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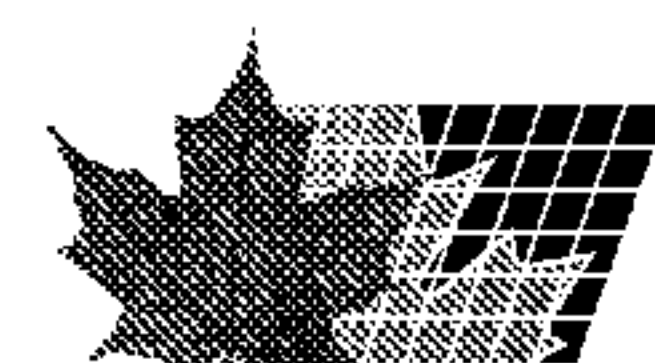
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(54) Title: NOJIRIMYCIN DERIVATIVES

(57) Abrégé/Abstract:

This invention relates to novel N-derivatives of 1-deoxy nojirimycin, to the method for their preparation and to their use in the treatment of diabetes and the use against retro-viruses, particularly in the treatment of acquired immuno-deficiency syndrome (AIDS).



ABSTRACT OF THE DISCLOSURE

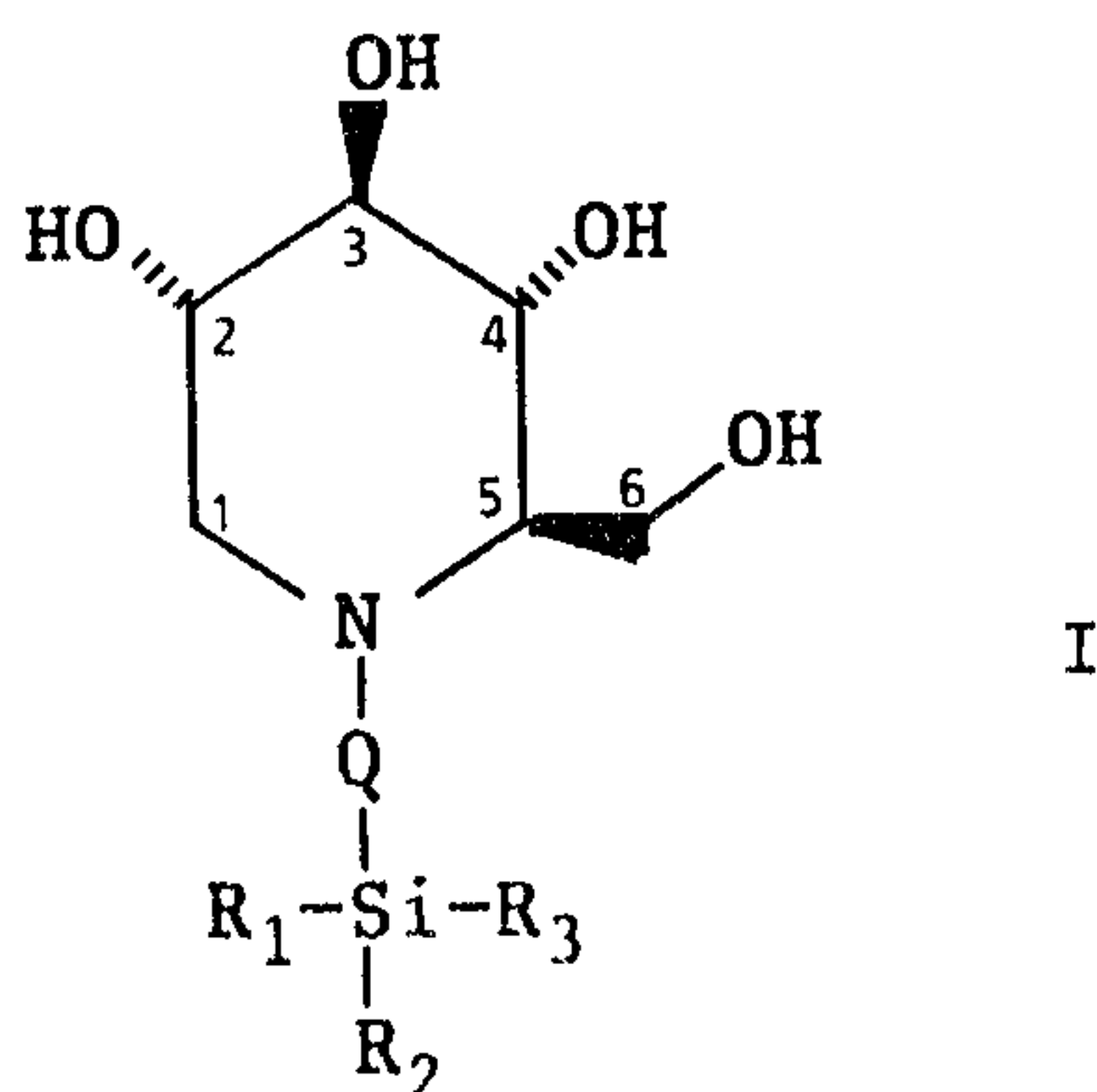
This invention relates to novel N-derivatives of 1-deoxy
nojirimycin, to the method for their preparation and to
their use in the treatment of diabetes and the use against
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NOVEL NOJIRIMYCIN DERIVATIVES

5 This invention relates to novel N-derivatives of 1-deoxy
nojirimycin, to the method for their preparation and to
their use in the treatment of diabetes and their use against
retro-viruses, particularly in the treatment of acquired
immuno-deficiency syndrome (AIDS).

10 More specifically the invention relates to 1-deoxy
nojirimycin derivatives of the formula



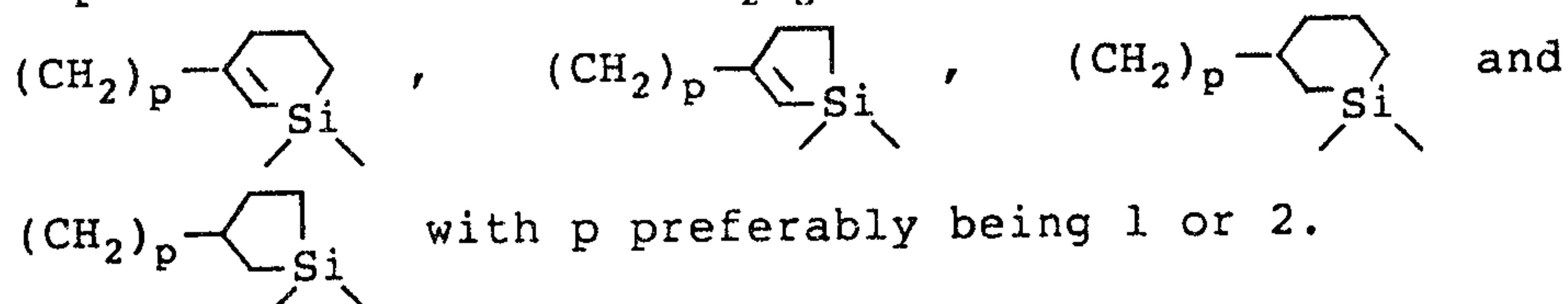
the isomeric forms thereof, and the pharmaceutically
acceptable salts thereof wherein

- Q is C_{1-7} alkylene, $(CH_2)_mCH=CH(CH_2)_n$, $(CH_2)_mC\equiv C(CH_2)_n$, $(CH_2)_mCH=C=CH(CH_2)_n$, $(CH_2)_p$ phenylene, $(CH_2)_m$ cyclopentenylene, $(CH_2)_m$ cyclohexenylene, $(CH_2)_pT$, wherein T, together with the silicon atom to which it is attached forms a 5 to 6 atom cyclic silicane, said cyclic silicane optionally having a double bond, with m being 1, 2 or 3, n being 0, 1 or 2, p being 0, 1, 2, 3 or 4,
- R_1 is C_{1-7} alkyl, C_{1-7} alkoxy, mono- or polyhydroxy C_{1-6} alkyl, mono- or polyalkoxy C_{1-6} alkyl, chloro C_{1-6} alkyl,
- R_2 and R_3 are C_{1-10} alkyl, $(CH_2)_p-X,Y$ -substituted phenyl, with X and Y each being H, OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, CF_3 , CN, NO_2 , SH or $-S-C_{1-6}$ alkyl, with the proviso that when Q is $(CH_2)_pT$, then one of R_1 , R_2 or R_3 is deleted.

As used herein, Q is a divalent moiety bridging the 1-deoxy-nojirimycin with the silicon atom to which Q is attached. In all instances the moieties of Q are directly attached to the nitrogen atom of the 1-deoxy nojirimycin. The C_{1-7} alkylene moiety includes the straight, branched and cyclized manifestations of saturated lower aliphatic hydrocarbons including such alkylene moieties derived from alkyl radicals such as methyl, ethyl, n-propyl, isopropyl, n-butyl, cyclopropyl, pentyl, hexyl, cyclohexyl, cyclohexylmethyl, preferably n-butyl, n-propyl, methyl or ethyl, (yielding, of course such moieties as for example $(-CH_2-)$, $(-CH_2-CH_2-)$, $(-CH_2CH_2CH_2-)$, $(-CH_2-(C_6H_{10})-)$ wherein the silicon is preferably attached at the meta-position of the cyclohexyl moiety, and the like). Preferably the moiety of $(CH_2)_mCH=CH(CH_2)_n$ is in its trans configuration, and preferably m is 1 and n is zero. Preferably, the $(CH_2)_m$ cyclopentenylene and cyclohexenylene moieties have their unsaturation at the carbon atom to which the silicon is

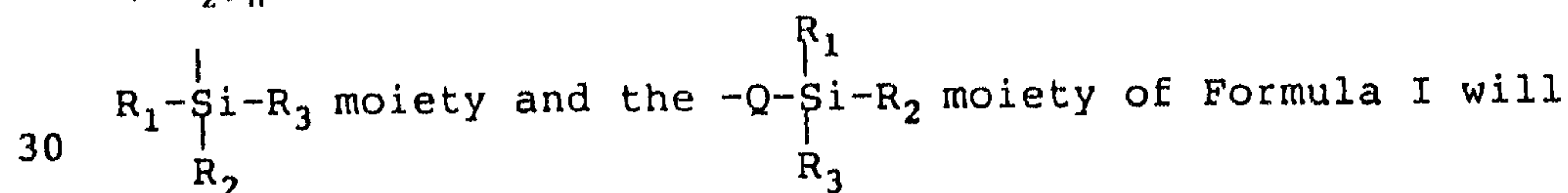
attached [e.g. $\text{CH}_2-\text{C}_6\text{H}_4-\text{Si}$ or $\text{CH}_2-\text{C}_6\text{H}_4-\text{Si}$].

Preferably, for the $(\text{CH}_2)_p$ phenylene moiety, p is 1 or 2 and the $-\text{SiR}_1\text{R}_2\text{R}_3$ moiety is attached to the phenyl moiety at its 3-position. Preferred $(\text{CH}_2)_n\text{T}$ moieties are illustrated as



10

In those instances wherein R_1 is C_{1-7} alkyl or C_{1-7} alkoxy, methyl, ethyl, methoxy and ethoxy are preferred. When R_1 is hydroxy C_{1-6} alkyl, hydroxymethyl is preferred. When R_1 is polyhydroxy C_{1-6} alkyl it is preferred that there be 1, 2 or 3 OH radicals, each one of which is attached to a different carbon atom of the C_{1-6} alkyl moiety and in such instances it is preferred that the hydroxy be located on carbon atoms other than the carbon atom attached directly onto the silicon atom; the same concepts also be true for the mono- and polyalkoxy substituted C_{1-6} alkyl moieties in which case methoxy is preferred. Preferably the $(\text{CH}_2)_p\text{X,Y}$ -substituted phenyl moieties are those wherein both X and Y are H, or one is H and the other is OH, chloro, methyl or methoxy or both are OH, Cl, methyl or methoxy. In general, in those instances wherein the Q radical contains a $(\text{CH}_2)_m$ moiety it is preferred that m be 1 or 2, and when Q contains $(\text{CH}_2)_n$ moieties n preferably is zero or 1. For convenience, the



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also be referred to as $-\text{SiR}_1\text{R}_2\text{R}_3$ and $-\text{Q}-\text{Si}-\text{R}_1\text{R}_2\text{R}_3$, respectively. In general the trans- isomers are preferred over the cis- isomers.

The pharmaceutically acceptable salts of the compounds of formula I include salts formed with non-toxic organic or

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inorganic acids such as, for example, from the following
acids: hydrochloric, hydrobromic, sulfonic, sulfuric, phos-
phoric, nitric, maleic, fumaric, benzoic, ascorbic, pamoic,
succinic, methanesulfonic acid, acetic, propionic, tartaric,
5 citric, lactic, malic, mandelic, cinnamic, palmitic,
itaconic and benzenesulfonic and the like.

