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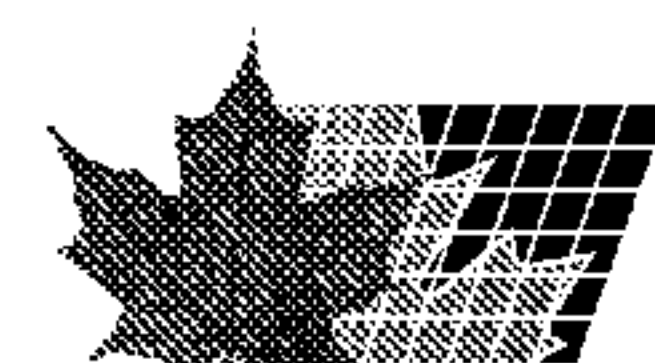
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(54) Title: SYNTHESIS OF MANNOJIRIMYCIN DERIVATIVES

(57) Abrégé/Abstract:

α -Homojirimycin and 6-dpi-homojirimycin are each synthesized from 2-azido-2-deoxy-3,4:6,7-di-O- isopropylidene-D-glycero-D-talo-heptono-1,5-lactone in which the side chain acetonide is hydrolyzed to give the corresponding diol which is then protected with a silyl protecting agent to form a silyl ether. The latter compound is used as a divergent intermediate in which the piperidine ring is formed by joining the nitrogen function at C-2 to C-6 (A) with inversion of configuration at C-6 to form 6- epi-homomannojirimycin or (B) with retention of configuration at C-6 to form α -homomannojirimycin.



SYNTHESIS OF MANNOJIRIMYCIN DERIVATIVESAbstract of the Disclosure

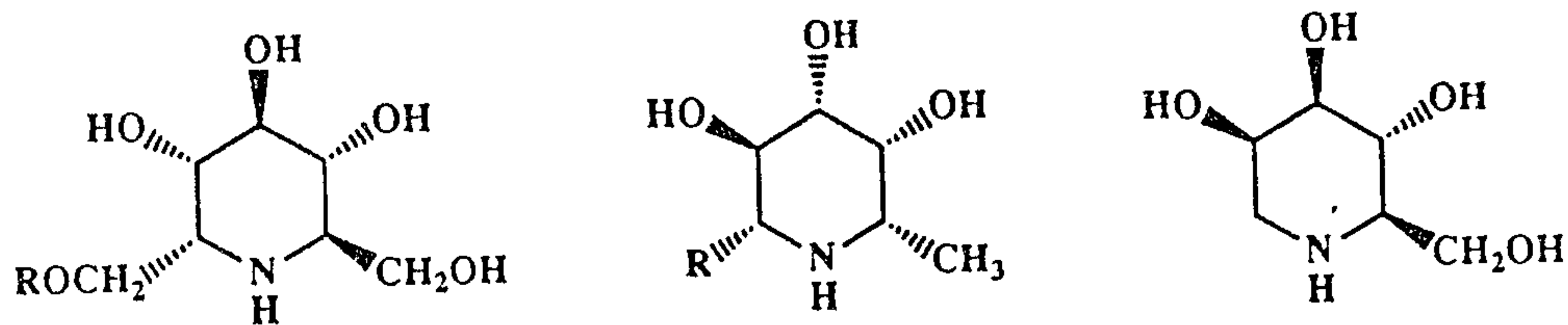
5 α -Homojirimycin and 6-dpi-homojirimycin are
each synthesized from 2-azido-2-deoxy-3,4:6,7-di-O-
isopropylidene-D-glycero-D-talo-heptono-1,5-lactone
in which the side chain acetone is hydrolyzed to
give the corresponding diol which is then protected
with a silyl protecting agent to form a silyl ether.
The latter compound is used as a divergent
10 intermediate in which the piperidine ring is formed
by joining the nitrogen function at C-2 to C-6 (A)
with inversion of configuration at C-6 to form 6-
epi-homomannojirimycin or (B) with retention of
configuration at C-6 to form α -homomannojirimycin.

SYNTHESIS OF MANNOJIRIMYCIN DERIVATIVESBackground of the Invention

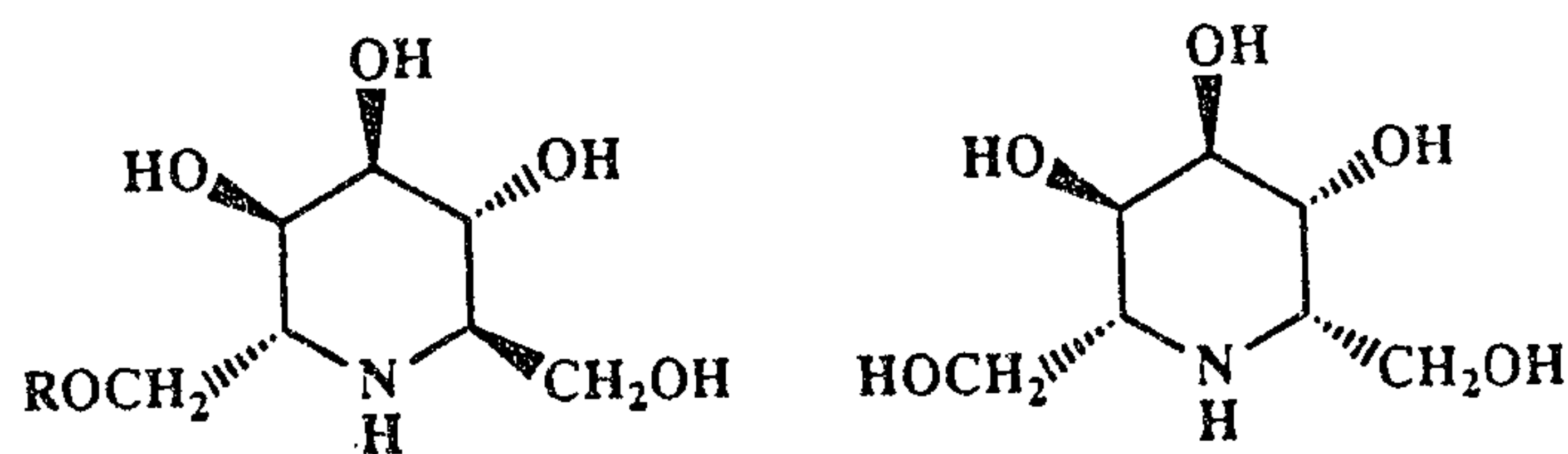
This invention relates to a method for the synthesis of mannojirimycin derivatives and, more particularly, to the synthesis of α -homomannojirimycin and 6-epi-homomannojirimycin from the azidolactone, 2-azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone.

Iminoheptitols, such as α -homonojirimycin (1) may constitute a general class of glycosidase inhibitors in which it is possible to use the anomeric substituent to obtain additional potency and/or specificity in comparison to the corresponding azohexoses that lack such a substituent. For example, the β -glucopyranosyl derivative (2) [Anzeveno et al., J. Org. Chem., 54, 2539 (1989); Liu, J. Org. Chem., 52, 4717 (1987)] of α -homonojirimycin (1), the first example of a naturally occurring azoheptose [Kite, et al., Tetrahedron Lett., 29, 6483 (1988)], is a powerful α -glucosidase inhibitor and is a drug candidate for antidiabetic therapy [Rhinehart et al., J. Pharmacol. Exp. Therap., 241, 915 (1987)]. Also, homofuconojirimycin (3) [Fleet et al., Tetrahedron Lett., 30, 4439 (1989)] is as powerful an inhibitor of human liver α -fucosidase as is deoxy-fuconojirimycin (4) [Winchester et al., Biochem. J., 259, in press (1989)].

Deoxymannojirimycin (DMJ) (5) is a major biochemical tool for the investigation and inhibition of mannosidases of glycoprotein processing [Elbein, Ann. Rev. Biochem., 56, 497 (1987)], although it is a relatively weak inhibitor of α -mannosidases in general. It has been suggested that DMJ may attenuate the infectivity of HIV-1 [Montefiori et al., Proc. Natl. Acad. Sci. USA 85, 9248 (1988)] due to its inhibition of processing mannosidases, and molecular graphics studies have been reported in an attempt to design mannosidase inhibitors as potential anti-HIV agents [Winkler and Holan, J. Med. Chem. 32, 2084 (1989)]. In fact, DMJ is a better inhibitor of α -fucosidases than of α -mannosidases [Evans et al. Phytochemistry, 24, 1953 (1985)]. This is presumably due to the correspondence of the stereochemistry of the hydroxyl functions at C-2, C-3 and C-4 of DMJ with those in both mannose and fucose and the less stringent structural requirements for the inhibition of α -fucosidase than of α -mannosidase. α -Homomannojirimycin (HMJ) (6) may be a more specific inhibitor of mannosidase than is DMJ (5) because of the additional interaction of the anomeric substituent with the active site of α -mannosidases. Furthermore, HMJ (6) should be a relatively weak inhibitor of α -fucosidases since the configurations at C-2 and C-6 are incorrect in relation to α -fuco configuration; the presence of the polar hydroxymethyl - rather than a methyl - substituent at C-6 should also decrease fucosidase inhibition. Additionally, HMJ should allow the preparation of a number of α -mannosyl derivatives (7) which might allow differential inhibition of the different mannosidases of glycoprotein processing, depending on the nature of the link to the mannose residue.

