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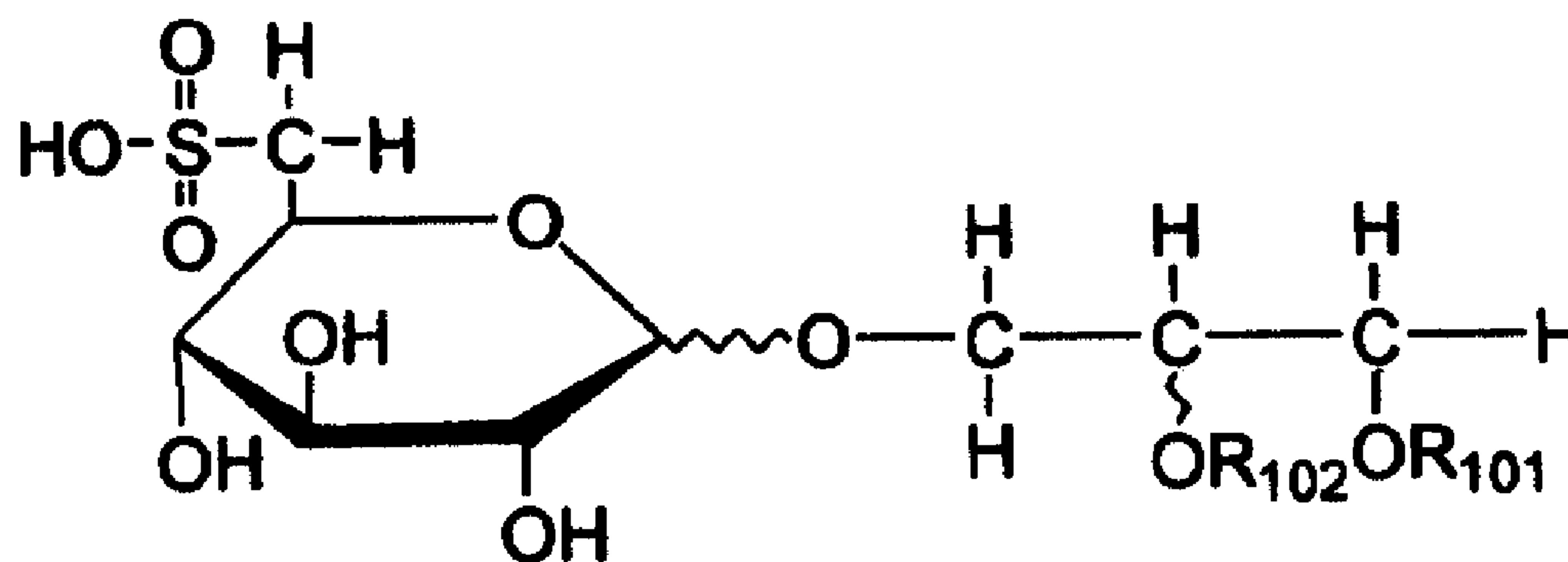
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(54) Title: NOVEL IMMUNOSUPPRESSIVE AGENT



(1)

(57) Abrégé/Abstract:

An immunosuppressive agent containing, as an active ingredient, at least one compound selected from the group consisting of compounds represented by Formula (1): (see formula 1) where R₁₀₁ and R₁₀₂ are independently an acyl residue of a higher fatty acid, and a pharmaceutically acceptable salt thereof.

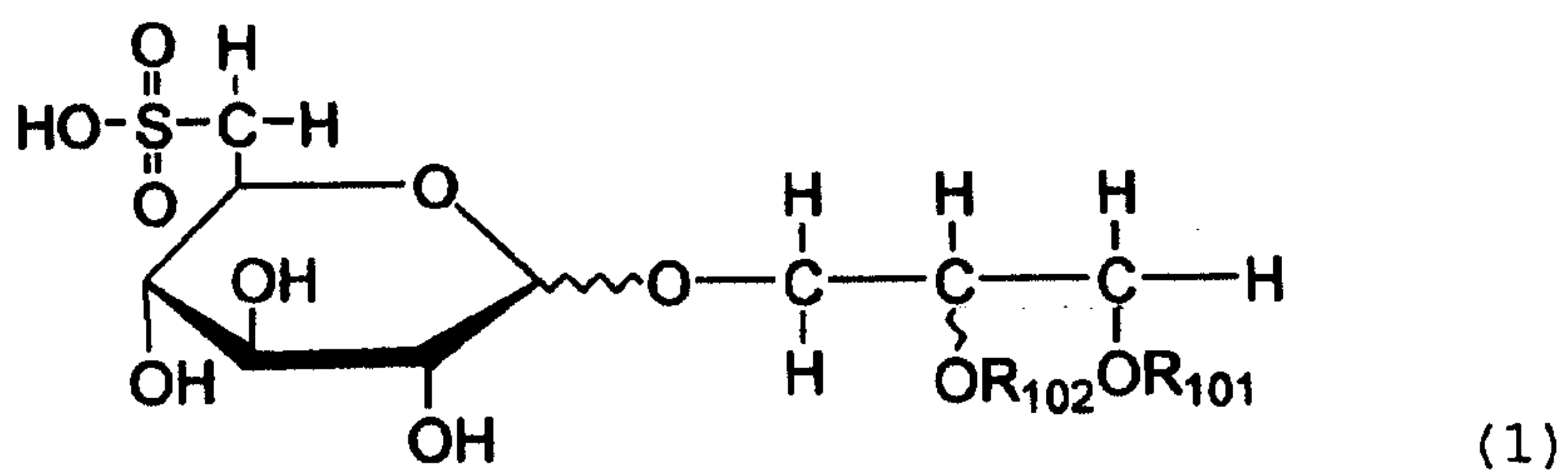


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A B S T R A C T

An immunosuppressive agent containing, as an active ingredient, at least one compound selected from the group consisting of compounds represented by

5 Formula (1):



where R₁₀₁ and R₁₀₂ are independently an acyl residue of a higher fatty acid, and a pharmaceutically

10 acceptable salt thereof.

D E S C R I P T I O N

NOVEL IMMUNOSUPPRESSIVE AGENT

5

Technical Field

The present invention relates to a novel immunosuppressive agent.

Background Art

10 In clinical treatment presently performed, transplantation can be employed to treat chemotherapeutically untreatable diseases. Transplantation is the technology for treating a disease by replacing partly or entirely of a diseased organ with a healthy organ taken from another
15 individual. Organ transplantation has been performed with respect to a wide variety of organs such as kidney, liver, lung, intestine, heart, pancreas, and cornea. The number of organ transplantations has been increased.

The immune response of skin is inherently high.
20 However, skin transplantation can be made successfully if a graft skin transplanted from one person to another can be kept alive for at least a few weeks. This is because new dermal tissue, if a graft epidermis is kept alive for a few weeks, can regenerate itself, thereby
25 recovering from a dermal tissue damage. Therefore, it is possible to make physical recuperation of serious and extensive burn or laceration by transplanting a

dermal tissue from another person.

The most fearful problem residing in tissue or organ transplantation is a rejection caused by a recipient's immune response.

5 Under these circumstances, in order to develop an immunosuppressive agent capable of preventing the rejection in a recipient, thereby attaining permanent fixation of a transplanted organ, intensive studies have been conducted since the 1970s, particularly in
10 European countries and U.S.A.

On the other hand, an immunosuppressive agent may also be important in treating autoimmune diseases such as rheumatism and collagen disease, since it can mitigate the symptoms to a certain degree.

15 Up to the present, cyclosporin A and FK506, etc., have been developed as immunosuppressive agents. However, the functional mechanisms of these immunosuppressive agents resemble each other and their chronic toxicity is a matter of concern. Thus, to
20 attain prolonged life in next-generation organ transplantation, another type of immunosuppressive agent is desired which has a lower toxicity based on a different chemical structure, and thus, different functional mechanism can be expected.

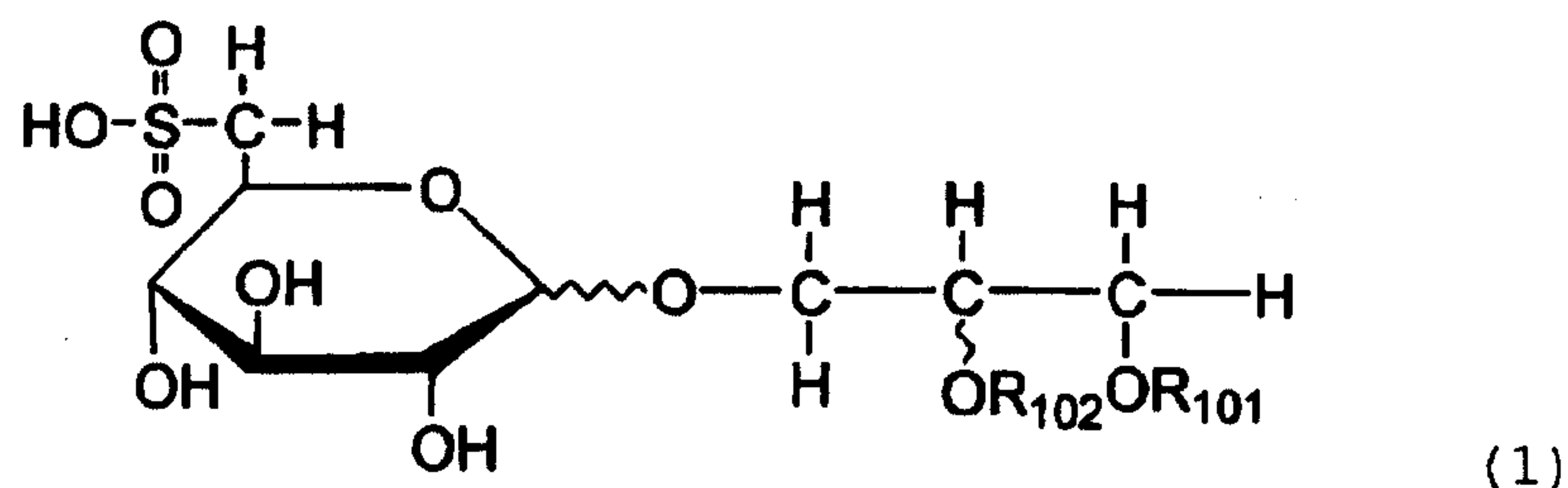
25 It has been found that naturally-occurring sulfur-containing glycolipids have pharmaceutical activities such as an anticancer effect (Sahara et al., British

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20

25



where R_{101} and R_{102} independently represent an acyl residue of a higher fatty acid, and

a pharmaceutically acceptable salt thereof.

Brief Description of Drawings

FIG. 1 shows the relationship between the concentration of the compound (SQAG 3) represented by Formula (1) and the immunosuppressive activity;

FIG. 2 shows the relationship between the concentration of the compound (SQAG 5) represented by Formula (1) and the immunosuppressive activity;

FIG. 3 shows the relationship between the concentration of the compound (SQAG 7) represented by Formula (1) and the immunosuppressive activity; and

FIG. 4 shows the relationship between the concentration of the compound (SQAG 9) represented by Formula (1) and the immunosuppressive activity.

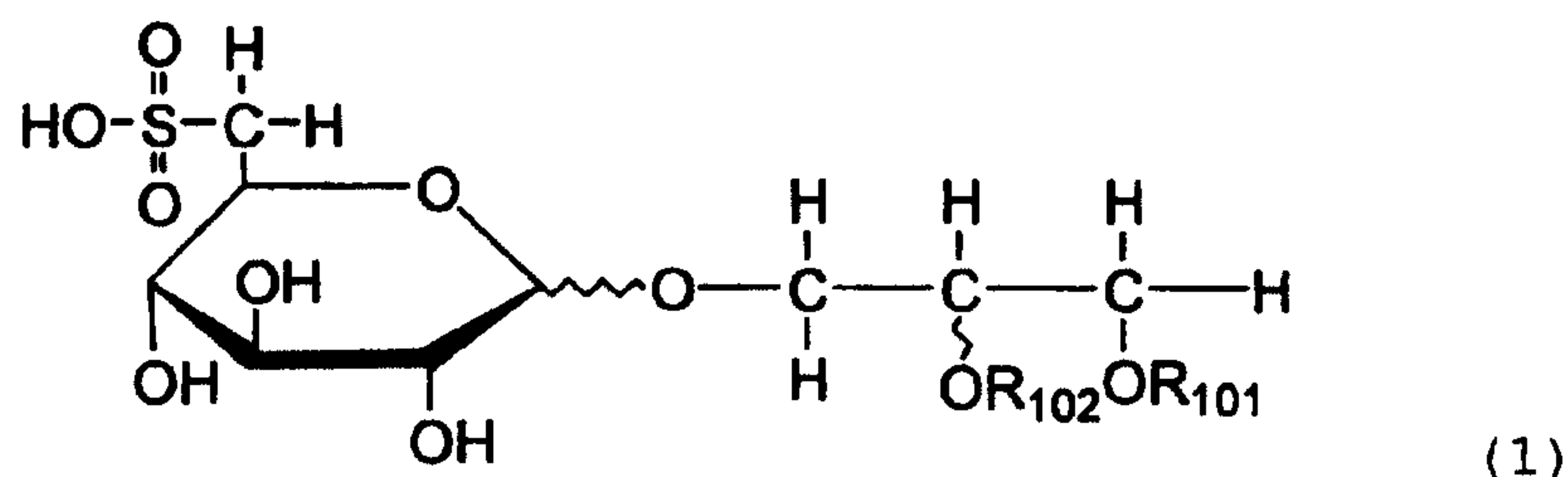
Best Mode for Carrying Out of the Invention

In the specification, the term "carbon atoms" of a protecting group refers to the number of carbon atoms assuming that the protecting group is unsubstituted. To be more specific, when the group represented by R^6 is a substituted alkyl group, its number of carbon atoms is that of the alkyl group itself, and the number

of carbon atoms of the substituent on the alkyl group is not counted. The same conditions are applicable to the case where the protecting group is other than the alkyl group.

