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Iminoheptitols as Glycosidase Inhibitors: Synthesis of α-Homomannojirimycin, 6-*epi*-α-Homomannojirimycin and of a Highly Substituted Pipecolic Acid

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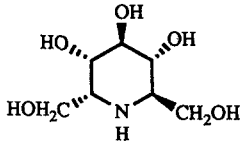
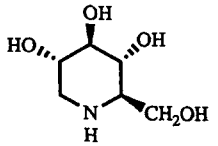
Abstract: In a search for a mannopyranose analogue which inhibits α-mannosidases but not α-fucosidases, α-homonojirimycin was prepared; the syntheses of 6-*epi*-α-homonojirimycin and of 2,6-dideoxy-2,6-imino-L-*glycero*-D-*talo*-heptonic acid (a highly substituted pipecolic acid) are also reported.

The analogues of pyranoses in which the ring oxygen is replaced by nitrogen and the anomeric hydroxyl group is removed are almost[1] always[2] inhibitors of the corresponding glycosidases. α-Homonojirimycin (HNJ) (1), the homologue of deoxynojirimycin (DNJ) (2), was isolated from *Omphalea diandra* and shown to be an inhibitor of several α-glucosidases;[3] HNJ has, like other amino sugar glycosidase inhibitors, been shown to accumulate in moths feeding on such plants.[4] Before the natural product (1) was isolated, the β-glucopyranosyl derivative (3) had been designed as a potential chemotherapeutic agent for controlling blood glucose levels;[5] the glucoside (3) has also been shown to inhibit preferentially an α- glucosidase II of glycoprotein processing[6] and to exhibit time-dependent inhibition of porcine kidney trehalase.[7] The introduction of an hydroxymethyl group at the anomeric position of piperidine derivatives such as DNJ (2) provides an opportunity for altering and, hopefully, increasing the specificity of inhibition of individual glycosidases. Deoxymannojirimycin (DMJ) (4) is a potent inhibitor of glycoprotein processing α-mannosidase I[8] but is in general a much better inhibitor of α-fucosidases[9] than of α-mannosidases. A series of derivatives of DMJ, such as the methyl derivative (5), in which a β-carbon substituent is introduced at the anomeric position, lose all ability to inhibit α-mannosidases but are powerful α-fucosidase inhibitors;[10] usually, any mono- or bi-cyclic nitrogen heterocycle, in which the secondary hydroxyl groups of a piperidine ring have the same absolute configuration as those of DMJ, will be a strong inhibitor of most α-fucosidases.[11] It was considered that α-homomannojirimycin (HMJ) (6) should be a promising candidate for a mannopyranoside analogue which might inhibit α-mannosidases but not inhibit α-fucosidases; the α-hydroxymethyl substituent might mimic an α- mannopyranoside link, but the polar hydroxyl group of this substituent would be thrust into the part of the fucosidase active site which usually accommodates the methyl group of the fucopyranoside.



(1)



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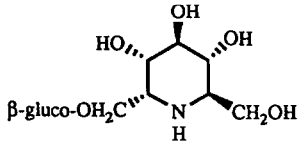

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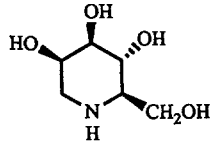
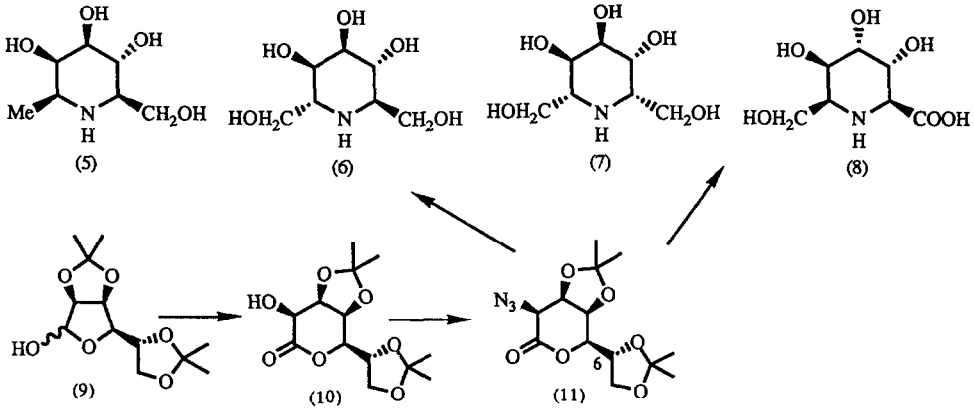