In general the compounds of this invention are prepared
by chemical reactions and procedures which are analogously
known in the art and the selection of a particular route to
10 any specific compound is governed by principles well known
and appreciated by those of ordinary skill in the art.

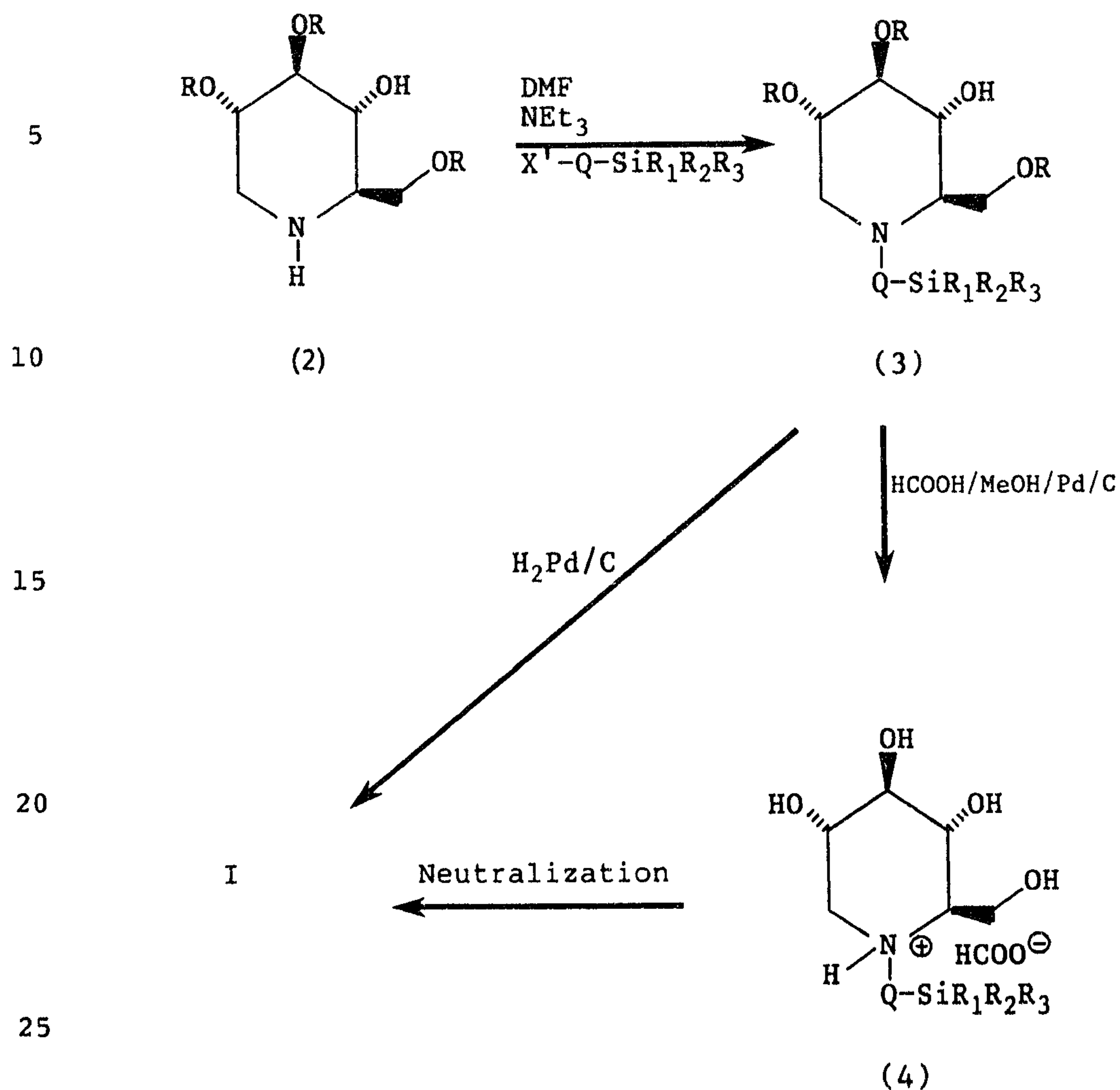
In general the compounds of this invention may be
prepared according to the reaction scheme outlined below.
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Reaction Scheme A

wherein Q-SiR₁R₂R₃ is as previously defined, R is H or Bz, Bz is benzyl, a preferred hydroxy-protecting group, X' is halogeno, mesylate or tosylate.

The synthesis of Reaction Scheme A is initiated by the condensation of an optionally hydroxy-protected 1-deoxy nojirimycin with an excess quantity ($\approx$ three times) of the appropriate X'-Q-SiR₁R₂R₃ reactant in the presence of an

excess of triethylamine (NEt_3) in dimethyl formamide (DMF). Preferably X' is the iodide. The so-produced compounds (3) are purified, preferably using chromatographic techniques and are then deprotected according to standard procedures well known in the art. Preferably deprotection is effected by using transfer hydrogenation with formic acid in methanol with Pd/C or by catalytic hydrogenation, preferably using palladium on carbon in an appropriate solvent, e.g. ethanol. When transfer hydrogenation is utilized, the deprotected products (4) are in the form of quaternary salts with the $\text{HCOO}^\ominus$ anion and thus must be neutralized; the neutralization preferably being effected using an ion exchange resin such as *Dowex AX-8.

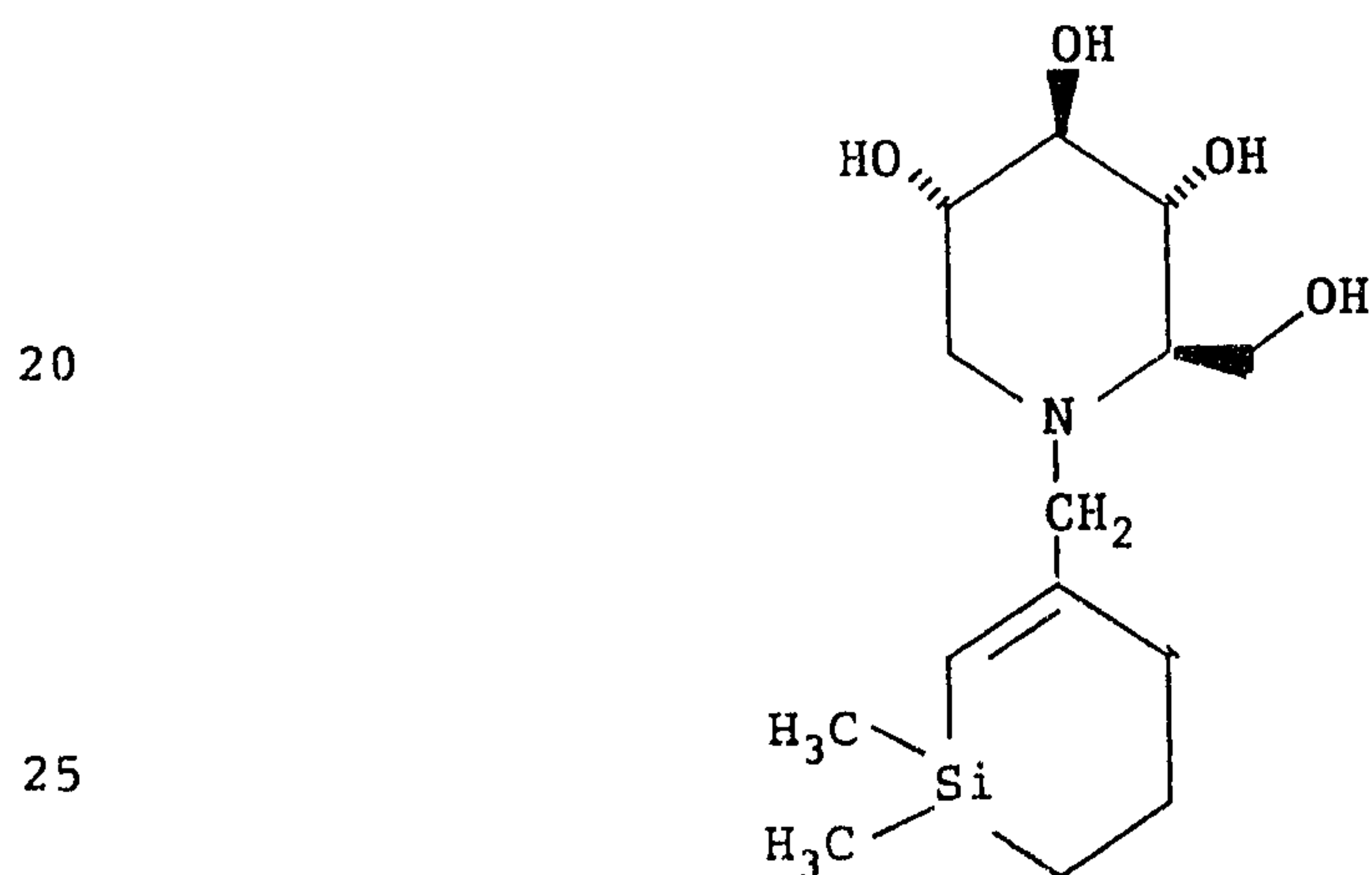
In those instances wherein Q represents a bridging moiety containing an unsaturation (e.g., allylic, allenic, acetylenic, cyclopentenylene, cyclohexenylene or the unsaturated $(\text{CH}_2)_p\text{T}$ moieties) it is preferred that the 2-, 3- and 6-position hydroxy groups not be protected in view of the difficulties encountered when removing the benzyl protecting groups unless special procedures are employed (e.g., when Q contains such unsaturated moieties a process using sodium in ammonia is preferred). In those instances wherein Q is other than an unsaturated moiety, and it is preferred that the 2-, 3- and 6-positions bear a benzyl protecting group, "normal" procedures (as outlined above) may be employed for their removal. The benzyl groups may also serve as a means for obtaining the products in a more purified form. Although not required the 4-position OH group may also bear a protecting group.

It should be noted that when the above comment is made concerning the protection of the 2-, 3- and 6-OH functions, the nomenclature is that which is used in sugar chemistry using the positions of glucitol as shown in Formula I. In that instance, the OH radical of the hydroxymethyl moiety is

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at the 6-position, the other beta OH is at the 3-position and the two alpha OH groups are at the 2- and 4-positions. In that instance it is the 2-, 3- and 6-position hydroxy groups which would be protected prior to the condensation
 5 reaction (the 4-position OH group, in any situation, normally need not be protected). In the instances wherein the compounds are named as piperidine derivatives the compounds (1 and 4) would be 2(β)-hydroxymethyl-1-
 10 [$R_1R_2R_3Si-Q$]-3 α ,4 β ,5 α -piperidinetriols and thus for Structures 2 and 3 the OH functions at the 2-, 4- and 5-positions of the piperidine would be protected with a benzyl protecting group.

15 To illustrate the nomenclature of the compounds of this invention as piperidine derivatives the structured compound



would be named [2R-(2 β ,3 α ,4 β ,5 α)-2-hydroxymethyl-1-[1-(3,3-dimethyl-3-sila-1-cyclohexenyl)methyl]-3,4,5-piperidinetriol.

30 1-Deoxy nojirimycin may be obtained by reducing nojirimycin (5-amino-5-deoxy-D-glucopyranose) using the method of Tetrahedron Letters, 24, 2125-2144, 1968, as referenced in European Patent Application 89 112284.8 published on January 10, 1990, with publication No. 0350012.
 35 The preparation of 1-deoxy nojirimycin and its hydroxy-

protected analogs (2) are also disclosed in the specific examples disclosed herein.

5 The X-Q-SiR₁R₂R₃ reactant are either known compounds or may be prepared by methods analogously known in the art.

The following examples illustrate the preparation of the compounds of this invention.

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EXAMPLE 1

Preparation of

3-(TRIMETHYLSILYL)-1-PROPANOL, METHANESULFONATE

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Methanesulfonylchloride (0.73 ml, 9 mmol) was added dropwise to a solution of 3-(trimethylsilyl)-1-propanol (1.2 ml, 7.56 mmol) cooled at 0°C in 20 ml of dichloromethane. After 45 minutes stirring, the reaction mixture was partitioned between water and dichloromethane, the organic phase was separated, the solvent was evaporated under reduced pressure to afford the expected 3-(trimethylsilyl)-1-propanol, methanesulfonate in crude quantitative yield.