(1) R = H (2) R = β -glucopyranosyl(3) R = CH₂OH (4) R = H

(5)



(6) R = H (7) R = linked mannose

(8)

Homomannojirimycin contains five adjacent chiral centers and seven adjacent carbon atoms, bearing functional groups. Previous syntheses of this class of compounds [Anzeveno et al., *supra*; Liu, *supra*; and Fleet et al., *Tetrahedron Lett.* 30, 4439 (1989)], begin with hexose derivatives and add the additional carbon atom relatively late in the synthesis.

Brief Description of the Invention

In accordance with the present invention, α -homomannojirimycin (6) and 6-epi-homomannojirimycin (8) are each synthesized from the protected azidolactone, 2-azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone (10), in which the nitrogen is introduced at C-2. The respective systematic names for α -homomannojiri-

mycin (6) and 6-epi-homomannojirimycin (8) are
2,6-dideoxy-2,6-imino-D-glycero-D-talo-heptitol and
2,6-dideoxy-2,6-imino-L-glycero-D-talo-heptitol.

5 The azidolactone (10) which is used as a
starting material in the method of the invention and
its method of synthesis are described hereinbelow and
by Bruce et al., in Tetrahedron 46, In Press 1989.
Briefly, the azidolactone (10) was prepared from
diacetone mannose which is converted to the protected
10 heptonolactone (9) by the Kiliani reaction [Kiliani,
Ber. 18, 3066 (1885); Fischer, Ber. 22, 2204 (1889)].
Esterification of the protected heptonolactone (9)
with triflic anhydride, followed by treatment with
sodium azide resulted in overall displacement at C-2
15 with retention of configuration to give the azido-
lactone (10) in 76% yield

In accordance with the present invention,
the side chain acetonide in azidolactone (10) is acid
20 hydrolyzed to give the corresponding diol (11) which
is then reacted with a silyl protecting agent, e.g.
t-butyldimethylsilyl chloride, to give the silyl
ether, 2-azido-7-O-tert-butyldimethylsilyl-2-deoxy-3,
4-O-isopropylidene-D-glycero-D-talo-heptono-1,5-
25 lactone (12). The silyl ether (12) is then used as a
divergent intermediate as follows:

A. to produce 6-epi-homomannojirimycin (8)
by a synthetic method which comprises formation of
the piperidine ring by joining the nitrogen function
30 at C-2 to C-6 with inversion of configuration at C-6,
or

B. to produce α -homomannojirimycin (6) by a synthetic method which comprises formation of the piperidine ring by joining the nitrogen function at C-2 to C-6 with retention of configuration at C-6.

5 In a preferred embodiment of the synthesis of 6-epi-homomannojirimycin (8), the following reaction steps are carried out:

10 a. Reacting silyl ether (12) with trifluoromethanesulfonic anhydride to give the azidotriflate (13),

b. Subjecting the azidotriflate (13) to palladium catalyzed reductive hydrogenation to form the bicyclic lactone (15),

15 c. Reducing the bicyclic lactone (15) with lithium aluminum hydride to give the protected iminoheptitol (16),

20 d. Removing the protecting groups from iminoheptitol (16) by acid hydrolysis, e.g. with trifluoroacetic acid, to give the desired 6-epi-homomannojirimycin (8).

In a preferred embodiment of the synthesis of α -homomannojirimycin (6), the following reaction steps are carried out:

25 a. Oxidizing the secondary alcohol function in silyl ether (12) to give the corresponding ketoazide (17),

b. Reducing the ketoazide (17) with triethylphosphite to give the bicyclic imine (18),

c. Reducing the bicyclic imine (18) by lithium borohydride to afford the protected α -homomannojirimycin (19),

5 d. Removing the protecting groups from the protected α -homomannojirimycin (19) by acid hydrolysis, e.g. with trifluoroacetic acid, to give the desired α -homomannojirimycin (6).

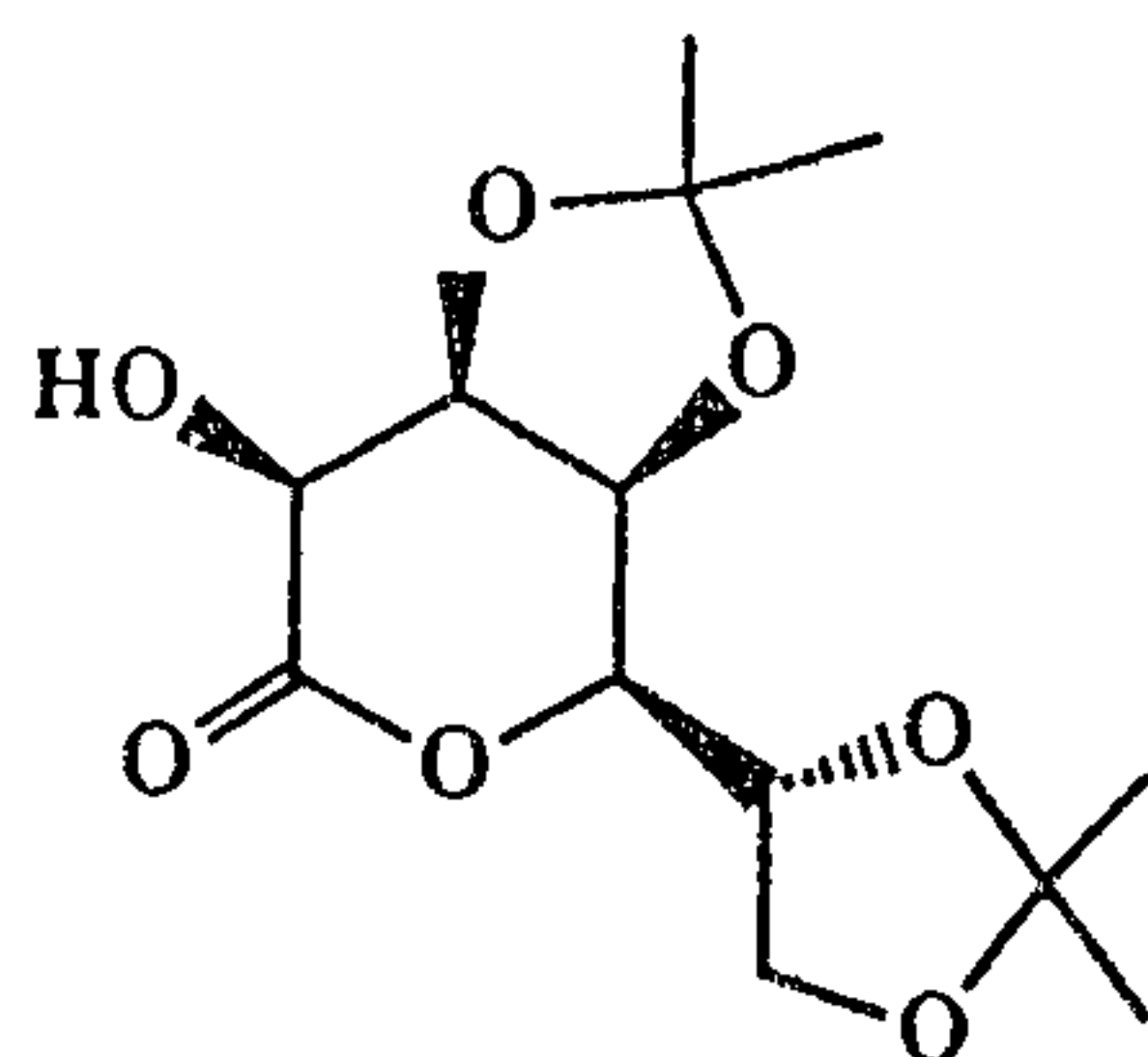
10 Other such suitable reactants for use in the foregoing syntheses of 6-epi-homomannojirimycin and α -homomannojirimycin will be apparent to the person skilled in the art after reading the present disclosure. These reactants are generally used in proportions such as to satisfy the stoichiometry of the above reaction steps.

15 Detailed Description of the Invention

The invention is conveniently illustrated by the following description of preferred embodiments in which the azidolactone, 2-azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone
20 (10), is used to prepare the 6-epi-homomannojirimycin (8) and α -homomannojirimycin (6).

