim 1 which is a C-phenyl glucitol compound represented by Formula (II) below or a pharmaceutically acceptable salt thereof, or a hydrate thereof,



(II)

where R^1, R^2, R^3, Y and Z are the same as defined in Claim 1.

3. The C-phenyl glycitol compound or a pharmaceutically acceptable salt thereof, or a hydrate thereof according to claim 2, wherein R^1 is a hydrogen atom, a hydroxyl group, a C_{1-4} alkyl group or a C_{1-4} alkoxy group, and R^2 is a C_{1-4} alkyl group or a halogen atom.

4. The C-phenyl glycitol compound according to claim 2 or 3 or a pharmaceutically acceptable salt thereof, or a hydrate thereof, where R^3 is a hydrogen atom.

5. The C-phenyl glycitol compound or a pharmaceutically acceptable salt thereof, or a hydrate thereof according to claim 3 or 4, wherein Y is a C_{1-6} alkylene group or -O-(CH_2)n- (n is an integer of 2 to 4), and Z is -NHCON(R^B)R^C wherein R^B and R^C are as defined in Claim 1.

6. The C-phenyl glycitol compound or a pharmaceutically acceptable salt thereof, or a hydrate thereof according to claim 3 or 4, wherein
Y is a C_{1-6} alkylene group or -O-(CH_2)n- (n is an integer of 2 to 4), and Z is -NHCON(R^B)R^C,

where

R^B is

(1) a C_{1-6} alkyl group which may be substituted with 1 to 3 substituents selected from Group A,

(2) a C_{3-12} cycloalkyl group which may be substituted with 1 to 3 substituents selected from a hydroxyl group and a C_{1-6} hydroxyalkyl group,

(3) a 3 to 12-membered heterocycloalkyl group or a 5 to 13-membered heteroaryl group that may be partially saturated, each of which contains one to three ring-constituting atom(s) selected from the group consisting of O, N, S and NR^{10} (R^{10} is a hydrogen atom, a C_{1-6} alkyl group, a phenyl-C_{1-6} alkyl group or a C_{2-6} alkoxycarbonyl group) and may be substituted with 1 to 3 subtitituents selected from the group consisting of a hydroxyl group and a C_{1-6} hydroxyalkyl group, or

(4) a 6 to 13-membered aryl group which may be partially saturated and may be substituted with 1 or 2 substituents selected from a hydroxyl group, and a C_{1-6} alkyl group, a phenyl-C_{1-6} alkyl group and a C_{1-6} alkylsulfonyl group, each of which may be substituted with a hydroxyl group(s)

in which

Group A consists of

a halogen atom, a hydroxyl group, a C_{1-6} alkoxy group which may be substituted with a hydroxyl group(s), a C_{2-6} alkoxycarbonyl group, a carbamoyl group, a di-C_{1-6} alkylamino group, a C_{1-6} alkylthio group which may be substituted with a hydroxyl group(s),

a phenoxy group, a thienyl group, benzothienyl group, furyl group,

a phenyl group which may be substituted with 1 to 3 substituents selected from the group consisting of a hydroxyl group, a halogen atom, a C_{1-6} alkoxy group, a C_{1-6} alkyl group which may be substituted with a hydroxyl group(s), a C_{1-6} alkylthio group, a phenylthio group which may be substituted with a hydroxyl group(s) or a C_{1-6} hydroxyalkyl group(s), and a piperidino group which may be substituted with a hydroxyl group(s) or a C_{1-6} hydroxyalkyl group(s),

a C_{3-12} cycloalkyl group which may be substituted with 1 to 3 subtitituents selected from the group consisting of a hydroxyl group and a C_{1-6} hydroxyalkyl group,

a 3 to 12-membered heterocycloalkyl group which contains one to three ring-constituting atom(s) selected from the group consisting of O, N, S and NR^{10} (R^{10} is a hydrogen atom, a C_{1-6} alkyl group, a phenyl-C_{1-6} alkyl group or a C_{2-6} alkoxycarbonyl group) and may be substituted with 1 to 3 subtitituents selected from the group consisting of a hydroxyl group and a C_{1-6} hydroxyalkyl group, and

4-C_{1-6} alkylpiperadine-1-ylcarbonyl group,

R^C is a hydrogen atom, and

R^B and R^C together with the nitrogen atom to which they are attached may form a piperidine group which may be

substituted with a pyrrolidinyl group or a C_{1-6} alkyl group which is substituted with a diC_{1-6}alkylamino group or a pyrrolidin-1-yl group, or a thiomorpholine group or a decahydroisoquinoline group.

7. The C-phenyl glycitol compound or a pharmaceutically acceptable salt thereof or a hydrate thereof according to any one of claims 2 to 4,

wherein

Y is a C_{1-6} alkylene group,

Z is $-CONHR^A$,

where

R^A is a C_{1-6} alkyl group substituted with 1 to 3 substituents selected from the group consisting of a hydroxyl group and a carbamoyl group.

8. The C-phenyl glycitol compound or a pharmaceutically acceptable salt thereof or a hydrate thereof according to any one of claims 2 to 4, wherein

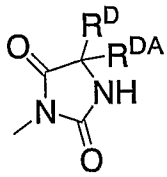
Y is a C_{1-6} alkylene group, and

Z is $-NHC(=NH)NH_2$.