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EXAMPLE 2

Preparation of

(3-IODOPROPYL)TRIMETHYSILANE

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An ethereal solution of magnesium iodide was prepared by adding 4.85 g (19 mmol) of iodine to 0.46 g (19 mmol) of magnesium in suspension in 40 ml of dry ether. 28 ml of this solution was added to a solution containing the crude 35 3-(trimethylsilyl)-1-propanol, methanesulfonate in 10 ml of ether. The reaction mixture was stirred for 3 hours at room

temperature and then partitioned between ether and water, the organic phase was separated and further washed with aqueous sodium thiosulfate. After evaporation of the solvent, 1.6 g of (3-iodopropyl)trimethylsilane was obtained
5 as a colorless liquid.

EXAMPLE 3

Preparation of

10 (3-BROMOPROPYL)TRIMETHYLSILANE

1.02 ml (10.9 mmol) of phosphorous tribromide in 20 ml of ether was added to a cooled (0°C, -10°C) solution of 4 g (30.2 mmol) of 3-(trimethylsilyl)-1-propanol in 40 ml of dry
15 ether. The reaction mixture was brought back to room temperature and refluxed for 15 minutes. After bulb to bulb distillation of the crude reaction mixture 4.3g of (3-bromopropyl)trimethylsilane were isolated as a colorless liquid.

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EXAMPLE 4

Preparation of

25 4-(TRIMETHYLSILYL)-BUTANOIC ACID

A solution containing 3 g (15.4 mmol) of (3-bromopropyl)-trimethylsilane in 3 ml of dry ether was added to 0.375 g (15.4 mmol) of magnesium turnings in ether (40 ml final volume of solution). After 1 hour of reflux gaseous
30 carbondioxide was bubbled through the reaction mixture (3 g, 77 mmol of dry ice). After 2 hours of stirring at room temperature the reaction mixture was partitioned between aqueous ammonium chloride and ether. The organic phase was separated, the aqueous phase was further acidified with
35 hydrochloric acid 1N and extracted with ether. Ethereal phases were pooled and the solvent was removed under reduced

pressure. Separation of the expected 4-trimethylsilyl-
butanoic acid from dimer of starting (3-bromopropyl)tri-
methylsilane was finally performed by acid base extraction.
0.62 g of 3-(trimethylsilyl)-butanoic acid was isolated as a
5 colorless liquid.

EXAMPLE 5

Preparation of

10 4-(TRIMETHYLSILYL)-1-BUTANOL

1.5 ml (11.4 mmol) of a 1 molar solution of borane
dimethylsulfide was added to a cooled (0°C) solution of
0.61 g (3.8 mmol) of 4-(trimethylsilyl)-butanoic acid in
15 20 ml of dry tetrahydrofuran. After work-up using the
standard procedure (methanol, tetramethylethylene diamine)
and flash chromatography purification on silica gel eluted
with a 9:1 mixture of hexane and ethyl acetate, 0.4 g of
4-(trimethylsilyl)-1-butanol was obtained as a colorless
20 liquid.

EXAMPLE 6

Preparation of

25

4-(TRIMETHYLSILYL)-1-BUTANOL, METHANESULFONATE

Starting from 0.4 g (2.53 mmol) of 4-(trimethylsilyl)-1-
butanol, 0.245 ml (3.16 mmol) of methanesulfonyl chloride
30 and 0.528 ml (4.3 mmol) of triethylamine, and using the same
procedure as for the preparation of 3-(trimethylsilyl)-1-
propanol, methanesulfonate, 0.5 g of the expected 4-(tri-
methylsilyl)-1-butanol, methanesulfonate was obtained.

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EXAMPLE 7

Preparation of

5 4-(IODOBUTYL)TRIMETHYLSILANE

Using the same procedure as described for the preparation of 3-(iodopropyl)trimethylsilane, starting from 0.5 g (2.53 mmol) of 4-(trimethylsilyl)-1-butanol methane sulfonate and 12 ml of a 0.34 M ethereal solution of
10 magnesium iodide, 0.5 g of 4-(iodobutyl)trimethylsilane was isolated as a colorless liquid.

15 EXAMPLE 8

Preparation of

(4-BROMO-2-BUTYNYL)TRIMETHYLSILANE

20 4-(trimethylsilyl)-2-butynol [J. Pernet, B. Randrianoelina, and L. Miginiac, Tetrahedron Letters, 25, 651, (1984)] (10 g, 70 mmol) is dissolved in dry diethyl ether (150 ml) and phosphorous tribromide (2.2 ml, 23.3 mmol) is added dropwise. Then the mixture is refluxed,
25 protected from the light during 2.5 hours. The reaction is washed twice with water, once with aqueous sodium bicarbonate and then once with water. The organic layer is dried over sodium sulfate. The solvent is evaporated under reduced pressure to afford the expected bromide (4-bromo-2-
30 butynyl)trimethylsilane (1.4 g, 97%) which is used without purification.

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EXAMPLE 9

Preparation of

5 (4-BROMO-2-(E)BUTENYL)TRIMETHYLSILANE

4-(Trimethylsilyl)-2(E)-butene-1-ol [H. Mastalerz, J. Org. Chem., 49, 4094, (1984)] (10 g, 70 mmol) is dissolved in dry diethyl ether (150 ml) and phosphorous tribromide (2.2 ml, 23.3 mmol) is added dropwise. Then the mixture is
10 refluxed, protected from the light during 2.5 hours. The reaction is washed twice with water, once with aqueous sodium bicarbonate and then once with water. The organic layer is dried over sodium sulfate. The solvent is evaporated under reduced pressure to afford the expected
15 bromide (4-bromo-2-(E)butenyl)-trimethylsilane (1.4 g, 97%) which is used without purification.

20 EXAMPLE 10

Preparation of

DIMETHYL(3-IODOPROPYL)PHENYLSILANE

25 Dimethyl(3-chloropropyl)phenylsilane [J.W. Wilt, W.K. Chwang, C.F. Dockus and N.M. Tomiuk, J. Am. Chem. Soc., 100, 5534, (1978)] (9 g, 48.8 mmol) and sodium iodide (29.5 g, 195 mmol) are refluxed in acetone during 24 hours. The mixture is filtered and the solvent is evaporated under
30 reduced pressure. The residue is dissolved in diethyl ether and washed with water. The organic layer is dried with sodium sulfate, filtered and concentrated under reduced pressure to afford pure dimethyl(3-iodopropyl)phenylsilane as a slightly yellow oil (12.5 g, 93%).

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EXAMPLE 11

Preparation of

5 BENZYL(IODOMETHYL)DIMETHYLSILANE

Benzyl(bromomethyl)dimethylsilane [Colm, Earborn and Foad M.S., Malmoud J. Organomet. Chem., 209, 13 (1981)] (12 g, 0.05 mmol) and sodium iodide (45 g, 0.3 mmol) are refluxed with stirring in acetone (500 ml) during 24 hours.
10 The reaction mixture is cooled, filtered and the solvent is evaporated under reduced pressure. The residue is dissolved in ether and washed with water. The organic layer is dried over sodium sulfate, filtered and concentrated under reduced pressure to afford benzyl(iodomethyl)dimethylsilane (13.7 g,
15 95%) as a slightly yellow oil.

EXAMPLE 12

20

Preparation of

t-BUTYL(IODOMETHYL)DIMETHYLSILANE

t-Butyl(chloromethyl)dimethylsilane [Makoto Kumada, Mitsuo Ishikawa, Sajiro Meada and Katsuyata Ikura, J.
25 Organometal. Chem. 2, 146, (1964)] (16.4 g, 0.1 mmol) and sodium iodide (60 g, 0.4 mmol) in acetone (500 ml) are refluxed with stirring during 24 hours. The reaction mixture is cooled, filtered and the solvent is evaporated under
30 reduced pressure. The residue is dissolved in ether and washed with water. The organic layer is dried over sodium sulfate, filtered and concentrated under reduced pressure to afford t-butyl(iodomethyl)dimethylsilane (20.9 g, 80%) as a slightly yellow oil.

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EXAMPLE 13

Preparation of

5 5-AZIDO-3,6-DI-O-BENZYL-5-DEOXY-D-GLUCOFURANOSE

The azide 5-azido-3,6-di-O-benzyl-5-deoxy-1,2-O-isopropylidene- α -D-glucofuranoside (U.G. Nayak and R.L. Whisler, J. Org. Chem., 33, 3582 (1968) (15.02 g, 35.3 mmol) was dissolved at 0°C in 100 ml of a 9:1 mixture of
10 trifluoro-acetic acid and water. The mixture was stirred at 0°C during 2 h. The trifluoroacetic acid was evaporated under reduced pressure at room temperature. The residue was taken with ether and washed with water. The organic layer was dried over sodium sulfate, filtered and concentrated
15 under reduced pressure. Flash chromatography on silica gel and elution with a 1:1 mixture of hexane and ethyl acetate, followed by recrystallization in a mixture of hexane and ethyl acetate afforded the expected compound 5-azido-3,6-di-O-benzyl-5-deoxy-D-glucofuranose.
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EXAMPLE 14

Preparation of

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METHYL 5-AZIDO-3,6-DI-O-BENZYL-5-DEOXY-D-GLUCOFURANOSIDE

To a solution of 5-azido-3,6-di-O-benzyl-5-D-glucofuranose (10.23 g, 26.5 mmol) in methylene chloride (170 ml) was added methanol (11 ml) and borontrifluoroetherate
30 (1.5 ml). The mixture was stirred 24 h at room temperature. The reaction mixture was successively washed with a saturated aqueous solution of sodium bicarbonate and then with brine. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. Flash
35 chromatography on silica gel and elution with a 1:1 mixture

of hexane and ethyl acetate afforded methyl 5-azido-3,6-di-O-benzyl-5-deoxy-D-glucofuranoside as a colorless oil (9.15 g, 85%).

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EXAMPLE 15

Preparation of

10 METHYL 5-AZIDO-2,3,6-TRI-O-BENZYL-5-DEOXY-D-GLUCOFURANOSIDE

15 To a suspension of sodium hydride (1.2 g, 27.5 mmol), 55% in mineral oil, washed three times with pentane) in anhydrous tetrahydrofuran (200 ml) was added quickly dropwise the alcohol methyl 5-azido-3,6-di-O-benzyl-5-deoxy-D-gluco-furanoside (9.15 g, 22.9 mmol) in tetrahydrofuran (50 ml) at room temperature and under nitrogen. The mixture was stirred during 3 h at room temperature. the mixture was yellow. Then $n\text{-Bu}_4\text{N}^+\text{I}^-$ (76 mg, 0.20 mmol) was added followed by benzyl bromide (3.30 ml, 27.5 mmol) added dropwise. The 20 mixture was stirred overnight at room temperature. After hydrolysis with saturated aqueous ammonium chloride tetrahydrofuran was evaporated under reduced pressure. The residue was diluted with water and extracted three times with ether. The organic phase was dried over sodium sulfate. 25 Filtration and evaporation under reduced pressure afforded an oil. Flash chromatography on silica gel and elution with a 20:80 mixture of ethyl acetate and hexane afforded the expected compound methyl 5-azido-2,3,6-tri-O-benzyl-5-deoxy-D-glucofuranoside as a colorless oil (10.88 g, 97%). 30

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EXAMPLE 16

Preparation of

5 5-AZIDO-2,3,6-TRI-O-BENZYL-5-DEOXY-D-GLUCOFURANOSE

Methyl 5-azido-2,3,6-tri-O-benzyl-5-deoxy-D-glucofuranoside (10.8 g, 22.2 mmol) was dissolved at room temperature in tetrahydrofuran (20 ml). The solution was cooled at -10°C and trifluoroacetic acid (120 ml) was added dropwise
10 followed by addition of water (20 ml). The mixture was stirred at 0°C during 24 h. The mixture was evaporated under reduced pressure without heating. The residue was taken with ether and washed with water. The organic layer was dried
15 over sodium sulfate, filtered and concentrated under reduced pressure. Flash chromatography on silica gel and elution with a 20:80 mixture of ethyl acetate and hexane afforded 5-azido-2,3,6-tri-O-benzyl-5-deoxy-D-glucofuranose as a colorless oil (9.63 g, 90%).

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EXAMPLE 17

Preparation of

25 5-AZIDO-2,3,6-TRI-O-BENZYL-5-DEOXY-D-GLUCONIC ACID-γ-LACTONE

To a solution of the lactol 5-azido-2,3,6-tri-O-benzyl-5-deoxy-D-glucofuranose (9.36 g, 20 mmol) in acetone (240 ml) cooled to 0°C, Jones' reagent 2 M (11.5 ml) was
30 added dropwise until the color was orange. The excess of Jones' reagent was destroyed with 2-propanol (0.5 ml). The mixture was concentrated under reduced pressure. The residue was taken with water and extracted with ether. The organic phase was dried with sodium sulfate, filtered and
35 concentrated under reduced pressure so as to afford an oil. Flash chromatography on silica gel and elution with a 1:9

mixture of ethyl acetate and hexane afforded the γ -lactone 5-azido-2,3,6-tri-O-benzyl-5-deoxy-D-gluconic acid- γ -lactone.