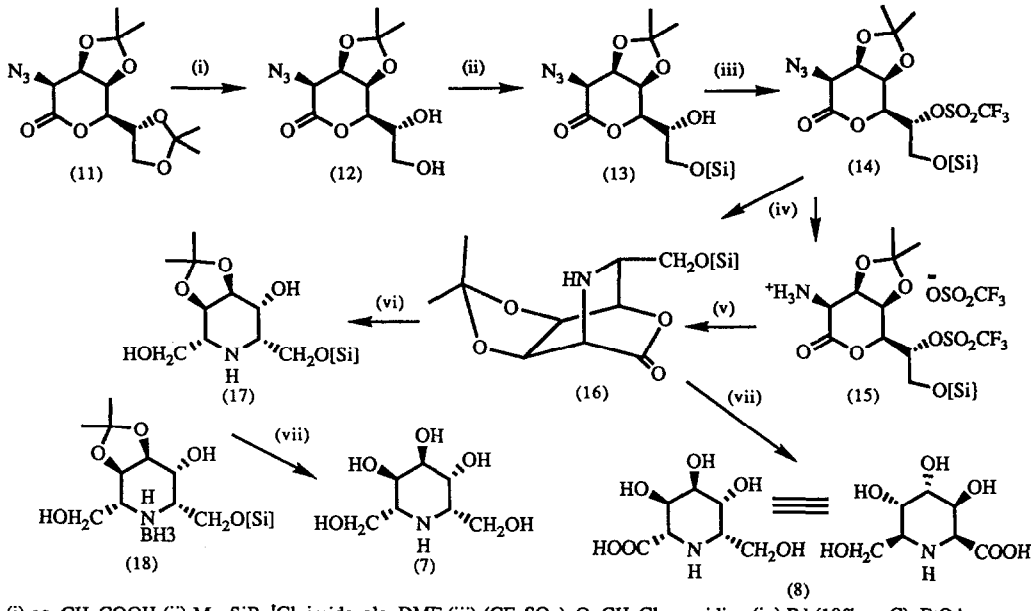
(4)

The synthesis of iminoheptitols, such as (3)[12] and (5),[13] has usually been accomplished by the addition of a one carbon unit at a relatively late stage; however, HNJ (1) has been prepared from an allylic alcohol[14] and HMJ (6) by a route in which the key step involves an aldolase.[15] This paper describes the syntheses of HMJ (6), 6-*epi*-HMJ (7) and the highly substituted pipecolic acid (8) from the readily available seven carbon azidolactone (11); some of this work has been published in a preliminary form.[16]



The azidolactone (11) is easily prepared from diacetone mannose (9) by a cyanide chain extension to give (10),[17] followed by conversion of the remaining free hydroxyl group into the corresponding azide.[18] The value of the azide (11) in the synthesis of highly functionalised pyrrolidines has been demonstrated in the preceding paper.[19] For the preparation of the synthetic targets in this paper, the nitrogen function at C-2 must be joined to C-6 with either inversion of configuration [for (7) and (8)] or retention of configuration [for HMJ (6)].