9. The C-phenyl glucitol compound or a pharmaceutically acceptable salt thereof or a hydrate thereof according to any one of claims 2 to 4, wherein

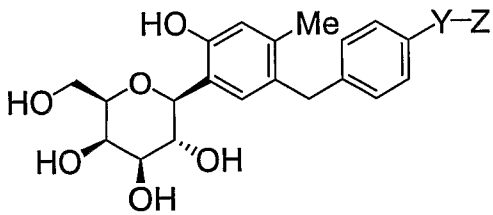
Y is a C_{1-6} alkylene group, and

Z is



R^D is a C_{1-6} alkyl group which is substituted with a C_{3-12} cycloalkyl group or a phenyl group and R^{DA} is a hydrogen atom or a C_{1-6} alkyl group.

10. The C-phenyl glycitol compound according to claim 1 which is a C-phenyl galacitol compound represented by Formula (III) below or a pharmaceutically acceptable salt thereof or a hydrate thereof,



(III)

where

Y is

a C_{1-6} alkylene group, and

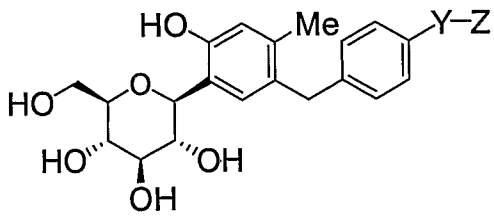
Z is

$-CONHR^A$,

where

R^A is a C_{1-6} alkyl group substituted with 1 to 3 substituents selected from the group consisting of a hydroxyl group and a carbamoyl group.

11. The C-phenyl glycitol compound according to claim 1 which is a C-phenyl glucitol compound represented by Formula (IV) below or a pharmaceutically acceptable salt thereof or a hydrate thereof,



(IV)

where

Y is a C_{1-6} alkylene group, and

Z is $-CONHR^{A1}$, $-NHC(=NH)NH_2$ or $-NHCOR^{B1}$,

where

R^{A1} is a C_{1-6} alkyl group substituted with 1 to 3 substituents selected from the group consisting of a hydroxyl group, an amino group and a carbamonyl group, and

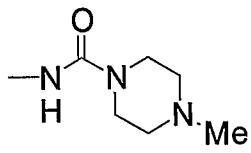
R^{B1} is

a C_{1-6} alkylamino group which may be substituted with 1 to 3 hydroxyl groups or a 4-C_{1-6} alkylpiperazin-1-yl-carbonyl group, or a 4-C_{1-6} alkylpiperazin-1-yl group.

12. The C-phenyl glycitol compound according to claim 11 or a pharmaceutically acceptable salt thereof or a hydrate thereof, wherein,

Y is a C_{1-6} alkylene group,

Z is $-CONHR^{A1}$ or $-NHC(=NH)NH_2$, or



where

R^{A1} is a C_{1-6} alkyl group substituted with 1 to 3 substituents selected from the group consisting of a hydroxyl group, an amino group and a carbamonyl group.

13. The C-phenyl glycitol compound according to claim 11 or a pharmaceutically acceptable salt thereof or a hydrate thereof, wherein

Y is a C_{1-6} alkylene group, and

Z is $-CONHR^{A1}$

where R^{A1} is a C_{1-6} alkyl group substituted with 1 to 3 substituents selected from the group consisting of a hydroxyl group, an amino group and a carbamonyl group.

14. The C-phenyl glycitol compound according to claim 11 or a pharmaceutically acceptable salt thereof or a hydrate thereof, wherein

Y is a C_{1-6} alkylene group, and

Z is $-NHC(=NH)NH_2$.

15. The C-phenyl glycitol compound according to claim 11 or a pharmaceutically acceptable salt thereof or a hydrate thereof, wherein

Y is a C_{1-6} alkylene group, and

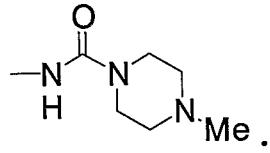
Z is $-NHCOR^{B1}$ (where R^{B1} is a C_{1-6} alkylamino group

substituted with 1 to 3 hydroxyl groups or a 4-C_{1-6} alkylpiperazin-1-yl-carbonyl group, or a 4-C_{1-6} alkylpiperazin-1-yl group).

16. The C-phenyl glycitol compound according to claim 11 or a pharmaceutically acceptable salt thereof or a hydrate thereof, wherein

Y is a C_{1-6} alkylene group, and

Z is represented by



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17. A pharmaceutical preparation, which comprises the C-phenyl glycitol compound according to any one of claims 1 to 16 or a pharmaceutically acceptable salt thereof or a hydrate thereof as an active ingredient.

18. The pharmaceutical preparation according to claim 17, which is an inhibitor of a sodium dependent glucose cotransporter 1 (SGLT1) activity and a sodium dependent glucose cotransporter 2 (SGLT2) activity.

19. The pharmaceutical preparation according to claim 17, which is a prophylactic or therapeutic agent for diabetes.