5

EXAMPLE 18

Preparation of

10 2,3,6-TRI-O-BENZYL-5-DEOXY-D-GLUCONIC ACID- δ -LACTAM

To a solution of the lactone 5-azido-2,3,6-tri-O-benzyl-5-deoxy-D-gluconic acid- γ -lactone (8.16 g, 17 mmol) in ethanol (180 ml) was added lindlar catalyst (1.7 g). The mixture was hydrogenated under atmospheric pressure during
15 24 h. Filtration and evaporation under reduced pressure afforded an oil which was crystallized in a mixture of hexane and ether. The lactam 2,3,6-tri-O-benzyl-5-deoxy-D-gluconic acid- δ -lactam was obtained as white crystals
20 (7.4 g, 96%). mp: 85-85.5°C.

EXAMPLE 19

Preparation of

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2,3,6-TRI-O-BENZYL-1,5-DIDEOXY-1,5-IMINO-D-GLUCITOL

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To a solution of 2,3,6-tri-O-benzyl-5-deoxy-D-gluconic acid δ -lactam (compound described in Example 18) (0.75 g, 1.6 mmol) in dry tetrahydrofuran (15ml) was added a 10 M solution of borane in methyl sulfide (0.58 ml) under nitrogen at 0°C. The mixture was stirred 15 min at 0°C, 30 min at room temperature, then refluxed during 6 h and finally stirred overnight at room temperature. The mixture was cooled to 0°C and the excess of borane was destroyed with methanol and stirred 1 h at room temperature. The

reaction mixture was treated with gaseous hydrochloric acid and refluxed during 1 h. The solvents were evaporated under reduced pressure. The residue was dissolved in ethyl acetate and washed with a saturated aqueous solution of sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure to afford an oil. Flash chromatography on silica gel and elution with ethyl acetate afforded 2,3,6-tri-O-benzyl-1,5-dideoxy-1,5-imino-D-glucitol which crystallized in methanol (0.655 g, 90%); m.p. 73-74°C.

EXAMPLE 20

Preparation of

1,5-DIDEOXY-1,5-{[4-(TRIMETHYLSILYL)-2-BUTYNYL]IMINO}-D-GLUCITOL

A solution of 1,5-dideoxy-1,5-imino-D-glucitol (0.5 g, 3.06 mmol) and (4-bromo-2-butyne)trimethylsilane (0.943 g, 4.6 mmol) is dissolved in dimethylformamide (15 ml) containing water (0.5 ml). Triethylamine (0.85 ml) is added. The mixture is heated at 80°C during 24 hours. The solvent is evaporated under reduced pressure. Flash chromatography on silica gel and elution with a 8:2 mixture of chloroform and methanol affords 1,5-dideoxy-1,5-{[4-(trimethylsilyl)-2-butyne]imino}-D-glucitol as an amorphous solid (0.24 g, 27%).

EXAMPLE 21

Preparation of

5 1,5-DIDEOXY-1,5-{[4-(TRIMETHYLSILYL)-2(Z)-BUTENYL]IMINO}-D-
GLUCITOL

1,5-Dideoxy-1,5-{[4-(trimethylsilyl)-2-butyryl]imino}-D-glucitol (0.1 g, 0.35 mmol) is dissolved in methanol (5 ml) and lindlar catalyst (25 mg) is added. The mixture is
10 hydrogenated at atmospheric pressure overnight. The catalyst is filtered off and the solvent is evaporated under reduced pressure to afford 1,5-dideoxy-1,5-{[4-(trimethylsilyl)-2(Z)-butenyl]imino}-D-glucitol as an amorphous solid
15 (0.09 g, 90%).

EXAMPLE 22

Preparation of

20 1,5-DIDEOXY-1,5-{[4-(TRIMETHYLSILYL)-2(E)-BUTENYL]IMINO}-D-
GLUCITOL

A solution of 1,5-dideoxy-1,5-imino-D-glucitol (also
25 known as 1-deoxynojirimycin) (0.5 g, 3.06 mmol) and (4-bromo-2-(E)butenyl)trimethylsilane (0.95 g, 4.6 mmol) in a mixture of dimethylformamide (10 ml), water (0.5 ml) and triethylamine (0.85 ml) is heated at 80°C during 24 hours. The solvents are evaporated under reduced pressure. Flash
30 chromatography on silica gel and elution with a 8:2 mixture of chloroform and methanol affords 1,5-dideoxy-1,5-{[4-(trimethylsilyl)-2(E)-butenyl]-imino}-D-glucitol as a foam
(0.12 g, 14%).

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EXAMPLE 23

Preparation of

5 1,5-DIDEOXY-2,3,6-TRI-O-BENZYL-1,5-{[3-(DIMETHYLPHENYL-SILYL)-PROPYL]IMINO}-D-GLUCITOL

10 A solution of 1,5-dideoxy-2,3,6-tri-O-benzyl-1,5-imino}-D-glucitol (0.433 g, 1 mmol) and dimethyl(3-iodopropyl)-phenylsilane (0.912 g, 3 mmol) in a mixture of dimethyl-formamide (6 ml) and triethylamine (0.42 ml) is heated at 80°C during 24 hours. The solvents are evaporated under reduced pressure. The residue is dissolved in ethyl acetate, washed with water. The organic layer is dried over sodium sulfate, filtered and concentrated under reduced pressure to
15 afford an oil. Flash chromatography on silica gel and elution with a 8:2 mixture of hexane and ethyl acetate affords the expected product 1,5-dideoxy-2,3,6-tri-o-benzyl-1,5-{{3-(dimethylphenylsilyl)-propyl}imino}-D-glucitol as a colorless oil (0.493 g, 81%).
20

EXAMPLE 24

Preparation of

25 1,5-DIDEOXY-1,5-{{3-(DIMETHYLPHENYLSILYL)PROPYL}IMINO}-D-GLUCITOL

30 1,5-Dideoxy-2,3,6-tri-O-benzyl-1,5-{{3-(dimethylphenylsilyl)propyl}imino}-D-glucitol (0.45 g, 0.74 mmol) is dissolved in a 9:1 mixture of methanol and formic acid (10 ml), and palladium 10% on charcoal (0.45 g) is added. The mixture is stirred overnight at room temperature. The catalyst is removed by filtration. The solvents are
35 evaporated under reduced pressure. The residue is dissolved in water and passed through a column of *Amberlyst A26 OH^o.

* Trade-mark

Water is evaporated under reduced pressure and flash chromatography on silica gel and elution with a 8:2 mixture of chloroform and methanol affords the expected product 1,5-dideoxy-1,5-[[3-(dimethylphenylsilyl)-propyl]imino]-D-glucitol as an amorphous solid (0.208 g, 83%).

EXAMPLE 25

10 Preparation of

1,5-DIDEOXY-2,3,6-TRI-O-BENZYL-1,5-[[(BENZYLDIMETHYLSILYL)-METHYL]IMINO]-D-GLUCITOL

15 A solution of 1,5-dideoxy-2,3,6-tri-O-benzyl-1,5-imino-D-glucitol (0.433 g, 1 mmol) and benzyl(iodomethyl)dimethylsilane (0.87 g, 3 mmol) in a mixture of dimethylformamide (6 ml) and triethylamine (0.42 ml) is heated at 80°C during 24 hours. The solvents are evaporated under reduced pressure. The residue is dissolved in ethyl acetate, washed
20 with water. The organic layer is dried over sodium sulfate, filtered and concentrated under reduced pressure to afford an oil. Flash chromatography on silica gel and elution with a 8:2 mixture of hexane and ethyl acetate affords the expected product 1,5-dideoxy-2,3,6-tri-O-benzyl-1,5-
25 [[(benzyldimethylsilyl)methyl]imino]-D-glucitol as a colorless oil (0.386 g, 65%).

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EXAMPLE 26

Preparation of

5 1,5-DIDEOXY-1,5-{[(BENZYLDIMETHYLSILYL)METHYL]IMINO}-D-
GLUCITOL

1,5-Dideoxy-2,3,6-tri-O-benzyl-1,5-{[(benzyldimethyl-
silyl)methyl]imino}-D-glucitol (0.3 g, 0.5 mmol) is
dissolved in a 9:1 mixture of methanol and formic acid
10 (10 ml), and palladium 10% on charcoal (0.3 g) is added. The
mixture is stirred overnight at room temperature. The
catalyst is removed by filtration. The solvents are
evaporated under reduced pressure. The residue is dissolved
in water and passed through a column of Amberlyst A26 OH[®].
15 Water is evaporated under reduced pressure and flash
chromatography on silica gel and elution with a 8:2 mixture
of chloroform and methanol affords the expected product 1,5-
dideoxy-1,5-{[(benzyldimethylsilyl)-methyl]-imino}-D-
glucitol as an amorphous solid (0.09 g, 55%).
20

EXAMPLE 27

Preparation of

25 1,5-DIDEOXY-2,3,6-TRI-O-BENZYL-1,5-{[(t-BUTYLDIMETHYLSILYL)-
METHYL]IMINO}-D-GLUCITOL

A solution of 1,5-dideoxy-2,3,6-tri-O-benzyl-1,5-imino-
D-glucitol (0.433 g, 1 mmol) and t-butyl(iodomethyl)dimethyl-
30 silane (0.77 g, 3 mmol) in a mixture of dimethylformamide
(6 ml) and triethylamine (0.42 ml) is heated at 80°C during
24 hours. The solvents are evaporated under reduced
pressure. The residue is dissolved in ethyl acetate, washed
with water. The organic layer is dried over sodium sulfate,
35 filtered and concentrated under reduced pressure to afford

an oil. Flash chromatography on silica gel and elution with a 8:2 mixture of hexane and ethyl acetate affords the expected product 1,5-dideoxy-2,3,6-tri-O-benzyl-1,5-[[t-butyldimethylsilyl)-methyl]imino]-D-glucitol as a colorless
5 oil (0.42 g, 75%).

EXAMPLE 28

10 Preparation of

1,5-DIDEOXY-1,5-[[t-BUTYLDIMETHYLSILYL)METHYL]IMINO]-D-GLUCITOL

15 1,5-Dideoxy-2,3,6-tri-O-benzyl-1,5-[[t-butyldimethylsilyl)methyl]imino]-D-glucitol (0.4 g, 0.72 mmol) is dissolved in a 9:1 mixture of methanol and formic acid (10 ml), and palladium 10% on charcoal (0.5 g) is added. The mixture is stirred overnight at room temperature. The catalyst is removed by filtration. The solvents are
20 evaporated under reduced pressure. The residue is dissolved in water and passed through a column of Amberlyst A26 OH[®]. Water is evaporated under reduced pressure and flash chromatography on silica gel and elution with a 8:2 mixture of chloroform and methanol affords the expected product 1,5-
25 dideoxy-1,5-[[t-butyldimethylsilyl)-methyl]imino]-D-glucitol as an amorphous solid (0.127 g, 61%).

30

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EXAMPLE 29

Preparation of

5 1,5-DIDEOXY-2,3,6-TRI-O-BENZYL-1,5-{[(DIMETHYLPHENYLSILYL)-
METHYL]IMINO}-D-GLUCITOL

10 A solution of 1,5-dideoxy-2,3,6-tri-O-benzyl-1,5-imino-D-glucitol (0.433 g, 1 mmol) and phenyl(iodomethyl)dimethylsilane [Chih-Tang Huang and Pao-Jen Wang, Hua Hsüeh Hsüeh Pao, 25, 341, (1959)] (0.77 g, 3 mmol) in a mixture of dimethylformamide (6 ml) and triethylamine (0.42 ml) is heated at 80°C during 24 hours. The solvents are evaporated under reduced pressure. The residue is dissolved in ethyl acetate, washed with water. The organic layer is dried over
15 sodium sulfate, filtered and concentrated under reduced pressure to afford an oil. Flash chromatography on silica gel and elution with a 8:2 mixture of hexane and ethyl acetate affords the expected product 1,5-dideoxy-2,3,6-tri-O-benzyl-1,5-{[(dimethylphenylsilyl)-methyl]imino}-D-
20 glucitol as a colorless oil (0.37 g, 64%).