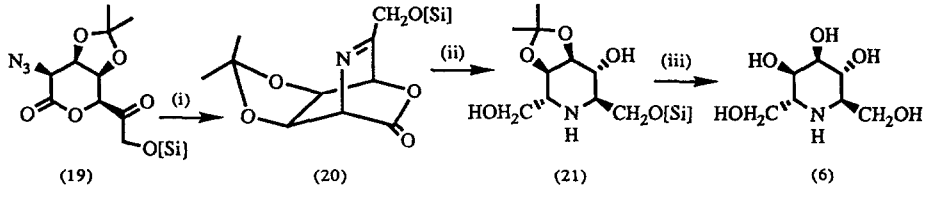
Treatment of the diacetonide (11) with aqueous acetic acid (Scheme 1) resulted in removal of the side chain acetonide to give the diol (12) [94% yield] which, with *tert*-butyldimethylsilyl chloride in dimethyl formamide in the presence of imidazole, afforded the silyl ether (13) [79% yield]. Esterification of the remianing hydroxyl group in (13) with trifluoromethanesulphonic anhydride in dichloromethane in the presence of pyridine gave the stable triflate (14) [95% yield]. When the azide (14) was hydrogenated in ethyl acetate in the presence of 10% palladium on carbon, both the bicyclic amine (16) [52% yield] and the aminotriflate triflate salt (15) [43% yield] were formed; surprisingly, the triflate salt (15) was purified by flash chromatography using ethyl acetate:hexane (2:1) and was only slightly less polar than the bicyclic amine (16). Treatment of the aminotriflate salt (15) with either anhydrous sodium acetate in dimethyl formamide or anhydrous sodium carbonate in tetrahydrofuran induced cyclisation of the amine to (16) in approximately 80% yields; (16) was obtained in 96% yield by hydrogenation of the azidotriflate (14) in ethyl acetate in the presence of 10% palladium on carbon and a four-fold excess of anhydrous sodium acetate. Removal of all the protecting groups from (16) by aqueous trifluoroacetic acid gave, after purification by ion exchange chromatography, the tetrahydroxy pipecolic acid (8); this provides a further example of the value of sugar azido-lactones in the synthesis of highly substituted cyclic α-amino acids.[20] Reduction of the bicyclic lactone (16) with lithium aluminum hydride in tetrahydrofuran gave the protected secondary amine (17) [54% yield]; reduction of (16) with lithium borohydride in tetrahydrofuran gave both (17) and the corresponding borane (18) in a combined yield of 58%. Treatment of (17) and (18) with aqueous trifluoroacetic acid gave 6-*epi*-HMJ (7) [85%], most conveniently handled as the crystalline hydrochloride.



(i) aq. CH_3COOH (ii) Me_2SiBu^tCl, imidazole, DMF (iii) $(CF_3SO_2)_2O$, CH_2Cl_2, pyridine (iv) Pd (10% on C), EtOAc (v) NaOAc (vi) $LiAlH_4$ or $LiBH_4$ in THF (vii) aq. CF_3COOH

Scheme 1

The synthesis of α-homomannojirimycin (6) (Scheme 2) requires a nitrogen bond to be made to C-6 with overall retention of configuration. Thus oxidation of the secondary hydroxyl function in (13) by pyridinium chlorochromate gave the ketone (19) [74% yield]. Reduction of the azide in (19) with triethylphosphite gave an intermediate iminophosphorane which spontaneously underwent an intramolecular aza-Wittig reaction[21] to give the stable but moisture-sensitive bicyclic imine (20) [89% yield]. Treatment of the imine (20) with lithium borohydride in tetrahydrofuran caused reduction both of the imine and lactone functionalities to give as the major product (21) [46% yield], together with a small amount of the epimer (17) [2% yield]. This result may imply that the imine functionality is predominantly reduced in the bicyclic form from the least hindered side, before the lactone ring is opened. Removal of the silyl and isopropylidene protecting groups gave the required HMJ (6) in 92% yield.