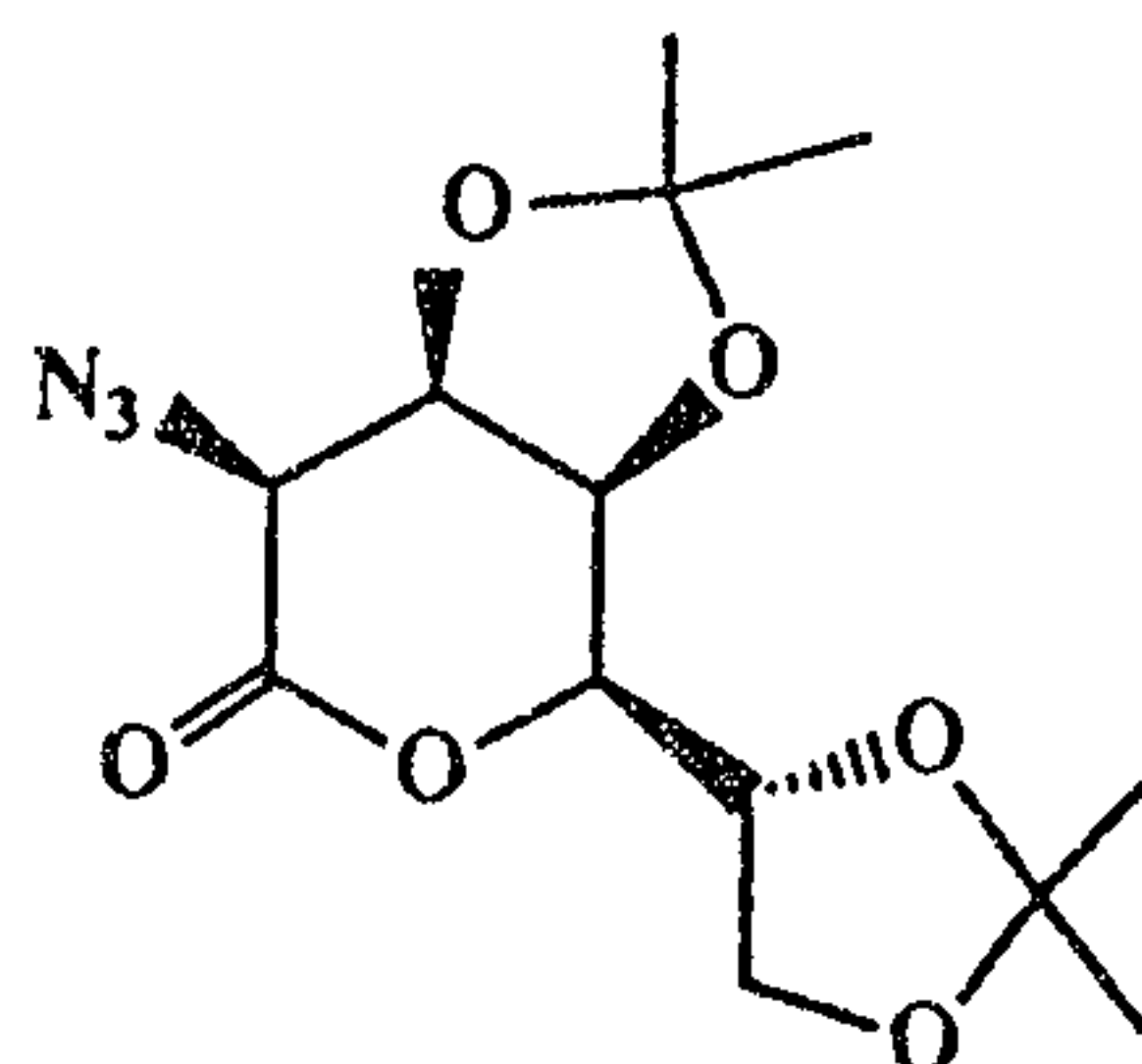
These illustrative embodiments of the invention were carried out by reactions, as follows, in which compound numbers in parenthesis correspond
25 to the compounds shown by structures herein.

A. Synthesis of the divergent intermediate
silyl ether (12).

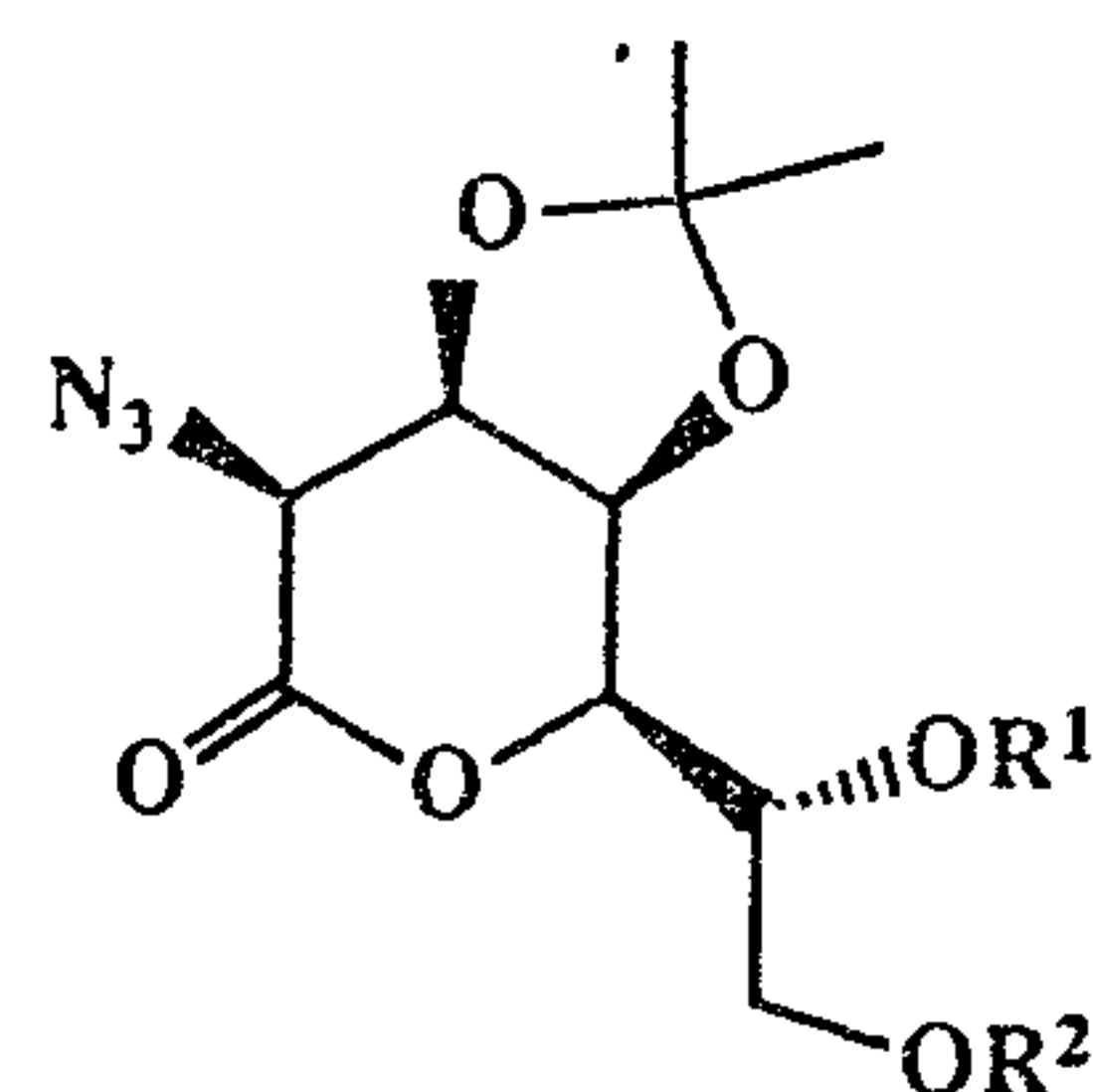


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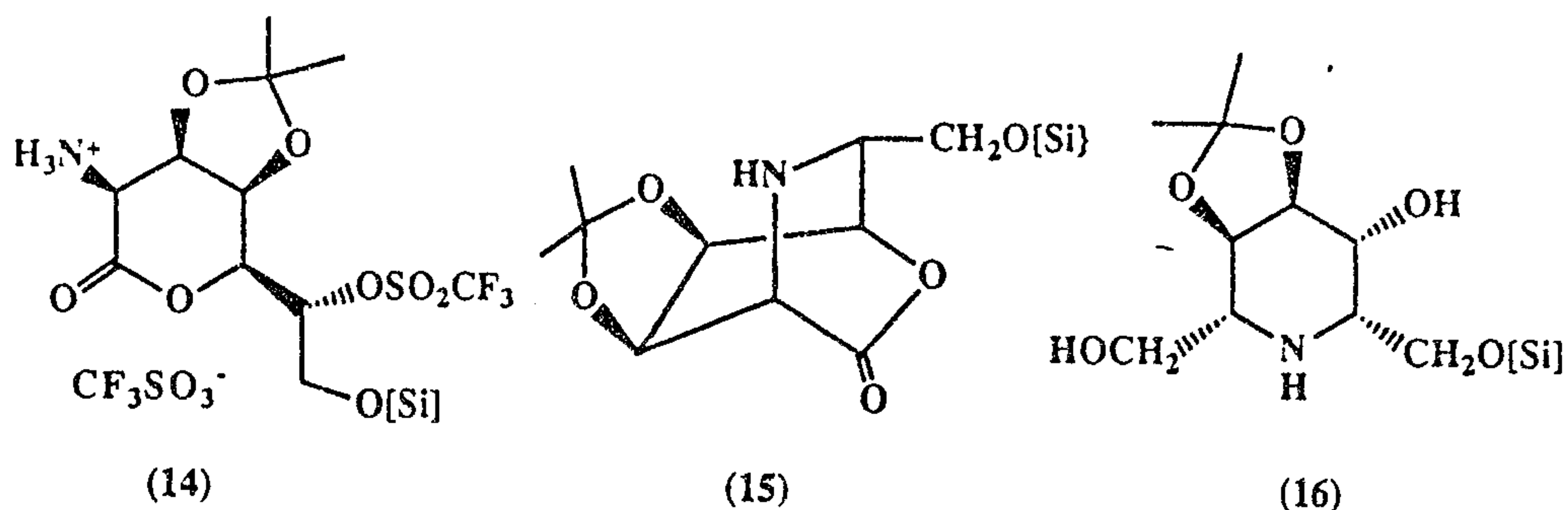
[Si] = Me₂Bu^tSi



(10)

(11)R¹ = R² = H(12)R¹ = H; R² = [Si](13)R¹ = O₂SCF₃; R² = [Si]