EXAMPLE 30

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Preparation of

1,5-DIDEOXY-1,5-{[(DIMETHYLPHENYLSILYL)METHYL]IMINO}-D-
GLUCITOL

30 1,5-Dideoxy-2,3,6-tri-O-benzyl-1,5-{[(dimethylphenylsilyl)methyl]imino}-D-glucitol (0.35 g, 0.60 mmol) is dissolved in a 9:1 mixture of methanol and formic acid (10 ml), and palladium 10% on charcoal (0.35 g) is added. The mixture is stirred overnight at room temperature. The catalyst is removed by filtration. The solvents are
35 evaporated under reduced pressure. The residue is dissolved

in water and passed through a column of Amberlyst A26 OH^o. Water is evaporated under reduced pressure and flash chromatography on silica gel and elution with a 8:2 mixture of chloroform and methanol affords the expected product 1,5-dideoxy-1,5-[[dimethylphenylsilyl]-methyl]imino}-D-glucitol as an amorphous solid (0.139 g, 75%).

EXAMPLE 31

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Preparation of

1,5-DIDEOXY-2,3,6-TRI-O-BENZYL-1,5-[[TRIMETHYLSILYL)-METHYL]IMINO}-D-GLUCITOL

15

A solution of 1,5-dideoxy-2,3,6-tri-O-benzyl-1,5-imino-D-glucitol (0.1 g, 0.24 mmol) and (iodomethyl)trimethylsilane (0.45 ml, 3.1 mmol) in a mixture of dimethylformamide (3 ml) and triethylamine (0.44 ml) is heated at 80°C during 24 hours. The solvents are evaporated under reduced pressure. The residue is dissolved in ethyl acetate, washed with water. The organic layer is dried over sodium sulfate, filtered and concentrated under reduced pressure to afford an oil. Flash chromatography on silica gel and elution with a 8:2 mixture of hexane and ethyl acetate affords the expected product 1,5-dideoxy-2,3,6-tri-O-benzyl-1,5-[[trimethylsilyl)methyl]imino}-D-glucitol as a colorless oil (0.09 g, 75%).

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EXAMPLE 32

Preparation of

5 1,5-DIDEOXY-1,5-{[(TRIMETHYLSILYL)METHYL]IMINO}-D-GLUCITOL

1,5-Dideoxy-2,3,6-tri-O-benzyl-1,5-{[(trimethylsilyl)-methyl]imino}-D-glucitol (0.075 g, 0.14 mmol) is dissolved in a 9:1 mixture of methanol and formic acid (12 ml), and palladium 10% on charcoal (0.3 g) is added. The mixture is
10 stirred overnight at room temperature. The catalyst is removed by filtration. The solvents are evaporated under reduced pressure. The residue is dissolved in water and neutralized with AG1-X8, 20-50 mesh, OH^o form. The resin is removed by filtration, water is removed by lyophilization
15 and the expected product 1,5-dideoxy-1,5-{[(trimethylsilyl)-methyl]imino}-D-glucitol is obtained as an amorphous solid (0.016 g, 45%).

20

EXAMPLE 33

Preparation of

25 1,5-DIDEOXY-2,3,6-TRI-O-BENZYL-1,5-{[3-(TRIMETHYLSILYL)-PROPYL]IMINO}-D-GLUCITOL

A solution of 1,5-dideoxy-2,3,6-tri-O-benzyl-1,5-imino-D-glucitol (0.34 g, 0.78 mmol) and (3-iodopropyl)trimethylsilane (0.57 gr, 2.34 mmol) in a mixture of dimethylformamide (5 ml) and triethylamine (0.33 ml) is stirred at room
30 temperature during 24 hours. The solvents are evaporated under reduced pressure. The residue is dissolved in ethyl acetate, washed with water. The organic layer is dried over sodium sulfate, filtered and concentrated under reduced
35 pressure to afford an oil. Flash chromatography on silica gel and elution with a 8:2 mixture of hexane and ethyl

acetate affords the expected product 1,5-dideoxy-2,3,6-tri-O-benzyl-1,5-[[3-(trimethylsilyl)-propyl]imino]-D-glucitol as a colorless oil (0.405 g, 94%).

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EXAMPLE 34

Preparation of

10 1,5-DIDEOXY-1,5-[[3-(TRIMETHYLSILYL)PROPYL]IMINO]-D-GLUCITOL

1,5-Dideoxy-2,3,6-tri-O-benzyl-1,5-[[3-(trimethylsilyl)-propyl]imino]-D-glucitol (0.39 g, 0.7 mmol) is dissolved in a 9:1 mixture of methanol and formic acid (30 ml), and palladium 10% on charcoal (2 g) is added. The mixture is
15 stirred overnight at room temperature. The catalyst is removed by filtration. The solvents are evaporated under reduced pressure. The residue is dissolved in water and neutralized with AG1-X8, 20-50 mesh, OH^o form. The resin is removed by filtration, water is removed by lyophilization
20 and the expected product 1,5-dideoxy-1,5-[[3-(trimethylsilyl)-propyl]imino]-D-glucitol is obtained as an amorphous solid (0.17 g, 85%).

25

EXAMPLE 35

Preparation of

30 1,5-DIDEOXY-2,3,6-TRI-O-BENZYL-1,5-[[4-(TRIMETHYLSILYL)-BUTYL]-IMINO]-D-GLUCITOL

A solution of 1,5-dideoxy-2,3,6-tri-O-benzyl-1,5-imino-D-glucitol (0.043 g, 0.1 mmol) and (4-iodobutyl)trimethylsilane (0.088 g, 0.3 mmol) in a mixture of dimethylformamide
35 (0.8 ml) and triethylamine (0.04 ml) is stirred at room temperature during 24 hours. The solvents are evaporated

under reduced pressure. The residue is dissolved in ethyl acetate, washed with water. The organic layer is dried over sodium sulfate, filtered and concentrated under reduced pressure to afford an oil. Flash chromatography on silica gel and elution with a 8:2 mixture of hexane and ethyl acetate affords the expected product 1,5-dideoxy-2,3,6-tri-O-benzyl-1,5-[[4-(trimethylsilyl)butyl]imino]-D-glucitol as a colorless oil (0.05 g, 90%).

10

EXAMPLE 36

Preparation of

1,5-DIDEOXY-1,5-[[4-(TRIMETHYLSILYL)BUTYL]IMINO]-D-GLUCITOL

1,5-Dideoxy-2,3,6-tri-O-benzyl-1,5-[[4-(trimethylsilyl)-butyl]imino]-D-glucitol (0.05 g, 0.09 mmol) is dissolved in a 9:1 mixture of methanol and formic acid (15 ml), and palladium 10% on charcoal (0.2 g) is added. The mixture is stirred overnight at room temperature. The catalyst is removed by filtration. The solvents are evaporated under reduced pressure. The residue is dissolved in water and neutralized with AG1-X8, 20-50 mesh, OH[⊖] form. The resin is removed by filtration, water is removed by lyophilization and the expected product 1,5-dideoxy-1,5-[[4-(trimethylsilyl)butyl]imino]-D-glucitol is obtained as an amorphous solid (0.02 g, 75%).

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EXAMPLE 37

Preparation of

5 1,5-DIDEOXY-1,5-IMINO-D-GLUCITOL: DEOXYNOJIRIMYCIN

2,3,6-Tri-O-benzyl-1,5-dideoxy-1,5-imino-D-glucitol (0.2 g, 0.46 mmol) is dissolved in a 9:1 mixture of methanol and formic acid (10 ml) under an inert atmosphere and palladium 10% on charcoal (0.4 g) is added. The mixture is
10 stirred overnight at room temperature. The catalyst is removed by filtration. The solvents are evaporated under reduced pressure. The residue is dissolved in methanol and the solution is filtered through a membrane (Millex-SR 0.5µM). Evaporation of solvent gives a sticky solid which is
15 further triturated in ethanol to give the expected 1,5-dideoxy-1,5-imino-D-glucitol as a beige powder (60 mg, 80%).

20

EXAMPLE 38

Preparation of

(E)-3-TRIMETHYLSILYL-2-PROPEN-1-OL

25

2 g (15.6 mmol) of 1-trimethylsilyl-2-propyn-1-ol in 10 ml of dry ether are added dropwise to an ice-cooled solution of sodium bis(2-methoxyethoxy) aluminum [Red-Al. 3.4 M in toluene, (7.3 ml, 25.1 mmol)] in 10 ml of dry
30 ether. The reaction mixture is then further stirred during 2½ hours at room temperature and poured into an ice-cooled sulfuric acid (1 N) ether mixture. If necessary the pH is adjusted to be slightly basic, the organic phase is then removed and the aqueous phase is further extracted with
35 ether. The combined organic phases are dried over sodium sulfate, filtered and concentrated under reduced pressure.

* Trade-mark

Rapid flash chromatography of the residue on a silica gel column eluted with a 8:2 mixture of hexane and ethyl acetate affords the expected (E)-3-trimethylsilyl-2-propen-1-ol as a colorless liquid (1.8 g, 90%).

5

EXAMPLE 39

Preparation of

10

(E)-3-TRIMETHYLSILYL-2-PROPEN-1-OL, METHANESULFONATE

15

1.6 ml (11.5 mmol) of triethylamine and 0.74 ml (9.6 mmol) of methanesulfonylchloride in 10 ml of dry dichloromethane are successively added to an ice-cooled solution of 1 g (7.6 mmol) of (E)-3-trimethylsilyl-2-propen-1-ol in 20 ml of dry dichloromethane. The reaction mixture is then further stirred during 3 hours at room temperature and poured into a water-dichloromethane mixture, the organic phase is removed, the aqueous phase is further extracted with dichloromethane. The organic phases are combined and washed with sodium bicarbonate, dried over sodium sulfate, filtered and concentrated under reduced pressure to give 1.1 g of a yellowish liquid which is further bulb to bulb distilled under reduced pressure (water pump, oven temperature 150-200°C) to afford 0.8 g (50%) of the expected (E)-3-trimethylsilyl-2-propen-1-ol, methanesulfonate.

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EXAMPLE 40

Preparation of

5 1,5-DIDEOXY-1,5-[[3-(TRIMETHYLSILYL)-2-PROPENYL]IMINO]-D-
GLUCITOL

10 A solution of 1,5-dideoxy-1,5-imino-D-glucitol (0.052 g, 0.32 mmol) and (E)-3-trimethylsilyl-2-propen-1-ol, methane-sulfonate (0.133 g, 0.63 mmol) in a mixture of dimethyl-formamide (2 ml) and triethylamine (0.09 ml, 0.63 mmol) is heated at 80°C during 20 hours. Solvents are evaporated under reduced pressure and the residue is flash chromatographed on a silica gel column, eluted with dichloromethane: ethanol 9:1 to 7:3 to give 0.022 g (35%) of the expected
15 1,5-dideoxy-1,5-[[3-(trimethylsilyl)-2-propenyl]imino]-D-glucitol as a white powder.

EXAMPLE 41

20

Preparation of

1-METHYL-3-TRIMETHYLSILYL-BENZENE

25 A mixture of 9.2 g (50 mmol) of 3-bromo-toluene and 5.84 g (50 mmol) of chlorotrimethylsilane in 100 ml of dry ether are added dropwise to 1.2 g (50 mmol) of magnesium turnings in a few milliliters of ether, some crystals of iodine are added to start the reaction. The reaction mixture is refluxed for 20 hours after the end of the addition and
30 then poured into a saturated solution of ammonium chloride (200 ml). The aqueous solution is further extracted with ether, the ethereal extracts are combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to afford 4.4 g of a yellowish liquid. Flash chromatography on
35

a silica gel column and elution with petroleum ether give 2.3 g (30%) of the expected 1-methyl-3-trimethylsilyl-benzene as a colorless liquid.

5

EXAMPLE 42

Preparation of

10 1-BROMOMETHYL-3-TRIMETHYLSILYL-BENZENE

A mixture of 2.5 g (15 mmol) of 1-methyl-3-trimethylsilyl-benzene and 3.1 g (16.5 mmol) of N-bromosuccinimide in 80 ml of carbon tetrachloride are refluxed in the presence of a catalytic amount of benzoyl peroxide. When succinimide
15 has totally precipitated at the surface, the hot mixture is filtered. The filtrate is evaporated under reduced pressure, the residue obtained is dissolved in a brine-chloroform mixture. The organic phase is separated, dried over sodium sulfate, filtered and evaporated to afford 4 g of a
20 yellowish liquid. Flash chromatography on silica gel and elution with petroleum ether give 2 g (60%) of the expected 1-bromomethyl-3-trimethylsilyl-benzene as a colorless liquid.