5 In the first place, we will more specifically explain the active ingredient contained in the immunosuppressive agent of the present invention, that is, a sulfoquinovosyldiacylglycerol derivative represented by Formula (1):

10



where R₁₀₁ and R₁₀₂ independently represent an acyl residue of a higher fatty acid.

15 In Formula (1), R₁₀₁ represents an acyl residue of a higher fatty acid. Fatty acids giving the acyl residue represented by R₁₀₁ include straight-chain or branched-chain, saturated or unsaturated higher fatty acids.

20 The acyl residues of straight-chain or branched-chain higher fatty acids represented by R₁₀₁ include groups represented by R-C(=O), where R represents an alkyl or alkenyl group having 13 or more carbon atoms. The number of carbon atoms of the alkyl and alkenyl groups represented by R of R-C(=O) is preferably 13 or

more and 25 or less, and more preferably, an odd number within 15-25. This is because if the number of carbon atoms of R exceeds 25, the manufacturing cost increases.

In Formula (1), R₁₀₂ has the same meaning as R₁₀₁.

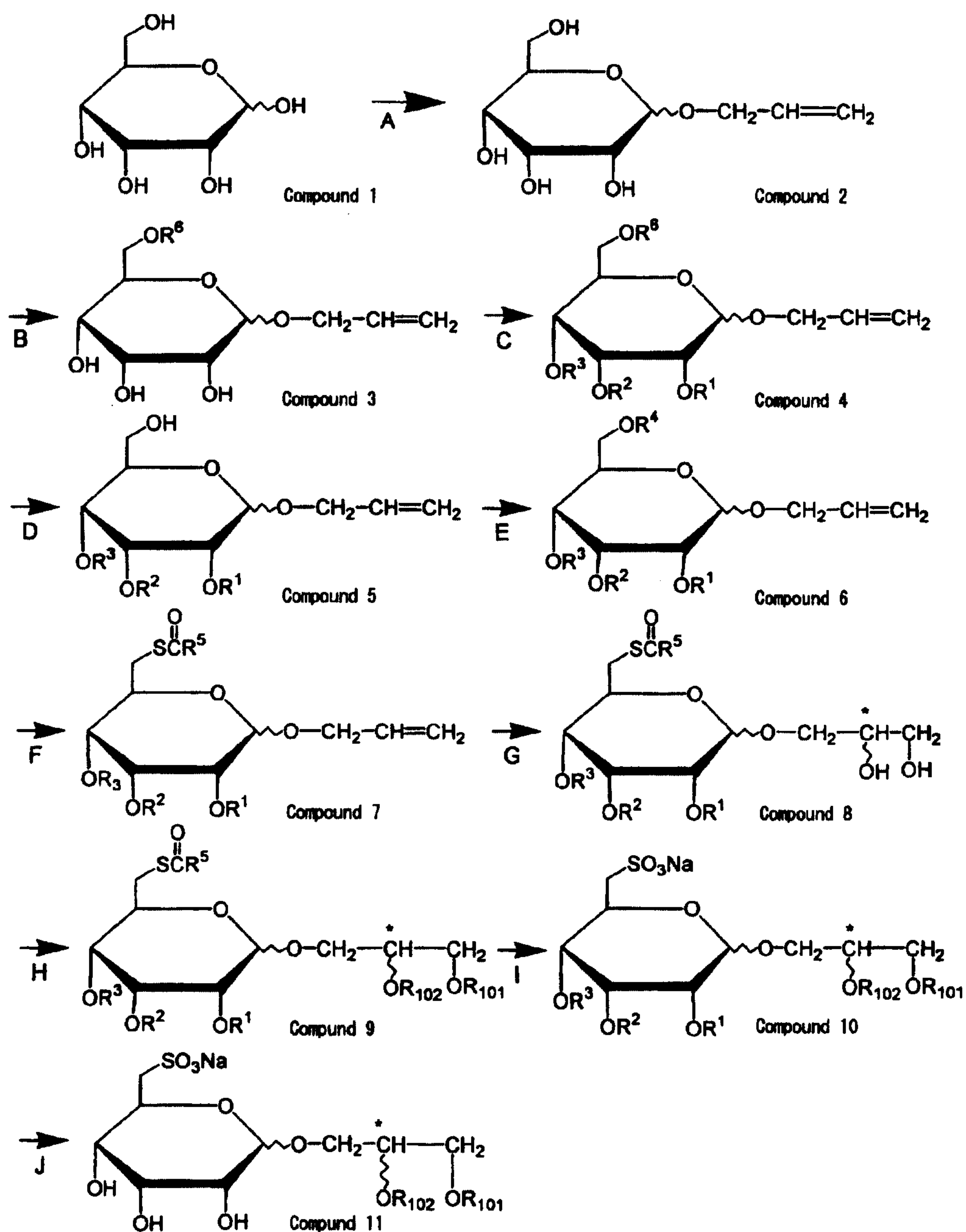
5 R₁₀₁ and R₁₀₂ may be the same or different.
However, they are preferably the same in view of manufacturing facility.

The sugar skeleton of sulfoquinovoside in Formula (1) may take either a boat or chair
10 conformation. However, the chair conformation is preferable in view of stability. The absolute configuration of the carbon (asymmetric carbon) at the 2-position of the glycerol moiety may be either the S- or R-configuration.

15 The bonding between sulfoquinovoside and glycerol is either an α - or β -bonding. However, the β -bonding is preferable judging from the results of the immunosuppressive activity assay using cultured cells.

The sulfoquinovosyldiacylglycerol derivatives of
20 the present invention can be prepared via (Step A) to (Step J) in accordance with the following reaction procedure.

Scheme 1



5

(Step A) The hydroxyl group bonded to the C1 carbon of D-glucose is converted into a 2-propenyl group. (Step B) The hydroxyl group of the C6 carbon of the glucose is protected. (Step C) The hydroxyl groups

bonded to the C2, C3 and C4 carbons of the glucose are protected. (Step D) The protecting group of the C6 carbon previously protected is deprotected. (Step E) The hydroxyl group bonded to the C6 carbon is

5 substituted with a group (for example, an alkylsulfonyloxy group or arylsulfonyloxy group) which can be converted to a carbonylthio group. (Step F) The C6 carbon is converted into a carbonylthio group.

(Step G) The 2-propenyl group bonded to the C1 carbon

10 is converted into a diol. (Step H) Each of the hydroxyl groups of the diol thus obtained is esterified with a desired higher fatty acid. (Step I) The carbonylthio group at the C6 carbon is converted into a sulfonate salt. (Step J) The protecting groups of C2,

15 C3 and C4 carbons of the sulfonate salt obtained are deprotected. As a result, a salt of a sulfoquinovosyldiacylglycerol derivative of the present invention can be produced. The salt thus obtained is subjected to titration with an acid such as

20 hydrochloric acid to give the sulfoquinovosyldiacylglycerol derivative of the present invention.

The aforementioned Steps A-J will be further explained in detail.

25 In Step A, the 2-propenylation is carried out by reacting the glucose with allyl alcohol in the presence of a strong acid, such as trifluoromethanesulfonic acid,

usually at room temperature to 100°C, preferably from 80 to 90°C, for a half day to two days. However, the reaction time varies depending upon the reaction conditions.

5 In Step B, the hydroxyl group bonded to the C6 carbon is protected to obtain the compound to which -OR⁶ is bonded at the C6 carbon (where R⁶ represents an alkyl or substituted silyl group).

10 As the compound capable of protecting the hydroxyl group, a compound can be used which can provide an alkyl or substituted silyl group as the R⁶ group.

15 Examples of the alkyl group represented by R⁶ preferably include bulky and substituted lower alkyl groups. The substituents of the bulky and substituted alkyl groups include methyl and phenyl groups. The specific examples of the substituted alkyl group include t-butyl and trityl groups.

20 When the group represented by R⁶ represents a substituted silyl group, examples of substituents of the substituted silyl group include lower alkyl groups, preferably alkyl groups having 1-4 carbon atoms (for example, methyl, ethyl, isopropyl and t-butyl groups); and aryl groups, preferably aryl groups having 6 carbon atoms (for example, a phenyl group). The substituted
25 silyl group represented by R⁶ preferably includes tri-substituted silyl groups, more preferably, a t-butyldiphenylsilyl group.

When the compound 3, where R^6 represents an alkyl group, is to be obtained, the protection of the hydroxyl group in Step B can be carried out by adding a compound represented by R^6-X (where R^6 represents the alkyl group defined above, and X represents a halogen atom such as chlorine atom) to a solution of the compound 2 dissolved in an organic solvent, such as anhydrous pyridine, and reacting the solution mixture at room temperature in the presence of a catalyst such as p-dimethylaminopyridine (DMAP). As the compound R^6-X , trityl chloride is preferably used in view of manufacturing cost and reaction facility.

When the compound 3, where R^6 represents a substituted silyl group, is to be obtained, t-butylldiphenylsilyl chloride, for example, is used as the compound R^6-X , and the reaction is carried out in the presence of a catalyst, such as imidazole, at room temperature for a half day to two days. Note that the reaction time varies depending upon the reaction conditions.

In Step C, the hydroxyl groups bonded to the C2, C3 and C4 carbons are protected and converted into $-OR^1$, $-OR^2$ and $-OR^3$, respectively, where R^1 to R^3 independently represent an alkyl or substituted silyl group. The protection of these hydroxyl groups can be carried out by activating, with sodium hydride, the hydroxyl groups bonded to the C2, C3 and C4 carbons of

the compound 3 dissolved in an organic solvent, such as N, N-dimethylformamide (DMF), and reacting with the compound capable of protecting these hydroxyl groups at room temperature.

5 As the compound capable of protecting the hydroxyl groups, benzyl bromide, p-methoxybenzyl bromide, t-butyldimethylsilyl chloride or triethylsilyl chloride may be used. The reaction using the compound capable of protecting the hydroxyl groups can be carried out
10 under a suitable reaction condition for each of the protecting groups.

 The deprotection of the protecting group bonded to the C6 carbon in Step D may be carried out by reacting a solution of the compound 4 dissolved in an organic
15 solvent, such as methanol, in the presence of a catalyst, such as p-toluenesulfonic acid, for a half day to one day at room temperature. The reaction time varies depending upon the reaction conditions.

 In Step E, R^4 , that is, an alkylsulfonyl or
20 arylsulfonyl group is bonded to the hydroxyl group at the C6 carbon of the compound 5, so that the hydroxyl group is converted into $-OR^4$ to give the compound 6.

 The reaction to give the $-OR^4$ group is performed by adding a compound having the alkylsulfonyl group or
25 a compound having the arylsulfonyl group to a solution of the compound 5 dissolved in an organic solvent, and reacting them. The alkyl groups of the compound having

the alkylsulfonyl group preferably include unsubstituted alkyl groups, more preferably, lower alkyl groups, much more preferably, alkyl groups having 1-2 carbon atoms (methyl and ethyl groups). The compound having an alkylsulfonyl group can be represented by $R^{4'}-X$, where $R^{4'}$ represents an alkylsulfonyl group, and X represents a halogen atom. Specific examples include methanesulfonyl chloride and ethanesulfonyl chloride.

On the other hand, the aryl group of the compound having the arylsulfonyl group may include unsubstituted and substituted aryl groups, preferably aryl groups having 6 carbon atoms (e.g., a phenyl group). In the case of the substituted aryl group, examples of the substituent thereof include p-methyl and p-methoxy groups. Examples of the compound having an arylsulfonyl group include compounds represented by $R^{4''}-X$, where $R^{4''}$ represents an arylsulfonyl group, and X represents a halogen atom. Specific examples include p-toluenesulfonyl chloride, p-methoxybenzenesulfonyl chloride and benzenesulfonyl chloride.

Of the compounds having an alkylsulfonyl or arylsulfonyl group, a compound having a tosyl group is preferably used from the viewpoint of reaction facility.

In the reaction of Step E, as an organic solvent, for example, pyridine or dichloromethane may be used.