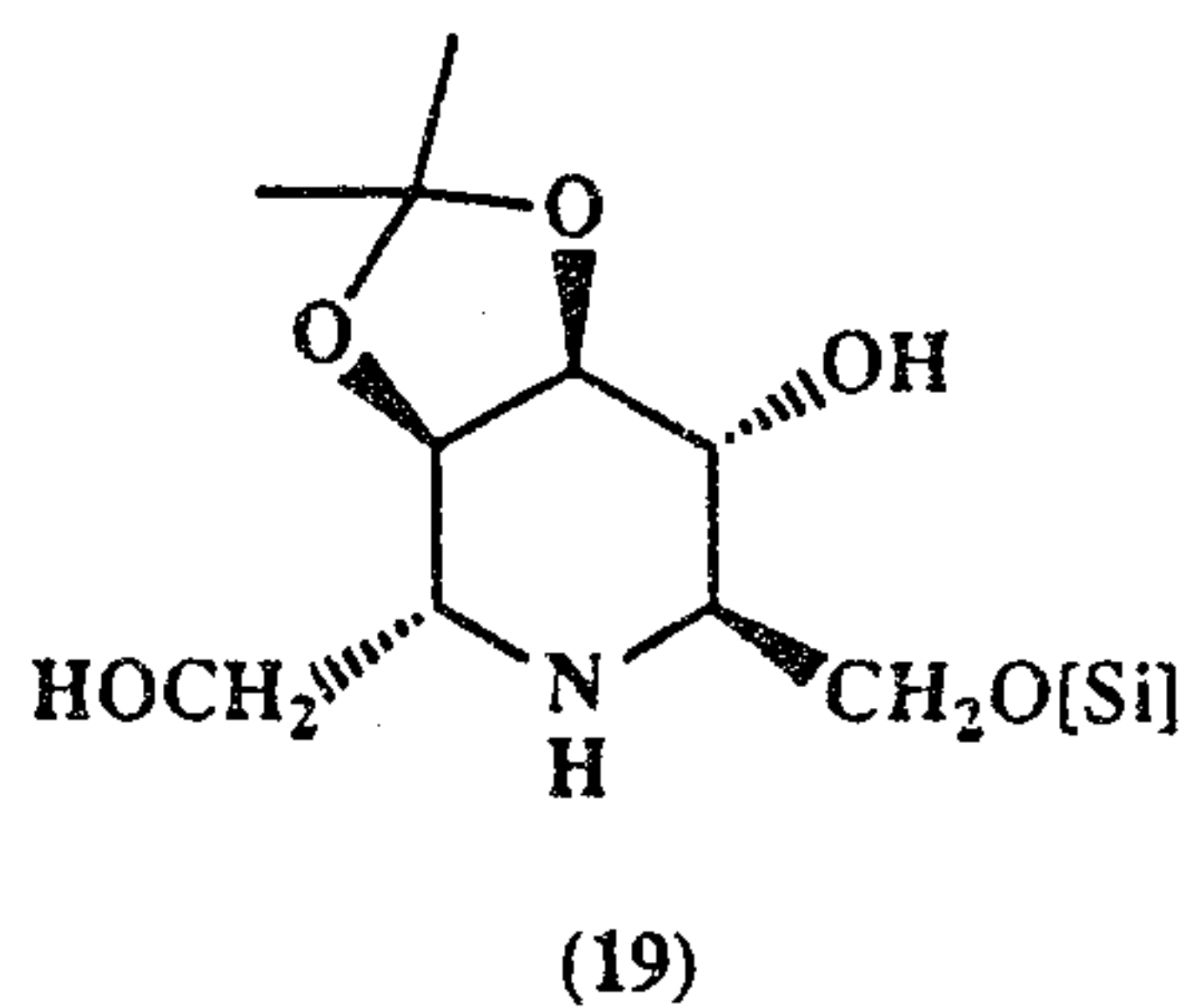
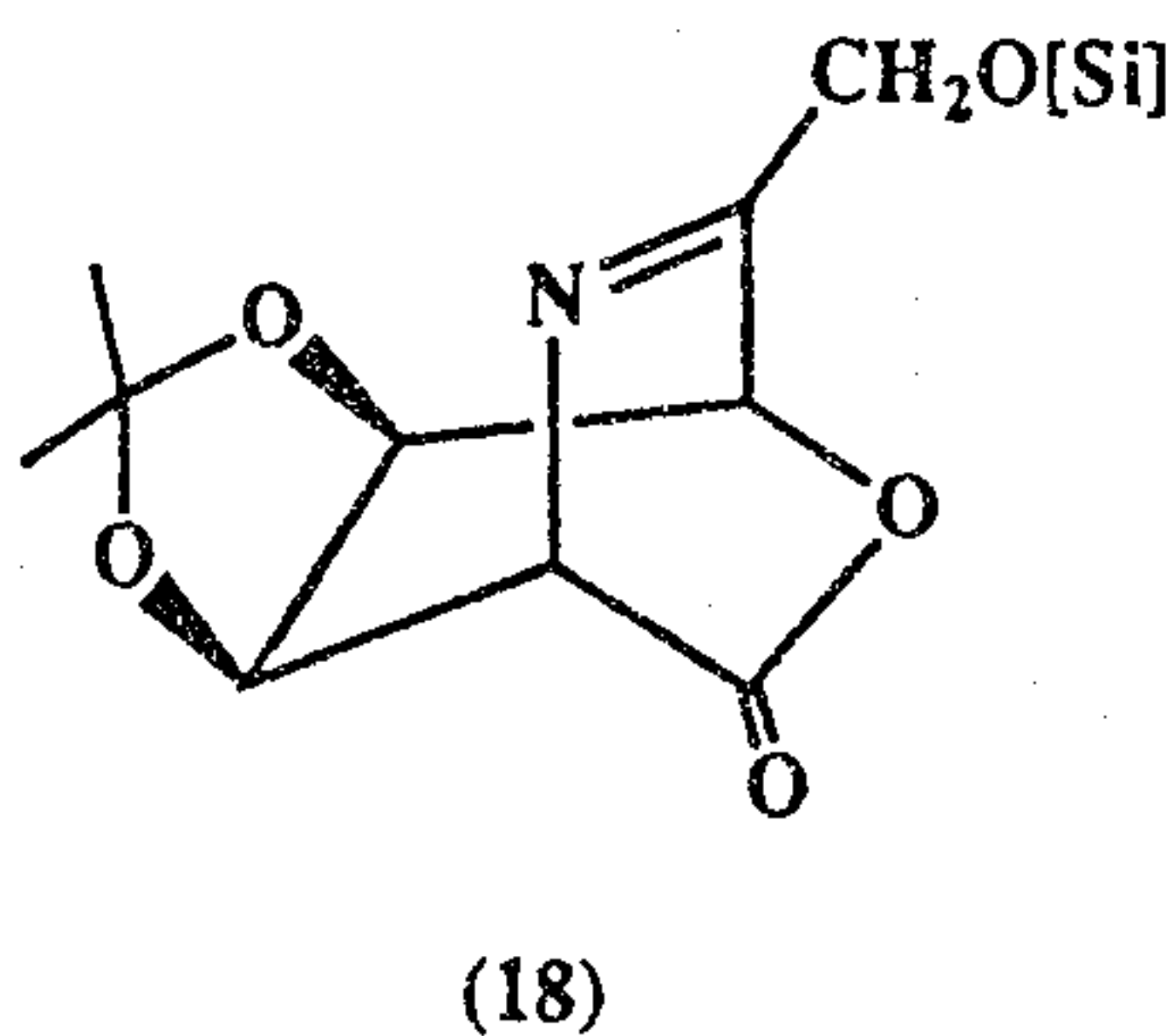
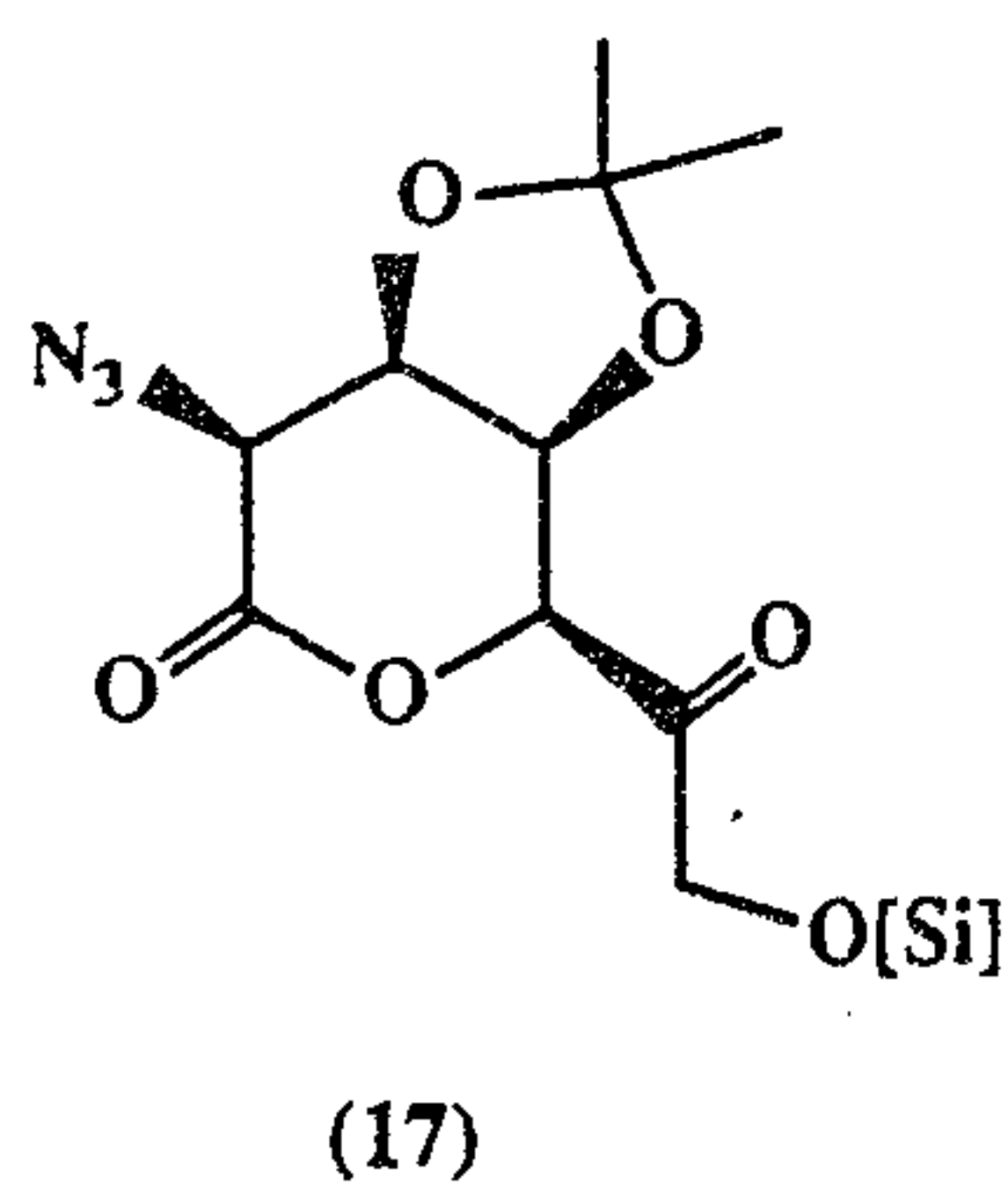
Hydrolysis of the side chain acetonide in (10) by 80% aqueous acetic acid gave the diol (11), m.p. 126°-127°C, (94% yield) which, with tert-butyl-dimethylsilyl chloride in dimethylformamide in the presence of imidazole, afforded the silyl ether (12), m.p. 138°-139°C, $[\alpha]_D^{20} +109.6^\circ$ (c, 0.99 in CHCl₃), (79% yield). The silyl ether (12) is a divergent intermediate for both the synthesis of HMJ (6) and of 6-*epi*-HMJ.