25

EXAMPLE 43

Preparation of

30 1,5-DIDEOXY-1,5-[[[3-(TRIMETHYLSILYL)PHENYL]METHYL]IMINO]-D-GLUCITOL

A solution of 1,5-dideoxy-1,5-imino-D-glucitol (0.128 g, 0.78 mmol) and 1-bromomethyl-3-trimethylsilyl-benzene
35 (0.3 g, 1.23 mmol) in a mixture of dimethylformamide (5 ml) and triethylamine (0.17 ml) is heated at 100°C during

20 hours. Solvents are evaporated under reduced pressure and the residue is flash chromatographed on a silica gel column, eluted with dichloromethane:ethanol 9:1 to 7:3 to give 0.1 g (40%) of the expected 1,5-dideoxy-1,5-[[3-(trimethylsilyl)-phenyl]methyl]imino]-D-glucitol as a white powder.

EXAMPLE 44

10 Preparation of

1,5-DIDEOXY-1,5-[[3-(TRIMETHYLSILYL)PROPYL]IMINO]-D-GLUCITOL

Step A:

15 3-Iodopropyltrimethylsilane

A stirred solution of 3-chloropropyltrimethylsilane (5.0 g, 33 mmol) and NaI (7.5 g, 50 mmol) in acetone (45 ml) was heated at a reflux for 16 hours. The solution became dark yellow (iodine) with a white precipitate (NaCl). The resultant mixture was cooled to room temperature and filtered to remove the NaCl. The salt was washed with acetone (3 x 5 ml). The washings were combined with the filtrate and concentrated (25°C/10 Torr) leaving a two-phase mixture. The concentrate was partitioned in ethyl acetate (50 ml) and water (25 ml). The organic layer was separated, washed with aqueous sodium metabisulfite 10% (10 ml), water (20 ml), dried (MgSO₄), and concentrated (250°C/10 Torr) to give 6.0 g of a pale yellow oil. This crude oil was distilled through a six-inch Vigreux column (removing some unreacted chloropropyltrimethylsilane) under water aspirator vacuum giving 4.2 g (50%) of a colorless oil: b.p. 72°C/10 Torr.

35

Step B:1,5-Dideoxy-1,5-[[3-(trimethylsilyl)propyl]imino]-D-glucitol

5 A well stirred mixture of 1,5-dideoxy-1,5-imino-D-glucitol (0.50 g, 3.1 mmol), 3-iodopropyltrimethylsilane (1.1 g, 4.6 mmol) and sodium bicarbonate (0.38 g, 4.6 mmol) in sulfolane (5 ml) was heated at 90°C for 3 hours and then cooled to room temperature. The mixture was diluted with
10 water (5 ml), acidified with 1 M HCl (5 ml) to pH 2-3, and allowed to stir at room temperature for 1 hour. The mixture was washed with hexane (3 x 5 ml) and adjusted to pH 8 with 1 M sodium hydroxide (3.2 ml) precipitating the crude
15 product. The mixture was cooled to 5°C (ice-water bath), filtered, and the filter cake was washed with ice-water (2 x 3 ml) and air-dried for 1 hour to give 0.64 g of a white solid. The solid was dissolved in hot (80°C) water (12 ml) and cooled to give 0.56 g (66%) of the desired product as white plates.

20

Enzymes which catalyze the hydrolysis of complex carbohydrates, e.g. α -glycosidases, convert non-absorbable
25 carbohydrates into absorbable sugars. The rapid action of these enzymes, particularly following the intake of high levels of carbohydrates, lead to acute high levels in blood glucose which, in the case diabetics, lead to undesirable manifestations, thus it has been a long-sought goal to find
30 compounds which will obviate the hyperglycemia caused by dietary improprieties. Similarly, in the case of obesity the control of high levels of blood glucose, with its subsequent conversion to fat, caused by the catalysis of carbohydrates has inspired the quest for compounds which will obviate the
35 problems associated with dietary improprieties. "Dietary

improprieties" means eating habits associated with overeating, overdrinking, and failure to maintain a balanced diet such as the excessive intake of carbohydrates, which metabolize to glucose and which lead to obesity.

5 The compound of the present invention are administered to subjects in need of such therapy, e.g., mammals such as humans. The compounds of this invention (I) are potent and long-lasting inhibitors of α -glucosidase and, by standard
10 laboratory methods for determining serum glucose levels, are shown to be useful for the treatment of disease states caused by the underutilization and/or overproduction of serum glucose without adversely affecting the rate of transport across cell membranes. Thus, the compounds are
15 useful in the treatment of diabetes and obesity.

 In the practice of this invention, an effective amount of a compound of this invention is that amount required to reduce the amount of serum glucose (relative to a control) following the ingestion of carbohydrates convertible to
20 absorbable glucose. The specific dosage for the treatment of any specific patient suffering from either disease state will depend upon such factors as size, type and age of the patient as well as the patients' dietary habits and the severity of the disease state, all of which are factors
25 normally familiar to and considered by the attending diagnostician treating the patient. Generally, the compounds are to be administered orally at a dose of 0.01 to 2 milligrams per kilogram of body weight (MPK) with a dose of 0.025 to 0.5 MPK being preferred. The compounds
30 preferably are to be administered orally at mealtimes in single or multiple unit doses containing 1 mg to 10 mg. Of course, in the treatment of obesity, the term includes the practice of treating the disease as well as continued administration of dose regimens suitable for the maintenance
35 of the desired weight for the patient.

It is also to be found that the compounds of the instant invention (I) will exert an inhibitory effect on glycosidase enzymes that are essential for elaboration of the final structure of the oligosaccharide side-chains of glyco-
5 proteins, particularly the HIV (gp 120) glycoprotein. Suitable assay techniques, e.g. syncytial formation, the reverse transcriptase assay, immunofluorescence tests and electron microscopy, may be used to evaluate the effects on HIV viral growth and for determining dose regimens. Anti-
10 viral effects may be confirmed by immunofluorescence with serum for virally infected patients. In the treatment of the HIV related disease states (e.g., AIDS), as well as other retroviral glyco-protein-related disease states, unlike the treatment of diabetes and obesity, the compounds of this
15 invention may be administered by parenteral means; specific doses being within the above stated dose range for treatment of diabetes and obesity. In addition to treating AIDS with the compounds of this invention, the compounds of this
20 invention may also be effectively utilized in conjunctive therapy with compounds known to be useful in treating patients with AIDS such as for example 2,3-dideoxycytidine, 2,3-dideoxyadenine, interferon, interleukin-2 and the like.

In practising the end-use application of the compounds
25 of this invention, the compounds are preferably incorporated in a pharmaceutical formulation comprising a pharmaceutical carrier in admixture with a compound of this invention. The term "pharmaceutical carrier" refers to known pharmaceutical excipients useful in formulating pharmaceutically active
30 compounds for internal administration to animals, and which are substantially non-toxic and non-sensitizing under conditions of use. The compositions can be prepared by known techniques for the preparation of tablets, capsules, elixirs, syrups emulsions, dispersions and wettable and
35 effervescent powders, and can contain suitable excipients known to be useful in the preparation of the particular type

of composition desired. Suitable pharmaceutical carriers and formulation techniques are found in standard texts, such as Remington's Pharmaceutical Sciences, Mack Publishing Company, Easton, PA.

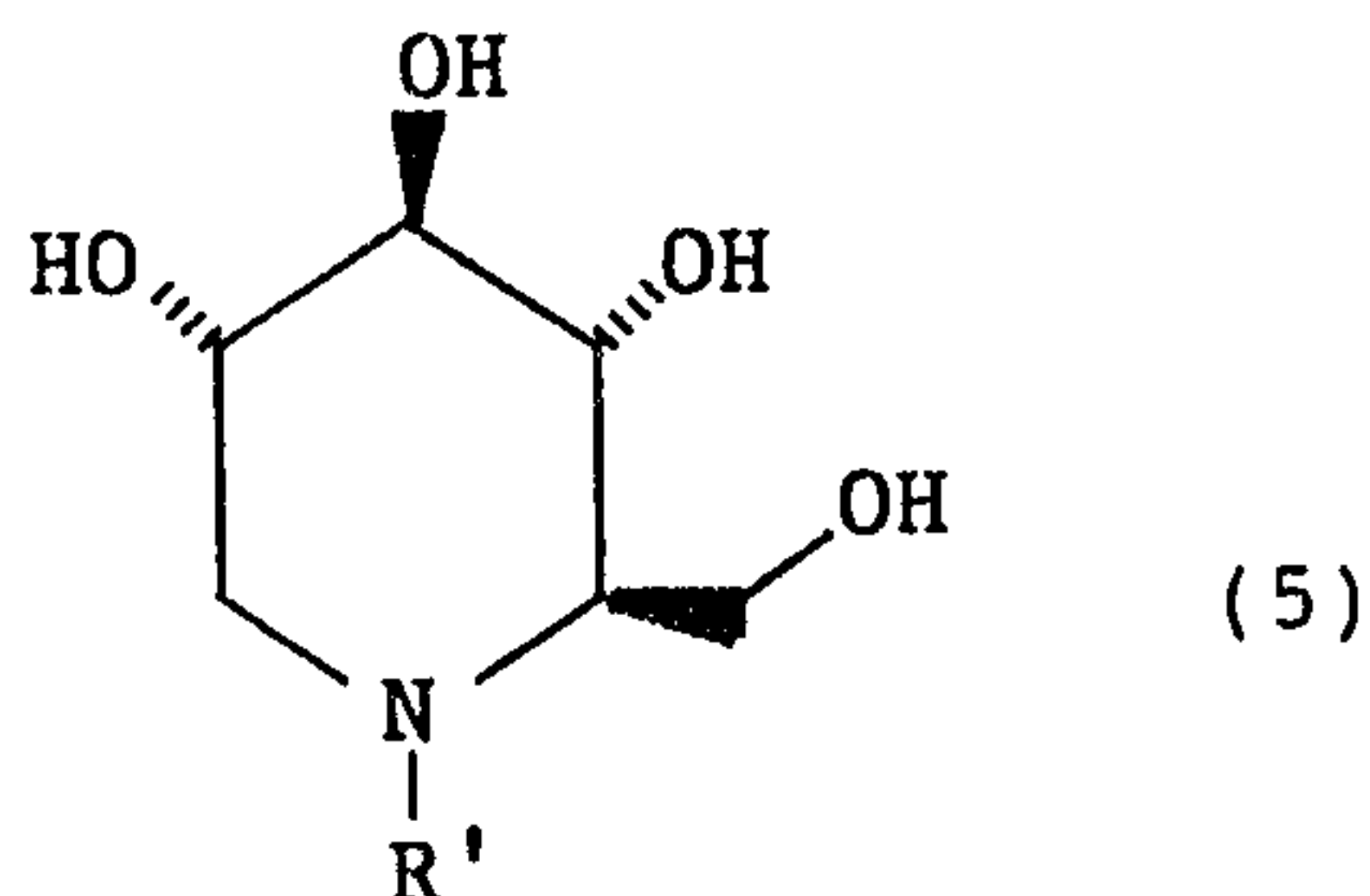
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As is true for most classes of therapeutic agents certain subgeneric groups and certain specific compounds are preferred. For the compounds embraced within this application the preferred sub-generic groups are those wherein Q is C₁₋₇ alkylene, (CH₂)_mCH=CH(CH₂)_n, (CH₂)_p phenylene, (CH₂)_m cyclopentenylene, (CH₂)_m cyclohexenylene or (CH₂)_p^T moieties. Preferred R₁ moieties are C₁₋₇ alkyl, phenyl or a hydroxylated alkyl, and preferred R₂ and R₃ moieties are C₁₋₁₀ alkyl, phenyl or benzyl.