The reaction mentioned above may be performed, as

the case may be, in the presence of a catalyst, such as DMAP, at room temperature for 2 hours to one day. The reaction time varies depending upon the reaction conditions.

5 In Step F, the sulfonyloxy group ($-OR^4$) of the compound 6 is replaced with a carbonylthio group represented by $-SC(=O)R^5$, where R^5 represents a hydrogen atom, an alkyl or aryl group.

10 In the reaction, a compound capable of substituting the alkylsulfonyloxy or arylsulfonyloxy group of the compound 6 with the carbonylthio group, is allowed to react in an organic solvent to give a compound 7. Hereinafter, this compound will be referred to as "O-substituted $\rightarrow$ S-substituted compound".

15 Examples of the O-substituted $\rightarrow$ S-substituted compound include alkali metal salts and alkali earth metal salts of a thiocarboxylic acid. Examples of the thiocarboxylic acid include thioformic acid, lower thiocarboxylic acids, preferably aliphatic
20 thiocarboxylic acids each having 1-5 carbon atoms in its aliphatic hydrocarbon moiety (for example, thioacetic acid or thiopropionic acid), and aromatic thiocarboxylic acids each having 6-10 carbon atoms in its aromatic hydrocarbon moiety (for example,
25 thiobenzoic acid).

The alkali metal that forms a salt with the thiocarboxylic acid includes potassium and sodium. The

alkali earth metal includes magnesium and calcium.

Of the above-mentioned O-substituted $\rightarrow$ S-substituted compounds, salts of thioacetic acid may be preferably used since a reaction can proceed stably and the sulfur atom can be easily oxidized in a later step.

Examples of an organic solvent used in the reaction include alcohol, for example, methanol, ethanol and propanol, N,N-dimethylformamide and dimethylsulfoxide.

The aforementioned reaction may be performed usually at room temperature to the boiling point of a solvent to be used while stirring for one hour to one day. Note that the reaction time varies depending upon the reaction conditions.

The dihydroxylation of Step G may be performed by adding an oxidizing agent, such as osmium tetroxide, to a solution of the compound 7 dissolved in a solvent mixture, such as a mixture of t-butanol and water, and then reacting the resultant mixture in the presence of a re-oxidizing agent, such as trimethylamine N-oxide, at room temperature for one hour to three days. Note that the reaction time varies depending upon the reaction conditions.

By the esterification of Step H, a sulfoquinovosyldiacylglycerol derivative having desired higher fatty acids each bonded, through an ester-bond, to its glycerol moiety can be obtained.

This reaction can be carried out by adding a higher fatty acid corresponding to a final product to a solution of the compound 8 dissolved in a suitable organic solvent, such as dichloromethane, and then
5 reacting the resultant mixture, if necessary, in the presence of a suitable catalyst, such as ethyldimethylaminopropylcarbodiimide (EDCI)-DMAP.

In the reaction of Step H, as the fatty acid to be added, use may be made of a higher fatty acid whose
10 acyl group is that represented by R₁₀₁ of Formula (1), i.e., a straight-chain or branched-chain, saturated or unsaturated higher fatty acid.

In the reaction of Step H, the compound 9 is obtained in the form of a mixture of a diacylester and
15 a monoacylester. The diacylester herein is represented by Formula (1) of the present invention where each of R₁₀₁ and R₁₀₂ is an acyl residue of the higher fatty acid added. The monoacylester herein has the acyl residue of the higher fatty acid added, as the R₁₀₁
20 only. Two or more higher fatty acids may be added, if desired, in the reaction of Step H. In this case, the resultant mixture contains diacylesters represented by Formula (1) where R₁₀₁ and R₁₀₂ are the same or different acyl residues, and monoesters having
25 different acyl residues as R₁₀₁.

If necessary, the mixture of the monoesters and diesters can be isolated from each other by, for

example, chromatography, and subjected to the next reaction Step I. Furthermore, production of the monoester is suppressed as much as possible by setting the addition amount of the fatty acid to 2-3 times
5 larger than that of the compound 8, in terms of mole, thereby the diester can be preferentially obtained.

In Step I, the conversion into a sulfonate salt can be carried out by adding an oxidizing agent, for example, OXONE (2KHSO₅, KHSO₄ and K₂SO₄) into a
10 solution of the compound 9 dissolved in an organic solvent, which is buffered with acetic acid and potassium acetate, and then allowing the resultant mixture to react at room temperature for a half day to two days. Note that the reaction time varies depending
15 upon the reaction conditions.

The deprotection of the protecting groups bonded to carbons at the C2 to C4 carbons in Step J can be carried out by a method suitable for a protecting group to be used and an acyl residue of the bonded higher
20 fatty acid. For example, when the protecting group is a benzyl group and each of R₁₀₁ and R₁₀₂ is an acyl residue of a saturated higher fatty acid, the deprotection can be conducted by reacting a solution of a compound 10 dissolved in an organic solvent, such as
25 ethanol, in the presence of a catalyst, such as palladium-activated carbon, under a hydrogen gas atmosphere at room temperature. Furthermore, when at

least one of the acyl residues of the higher fatty acids represented by R₁₀₁ and R₁₀₂ is an acyl residue of an unsaturated higher fatty acid, a deprotection method suitable for a protecting group used and capable of retaining the double bond of the unsaturated fatty acid may be employed. For example, when the protecting group is a silyl group, the deprotection can be conducted by use of an acid catalyst (e.g., trifluoroacetic acid).

10 Note that glucose of a starting material usually takes α - and β -anomer configurations in a solution. Therefore, the product in each step results in a mixture of α - and β -anomers. The mixture may be separated into α - and β -anomers by chromatography.

15 Prior to the step B, if a step of reacting the compound 2 with benzaldehyde is performed to form benzylidene, it is possible to selectively crystallize the α -anomer and thereby separate it. Furthermore, if halogen such as bromine is bonded to the C1 carbon before the 2-propenylation of Step A, the propenyl group can be introduced into a β -configuration in a later reaction. In this way, a β -anomers can be selectively synthesized.

25 The immunosuppressive agent of the present invention contains at least one compound selected from the group consisting of sulfoquinovosyldiacylglycerol derivatives represented by Formula (1) of the present

invention and pharmaceutically acceptable salts thereof, as an active ingredient. Examples of the pharmaceutically acceptable salts employed in the immunosuppressive agent of the present invention
5 include, but not limited to, a salt of a monovalent cation such as a sodium or potassium ion. Hereinafter, the compounds of the group consisting of sulfoquinovosyldiacylglycerol derivatives and pharmaceutically acceptable salts thereof are sometimes
10 referred to as "immunosuppressive substance of the present invention".

Examples of the sulfoquinovosylacylglycerol derivative contained in the immunosuppressive substance of the present invention as an active ingredient
15 include an isomer in which quinovose is bonded to glycerol with an α - or β -configuration, and an isomer having an asymmetric carbon at the C2 carbon of the glycerol moiety. The immunosuppressive substance of the present invention may include these isomers alone
20 or in combination of two or more types of isomers as long as they adversely affect the activity of the immunosuppressive substance.

The immunosuppressive substance of the present invention can be orally or parenterally administered.
25 Immunosuppressive substance of the present invention can be combined with, for example, a pharmaceutically acceptable excipient or diluent depending on an

administration route thereby to form a medicinal formulation.

The forms of the agent suitable for oral administration include, solid-, semi-solid, liquid- and gas-states. Specific examples include, but not limited to, tablet, capsule, powder, granule, solution, suspension, syrup and elixir agents.

In order to formulate the immunosuppressive substance of the present invention into tablets, capsules, powders, granules, solutions or suspensions, the substance is mixed with a binder, a disintegrating agent and/or a lubricant, and, if necessary, the resultant is mixed with a diluent, a buffer, a wetting agent, a preservative and/or a flavor, by a known method. Examples of the binder include crystalline cellulose, cellulose derivatives, cornstarch and gelatin. Examples of the disintegrating agent include cornstarch, potato starch and sodium carboxymethylcellulose. Examples of the lubricant include talc and magnesium stearate. Furthermore, additives such as lactose and mannitol may also be used as long as they are used conventionally.

Moreover, the immunosuppressive substance of the present invention may be administered in the form of aerosol or inhalant, which is prepared by charging the active substance of liquid- or fine powder-form, together with a gaseous or liquid spraying agent, and,

if necessary, a known auxiliary agent such as a wetting agent, into a non-pressurized container such as an aerosol container or a nebulizer. As the spraying agent, a pressurized gas, for example,
5 dichlorofluoromethane, propane or nitrogen may be used.

For parenteral administration, the immunosuppressive substance of the present invention can be administered by injection, percutaneously, rectally or intraocularly.

10 For the administration by injection, the immunosuppressive substance of the present invention can be injected, for example, hypodermically, intracutaneously, intravenously or intramuscularly. An injection preparation may be formulated by dissolving,
15 suspending or emulsifying the immunosuppressive substance of the present invention into an aqueous or non-aqueous solvent such as a vegetable oil, a synthetic glyceride with a fatty acid, an ester of a higher fatty acid or propylene glycol by a known method.
20 If desired, a conventional additive such as a solubilizing agent, an osmoregulating agent, an emulsifier, a stabilizer or a preservative, may be added to the preparation.

For formulating the immunosuppressive substance of
25 the present invention into solutions, suspensions, syrups or elixirs, a pharmaceutically acceptable solvent such as sterilized water for injection or a

normalized physiological saline solution may be used.

For the percutaneous administration, the immunosuppressive substance of the present invention may be administered in the form of ointment,
5 emulsifications, pastae, plasters, liniments, lotions, suspensions in accordance with the state of skin to be treated.

The ointments can be formulated by a known method by kneading the immunosuppressive substance of the
10 present invention with a hydrophobic base, such as Vaseline or paraffin, or a hydrophilic bas, such as hydrophilic Vaseline or macrogol. The emulsifying agents and other percutaneous agents may be formulated by a method conventionally used.

15 For the rectal administration, a suppository can be used. The suppository may be prepared by mixing the immunosuppressive substance of the present invention with an excipient that can be melted at body temperature but is solid at room temperature, such as
20 cacao butter, carbon wax or polyethylene glycol, and molding the resultant material, by a known method.

For the intraocular administration, ophthalmic formulations such as eye drops and eye ointments may be administered. The eye drops are formulated by
25 dissolving or suspending the immunosuppressive substance of the present invention in an aqueous solvent, such as sterilized water, and, if necessary,

adding a preservative, buffer, and surfactant.

The immunosuppressive substance of the present invention may be used together with a pharmaceutically acceptable compound having another activity, to prepare
5 a pharmaceutical preparation.

The dose of the immunosuppressive substance of the present invention may be appropriately set or adjusted in accordance with an administration form, an administration route, a degree or stage of a target
10 disease, and the like. For example, in the case of oral administration, a dose of the immunosuppressive substance may be set at 1 - 100 mg/kg body weight/day, preferably 1 - 10 mg/kg body weight/day. In the case of administration by injection, a dose of the
15 immunosuppressive substance may be set at 1 - 50 mg/kg body weight/day, more preferably, 1 - 5 mg/kg body weight/day. In the case of percutaneous administration, a dose of the immunosuppressive substance may be set at 1 - 100 mg/kg body weight/day, more preferably, 1 -
20 10 mg/kg body weight/day. In the case of rectal administration, a dose of the immunosuppressive substance may be set at 1 - 50 mg/kg body weight/day, more preferably 1 - 5 mg/kg body weight/day. In the case of intraocular administration, about a 0.01 - 3%
25 solution of the immunosuppressive substance may be applied dropwise to an eye several times per day. However, the doses are not limited to these.

Examples

The present invention will now be described by way of its Examples. However, the present invention is not limited to these Examples.

5 Synthesis example of a
sulfoquinovosyldiacylglycerol β derivative is set forth below, as an example of the active ingredients used in the immunosuppressive substance of the present invention.