B. Synthesis of 6-epi-homomannojirimycin (8).

For the synthesis of 6-epi-HMJ (8), the piperidine ring is constructed by joining the nitrogen function at C-2 in (12) to C-6, with inversion of configuration at C-6. Treatment of (12) with trifluoromethanesulphonic anhydride in the presence of pyridine in dichloromethane at 20°C gave the triflate (13), m.p. 79°-80°C (95% yield). Hydrogenation of the azidotriflate (13) in ethyl acetate in the presence of 10% palladium on carbon in the presence of sodium acetate resulted in reduction of azide to the corresponding amine followed by easy cyclization to the bicyclic piperidine (15), waxy solid, $[\alpha]_D^{20} -15.4^\circ$ (c, 1.2 in CHCl_3) in 96% yield; when the hydrogenation of (13) was carried out in the absence of sodium acetate, the bicyclic amine (15) was formed in 52% yield, together with the aminotriflate triflate salt (14), m.p. 77°-79°C, $[\alpha]_D^{20} +34.7^\circ$ (C, 0.63 in CHCl_3), in 43% yield. Reduction of the bicyclic lactone (15) with lithium

aluminum hydride in tetrahydrofuran gave the protected iminoheptitol (16), m.p. 112°-114°C, $[\alpha]_D^{20} +52.7^\circ$ (c, 01.0 in CHCl_3), in 54% yield. Removal of the protecting groups from (16) by treatment with aqueous trifluoroacetic acid gave, after purification by ion exchange chromatography, 6-epi-HMJ (8), $[\alpha]_D^{20} +26.4^\circ$ (c, 0.5 in H_2O) as a very hygroscopic solid in 85% yield [42% overall yield from (12)]; the corresponding hydrochloride of (8), m.p. 203°-205°C, $[\alpha]_D^{20} +31.1^\circ$ (c, 1.0 in H_2O), is an easily crystallized solid. ^{13}C NMR of 6-epi-HMJ (8) as free base (D_2O): δ 54.6 and 56.0 (2 x d, C-2 and C-6), 62.1 (two overlapping t, C-1 and C-7), 66.8, 70.1 and 71.7 (3 x d, C-3, C-4 and C-5). ^{13}C NMR of 6-epi-HMJ (8) as hydrochloride (D_2O): δ 56.1 and 56.4 (2 x d, C-2 and C-6), 58.3 and 59.1 (2 x t, C-1 and C-7), 63.5, 67.4 and 69.4 (3 x d, C-4 and C-5).

C. Synthesis of α -homomannojirimycin (6).



The synthesis of HMJ (6) from the silyl ether (12) requires the formation of the piperidine ring with retention of configuration at C-6. Oxidation of the secondary alcohol function in (12) with pyridinium chlorochromate in dichloromethane gave the ketone (17), m.p. 120°-122°C, $[\alpha]_D^{20} +5.4^\circ$ (c, 1.0 in CHCl_3), in 74% yield. Reduction of the ketoazide (17) with triethylphosphite [Takeuchi et al., J. Org. Chem. 54, 431 (1989)] gave an intermediate aza-ylid which underwent an intramolecular aza-Witting reaction [Eguchi and Takeuchi, J. Chem. Soc. Chem. Commun. 1989, 602] to give the bicyclic imine (18), oil, $[\alpha]_D^{20} +98.3^\circ$ (c, 1.0 in CHCl_3) in 89% yield. Reduction of the imine (18) by lithium borohydride in tetrahydrofuran gave predominant reduction from the less hindered face of the carbon-nitrogen double bond [Maruoka et al., J. Am. Chem. Soc. 105, 2835 (1983)] to afford the protected HMJ (19), m.p. 165-166°C, $[\alpha]_D^{20} -28.5^\circ$ (c, 1.0 in CHCl_3) (46% yield), together with a small amount of the C-6 epimer (16) (2% yield). Removal from (19) of all the protecting groups by aqueous trifluoroacetic acid gave HMJ (6) as a very hygroscopic solid $[\alpha]_D^{20} +7.45^\circ$ (c, 0.55 in H_2O), in 92% yield [28% overall yield from (12)]; the hydrochloride of HMJ is also a hygroscopic solid. ^{13}C NMR of HMJ (6) as free base (D_2O): δ 56.2 and 59.0 (2 x d, C-2 and C-6), 59.6 and 61.3 (2 x t, C-1 and C-7), 68.9, 69.4 and 72.2 (3 x d, C-3, C-4 and C-5).

Glycosidase Inhibition Tests.

The iminoheptitols (6) and (8) were assayed as inhibitors of 14 human liver glycosidases and the effects compared with those of deoxymannojirimycin (5) by conventional enzyme assay methods described by Daher et al., Biochem. J. 258, 613 (1989). The results are set forth in the Table, below, in which it can be seen that the specificity and potency of inhibition of human α -mannosidases by HMJ (6) and by DMJ (5) is very similar. Neither compound inhibited β -mannosidase. 6-epi-HMJ (8) did not inhibit any α -mannosidase, indicating that the correct configuration at C-5 is essential for the inhibition of α -mannosidases. In contrast, both DMJ (5) and 6-epi-HMJ (8) were powerful inhibitors of α -fucosidase, whereas HMJ (6) is only a weak inhibitor of this enzyme. The relative potencies of these compounds as fucosidase inhibitors may be understood by considering them as analogues of α -L-fucose; all three compounds have the correct chirality of the secondary hydroxyl groups - the minimum requirement for inhibition of α -fucosidase. However, their relative effectiveness as α -fucosidase inhibitors is determined by the stereochemistry of the substituents at C-2 and C-6; while DMJ (5) and 6-epi-HMJ (8) have only one substituent with the wrong configuration relative to α -L-fucose, both substituents at C-2 and C-6 of HMJ (6) are different from those in α -L-fucose. All the compounds are weaker inhibitors of α -fucosidase than is deoxyfuconojirimycin, since they all lack a lipophilic methyl substituent with correct configuration.

Thus HMJ (6) is a more selective inhibitor of α -mannosidases than DMJ (5). The enhanced specificity of HMJ (6), relative to DMJ and the

possibility of the formations of α -1,2-, α -1,2- and α -1,2-mannosyl derivatives attached to the anomeric hydroxymethyl group should make this a valuable compound for exploring the function and specificity of the processing mannosidases. In summary, the present invention demonstrates the use of the readily available heptonolactone (9) in the synthesis of highly functionalized compounds and further indicates the potential of iminoheptitols as glycosidase inhibitors.