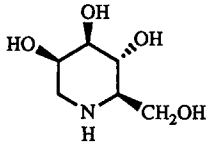
(i) $(EtO)_3P$, THF, 18 h, room temp (ii) $LiBH_4$, THF -78°C (iii) aq. CF_3COOH

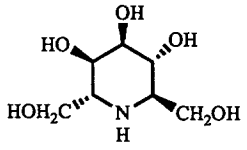
Scheme 2

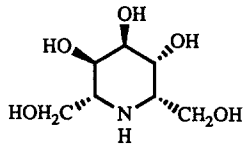
Glycosidase Inhibition

The objective of this work was to find a piperidine analogue of mannose which would inhibit α-mannosidases but not α-fucosidases and the compounds were assayed[22] as inhibitors of 13 human liver glycosidases [Table]. 6-*epi*-HMJ (7), with the wrong configuration for the side chain hydroxymethyl group of mannose, shows no inhibition of any of the α-mannosidases but, like DMJ (4) is a powerful inhibitor of α-fucosidase. In marked contrast, HMJ (6) is a very much weaker inhibitor of fucosidase than either (4) or (7) in spite of having the minimum structural requirement of the correct absolute stereochemistry of the three hydroxyl groups on the piperidine ring.[11]

Table % Inhibition of human liver α-fucosidase and α-mannosidases







Inhibitor (1 mM)	DMJ (4)	HMJ (6)	6-*epi*-HMJ (7)
lysosomal α-mannosidase	58%	49%	0%
Golgi α-mannosidase	45%	56%	0%
neutral α-mannosidase	21%	33%	0%
liver α-fucosidase	92%	29%	93%
	[Ki 5.0 μM]		[Ki 4.5 μM]

The specificity and potency of DMJ (4) and HMJ (6) as inhibitors of α-mannosidases are similar, although HMJ (6) is more selective in not showing any significant inhibition of any other glycosidase. The possibility of further functionalising the anomeric hydroxymethyl group of HMJ makes this an attractive candidate for the design of compounds to explore the function and specificity of processing α-mannosidases. The preceding paper compares the inhibition of α-mannosidases by (4) and (6).[19]

Experimental Melting points were recorded on a Kofler hot block and are corrected. Proton nuclear magnetic resonance (δ_H) spectra were recorded on Varian Gemini 200 (at 200 MHz) or Bruker WH 300 (300 MHz) or Bruker AM 500 (500 MHz) spectrometers. ^{13}C Nuclear magnetic resonance (δ_C) spectra were recorded on a Varian Gemini 200 (50 MHz) spectrometer and multiplicities were assigned using DEPT sequence. All chemical shifts are quoted on the δ-scale using residual solvent as an internal standard. Deuteriochloroform was used as solvent unless otherwise stated. For samples in D_2O, methanol (δ_C 49.5) was added as a reference. Infra-red spectra were recorded on a Perkin-Elmer 781, or on a Perkin-Elmer 1750 IR Fourier Transform spectrophotometer. Mass spectra were recorded on VG, ZAB 1F, or Trio-1 GCMS (DB-5 column) spectrometers using desorption chemical ionisation (NH_3,DCI), chemical ionisation (NH_3,CI) or fast atom bombardment. Optical rotations were measured on a Perkin-Elmer 241 polarimeter with a path length of 1 dm. Concentrations are given in g/100 ml. Microanalyses were performed by the microanalysis service of the Dyson-

Perrins laboratory. Thin layer chromatography was carried out on aluminium sheets coated with $60F_{254}$ silica or glass plates coated with silica Blend 41. Plates were developed using a spray of 0.2% w/v cerium (IV) sulphate and 5% ammonium molybdate in 2M sulphuric acid. Flash chromatography was carried out using Sorbsil C60 40/60 silica. Solvents and commercially available reagents were dried and purified before use according to standard procedures; dichloromethane was refluxed over, and distilled from, calcium hydride; methanol was distilled from magnesium methoxide; pyridine was distilled from, and stored over, potassium hydroxide; tetrahydrofuran was distilled, under nitrogen, from a solution dried in the presence of benzophenone. *N,N*-Dimethylformamide was distilled under reduced pressure from calcium hydride. Hexane was distilled at 68 °C before use to remove involatile fractions. All solvents were removed *in vacuo*. The azidolactone (11) was prepared as previously described.[17,18] The techniques for the determination of the inhibition of human liver glycosidases have been described elsewhere.[22]