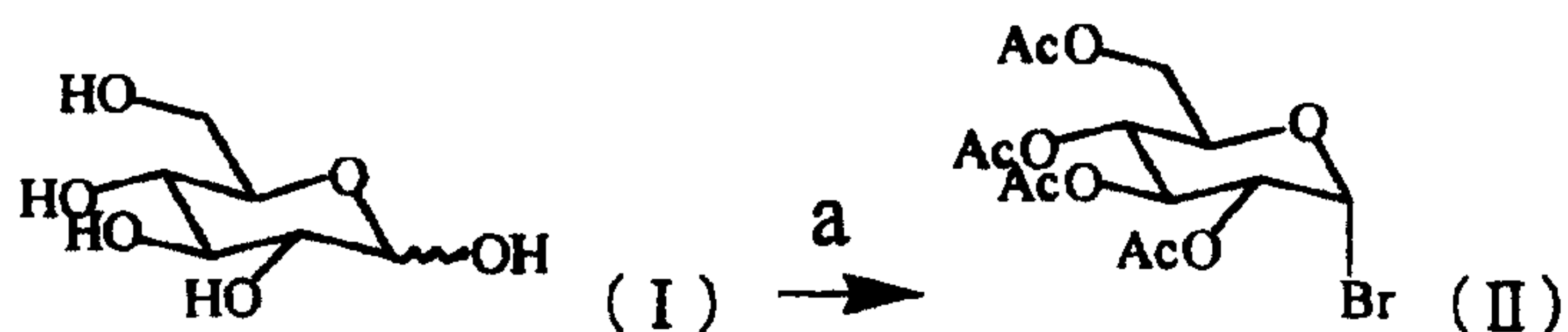
10 <Example 1>

Route a: 2,3,4,6-tetra-O-acetyl-D-glucopyranosyl bromide (II)

15 To 400 mL of acetic anhydride, 2.4 mL of 60% perchloric acid was added dropwise at 0°C. After the solution was returned to room temperature, 100g (0.56 mol) of D-glucose was added to the solution with stirring for about 30 minutes while keeping the solution temperature at 30-40°C. After the reaction solution was cooled to 20°C, 30g (1.0 mol) of red
20 phosphorus was added. While the solution temperature was maintained at 20°C or less, 180g (2.3 mol) of bromine, and then 36 mL of water were added dropwise. After the resultant mixture was allowed to stand at room temperature for 2 hours, 300 mL of cold chloroform
25 was added to the mixture. The reaction solution was filtrated by a funnel having a glass wool placed at the bottom. The filtrate was poured into cold water

(800 mL) and a chloroform layer was separated by a separatory funnel. The water layer was extracted with 50 mL of chloroform. The chloroform layers were combined and washed with cold water (300 mL). The resultant chloroform layer was poured into 500 mL of saturated sodium hydrogencarbonate solution, sufficiently shaken in a separatory funnel. The resultant chloroform layer was recovered, dried over anhydrous sodium sulfate, filtrated, and concentrated in vacuo to give a crystalline substance. The obtained crystalline substance was pulverized in a mortar together with a solution of petroleum ether : ether (2:1) and filtered off. The crude crystalline substance was dried in vacuo, recrystallized with cold diisopropylether. As a result, a pure crystal was obtained (yield: 152.6g, 0.37 mol, recovery: 66.7%).

Melting point: 88-90°C. Rf value: 0.338 (Hexan: ethyl acetate=4:1)

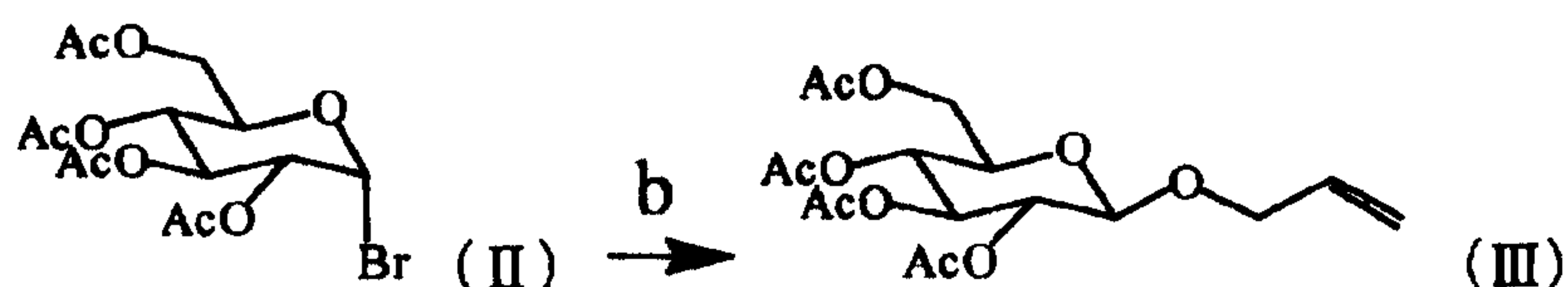


Route b: 2,3,4,6-tetra-O-acetyl-1-O-(2-propenyl)- β -D-glucose (III)

In 100 mL of allyl alcohol, 16.7g (40.6 mmol) of the compound (II) was dissolved, and 10.0g (39.6 mmol) of mercury cyanide was added thereto. The resultant mixture was stirred at room temperature overnight. The

reaction solution was concentrated in vacuo, shaken together with 100 mL of chloroform and cold water in a separatory funnel to allow the chloroform layer to separate. After the chloroform layer was dried over anhydrous sodium sulfate, filtrated, and concentrated in vacuo, the resultant syrup was dissolved in cold diisopropylether. To the resultant solution, a small amount of crystal seed was added and stood in an ice-cooled condition. As a result, a crystal was obtained (yield: 12.6g, 32.5 mmol, recovery: 80%)

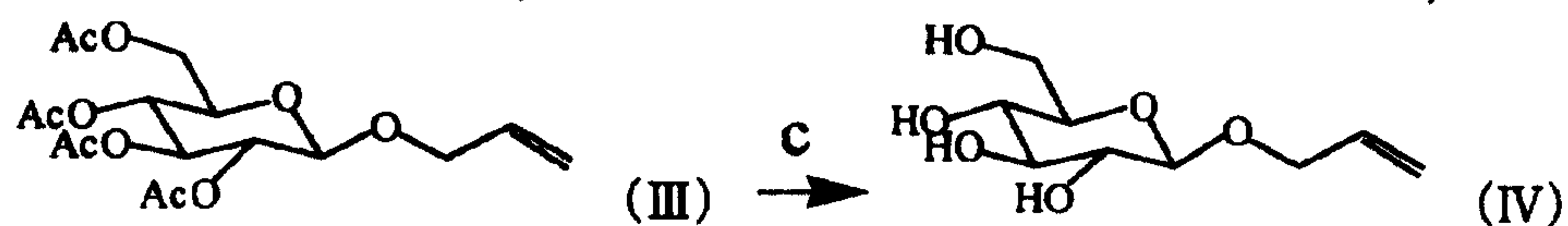
Melting point: 77-81°C, Rf value: 0.282 (benzene: ethyl acetate = 4:1)



Route c: 1-0-(2-propenyl)- β -D-glucose (IV)

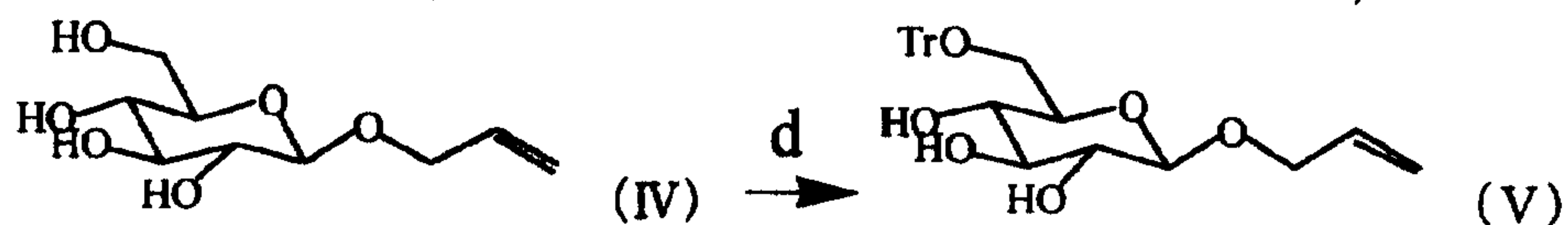
The compound (III) (30.3g, 78.1 mmol) was dissolved in 120 mL of methanol. To the solution mixture, a small amount of 28% sodium methoxide in methanol was added dropwise while stirring. The reaction mixture was reacted at room temperature for 4 hours, neutralized with 0.1N hydrochloric acid, dried over anhydrous sodium sulfate, filtrated, concentrated in vacuo, and purified by silica gel flash chromatography (chloroform : methanol = 4 : 1). As a result, a colorless and transparent oily substance was obtained (yield: 15.8g, 71.8 mmol, recovery: 91.9%).

Rf value: 0.407 (Chloroform : methanol = 4 : 1)



Route d: 1-O-(2-propenyl)-6-O-triphenylmethyl- β -
5 D-glucose (V)

The compound (IV) (15.8g, 71.8 mmol) was dissolved
in 120 mL of anhydrous pyridine. To the solution,
23.4g (83.9 mmol) of trityl chloride and 0.1g
(0.82 mmol) of p-dimethylaminopyridine (DMAP) were
10 added. The reaction mixture was reacted for 36 hours
at room temperature while stirring. Then, the reaction
was quenched by adding 300 mL of cold water and the
extracted with ethyl acetate (3 $\times$ 300 mL). The resultant
organic layers were combined, neutralized with 1.0N
15 hydrochloric acid to pH 4, washed with brine (2 $\times$ 300 mL),
dried over anhydrous sodium sulfate, filtered,
concentrated in vacuo, and purified by silica gel flash
chromatography (dichloromethane: methanol = 20 : 1)).
As a result, a pale yellowish oily substance was
20 obtained (yield: 28.7g, 62.1 mmol, recovery: 86.5%). Rf
value: 0.306 (chloroform : methanol= 19 : 1).



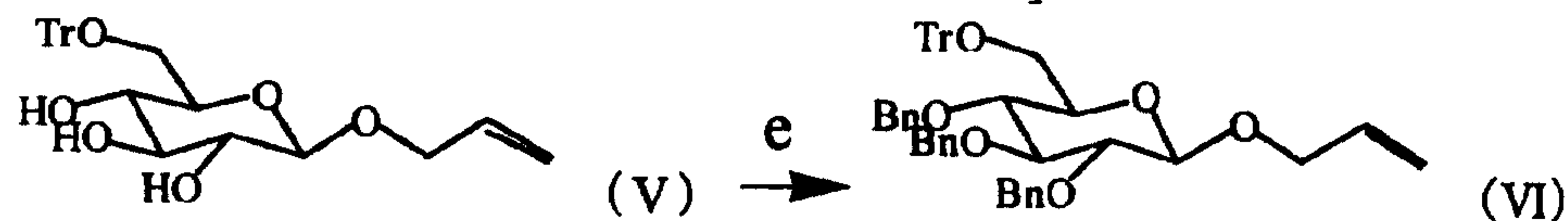
Route e: 2,3,4-tri-O-benzyl-1-O-(2-propenyl)-6-O-
25 triphenylmethyl- β -D-glucose (VI)

80% sodium hydride (3.2g, 133 mmol) dispersed in a mineral oil was put into a reaction vessel, and sufficiently washed with anhydrous hexane (50 mL).

After the hexane was removed, 14.2g (30.7 mmol) of the compound (V) dissolved in dry N,N-dimethylformamide was gradually added to the resultant suspension in an ice-cooled condition. After 15 minutes, the reaction mixture was returned to room temperature and the reaction was performed for one hour while stirring.

Next, 21.6g (126 mmol) of benzylbromide were gradually added to the reaction mixture under an ice-cooled condition again. After 15 minutes, the reaction mixture was returned to room temperature, and reacted for 3 hours while stirring. Then, 20 mL of methanol and 30 mL of cold water were added to the reaction mixture to quench the reaction. The reaction mixture was extracted with ethyl acetate (3×50 mL). The organic layers were combined, washed with brine (2×100 mL), dried over anhydrous sodium sulfate, filtered, concentrated in vacuo, and purified by silica gel flash chromatography (hexane : ethyl acetate = 10 : 1). As a result, a pale yellowish oily substance was obtained (yield: 21.6g, 29.5 mmol, recovery: 96.1%).

The R_f value: 0.410 (hexane : ethyl acetate = 4 : 1)



Route f: 2,3,4-tri-O-benzyl-1-O-(2-propenyl)- β -D-glucose (VII)

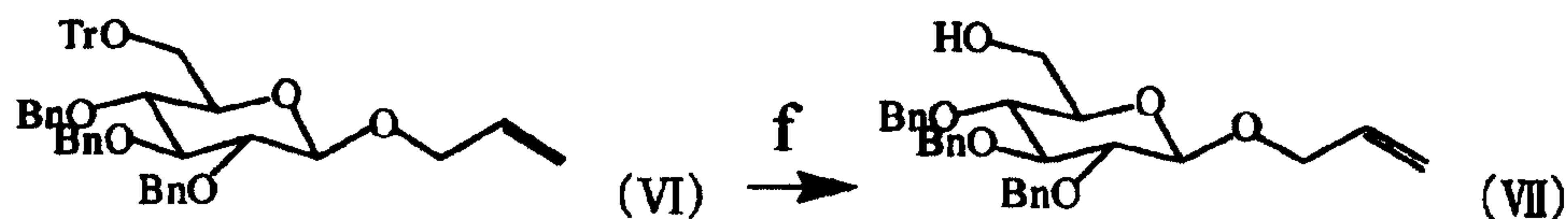
In 150 mL of methanol, the compound (VI) (21.6g, 29.5 mmol) was dissolved and 2.80g (14.7 mmol) of p-toluenesulfonic acid monohydrate was added. The solution was reacted overnight while stirring. Thereafter, the reaction was quenched by adding 100 mL of cold water and extracted with ethyl acetate (3 $\times$ 200 mL). The organic layers were combined, washed with brine (2 $\times$ 300 mL), dried over anhydrous sodium sulfate, filtered, concentrated in vacuo, and purified to silica gel flash chromatography (hexane : ethyl acetate = 4 : 1). As a result, a white crystalline substrate was obtained (yield 9.0g, 18.4 mmol, recovery 62.4%).