TABLE

% Inhibition of human liver α -fucosidase and α -mannosidase catalysed hydrolysis of 4-umbelliferyl pyrranosides at 1 mM concentration of inhibitor

15	Inhibitor	α -Mannosidases			α -Fucosidase
		Lysosomal	Golgi II	Neutral	
	Deoxymanno-jirimycin (5)	58%	45%	21%	91% [K_i 5.0 μ M]
20	Homomanno-jirimycin (6)	49%	56%	30%	29%
25	6-Epi-homo-manno-jirimycin (8)	0%	0%	0%	96% [K_i 4.5 μ M]

The following examples will further illustrate the invention in greater detail although it will be appreciated that the invention is not limited to these specific examples. Examples 1 to 3 illustrate the preparation of the azidolactone (10); Examples 4 and 5 illustrate the preparation of the divergent intermediate silyl ether (12); Examples 6 to 11 illustrate the preparation of 6-epi-homomannojirimycin (8); and Examples 12 to 15 illustrate the preparation of α -homomannojirimycin (6).

Example 1

3,4:6,7-Di-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone (9) and
15 3,4:6,7-Di-O-isopropylidene-D-glycero-D-galacto-heptano-1,5-lactone. D-Mannose was obtained from Sigma Chemical Company and was converted into 2,3:5,6-di-O-isopropylidene-D-mannofuranose in 80%-90% yield as previously described by Schmidt, Meth. Carbohydr. Chem. 2, 318 (1963). A mixture 2,3:5,6-di-O-isopropylidene-D-mannofuranose (10.8 g, 41.0 mmol), sodium cyanide (1.84 g, 38.0 mmol) and sodium hydrogen carbonate (3 g) in water (200 ml) was stirred at room temperature for 4 days after which
25 time a clear solution was obtained which was free of cyanide. The reaction mixture was then heated at 90°C for 1.5 h, cooled to room temperature and extracted with dichloromethane (2 x 20 ml); the dichloromethane layer was dried (sodium sulphate) and
30 the solvent removed to give unreacted diacetone mannose starting material (1.84 g, 17%). The aqueous layer was adjusted to pH 3 by dropwise addition of concentrated sulphuric acid and then extracted with ethyl acetate (3 x 150 ml). The combined ethyl

acetate extracts were dried (sodium sulphate) and the solvent removed to give a residue which, after purification by flash chromatography [ethyl acetate:hexane, 1:2], gave the following two products:

5

A

3,4:6,7-di-O-isopropylidene-D-glycero-D-galacto-heptono-1,5-lactone, R_f 0.7 (ethyl acetate:hexane, 2:1) and R_f 0.6 (ethyl acetate:hexane, 1:1), (0.78 g, 6.6% yield, 8% based on unrecovered starting material), m.p. 140°-141°C (ether:hexane), $[\alpha]_D^{20} +93.4^\circ$ (c, 1.2 in CHCl_3), $v_{\max}$ (CHCl_3): 3350 (OH), 1755 (C=O) cm^{-1} ; (Found: C, 54.17; H, 7.25. $\text{C}_{13}\text{H}_{20}\text{O}_7$ requires: C, 54.16; H, 7.01%), and

10

B

3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone (9). R_f 0.5 (ethyl acetate:hexane, 2:1) and R_f 0.3 (ethyl acetate:hexane, 1:1), 3.08 g, 26% yield, 31% based on unrecovered starting material), m.p. 157°-159°C (ethyl acetate:hexane), $[\alpha]_D^{20} +63.8^\circ$ (c, 1.3 in CHCl_3), $v_{\max}$ (CHCl_3): 3540 (OH), 1767 (C=O) cm^{-1} ; (Found: C, 54.12; H, 7.09. $\text{C}_{13}\text{H}_{20}\text{O}_7$ requires: C, 54.16; H, 7.01%).

20

Example 2

3,4:6,7-Di-O-isopropylidene-2-O-trifluoromethanesulphonyl-D-glycero-D-talo-heptono-1,5-lactone.

25

Dry pyridine (4 ml, 50 mmol) and trifluoromethanesulphonic anhydride (5.0 g, 18 mmol) were added over 5 min to a stirred solution of the talo-lactone product (9) of Example 1 (3.72 g, 13 mmol) in dichloromethane (75 ml) at -30°C under nitrogen; after a further 5 min, no starting material

30

remained and the reaction was quenched by addition of dilute aqueous hydrochloric acid (60 ml). The organic layer was washed with brine (2 x 60 ml) and dried (sodium sulphate); the solvent was removed to give the stable crude triflate (2), a cream solid, (5.1 g, 93%), which was used directly for the conversion to azide without further purification. A sample of the crude triflate was recrystallized to give
3,4:6,7-di-O-isopropylidene-2-O-trifluoromethane sulphonyl-D glycer-D-talo-heptono-1,5-lactone. m.p. 118°-119°C (dec.) (ether:hexane), $[\alpha]_D^{20} +37.0^\circ$ (c , 1.02 in CHCl_3), v_{max} (CHCl_3): 1793 (C=O) cm^{-1} ; Found: C, 40.05; H, 4.59. $\text{C}_{14}\text{H}_{19}\text{F}_3\text{O}_9\text{S}$ requires: C, 40.00; H, 4.56%).

15

Example 3

2-Azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone (10).

From talotriflate. The crude triflate (5.1 g, 12 mmol), prepared above in Example 2, in dimethyl formamide (25 ml) was stirred with sodium azide (1.0 g, 15 mmol) at room temperature for 4 h. The solvent was then removed and the residue partitioned between dichloromethane (60 ml) and brine (60 ml). The organic layer was dried (sodium sulphate) and the solvent removed to give, after purification by flash chromatography [ethyl acetate:hexane, 1:3], 2-azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone (10). [3.05 g, 81%, 75% from the talo-lactone (9)], as a colorless syrup which crystallized on standing, m.p. 103°-104°C (ether:hexane), $[\alpha]_D^{20} +96.7^\circ$ (c , 1.13 in CHCl_3), v_{max} (CHCl_3): 2125 (N_3), 1773 (C=O) cm^{-1} ; (Found: C, 49.81; H, 6.19; N, 13.70. $\text{C}_{13}\text{H}_{19}\text{N}_3\text{O}_6$ requires: C, 49.84; H, 6.11; N, 13.41%).

Example 4

2-Azido-2-deoxy-3,4-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone (11).
2-Azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-
5 D-talo-heptono-1,5-lactone (10) (815 mg, 2.6 mmol)
was stirred with 80% acetic acid (6 ml) for 3.5 h at
50°C. The solvent was removed and the residue was
purified by flash chromatography [ethyl
acetate:hexane, 4:1] to give 2-azido-2-deoxy-3,4-
10 O-isopropylidene-D-glycero-D-talo-heptono-1,5-
lactone (11), (672 mg, 94%), m.p. 126°-127°C (ethyl
acetate-hexane), $[\alpha]_D^{20} +131.5^\circ$ (c, 1.08 in MeOH).
 $\nu_{\max}$ (nujol): 3470 (OH), 2120 (N₃), 1750 (C=O) cm⁻¹.
(Found: C, 44.02; H, 5.47; N, 15.22. C₁₀H₁₅N₃O₆
15 requires: C, 43.96; H, 5.53; N, 15.38%).

Example 5

2-Azido-7-O-tert-butyldimethylsilyl-2-deoxy-3,4-
O-isopropylidene-D-glycero-D-talo-heptono-1,5-
lactone (12). A solution of tert-butyldimethyl-
20 silyl chloride (0.95 g, 6.3 mmol) in
dimethylformamide (5 ml) was added dropwise, under
nitrogen, to a stirred solution of the diol (11)
(1.15 g, 4.2 mmol) and imidazole (0.57 g, 8.4 mmol)
in dimethylformamide (15 ml) at -10°C. After 15 min
25 at -10°C the reaction was complete and the solvent
was removed. Purification by flash chromatography
[hexane:ethyl acetate, 4:1] gave 2-azido-7-O-tert-
butyldimethylsilyl-2-deoxy-3,4-O-isopropylidene-D-
glycero-D-talo-heptono-1,5-lactone (12). (1.29 g.
30 79%) a white solid, m.p. 138°-139°C (ether), $[\alpha]_D^{20}$

+109.6° (c , 0.99 in CHCl_3). ν_{max} (CHCl_3): 3550 (OH), 2120 (N_3), 1779 ($\text{C}=\text{O}$) cm^{-1} . (Found: C, 49.34; H, 7.77; N, 10.59. $\text{C}_{16}\text{H}_{29}\text{N}_3\text{O}_8\text{Si}$ requires: C, 49.59; H, 7.54; N, 10.84%).

5

Example 6

2-Azido-7-O-tert-butyldimethylsilyl-2-deoxy-3,4-O-isopropylidene-6-O-trifluoromethanesulphonyl-D-glycero-D-talo-heptono-1,5-lactone (13). Dry pyridine (0.8 ml, 10 mmol) and

10 trifluoromethanesulphonic anhydride (1.22 g, 4.3 mmol) were added to a stirred solution of 2-azido-2-deoxy-3,4-O-isopropylidene-7-O-tert-butyldimethylsilyl-D-glycero-D-talo-heptono-1,5-lactone (12) (1.29 g, 3.3 mmol) in dichloromethane (15 ml), under nitrogen,

15 at -20°C. After 30 min at -10°C, tlc [ether:hexane, 1:1] indicated complete consumption of starting material (R_f 0.2) to give a single product (R_f 0.6). The reaction was diluted with dichloromethane (20 ml), washed with dilute aqueous hydrochloric acid

20 (2 x 10 ml), followed by brine (20 ml), and dried (sodium sulphate). The solvent was removed to give the triflate (1.62 g, 95%), a yellow crystalline solid which was used without purification. A small sample was recrystallized to give colorless needles

25 of 2-azido-7-O-tert-butyldimethylsilyl-2-deoxy-3,4-O-isopropylidene-6-O-trifluoromethanesulphonyl-D-glycero-D-talo-heptono-1,5-lactone (13). m.p. 79°-80°C. $[\alpha]_D^{20}$ +41.1° (c , 0.95 in CHCl_3), ν_{max} (CHCl_3): 2125 (N_3), 1780 ($\text{C}=\text{O}$) cm^{-1} . (Found: C, 39.45; H, 5.43; N, 8.26. $\text{C}_{17}\text{H}_{28}\text{F}_3\text{N}_3\text{O}_8\text{SS}_1$ requires: C, 39.30; H, 4.53; N, 8.09%).