10

The following compounds of Formula 5 illustrate the preferred specific compounds:

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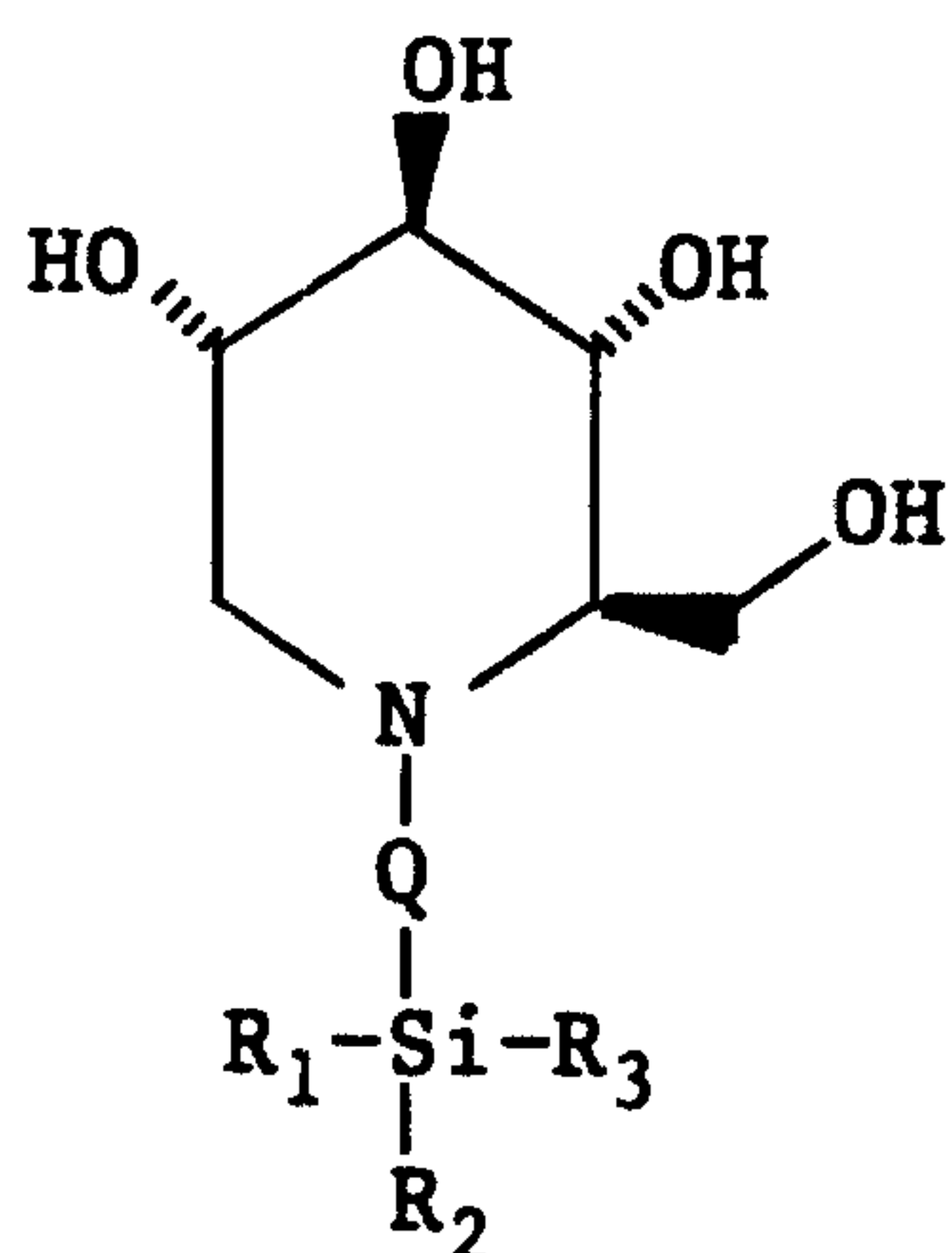
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	<u>R'</u>	<u>R'</u>
5	$-\text{CH}_2-\text{Si}(\text{CH}_3)_3$	$-\text{CH}_2-\text{C}_6\text{H}_{10}-\text{Si}(\text{CH}_3)_2$
	$-(\text{CH}_2)_3-\text{Si}(\text{CH}_3)_3$	
10	$-(\text{CH}_2)_4-\text{Si}(\text{CH}_3)_3$	$-\text{CH}_2-\text{C}_6\text{H}_{10}-\text{Si}(\text{CH}_3)_2$
	$-\text{CH}_2-\text{Si}(\text{CH}_3)_2\text{C}_6\text{H}_5$	
15	$-\text{CH}_2-\text{Si}(\text{CH}_3)_2\text{C}_2\text{H}_5$	$-\text{CH}_2-\text{C}_6\text{H}_9-\text{Si}(\text{CH}_3)_2$
	$-\text{CH}_2-\text{Si}(\text{CH}_3)_2\text{C}_3\text{H}_7$	
20	$-\text{CH}_2-\text{CH}=\text{CH}-\text{Si}(\text{CH}_3)_3$ (trans)	$-\text{CH}_2-\text{C}_6\text{H}_9-\text{Si}(\text{CH}_3)_2$
	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{Si}(\text{CH}_3)_3$	
25		$-\text{CH}_2-\text{C}_6\text{H}_4-\text{Si}(\text{CH}_3)_3$
	$-\text{CH}_2-\text{C}_6\text{H}_4-\text{Si}(\text{CH}_3)_3$	
30	$-(\text{CH}_2)_3-\text{Si}(\text{CH}_3)_2\text{CH}_2\text{OH}$	
	$-(\text{CH}_2)_3-\text{Si}(\text{CH}_3)_2\text{CH}_2\text{CHOHCH}_2\text{OH}$	
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WHAT IS CLAIMED IS:

1. A compound of the formula



or an isomeric form thereof, or a pharmaceutically acceptable salt thereof wherein

Q is C₁₋₇ alkylene, (CH₂)_mCH=CH(CH₂)_n, (CH₂)_mC≡C(CH₂)_n, (CH₂)_mCH=C=CH(CH₂)_n, (CH₂)_p phenylene, (CH₂)_m cyclopentenylene, (CH₂)_m cyclohexenylene, (CH₂)_pT, wherein T is a trivalent hydrocarbyl moiety which together with the silicon atom to which it is attached, forms a 5 to 6 atom cyclic silicane, said cyclic silicane optionally having a double bond, with m being 1, 2 or 3, n being 0, 1 or 2, p being 0, 1, 2, 3 or 4,

R_1 is C_{1-7} alkyl, C_{1-7} alkoxy, mono- or polyhydroxy C_{1-6} alkyl, mono- or polyalkoxy C_{1-6} alkyl, chloro C_{1-6} alkyl,

R_2 and R_3 are C_{1-10} alkyl, $(CH_2)_p$ -X,Y-substituted phenyl, with X and Y each being H, OH, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, CF_3 , CN, NO_2 , SH or -S- C_{1-6} alkyl, with the proviso that when Q is $(CH_2)_pT$, then one of R_1 , R_2 or R_3 is deleted.

2. The compound of Claim 1 wherein Q is a C_{1-7} alkylene.

3. The compound of Claim 2 wherein R_1 , R_2 and R_3 are C_{1-7} alkyl.

4. The compound of Claim 2 wherein the C_{1-7} alkyl is methyl.

5. The compound of Claim 2 wherein R_1 is a hydroxylated C_{1-7} alkyl.

6. The compound of Claim 1 wherein Q is $(CH_2)_mHC=CH(CH_2)_n$.

7. The compound of Claim 6 wherein R_1 , R_2 and R_3 are C_{1-7} lower alkyl.

8. The compound of Claim 1 wherein Q is $(CH_2)_pT$.

9. The compound of Claim 8 wherein R_1 and R_2 are C_{1-7} alkyl and R_3 is deleted.

10. The compound of Claim 9 wherein the cyclic silicane of $(CH_2)_pT$ is unsaturated.

11. The compound of Claim 1 wherein Q is $-\text{CH}_2\text{-phenylene}$ and R_1 , R_2 and R_3 are each C_{1-7} alkyl.

12. The compound of Claim 1 wherein $-\text{Q-Si-R}_1\text{R}_2\text{R}_3$ is $-\text{CH}_2\text{-Si-(CH}_3)_3$.

13. The compound of Claim 1 wherein $-\text{Q-Si-R}_1\text{R}_2\text{R}_3$ is $-(\text{CH}_2)_3\text{-Si(CH}_3)_3$.

14. The compound of Claim 1 wherein $-\text{Q-Si-R}_1\text{R}_2\text{R}_3$ is $-(\text{CH}_2)_4\text{-Si(CH}_3)_3$.

15. The compound of Claim 1 wherein $-\text{Q-Si-R}_1\text{R}_2\text{R}_3$ is $-\text{CH}_2\text{Si(CH}_3)_2\text{C}_6\text{H}_5$.

16. The compound of Claim 1 wherein $-\text{Q-Si-R}_1\text{R}_2\text{R}_3$ is $-\text{CH}_2\text{Si(CH}_3)_2\text{C}_2\text{H}_5$.

17. The compound of Claim 1 wherein $-\text{Q-Si-R}_1\text{R}_2\text{R}_3$ is $-\text{CH}_2\text{Si(CH}_3)_2\text{C}_3\text{H}_7$.

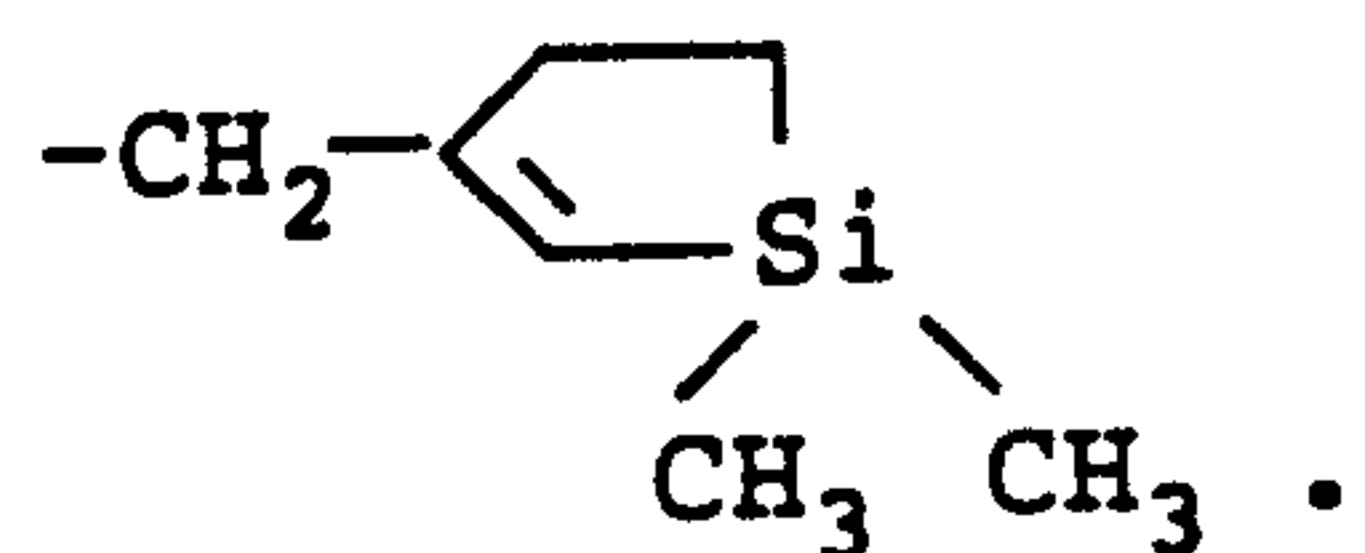
18. The compound of Claim 1 wherein $-\text{Q-Si-R}_1\text{R}_2\text{R}_3$ is $\text{trans-CH}_2\text{-CH=CH-Si(CH}_3)_3$.

19. The compound of Claim 1 wherein $-\text{Q-Si-R}_1\text{R}_2\text{R}_3$ is $-\text{CH}_2\text{-C}_6\text{H}_4\text{-meta-Si(CH}_3)_3$.

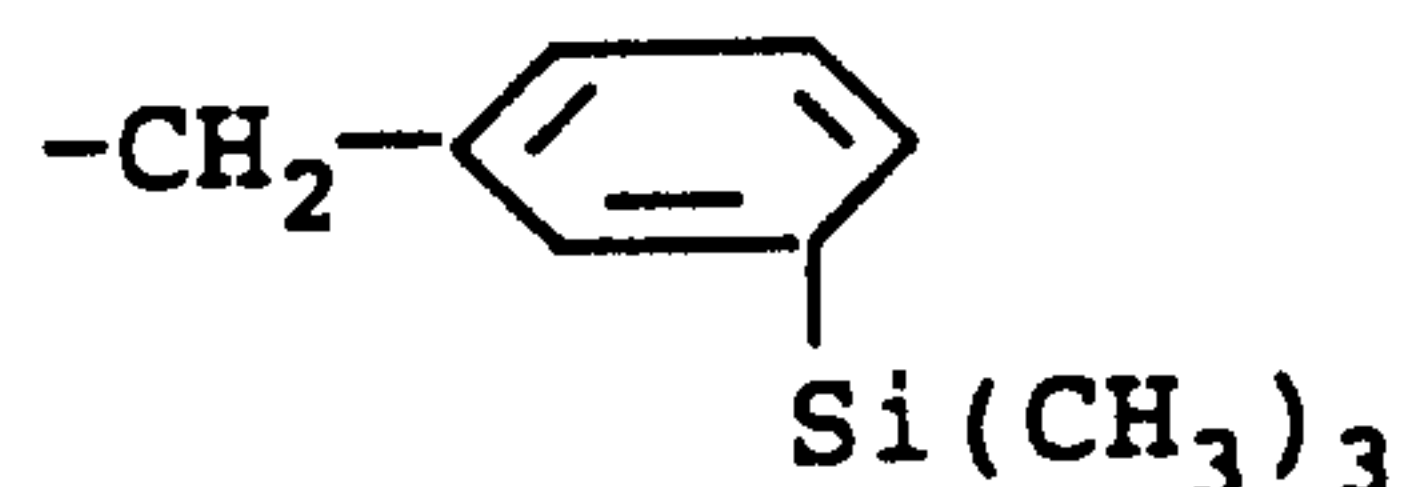
20. The compound of Claim 1 wherein $-\text{Q-Si-R}_1\text{R}_2\text{R}_3$ is $-(\text{CH}_2)_3\text{-Si(CH}_3)_2\text{CH}_2\text{OH}$.