Melting point: 80-82°C,

R_f value: 0.338 (hexane : ethyl acetate = 4:1)

$[\alpha]_D = +0.4^\circ$ (c 5.50 CHCl₃)

¹H NMR (300MHz, CDCl₃+TMS, δ) ; 7.36-7.23 (15H, m, Ar), 6.02-5.89 (1H, m, -CH=CH₂), 5.34 (1H, dd, J=1.5 & 17.2, -CH=CH₂), 5.22 (1H, dd, J=1.4 & 10.4, -CH=CH₂), 4.95 (1H, d, J=10.9, Ar-CH₂), 4.94 (1H, d, J=10.9, Ar-CH₂), 4.86 (1H, d, J=10.9, Ar-CH₂), 4.81 (1H, d, J=10.9, Ar-CH₂), 4.73 (1H, d, J=10.9, Ar-CH₂), 4.64 (1H, d, J=10.9, Ar-CH₂), 4.50 (1H, d, J=7.8, H-1), 4.43-4.13 (2H, m, -O-CH₂-CH=CH₂), 3.88-3.34 (6H, m, H-2 & H-3 & H-4 & H-5 & H-6a,b)



Route g: 2,3,4-tri-O-benzyl-1-O-(2-propenyl)-6-O-(4-tolylsulfonyl)- β -D-glucose (VIII)

5 In 200 mL of anhydrous pyridine, 9.80g (20.0 mmol) of the compound (VII) was dissolved, and then 24.4 mg (0.2 mmol) of DMAP and 11.4g (60.0 mmol) of p-toluenesulfonyl chloride were added. The solution was reacted at room temperature overnight while stirring.

10 Thereafter, the reaction was quenched by adding 300 mL of cold water and extracted with ethyl acetate (3 $\times$ 200 mL). The resultant organic layers were combined, neutralized to pH 4 with 1.0N and 0.1N hydrochloric acid, washed with brine (2 $\times$ 300 mL), dried over

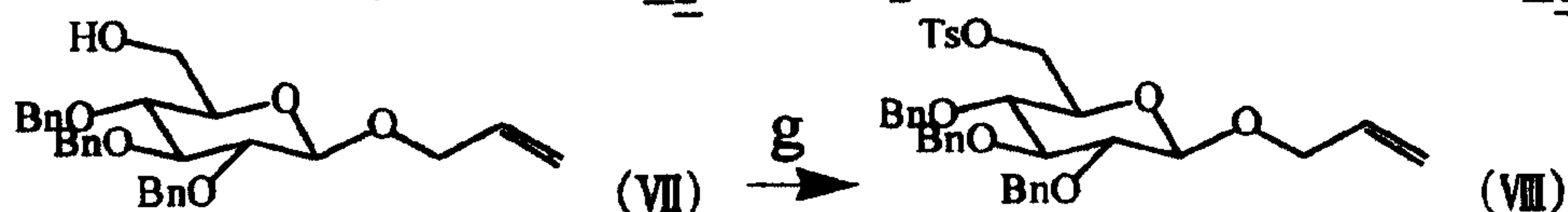
15 anhydrous sodium sulfate, filtered, concentrated in vacuo, and purified by silica gel flash chromatography (hexane : ethyl acetate = 4 : 1). As a result, a white crystalline substance was obtained (yield: 9.00g, 14.0 mmol, recovery 70.0%).

20 Melting point: 111-112°C, Rf value: 0.295 (hexane: ethyl acetate = 4 : 1)

¹H NMR (300MHz, CDCl₃+TMS, δ) ; 7.77 (2H, d, J=8.2, H at Ts Me), 7.31-7.25 (15H, m, Ar), 7.19-7.16 (2H, m, H at Ts SO₂), 5.98-5.85 (1H, m, -CH=CH₂), 5.35-5.19 (2H, m, -CH=CH₂), 4.92 (2H, d, J=10.9, Ar-CH₂), 4.81 (1H, d, J=10.8, Ar-CH₂), 4.75 (1H, d, J=10.9, Ar-CH₂), 4.68 (2H,

25

d, $J=10.9$, Ar-CH₂), 4.48 (1H, d, $J=10.8$, Ar-CH₂), 4.39 (1H, d, $J=7.8$, H-1), 4.34-3.38 (8H, m, H-2 & H-3 & H-4 & H-5 & H-6a,b & -O-CH₂-CH=CH₂), 2.42 (3H, s, Ts CH₃)



5

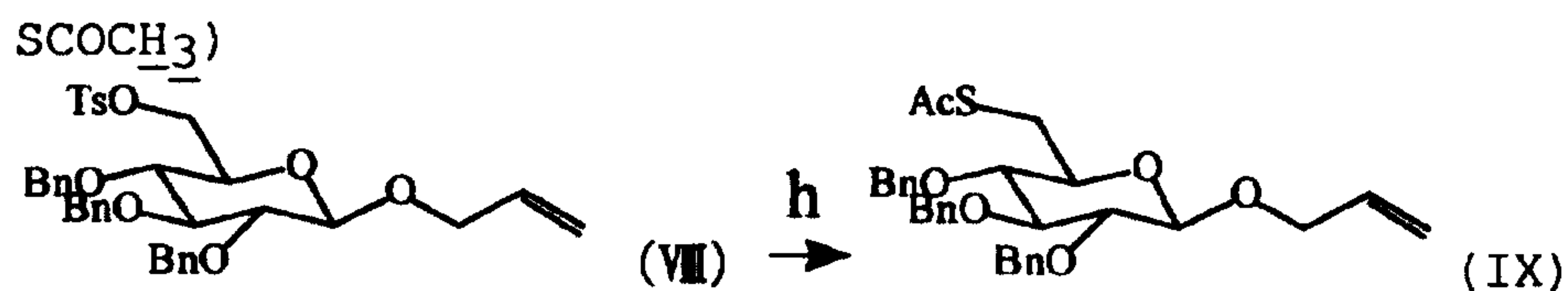
Route h: 2,3,4-tri-O-benzyl-1-O-(2-propenyl)-6-deoxy-6-acetylthio- β -D-glucose (IX)

In 250 mL of anhydrous ethanol, 9.00g (14.0 mmol) of the compound (VIII) was dissolved and then 4.80g (42.0 mmol) of potassium thioacetate was added. The solution was reacted under reflux for 3 hours while stirring. Thereafter, the reaction was quenched by adding 300 mL of cold water, and extracted with ethyl acetate (3 $\times$ 200 mL). The organic layers were combined, washed with brine (2 $\times$ 300 mL), dried over anhydrous sodium sulfate, filtered, concentrated in vacuo, purified by silica gel flash chromatography (hexane : ethyl acetate = 10 : 1). As a result, a white crystalline substance was obtained (yield: 6.60g, 12.0 mmol, recovery: 85.7%). Melting point: 70-73°C, Rf value: 0.295 (hexane : ethyl acetate= 4:1)

$[\alpha]_D = +26.7$ (c 0.75, CHCl₃)

¹H NMR (300MHz, CDCl₃+TMS, δ) ; 7.35-7.25 (15H, m, Ar), 6.00-5.89 (1H, m, -CH=CH₂), 5.35 (1H, dd, $J=1.5$ & 17.2, -CH=CH₂), 5.22 (1H, dd, $J=1.3$ & 10.4, -CH=CH₂), 4.95 (1H, d, $J=10.9$, Ar-CH₂), 4.93 (1H, d, $J=10.8$,

Ar-CH₂), 4.87 (1H, d, J=10.8, Ar-CH₂), 4.78 (1H, d, J=10.9, Ar-CH₂), 4.71 (1H, d, J=10.9, Ar-CH₂), 4.63 (1H, d, J=10.7, Ar-CH₂), 4.42 (1H, d, J=7.9, H-1), 4.37-3.33 (7H, m, H-2 & H-3 & H-4 & H-5 & H-6a & -O-CH₂-CH=CH₂),
 5 2.96 (1H, dd, J=6.9 & 13.6, H-6b) , 2.34 (3H, s,



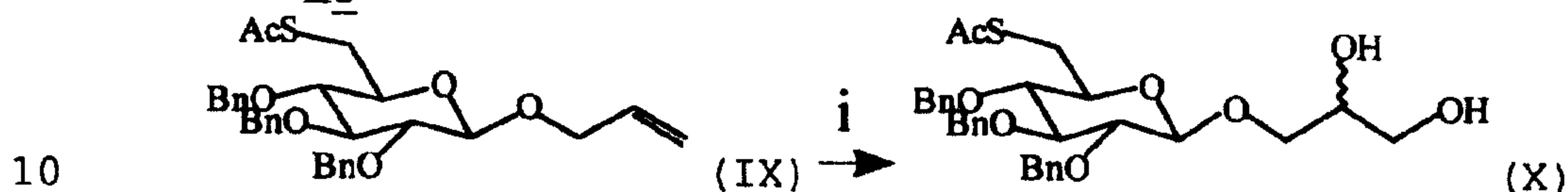
Route i: 3-O-(2,3,4-tri-O-benzyl-6-deoxy-6-acetylthio- β -D-glucopyranosyl)-glycerol (X)
 10

In a mixture of t-butanol : H₂O (4 : 1), 3.30g (6.02 mmol) of the compound (IX) was dissolved and then 1.34g (12.1 mmol) of trimethylamine N-oxide dihydrate and 1.7 mL of 0.04 M solution of osmium tetroxide in
 15 t-butanol were added. The solution was reacted at room temperature for 3 days while stirring. Thereafter, 5.8g of activated charcoal was added, and then the reaction mixture was allowed to stand while stirring for 1.5 hours. After filtration with suction, the
 20 reaction was quenched by adding 250 mL of cold water and extracted with ethyl acetate (3 $\times$ 200 mL). The organic layers were combined, washed with brine (2 $\times$ 300 mL), dried over anhydrous sodium sulfate, filtered, concentrated in vacuo, and purified by silica
 25 gel flash chromatography (hexane : ethyl acetate = 1 : 1). As a result, a white crystalline substance was

obtained (yield: 1.79g, 3.08 mmol, recovery 51.2%).

Melting point: 91-93°C, Rf value: 0.112 (hexane : ethyl acetate = 1 : 1), $[\alpha]_D = +18.0$ (c 0.75, CHCl₃)

¹H NMR (300MHz, CDCl₃+TMS, δ) ; 7.35-7.25 (15H, m, Ar), 4.94-4.61 (6H, m, Ar-CH₂), 4.38 (0.5H, d, J=7.8, H-1(R or S)), 4.37 (0.5H, d, J=7.8, H-1(R or S)), 3.83-3.37 (7H, m, H-2 & H-3 & H-4 & H-5 & H-6a & -O-CH₂-CH=CH₂), 2.96 (1H, dd, J=6.9 & 13.6, H-6b), 2.34 (3H, s, SC₃CH₃)



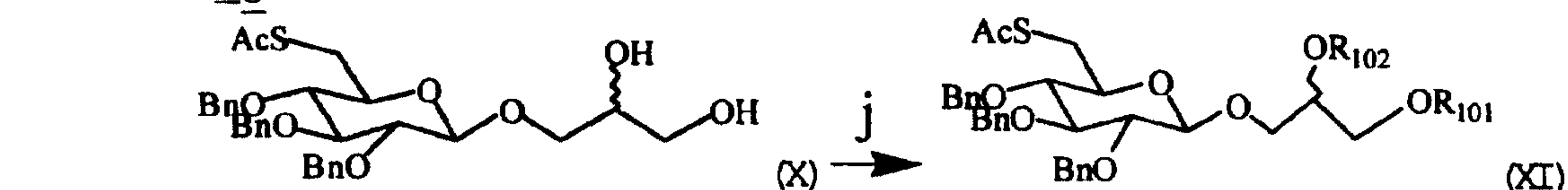
Route j: 3-O-(2,3,4-tri-O-benzyl-6-deoxy-6-acetylthio- β -D-glucopyranosyl)-1,2-di-O-stearoyl-glycerol (XI)

15 Into 100 mL of dichloromethane, 1.23g (2.12 mmol) of the compound (X) was dissolved and then 1.30g (6.79 mmol) of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (EDCI), 260 mg (2.13 mmol) of DMAP, and 1.75g (6.15 mmol) of stearic acid, were added. The
20 solution was reacted at room temperature for a day while stirring. Thereafter, the reaction was quenched by adding 100 mL of dichloromethane, washed with brine (2 $\times$ 50 mL), dried over anhydrous sodium sulfate, filtered, concentrated in vacuo, and purified by silica
25 gel flash chromatography (hexane : ethyl acetate = 10 : 1 $\rightarrow$ 8 : 1). As a result, a white non-crystalline

solid substance was obtained (yield: 2.10g, 1.88 mmol, recovery: 88.7%). Rf value: 0.487 (hexane; ethyl acetate = 4 : 1)