2-Azido-2-deoxy-3,4-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone (12). 2-Azido-2-deoxy-3,4:6,7-di-*O*-isopropylidene-D-*glycero*-D-*talo*-heptono-1,5-lactone (11) (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-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone (12)*, (672 mg, 94%), m.p. 126-127°C (ethyl acetate - hexane), $[\alpha]_D^{20}$ +131.5° (*c*, 1.08 in MeOH). ν_{max} (nujol): 3470 (OH), 2120 (N_3), 1750 (C=O) cm^{-1}; δ_H ($CDCl_3$): 1.41 (3H, s, Me), 1.48 (3H, s, Me), 1.95 (1H, t, OH-7, J 5.4 Hz), 2.61 (1H, d, OH-6, J 6.3 Hz), 3.88 (3H, m), 4.07 (1H, m, H-6), 4.20 (1H. dd. H-5, $J_{4,5}$ 1.4 Hz, $J_{5,6}$ 8.6 Hz), 4.81 (1H, dd, H-4, $J_{3,4}$ 7.8 Hz), 4.88 (1H, dd, H-3, $J_{2,3}$ 3.0 Hz). δ_C (D_2O): 24.0, 25.6 (2 x q, $\underline{Me}_2C$), 60.8 (d, C-2), 62.8 (t, C-7), 69.3, 72.9, 75.2, 76.4 (4 x d, 4 x CHO), 112.1 (s, $Me_2\underline{C}$), 171.4 (s, C-1). *m/z* (NH_3, DCI): 291 ($M+NH_4^+$, 45%), 246 (MH^+-N_2, 100%). (Found: C, 44.02; H, 5.47; N, 15.22. $C_{10}H_{15}N_3O_6$ requires: C, 43.96; H, 5.53; N, 15.38%).

2-Azido-7-O-tert-butyldimethylsilyl-2-deoxy-3,4-O-isopropylidene-D-glycero-D-talo-heptono-1,5-lactone (13). A solution of *tert*-butyldimethylsilyl chloride (0.95 g, 6.3 mmol) in dimethylformamide (5 ml) was added dropwise, under nitrogen, to a stirred solution of the diol (12) (1.15 g, 4.2 mmol) and imidazole (0.57 g, 8.4 mmol) in dimethylformamide (15 ml) at -10°C. After 15 min 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 (13)*, (1.29 g, 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), 1770 (C=O) cm^{-1}; δ_H ($CDCl_3$) 0.08 (6H, s, $SiMe_2$), 0.89 (9H, s, Si^tBu). 1.39 (3H, s, Me). 1.46 (3H, s, Me), 2.66 (1H, d, HO, J 6.0 Hz), 3.82 (3H, m), 4.03 (2H, m), 4.85 (2H, m). δ_C ($CDCl_3$): -5.7 (q, $\underline{Me}_2Si$), 18.1 (s, $\underline{C}Me_3$), 24.2 (q, Me), 25.7 (q, 4 x Me), 59.1 (d, C-2), 62.6 (t, C-7), 68.2, 72.2, 72.3. 75.4 (4 x d, 4 x CHO), 111.2 (s, $Me_2\underline{C}$), 166.4 (s, C-1). *m/z* (NH_3, DCI): 405 ($M+NH_4^+$, 55%), 360 (MH^+-N_2, 100%). (Found: C, 49.34; H, 7.77; N, 10.59. $C_{16}H_{29}N_3O_6Si$ requires: C, 49.59; H, 7.54; N, 10.84%).