30

Example 7

5 2-Amino-7-O-tert-butyldimethylsilyl-2-deoxy-3,4-O-
isopropylidene-6-O-trifluoromethanesulphonyl-D-
glycero-D-talo-heptono-1,5-lactone trifluoromethane-
sulphonate (14). A solution of the triflate (13)
(1.62 g, 3.12 mmol) in ethyl acetate (20 ml) was
stirred vigorously at room temperature, under
hydrogen, in the presence of 10% palladium on carbon
(100 mg). After 24 h no starting material remained
10 by tlc (R_f 0.6, ether:hexane, 1:1). The mixture was
filtered through celite, washing with ethyl acetate
(30 ml), to give a solution containing two products
(R_f , 0.95 and 0.4, ethyl acetate). The solvent was
removed and the residue was purified by flash
15 chromatography (ethyl acetate:hexane, 2:1) to give
two compounds; the first was the bicyclic amine (15)
(550 mg, 52%), identical in all respects to the
material prepared below. The second compound was
identified as the triflate salt, 2-Amino-7-O-tert-
20 butyldimethylsilyl-2-deoxy-3,4-O-
isopropylidene-6-O-trifluoromethanesulphonyl-D-
glycero-D-talo-heptono-1,5-lactone trifluoromethane-
sulphonate (14) (872 mg, 43%), a white solid, m.p.
77°-79°C (ether), $[\alpha]_D^{20} +34.7^\circ$ (c , 1.0 in CHCl_3),
25 ν_{max} (CHCl_3): 3500 br (NH_3^+), 1780 (C=O) cm^{-1} .
(Found: C, 33.46; H, 5.04; N, 2.13.
 $\text{C}_{18}\text{H}_{31}\text{F}_6\text{NO}_{11}\text{S}_2\text{Si}$ requires: C, 33.59; H, 4.85; N,
2.18%).

Example 8

7-O-tert-Butyldimethylsilyl-2,6-dideoxy-2,6-imino-
3,4-O-isopropylidene-L-glycero-D-talo-heptono-1,5-
lactone (15). The azido triflate (13) (605 mg, 1.16
5 mmol) in ethyl acetate (20 ml) was stirred vigorously
at room temperature, under hydrogen, in the presence
of anhydrous sodium acetate (380 mg, 4.6 mmol) and
10% palladium on carbon (50 mg). After 20 h. the
mixture was filtered through celite, washed with
10 ethyl acetate (20 ml), to give a colorless solution
showing one spot on tlc [ethyl acetate, R_f 0.9].
Flash chromatography (hexane:ethyl acetate, 1:1) gave
7-O-tert-butyldimethylsilyl-2,6-dideoxy-2,6-imino-
3,4-O-isopropylidene-L-glycero-D-talo-heptono-1,5-
15 lactone (15) (348 mg, 96%, a colorless syrup which
solidified to a white wax on standing. $[\alpha]_D^{20}$
-15.4° (c 1.2 in $CHCl_3$), ν_{max} (neat): 3360 (NH),
1781 (C=O) cm^{-1} ; (Found: C, 55.17; H, 8.79; N,
4.27. $C_{16}H_{29}NO_5Si$ requires: C, 55.95; H, 8.51; N,
20 4.08%).

Example 9

Cyclization of the triflate salt (14) to the bicyclic amine (15).

5 Method (i). The triflate salt (14) (105 mg, 0.16 mmol) was stirred with anhydrous sodium acetate (54 mg, 0.65 mmol) in dimethyl formamide (4 ml) at room temperature for 20 h. The solvent was removed and the residue was purified by flash chromatography (hexane: ethyl acetate, 2:1) to give the bicyclic
10 amine (15) (47 mg, 86%), identical in all respects to the material prepared above.

15 Method (ii). The triflate salt (14) (75 mg, 0.12 mmol) was stirred with anhydrous sodium carbonate (25 mg, 0.24 mmol) in dry tetrahydrofuran (3 ml). After 24 h at room temperature the reaction was worked up and purified as above to give the bicyclic amine (15) (30 mg, 79%).

Example 10

20 7-O-tert-Butyldimethylsilyl-2,6-dideoxy-2,6-imino-3,4-O-isopropylidene-L-glycero-D-talo-heptitol (16),

25 Method (i). Lithium aluminum hydride (50 mg, 1 mmol) was added to a stirred solution of the bicyclic amine (15) (167 mg, 0.48 mmol) in dry THF (3 ml) at 0°C. After 2 h at 0°C tlc (hexane:ethyl acetate, 2:1)
30 indicated complete consumption of starting material (R_f 0.6) to give a product at R_f 0.1 together with baseline material. The reaction was quenched with water (0.5 ml), diluted with ethyl acetate (10 ml) and filtered through *celite. The solvent was removed and the residue was purified by flash chromatography

*Trade-mark

(hexane:ethyl acetate, 3:2) to give 7-O-tert-butyl dimethylsilyl-2,6-dideoxy-2,6-imino-3,4-O-isopropylidene-L-glycero-D-talo-heptitol (16) (90 mg, 54%), m.p. 112°-114°C (ether-hexane), $[\alpha]_D^{20} +52.7^\circ$ (c , 1.0 in CHCl_3 , ν_{max} (CHCl_3): 3450 (NH cm^{-1}). (Found: C, 55.46; H, 9.51; N, 4.03. $\text{C}_{16}\text{H}_{35}\text{NO}_5\text{Si}$ requires: C, 55.30; H, 9.57; N, 4.03%).

Method (ii). Lithium borohydride (2 M in THF, 0.55 ml, 1.1 mmol) was added to a stirred solution of the bicyclic amine (15) (379 mg, 1.1 mmol) in THF (10 ml), under nitrogen, at -20°C. The solution was allowed to warm to room temperature and stirred for 2 h, after which time tlc (hexane:ethyl acetate, 1:1) indicated only a trace of starting material (R_f 0.7) and two products at R_f 0.6 and 0.1. The reaction was quenched with anhydrous ammonium chloride, filtered, and the solvent removed to give a solid (383 mg). Flash chromatography (hexane:ether, 2:1) gave two products; the first was the borane adduct (153 mg, 39%), m.p. 110°C (dec., ether-hexane), $[\alpha]_D^{20} +9.8^\circ$ (c 1.0 in CHCl_3), ν_{max} (CHCl_3): 3450, 3230 (NH and OH), 2380 (BH_3) cm^{-1} . (Found: C, 53.81; H, 10.34; N, 3.60. $\text{BC}_{16}\text{H}_{32}\text{NO}_5\text{Si}$ requires: C, 53.18; H, 10.04; N, 3.88%). The second product was identified as 7-O-tert-butyl dimethylsilyl-2,6-dideoxy-2,6-imino-3,4-O-isopropylidene-L-glycero-D-talo-heptitol (16) (74 mg, 18%), identical in all respects to the material prepared above.

Example 11

2,6-Dideoxy-2,6-imino-L-glycero-D-talo-heptitol
hydrochloride. 7-O-tert-Butyldimethylsilyl-2,6-
dideoxy-2,6-imino-3,4-O-isopropylidene-L-glycero-
5 D-talo-heptitol (16) (137 mg, 0.40 mmol) was stirred
in 50% aqueous trifluoroacetic acid (4 ml) for 20 h
at room temperature. The solvent was removed and the
crude trifluoroacetate salt was decomposed with
dilute aqueous sodium hydroxide. Purification by ion
10 exchange chromatography (*Dowex 50 x, 8-100, H⁺ form,
eluting with 0.5 M aqueous ammonia), followed by
freeze drying, gave 2,6-dideoxy-2,6-imino-L-
glycero-D-talo-heptitol (8), (66 mg, 85%), a very
hygroscopic solid, (R_f 0.8, EtOH : MeOH : 0.5 M NH₃
15 2:2:1), $[\alpha]_D^{20} +26.4^\circ$ (c , 0.5 in H₂O). Repeating
this procedure with the borane adduct (8) (125 mg,
0.35 mmol) gave an identical material to that above
(55 mg, 82%). The free base (16) (100 mg, 0.52 mmol)
was dissolved in methanol (3 ml) and acetyl chloride
20 (ca. 0.1 ml, 1 mmol) was added. Addition of
chloroform and cooling yielded crystals of
2,6-dideoxy-2,6-imino-L-glycero-D-talo-heptitol
hydrochloride, (91 mg, 76%), m.p. 203°-205°C
(methanol:chloroform), $[\alpha]_D^{20} +31.1^\circ$ (c , 1.0 in H₂O),
25 ν_{max} (KBr): 3500-2500 (NH, OH) cm⁻¹. Found: C,
36.61; H, 7.32; N, 5.88. C₇H₁₆NO₅Cl requires: C,
36.61; H, 7.02; N, 6.10%.