$[\alpha]_D = -21.3$ (c 0.15, CHCl_3)

5 ^1H NMR (300MHz, CDCl_3 +TMS, δ); 7.34-7.26 (15H, m, Ar), 5.28 (1H, m, Gly-H-2), 4.92-4.60 (6H, m, Ar- CH_2), 4.36 (0.5H, d, $J=7.7$, H-1(R or S)), 4.35 (0.5H, d, $J=7.8$, H-1(R or S)), 4.25-2.96 (10H, m, H-2 & H-3 & H-4 & H-5 & H-6a, b & Gly-H-1a, b & Gly-H-3a, b), 2.37 (1.5H, s, SCOCH_3 (R or S)), 2.35 (1.5H, s, SCOCH_3 (R or S)), 2.32-2.24 (4H, m, OCOCH_2), 1.65-1.58 (4H, m, $\text{OCOCH}_2\text{CH}_2$), 1.25 (56H, br, $-\text{CH}_2-$), 0.88 (6H, t, $J=6.3$, CH_3)



15 $R_{101}=R_{102}=\text{stealoyl}$

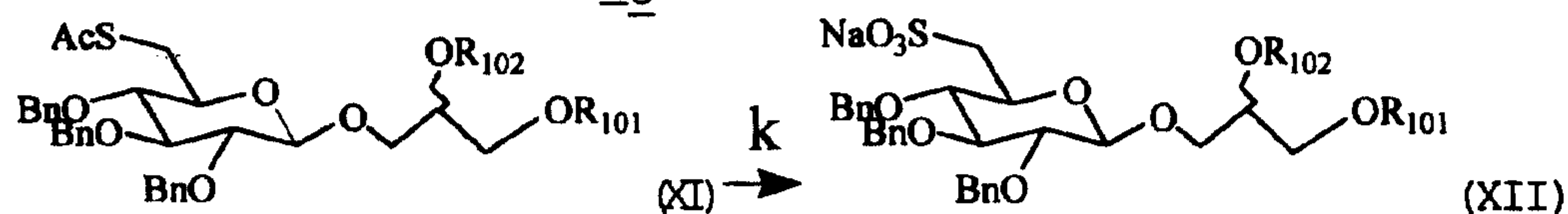
Route k: 3-O-(2,3,4-tri-O-benzyl-6-deoxy-6-sulfo- β -D-glucopyranosyl)-1,2-di-O-stealoyl-glycerol sodium salt (XII)

20 In 50 mL of acetic acid, 1.24g (1.11 mmol) of the compound (XI) was dissolved and then 1.5g of potassium acetate and 1.55g of OXONE (2KHSO_5 , KHSO_4 , K_2SO_4) were added. The solution was reacted overnight at room temperature while stirring.

25 Thereafter, the reaction was quenched by adding 100 mL of cold water, and extracted with ethyl acetate

(5×50 mL). The organic layers were combined, neutralized with saturated sodium hydrogencarbonate (2×100 mL), washed with brine (2×100 mL), dried over anhydrous sodium sulfate, filtered, concentrated in vacuo, and purified by silica gel flash chromatography (chloroform : methanol = 20 : 1 → 15 : 1). As a result, a white non-crystalline solid substance was obtained (yield: 773 mg, 0.677 mmol, recovery 61.0%). R_f value: 0.288 (dichlormethane: methanol = 10 : 1), [α]_D = +4.8° (c 0.17, CHCl₃)

¹H NMR (300MHz, CDCl₃+TMS, δ) ; 7.29-7.16 (15H, m, Ar), 5.31(1H, m, Gly-H-2), 4.91-4.56 (6H, m, Ar-CH₂), 4.50 (1H, d, J=7.6, H-1), 4.44-3.03 (10H, m, H-2 & H-3 & H-4 & H-5 & H-6a, b & Gly-H-1a, b & Gly-H-3a, b), 2.62(4H, br, OCOCH₂), 2.19-2.17 (4H, br, OCOCH₂CH₂), 1.49 (4H, br, OCOCH₂CH₂CH₂), 1.25 (52H, br, -CH₂-), 0.88 (6H, t, J=6.3, CH₃)



R₁₀₁=R₁₀₂=stearoyl

20

Route 1: 3-O-(6-deoxy-6-sulfo-β-D-glucopyranosyl)-1,2-di-O-stearoyl-glycerol sodium salt (XIII)

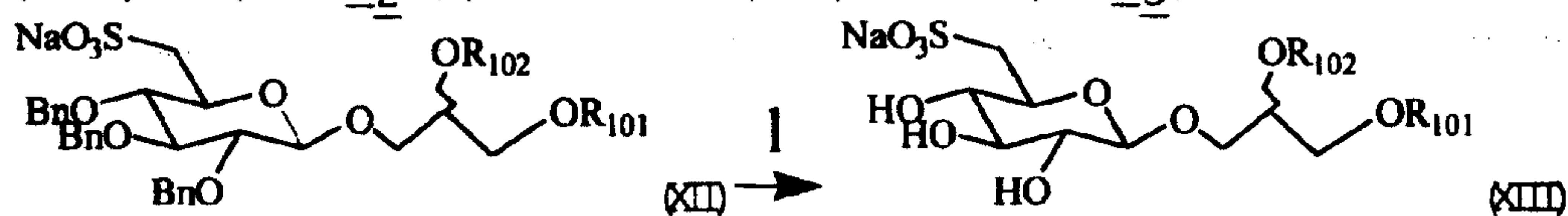
Into 50 mL of ethanol, 773 mg (0.677 mmol) of the compound (XII) was dissolved and then 2.00g of 10% palladium-activated carbon (Pd-C) was added. After the

25

atmosphere of the flask was substituted with hydrogen, the solution mixture was reacted at room temperature overnight while stirring. Then, the reaction mixture was filtered with suction using celite, concentrated in vacuo, and purified by silica gel flash chromatography (chloroform: methanol = 10 : 1 → chloroform: methanol: water = 70 : 30 : 4). As a result, a white non-crystalline solid substance was obtained (yield: 311 mg, 0.356 mmol, recovery 52.6%).

Rf value: 0.402 (chloroform : methanol : water = 65 : 25 : 4), $[\alpha]_D = -3.6^\circ$ (c 0.59, CHCl₃: CH₃OH:H₂O = 70:30:4).

¹H NMR (300MHz, CDCl₃+TMS, δ) ; 5.28(1H, m, Gly-H-2), 4.32 (1H, d, J=7.7, H-1), 4.27-3.11 (10H, m, H-2 & H-3 & H-4 & H-5 & H-6a, b & Gly-H-1a, b & Gly-H-3a, b), 2.36-2.30(4H, m, OCOCH₂), 1.60 (4H, m, OCOCH₂CH₂), 1.27 (56H, br, -CH₂-), 0.89 (6H, t, J=6.4, CH₃)



R₁₀₁=R₁₀₂=stearoyl

<Assay 1>

Mixed lymphocytes reaction

Lymphocytes serving as stimulator cells and responder cells were prepared from blood taken from individual healthy persons.

The responder cells were further separated from

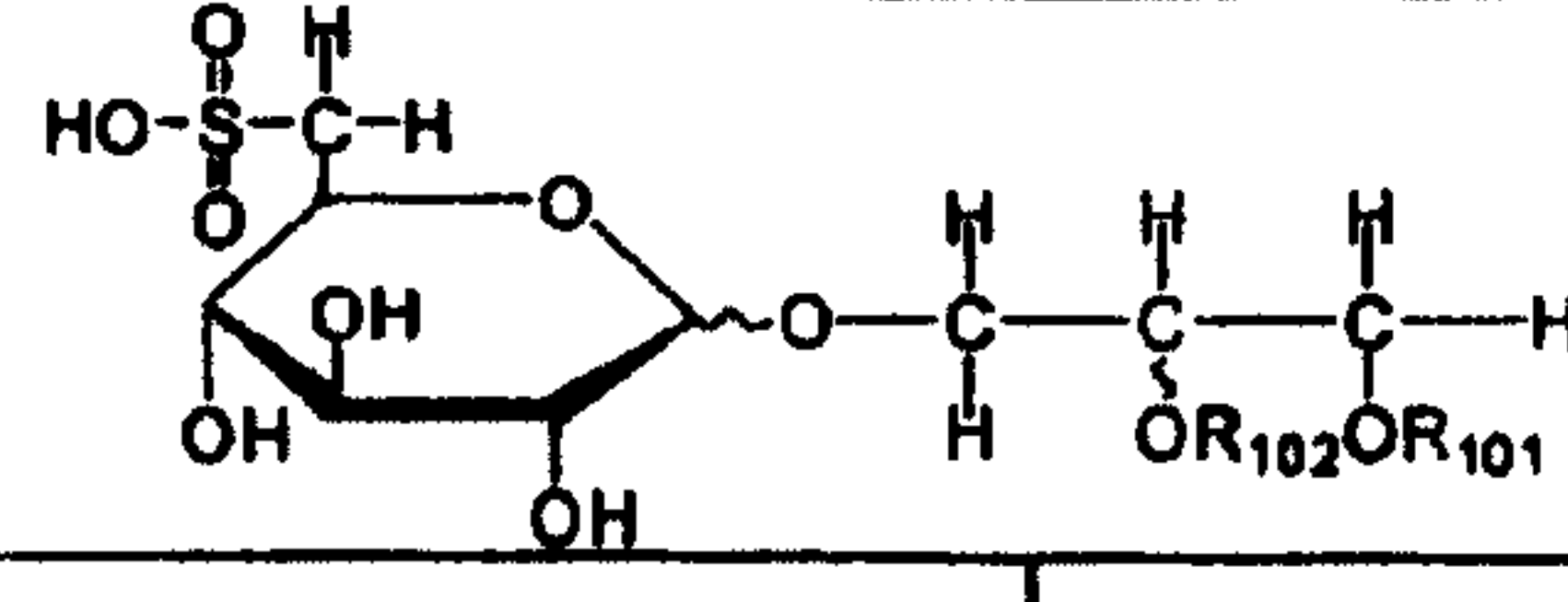
the lymphocyte cells to give T lymphocytes alone.

No treatment was applied to the responder cells.
10⁶/mL of the stimulator cells were treated with
10 µg/mL of mitomycin C to stop the cell growth.

5 Thereafter, the stimulator cells were washed with PBS
(phosphate buffer saline) 4 times.

Subsequently, the responder cells were inoculated
at a rate of 10⁵ cells per well and then test
substances (compounds SQAG 3, SQAG 5, SQAG 7, and
10 SQAG 9 listed in Table 1 below) were added to a
predetermined concentration. The reaction mixture was
cultured at 37°C for one hour. Thereafter, the
stimulator cells were added at a rate of 10⁵ cells per
well. The mixture was cultured in a CO₂ incubator at
15 37°C for 4 days. After the incubation, the
proliferation ability of the responder cells was
quantified as follows. First, [³H]-thymidine was
added to the responder cells and incorporated into the
nucleus of the cells by culturing the cells for
20 12 hours. Then, the amount of [³H]-thymidine uptake
into the cells was determined by a scintillation
counter.

Table 1

Compound			Bonding between glucose and glyceride
	R ₁₀₁ -	R ₁₀₂ -	
SQAG 3	CH ₃ (CH ₂) ₁₄ CO-	CH ₃ (CH ₂) ₁₄ CO-	α
SQAG 5	CH ₃ (CH ₂) ₁₆ CO-	CH ₃ (CH ₂) ₁₆ CO-	α
SQAG 7	CH ₃ (CH ₂) ₁₄ CO-	CH ₃ (CH ₂) ₁₄ CO-	β
SQAG 9	CH ₃ (CH ₂) ₁₆ CO-	CH ₃ (CH ₂) ₁₆ CO-	β

The results are shown in FIGS. 1-4.

5 FIGS. 1-4 show the amounts of [³H]-thymidine uptake when SQAG 3, SQAG 5, SQAG 7, and SQAG 9 are added. The lower the amount of [³H]-thymidine uptake, the higher the immunosuppressive activity. In each of the FIGS. 1-4, the vertical axis indicates the
10 intensity of radioactivity and the horizontal axis indicates the concentration of the test substance.

As is apparent from FIGS. 1-4, all test substances have significant immunosuppressive activities. In particular, SQAG 9 has a considerably higher
15 immunosuppressive activity than other compounds.