2-Azido-7-O-tert-butyldimethylsilyl-2-deoxy-3,4-O-isopropylidene-6-O-trifluoromethanesulphonyl-D-glycero-D-talo-heptono-1,5-lactone (14). Dry pyridine (0.8 ml, 10 mmol) and 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 (13) (1.29 g, 3.3 mmol) in dichloromethane (15 ml), under nitrogen, 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 (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 further purification; a small sample was recrystallised to give colourless needles of *2-azido-7-O-tert-butyldimethylsilyl-2-deoxy-3,4-O-isopropylidene-6-O-trifluoromethanesulphonyl-D-glycero-D-talo-heptono-1,5-lactone (14)*, m.p. 79-80°C. $[\alpha]_D^{20}$ +41.1° (*c*, 0.95 in $CHCl_3$), ν_{max} ($CHCl_3$): 2125 (N_3), 1780 (C=O) cm^{-1} ; δ_H ($CDCl_3$): 0.11 (6H, s, $SiMe_2$), 0.90 (9H, s Si^tBu), 1.40 (3H, s, Me), 1.49 (3H s, Me), 3.82 (1H, d, H-2, $J_{2,3}$ 3.2 Hz), 4.04 (1H, dd, H-7, $J_{6,7}$ 3.1 Hz, $J_{7,7'}$ 12.7 Hz), 4.14 (lH, dd, H-7', $J_{6,7'}$ 1.9 Hz), 4.57 (1H, d, H-5, $J_{5,6}$ 8.0 Hz), 4.68 (1H, d, H-4, $J_{3,4}$ 7.8 Hz), 4.93 (1H,dd, H-3), 5.16 (1H, br d, H-6). δ_C ($CDCl_3$): -5.9 (q, $\underline{Me}_2Si$), 18.0 (s, $\underline{C}Me_3$), 23.7 (q, Me), 25.5 (q, 4 x Me), 58.8 (d, C-2), 60.7 (t, C-7), 71.3, 72.3, 75.2 (3 x d, C-3, C-4, C-5), 83.9 (d, C-6), 111.7 (s, $\underline{C}Me_2$), 118.4 (q, CF_3, not proton decoupled), 165.5 (s, C-1). *m/z* (NH_3, DCI): 537 ($M+NH_4^+$, 100%), 492 (MH^+-N_2, 10%). (Found: C, 39.45; H, 5.43; N, 8.26. $C_{17}H_{28}F_3N_3O_8SSi$ requires: C, 39.30; H, 4.53; N, 8.09%) .

7-O-tert-Butyldimethylsilyl-2,6-dideoxy-2,6-imino-3,4-O-isopylidene-L-glycero-D-talo-heptono-1,5-lactone (16). The azido triflate (14) (605 mg, 1.16 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, washing with ethyl acetate (20 ml), to give a colourless solution showing one spot on tlc [ethyl acetate, R_f 0.9]. Flash chromatography [hexane:ethyl acetate, 1:1] gave *7-O-tert-butyl dimethylsilyl-2,6-dideoxy-2,6-imino-3,4-O-isopropylidene-L-glycero-D-talo-heptono-1,5-lactone (16)*, (348 mg, 96%), a colourless syrup which solidified to a white wax on standing. $[a]_D^{20}$ -15.4° (*c*, 1.2 in $CHCl_3$), ν_{max} (neat): 3360 (NH), 1781 (C=O) cm^{-1}; δ_H ($CDCl_3$): 0.06 (6H, s, $SiMe_2$), 0.89 (9H, s, Si^tBu), 1.41 (3H, s, Me), 1.16 (3H, s, Me), 2.34 (1H, br s, NH), 3.50 (3H, m), 3.67 (1H, d, H-2, $J_{2,3}$ 2.9 Hz), 4.39 (1H, dd, H-3, $J_{3,4}$ 8.0 Hz), 4.52 (1H, dd, H-4, $J_{4,5}$ 4.3 Hz), 4.84 (1H, d, H-5). δ_C ($CDCl_3$): -5.8 (q, $\underline{Me}_2Si$), 18.1 (s, $\underline{C}Me_3$), 24.3 (q, Me), 25.7 (q, 4 x Me), 48.3 (d, C-6), 54.1 (d, C-2), 62.6 (t, C-7), 71.3, 72.5, 74.7 (3 x d, 3 x CHO), 113.9 (s, $\underline{C}Me_2$), 170.7 (s, C-1). *m/z* (NH_3, DCI): 344 ($M+H^+$, 100%), 286 ($M^+-{}^tBu$). (Found: C, 55.71; H, 8.79; N, 4.27. $C_{16}H_{29}NO_5Si$ requires: C, 55.95; H, 8.15; N, 4.08%)