21. The compound of Claim 1 wherein $-\text{Q-Si-R}_1\text{R}_2\text{R}_3$ is $-(\text{CH}_2)_3\text{-Si(CH}_3)_2\text{CH}_2\text{CHOHCH}_2\text{OH}$.

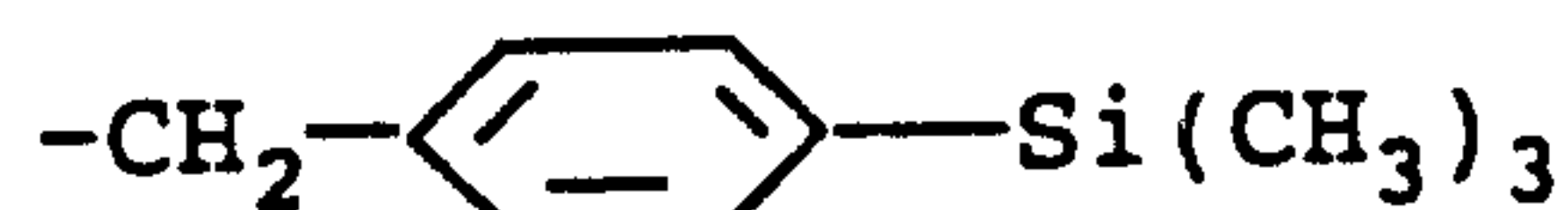
22. The compound of Claim 1 wherein $-Q-Si-R_1R_2R_3$ is



23. The compound of Claim 1 wherein $-Q-Si-R_1R_2R_3$ is



24. The compound of Claim 1 wherein $-Q-Si-R_1R_2R_3$ is



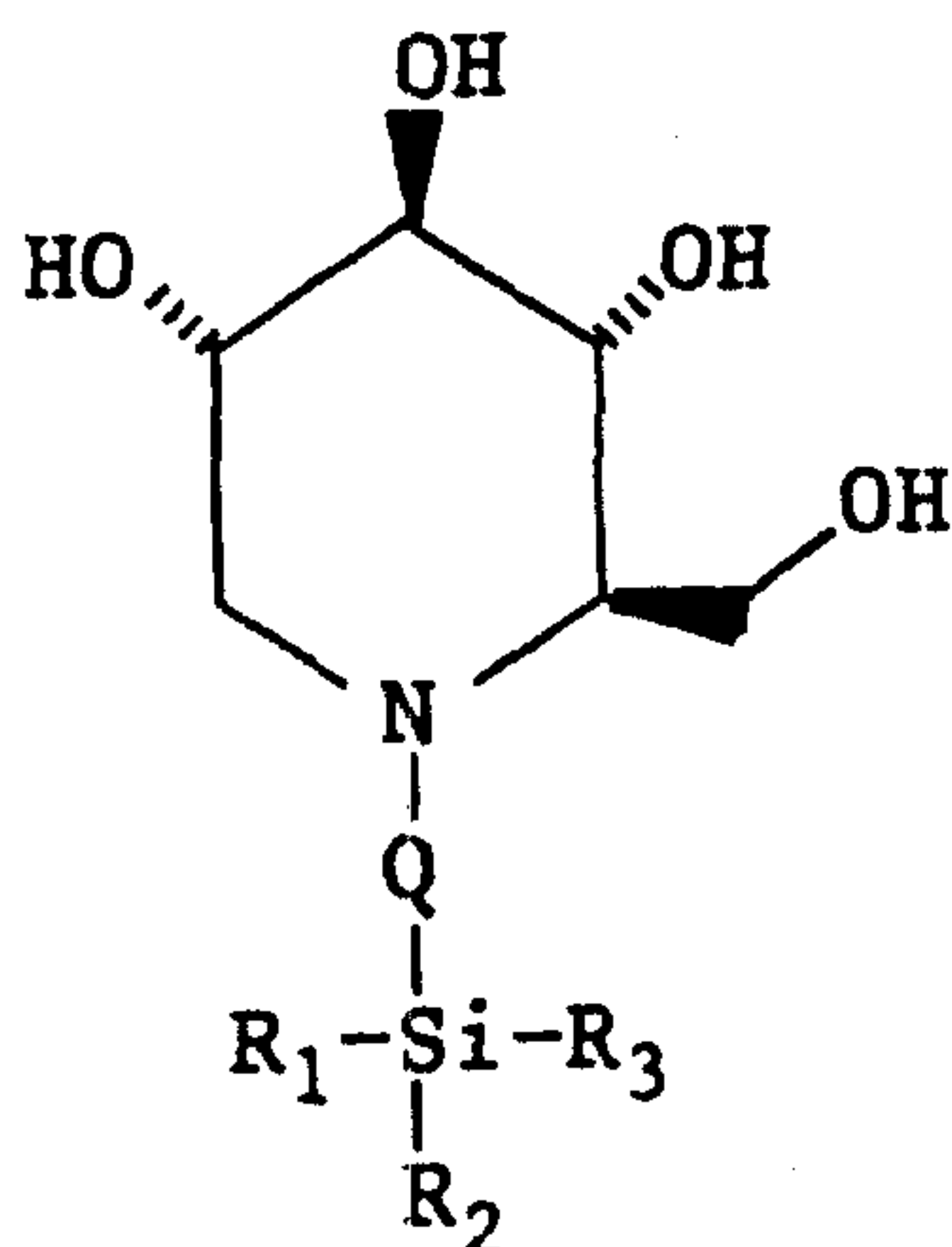
25. The compound of Claim 1 further comprising a pharmaceutically acceptable carrier.

26. The use of a therapeutically effective amount of a compound as claimed in any one of claims 1 to 24, or an isomer thereof, or a pharmaceutically acceptable salt thereof, for the treatment of hyperglycemia.

27. The use of a therapeutically effective amount of a compound as claimed in any one of claims 1 to 24, or an isomer thereof, or a pharmaceutically acceptable salt thereof, for the treatment of obesity associated with dietary improprieties.

28. The use of a therapeutically effective amount of a compound as claimed in any one of claims 1 to 24, or an isomer thereof, or a pharmaceutically acceptable salt thereof, for the treatment of AIDS.

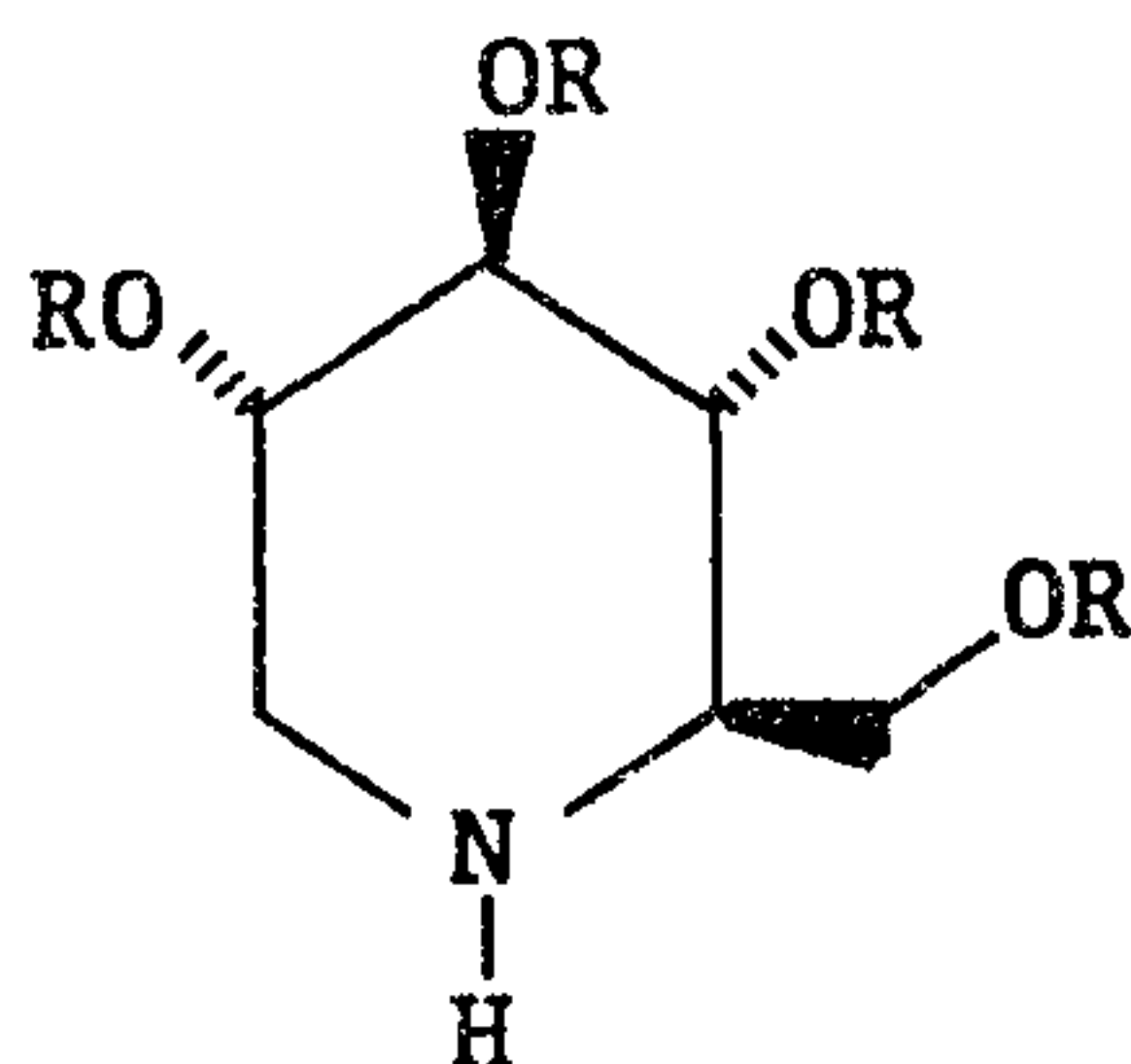
29. A process of preparing a compound of the formula



or an isomeric form thereof, or a pharmaceutically acceptable salt thereof wherein

- Q is C₁₋₇ alkylene, (CH₂)_mCH=CH(CH₂)_n, (CH₂)_mC≡C(CH₂)_n, (CH₂)_mCH=C=CH(CH₂)_n, (CH₂)_pphenylene, (CH₂)_mcyclopentenylene, (CH₂)_mcyclohexenylene, (CH₂)_pT, wherein T is a trivalent hydrocarbyl moiety which together with the silicon atom to which it is attached, forms a 5 to 6 atom cyclic silicane, said cyclic silicane optionally having a double bond, with m being 1, 2 or 3, n being 0, 1 or 2, p being 0, 1, 2, 3 or 4,
- R₁ is C₁₋₇ alkyl, C₁₋₇ alkoxy, mono- or polyhydroxy C₁₋₆ alkyl, mono or polyalkoxy C₁₋₆ alkyl, chloro C₁₋₆ alkyl,
- R₂ and R₃ are C₁₋₁₀ alkyl, (CH₂)_p-X, Y-substituted phenyl, with X and Y each being H, OH, halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy, CF₃, CN, NO₂, SH or -S-C₁₋₆ alkyl, with the proviso that when Q is (CH₂)_pT, then one of R₁, R₂ or R₃ is deleted,

which comprises condensing an optionally hydroxy-protected compound of the formula



wherein R is H or an optional protecting group with a reactant $X'-Q-SiR_1R_2R_3$ wherein X' is halogeno, mesylate or tosylate followed by the removal of any hydroxy-protecting group and, if necessary, neutralizing any anion formed during the deprotection process.

30. A pharmaceutical composition comprising an effective amount of a compound of Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24, or an isomer thereof, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier therefor.

31. A pharmaceutical composition for use in the treatment of hyperglycemia in a mammal which comprises a therapeutically effective amount of a compound of Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24, or an isomer thereof, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier therefor.

32. A pharmaceutical composition for use in the treatment of obesity in a mammal which comprises a therapeutically effective amount of a compound of Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24, or an isomer thereof, or a

pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier therefor.

33. A pharmaceutical composition for use in the treatment of AIDS in a mammal which comprises a therapeutically effective amount of a compound of Claim 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 or 24, or an isomer thereof, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier therefor.