<Assay 2>

Rejection test in skin graft

ACI rats and LEW rats were prepared and subjected to inhalation anesthesia of ether. After shaving the
20 dorsum of each ACI rat, posterior lateral skin (1×1 cm) was removed to form a skin-flayed wound, and then a hemostatic treatment was performed. On the other hand,

a piece of skin (1×1 cm) was obtained from the tail of each LEW rat. The donor skin was applied to the skin-flayed wound of each ACI rat and sutured with 5-0 nylon sutures. Then, gauze was applied to the surgically operated portion and a corset with a rubber bandage was further attached thereon to protect it. Such a skin transplantation operation was applied to all ten ACI rats in the same manner. Of the ten ACT rats, five rats were selected at random and classified as a control group, and the remaining five rats were classified as a test group to which test substances are to be administered. To the control group, 10 mL of physiological saline was intraperitoneally injected daily for five days after the surgery. To the test group, 10 mL solution of SQAG 9 dissolved in physiological saline at a concentration of 1 mg/mL was intraperitoneally injected daily for five days after the surgery in the same manner as in the control group.

On the seventh day after the operation, a graft was taken to prepare a tissue specimen. Subsequently, H-E staining was performed in accordance with the method of Fujita et al. (T. Fujita, S. Takahashi, A. Yagihashi, K. Jimbow, N. Sato, Transplantation, vol. 64, 922-925, 1997). The results were histologically examined.

As a result of histological observation, it was confirmed that the epidermal layer was removed from the

dermis in all five rats of the control group, and that necrosis of the epidermis had occurred. In contrast, necrosis of the epidermal layer was observed in three out of five rats in the SQAG 9 administered group.

5 However, in the remaining two rats, it was observed that some parts of the epidermis successfully adhered to the dermis even though other parts of the epidermal layer were partly removed from the dermis.

10 The present inventors consider that the skin graft rejection test is the most stringent method of evaluation for an immunosuppressive activity. It is considered that rejection occurred most severely when transplantation was made between the ACI series rats and the LEW series rats, as used in this assay.

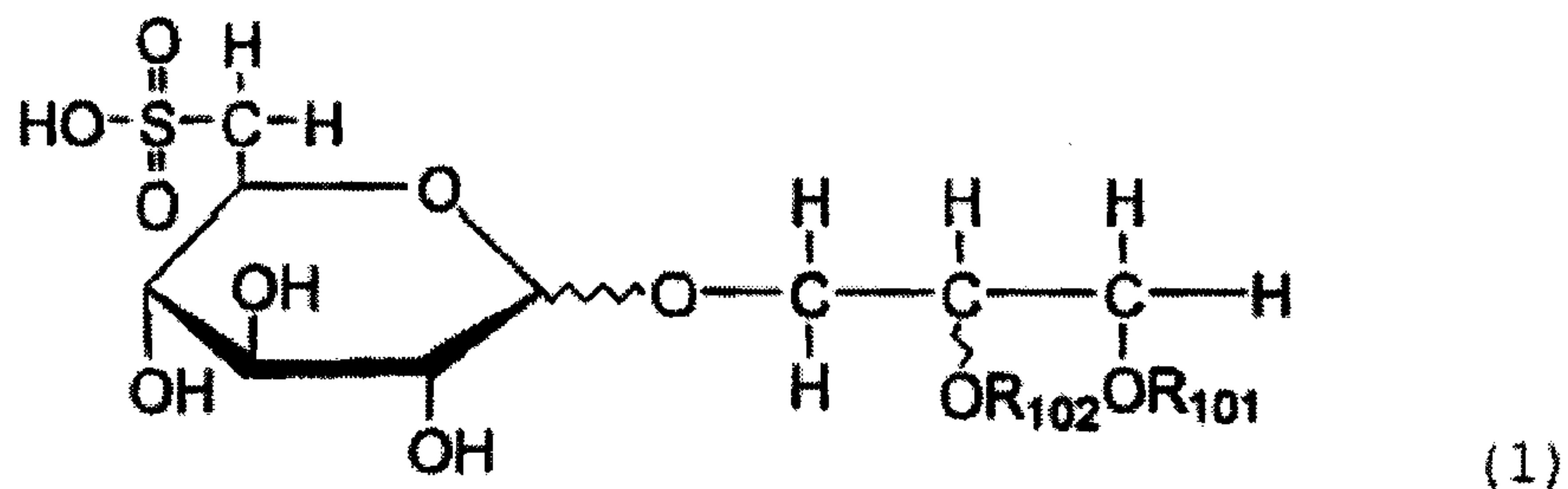
15 However, under such stringent conditions, the activity for suppressing the rejection was observed in two out of five rats in this assay. This fact demonstrates that SQAGs of the present invention are highly effective as an immunosuppressive agent.

20 In addition, none of the rats administered with SQAGs died from acute toxicity during the test period. Neither weight reduction nor malphysical conditions were visually observed. No abnormality was observed with respect to major organs in general pathological tests. It is therefore demonstrated that the
25 immunosuppressive agents of the present invention are extremely low in toxicity.

Of the commercially available immunosuppressive agents, a few (e.g., FK506) are known as effective in suppressing rejection in skin graft tests. However, highly effective immunosuppressive agents low in toxicity have not yet been reported.

C L A I M S

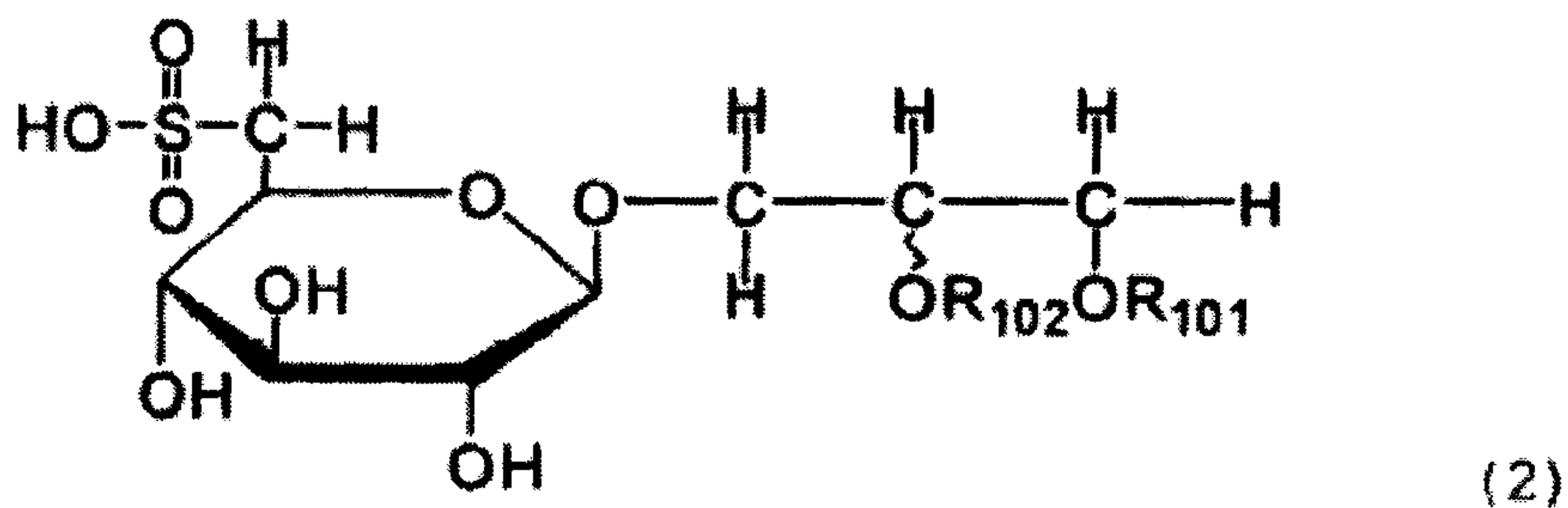
1. An immunosuppressive agent comprising a compound selected from the group consisting of:
compounds represented by Formula (1);



5

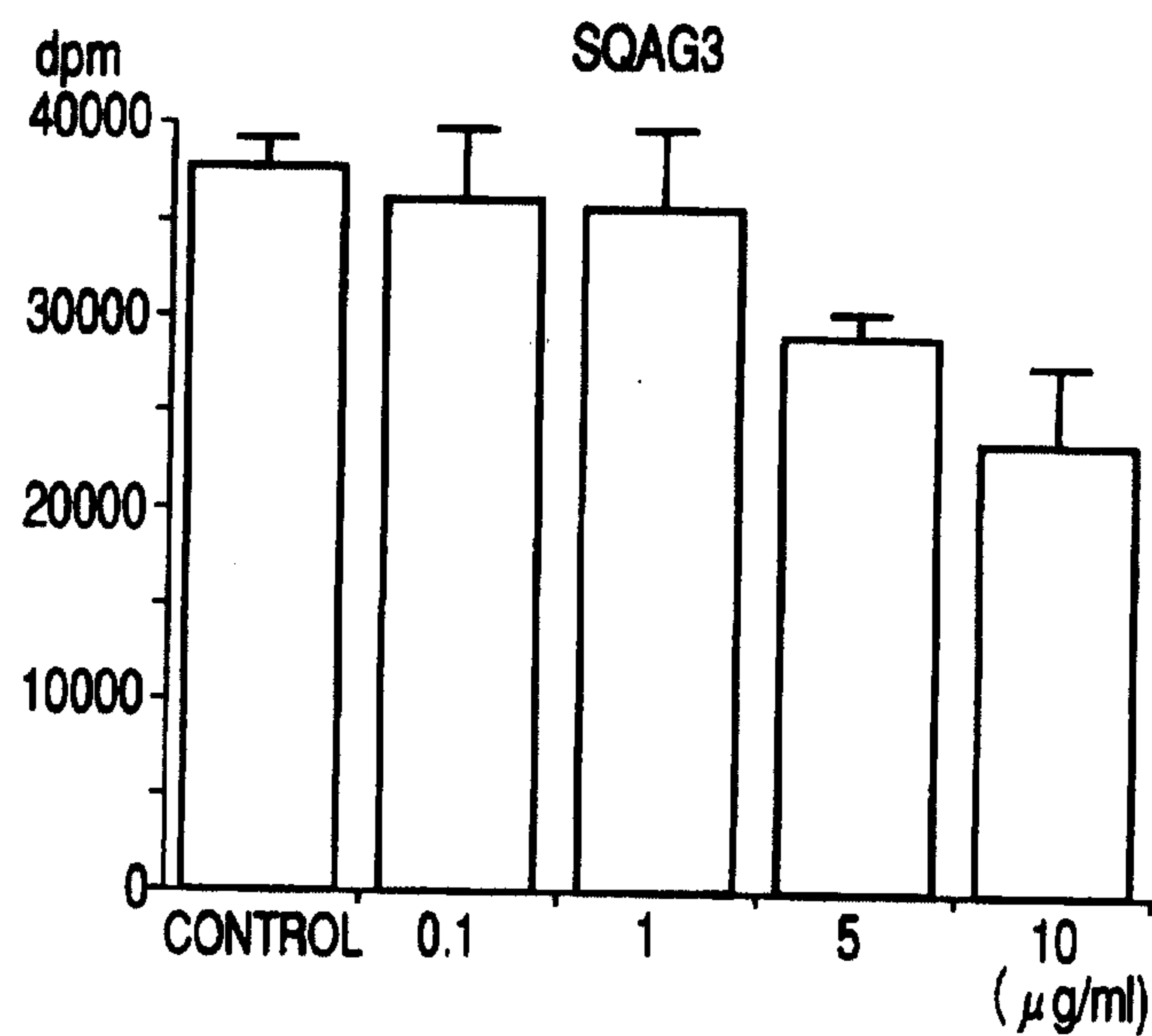
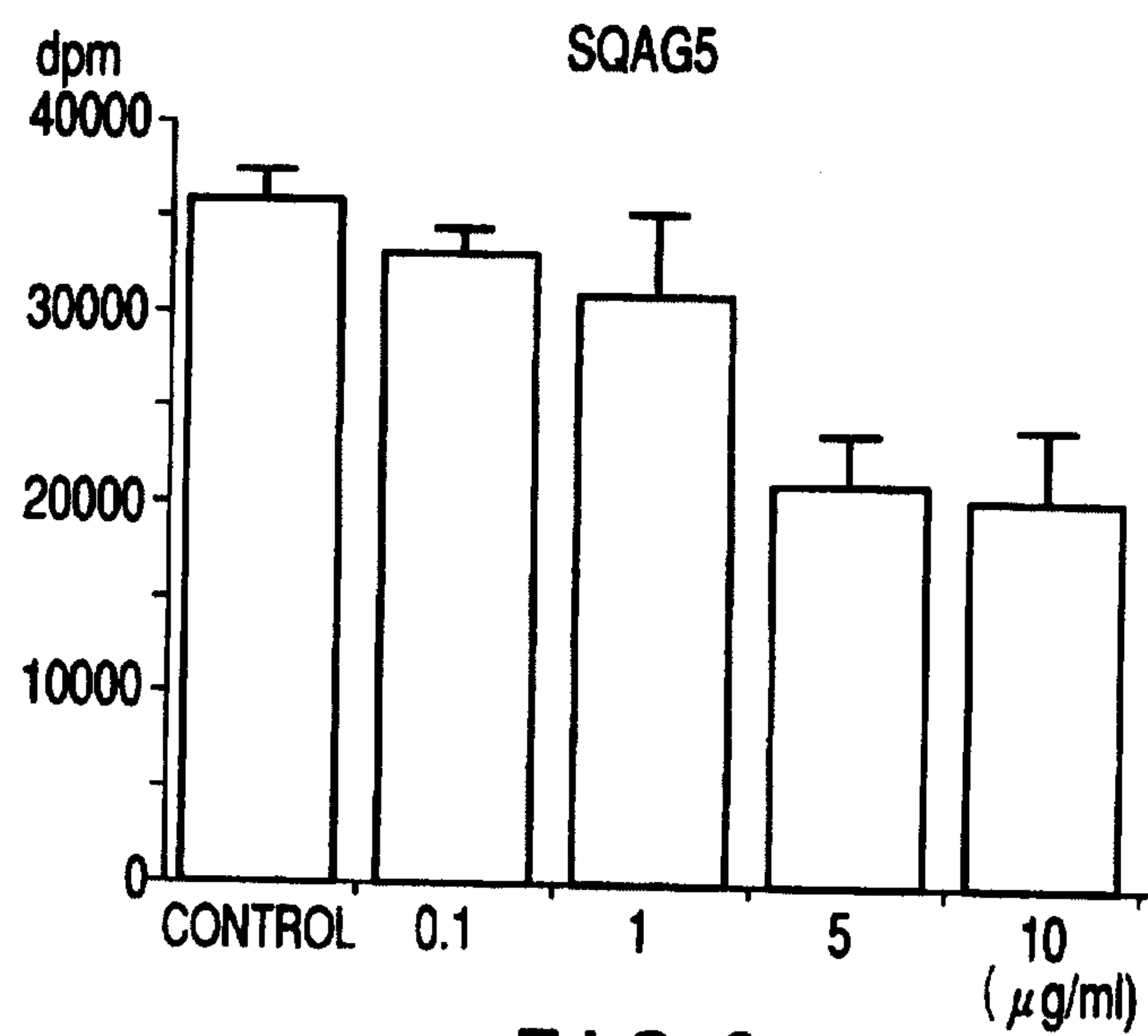
where R_{101} and R_{102} independently represent an acyl residue represented by $R-C(=O)-$, where R represents an alkyl or alkenyl group having 13 to 25 carbon atoms, and
a pharmaceutically acceptable salt thereof.