*Trade-mark

Example 12

2-Azido-7-O-tert-butyldimethylsilyl-2-deoxy-3,4-O-isopropylidene-D-talo-6-heptulosono-1,5-lactone (17). The alcohol (12) (2.07 g, 5.35 mmol) and pyridinium chlorochromate (3.45 g, 16 mmol) were stirred with powdered molecular sieve (2 g) in dichloromethane (50 ml), under nitrogen, at room temperature. After 18 h, tlc (hexane:ethyl acetate, 1:1) indicated complete consumption of starting material (R_f 0.35) to give a single product (R_f 0.5). The mixture was diluted with ether (50 ml), filtered through a celite plug and the solvent removed. Flash chromatography (hexane:ethyl acetate, 5:1) gave 2-Azido-7-O-tert-butyldimethylsilyl-2-deoxy-3,4-O-isopropylidene-D-talo-6-heptulosono-1,5-lactone (17), (1.53 g, 74%), m.p. 120°-122° (ether), $[\alpha]_D^{20} +5.4^\circ$ (c , 1.0 in $CHCl_3$), ν_{max} ($CHCl_3$): 2123 (N_3), 1780 (C=O), 1743 (C=O) cm^{-1} . (Found: C, 49.96; H, 7.32; N, 10.60. $C_{16}H_{27}N_3O_6Si$ requires: C, 49.85; H, 7.06; N, 10.90%).

Example 13Imine (18)

Triethyl phosphite (1.3 M in THF, 2.4 ml, 3.1 mmol) was added, under nitrogen, to a stirred solution of the ketone (17) (605 mg, 1.57 mmol) in dry THF (5 ml). After 18 h at room temperature, tlc (hexane:ethyl acetate, 5:1) indicated complete consumption of starting material (R_f 0.6) to give a single product (R_f 0.7). The solvent was removed and the residue was purified by flash chromatography (hexane:ethyl acetate, 5:1) to give the bicyclic imine (18), (477 mg, 89%), a colorless oil, $[\alpha]_D^{20} +98.3^\circ$ (c , 1.0 in $CHCl_3$), ν_{max} (film): 1780 (C=O),

1650 (C=N) cm^{-1} . (Found: C, 56.39; H, 8.02; N, 4.05. $\text{C}_{16}\text{H}_{27}\text{NO}_5\text{Si}$ requires: C, 56.28; H, 7.97; N, 4.10%).

Example 14

5 7-O-tert-Butyldimethylsilyl-2,6-dideoxy-2,6-imino-
 3,4-O-isopropylidene-D-glycero-D-talo-heptitol (19).
 Lithium borohydride (2 M in THF, 0.6 ml, 1.2 mmol) was
 added, under nitrogen, to a stirred solution of the
10 imine (18) (182 mg, 0.53 mmol) in dry THF (10 ml) at
 -78°C . The solution was allowed to warm to room
 temperature over a period of 1 h and stirred for an
 additional 4 h before quenching with saturated
 aqueous ammonium chloride (0.3 ml). The solution was
15 evaporated to dryness and the residue was purified by
 flash chromatography (gradient elution; hexane:ethyl
 acetate, 1:1 0:1) to give two products; the first
 (R_f 0.3, ethyl acetate) was 7-O-tert-butyldimethyl-
 silyl-2,6-dideoxy-2,6-imino-3,4-O-isopropylidene-D-
 glycero-L-talo-heptitol (16) (3 mg 2%), identical in
20 all respects to the material prepared above. The
 second compound was identified as 7-O-tert-butyldi-
 methyilsilyl-2,6-dideoxy-2,6-imino-3,4-O-isopropyl-
 idene-D-glycero-D-talo-heptitol (19), (85 mg, 46%),
 m.p. $165^\circ\text{--}166^\circ\text{C}$ (ethyl acetate:ether), $[\alpha]_D^{20}$
25 -28.5° (c , 1.0 in CHCl_3), ν_{max} (CHCl_3): 3450 (OH)
 cm^{-1} . Found: C, 55.56; H, 10.01; N, 3.99.
 $\text{C}_{16}\text{H}_{35}\text{NO}_5\text{Si}$ requires: C, 55.30; H, 9.57; N, 4.03%).

Example 15

2,6-Dideoxy-2,6-imino-D-glycero-D-talo-heptitol (6).

The protected iminoheptitol (19) (196 mg, 0.56 mmol) in 50% aqueous trifluoroacetic acid (4 ml) was stirred at room temperature for 20 h. After removing the solvent, the resulting trifluoroacetate salt was decomposed to the free base with dilute aqueous sodium hydroxide. Purification by ion exchange chromatography (Dowex 50 x, 8-100, H⁺ form, eluting with 0.5 M aqueous ammonia solution and then Amberlite CG-400, OH⁻ form, eluting with water) gave, after freeze drying, 2,6-dideoxy-2,6-imino-D-glycero-D-talo-heptitol (6) (99 mg, 92%), a very hygroscopic solid, $[\alpha]_D^{20} +7.45^\circ$ (c, 0.55 in H₂O).

Various other examples will be apparent to the person skilled in the art after reading the present disclosure without departing from the spirit and scope of the invention. It is intended that all such other examples be included within the scope of the appended claims.

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A method for the synthesis of 6-epi-homomannojirimycin comprising:

a. reacting 2-azido-7-O-tert-butyl-dimethylsilyl-2-deoxy-3,4-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone with trifluoromethanesulfonic anhydride to give an azidotriflate 2-azido-7-O-tert-butyl-dimethylsilyl-2-deoxy-3,4-O-isopropylidene-6-O-trifluoromethanesulphonyl-D-glycero-D-talo-heptono-1,5-lactone,

b. subjecting the azidotriflate to palladium catalyzed reductive hydrogenation to form a bicyclic lactone 7-O-tert-butyl-dimethylsilyl-2,6-dideoxy-2,6-imino-3,4-O-isopropylidene-L-glycero-D-talo-heptono-1,5-lactone,

c. reducing the bicyclic lactone with lithium aluminum hydride to give a protected iminoheptitol 7-O-tert-butyl-dimethylsilyl-2,6-dideoxy-2,6-imino-3,4-O-isopropylidene-L-glycero-D-talo-heptitol, and

d. removing the protecting groups from the iminoheptitol by acid hydrolysis to give 6-epi-homomannojirimycin.

2. A method for the synthesis of α -homomannojirimycin comprising

a. oxidizing the secondary alcohol function in 2-azido-7-O-tert-butyl-dimethylsilyl-2-deoxy-3,4-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone to give a corresponding ketoazide 2-azido-7-O-tert-butyl-dimethylsilyl-2-deoxy-3,4-O-isopropylidene-D-talo-6-heptulosono-1,5-lactone,

b. reducing the ketoazide with triethylphosphite to give a 2,6-bicyclic imine,

c. reducing said 2,6-bicyclic imine by lithium borohydride to afford a protected α -homomannojirimycin 7-O-tert-butyl-dimethylsilyl-2,6-dideoxy-2,6-imino-3,4-O-isopropylidene-D-glycero-D-talo-heptitol, and

d. removing the protecting groups from the protected α -homomannojirimycin by acid hydrolysis to give the α -homomannojirimycin.

3. The method of claim 1 including the additional steps in which the 2-azido-7-O-tert-butyldimethylsilyl-2-deoxy-3,4-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone is synthesized by

a) removing the side chain acetonide of 2-azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone by acid hydrolysis to give a corresponding diol 2-azido-2-deoxy-3,4-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone, and

b) reacting the diol with a silyl protecting agent to give 2-azido-7-O-tert-butyldimethylsilyl-2-deoxy-3,4-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone.

4. The method of claim 2 including the additional steps in which the 2-azido-7-O-tert-butyldimethylsilyl-2-deoxy-3,4-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone is synthesized by

a) removing the side chain acetonide of 2-azido-2-deoxy-3,4:6,7-di-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone by acid hydrolysis to give a corresponding diol 2-azido-2-deoxy-3,4-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone, and

b) reacting the diol with a silyl protecting agent to give a 2-azido-7-O-tert-butyldimethylsilyl-2-deoxy-3,4-O-isopropylene-D-glycero-D-talo-heptono-1,5-lactone.

5. α -homomannojirimycin.

6. 6-epi-homomannojirimycin.

7. 2-azido-7-O-tert-butyldimethylsilyl-2-deoxy-3,4-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone.

8. 7-O-tert-butyldimethylsilyl-2,6-dideoxy-2,6-imino-3,4-O-isopropylidene-L-glycero-D-talo-heptono-1,5-lactone.

9. 2-azido-7-O-tert-butyldimethylsilyl-2-deoxy-3,4-O-isopropylidene-D-talo-6-heptulosono-1,5-lactone.

10. 7-O-tert-butyldimethylsilyl-2,6-dideoxy-2,6-imino-3,4-O-isopropylidene-D-glycero-D-talo-heptitol.

11. A compound selected from the group consisting of: α -homomannojirimycin; 6-epi-homomannojirimycin; 2-azido-7-O-tert-butyldimethylsilyl-2-deoxy-3,4-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone; 7-O-tert-butyldimethylsilyl-2,6-dideoxy-2,6-imino-3,4-O-isopropylidene-L-glycero-D-talo-heptono-1,5-lactone; 2-azido-7-O-tert-butyldimethylsilyl-2-deoxy-3,4-O-isopropylidene-D-talo-6-heptulosono-1,5-lactone; and 7-O-tert-butyldimethylsilyl-2,6-dideoxy-2,6-imino-3,4-O-isopropylidene-D-glycero-D-talo-heptitol.