- 10 2. The immunosuppressive agent according to claim 1, wherein the compound represented by Formula (1) is represented by Formula (2):

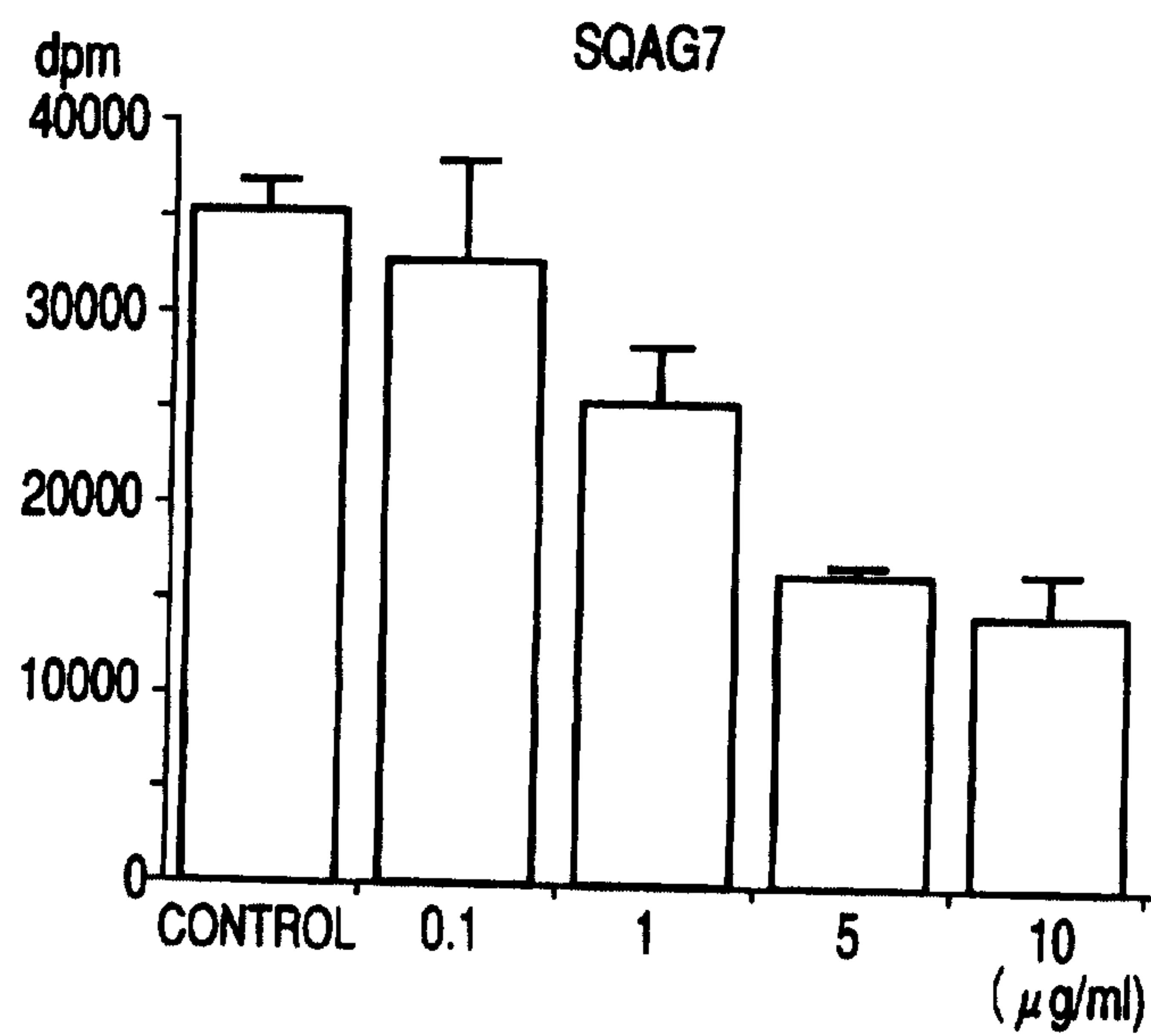
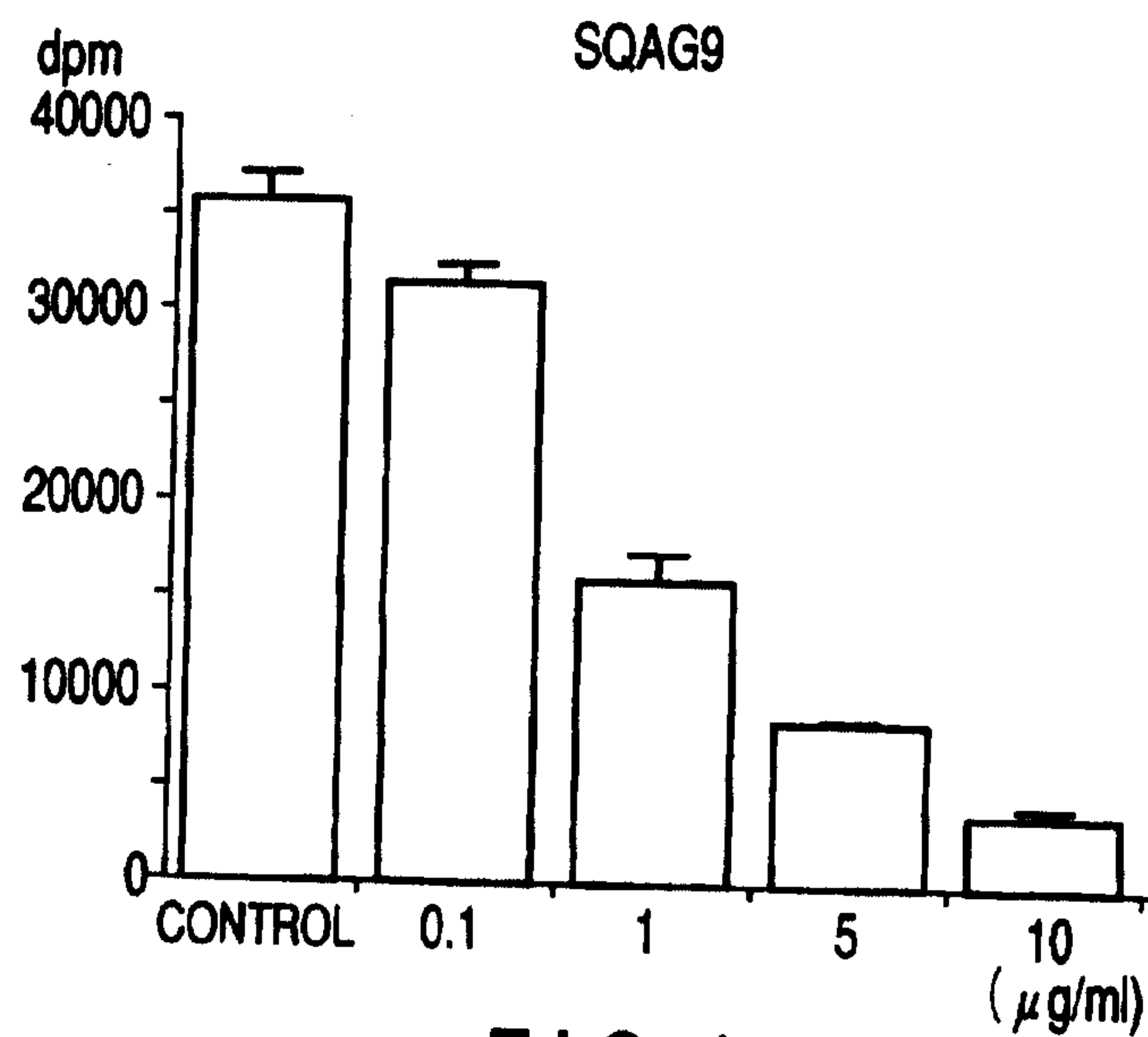


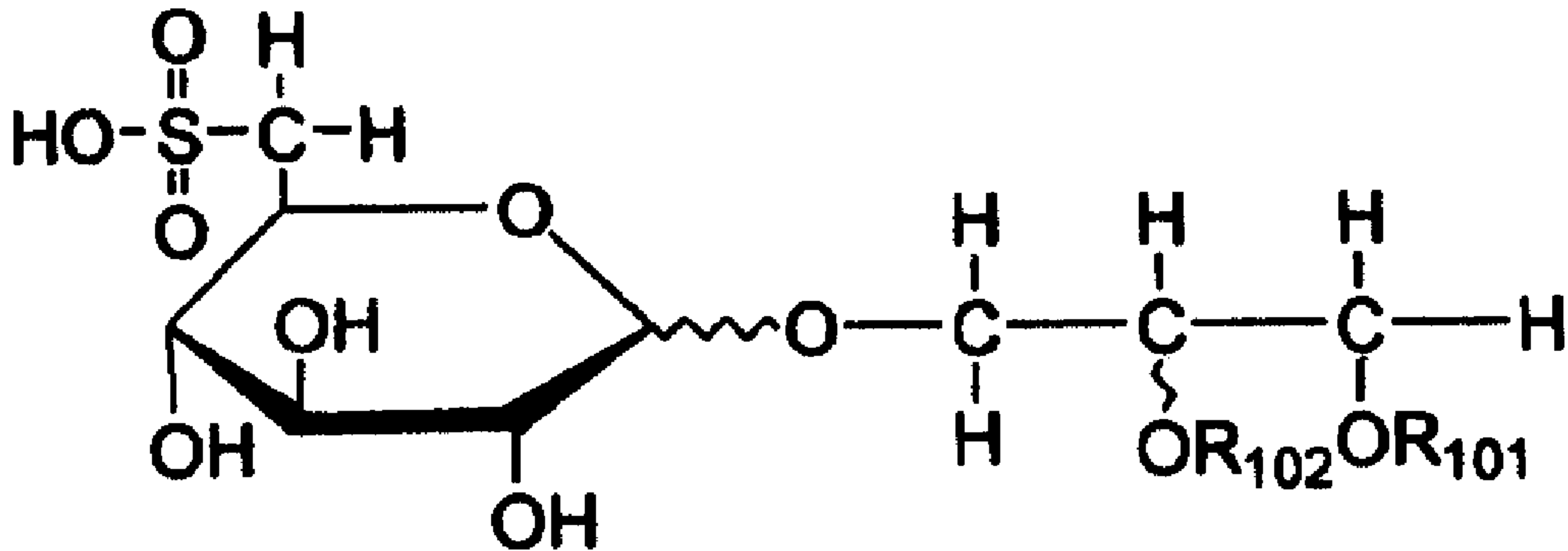
15 where R_{101} and R_{102} have the same meanings as defined in Formula (1).

1/2

**FIG. 1****FIG. 2**

2/2

**FIG. 3****FIG. 4**



(1)