2-Amino-7-O-tert-butyldimethylsilyl-2-deoxy-3,4-O-isopropylidene-6-O-trifluoromethanesulphonyl-D-glycero-D-talo-heptono-1,5-lactone trifluoromethanesulphonate (15). A solution of the triflate (14) (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 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 chromatography [ethyl acetate:hexane, 2:1] to give two compounds; the first was the bicyclic amine (16) (550 mg, 52%), identical in all respects to the material prepared above. The second compound was identified as the triflate salt, *2-amino-7-O-tert-butyldimethylsilyl-2-deoxy-3,4-O-isopropylidene-6-O-trifluoromethanesulphonyl-D-glycero-D-talo-heptono-1,5-lactone trifluoromethanesulphonate (15)* (872 mg, 43%), a white solid, m.p. 77-79°C (ether), $[\alpha]_D^{20}$ +34.7° (*c*, 1.0 in $CHCl_3$), ν_{max} ($CHCl_3$): 3500 br (NH_3^+), 1780 (C=O) cm^{-1}; δ_H ($CDCl_3$): 0.08 (3H,

s, Me), 0.09 (3H, s, Me), 0.90 (9H, s, Si^{t}Bu), 1.33 (3H, s, Me), 1.41 (3H, s, Me), 3.94 (1H, dd, H-7, $J_{6,7}$ 5.6 Hz, $J_{7,7'}$ 12.6 Hz), 4.15 (1H, d, H-7'), 4.64 (lH, d, H-2 $J_{2,3}$ 3.6 Hz), 4.76 (2H, m), 5.11 (2H, m). 7.4-7.7 (3H, br m, D_2O exchange, NH_3^+). δ_C ($CDCl_3$): -6.1 (q, $\underline{Me}_2Si$). 18.0 (s, Si$\underline{C}Me_3$), 23.1 (q, Me), 25.1 (q, Me), 25.5 (q, C$\underline{Me}_3$), 52.2 (d, C-2), 61.0 (t, C-7), 71.3, 71.5, 74.4 (3 x d, 3 x CHO). 85.0 (d, C-6), 112.2 (s, $\underline{C}Me_2$), 118.4, 119.8 (2 x q, 2 x CF_3, not proton decoupled), 165.5 (s, C-1). *m/z* (NH_3, DCI): 494 (MH^+-CF_3SO_3H, 50%), 344 (MH^+-[2 x CF_3SO_3H]). (Found: C, 33.46; H, 5.04; N, 2.13. $C_{18}H_{31}F_6NO_{11}S_2Si$ requires: C, 33.59; H, 4.85; N, 2.18%).

Cyclisation of the triflate salt (15) to the bicyclic amine (16). Method (i). The triflate salt (15) (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 amine (16) (47 mg, 86%), identical in all respects to the material prepared above. *Method (ii).* The triflate salt (15) (75 mg, 0.12 mmol) was stirred with anhydrous sodium carbonate (25 mg, 0.24 mg) 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 (16) (30 mg, 79 %).

2,6-Dideoxy-2,6-imino-L-glycero-D-talo-heptonic acid (8). The protected imino heptono-1,5-lactone (16) (180 mg, 0.52 mmol) was stirred in 50% aqueous trifluoroacetic acid (3 ml) at 20°C for 20 h. After removing the solvent and co-evaporating with toluene (2 x 5 ml), the residue was purified by ion exchange chromatography (Dowex 50x 8-100, H^+ form, eluting with 0.8 M aqueous pyridine) to give, after freeze drying, *2,6-dideoxy-2,6-imino-L-glycero-D-talo heptonic acid (8)* (47 mg, 48%), a white solid, m.p. 150-156°C (dec.), $[\alpha]_D^{20}$ +16.9° (*c*, 1.0 in H_2O), ν_{max} (KBr): 3400 (NH and OH), 1630 (C=O) cm^{-1}; δ_H (D_2O): 3.43 (1H, dt, H-6, $J_{5,6}$ 1.3 Hz, $J_{6,7}$ 6.9 Hz), 3.55 (1H, d, H-2, $J_{2,3}$ 10.9 Hz), 3.74 (2H, d, H-7), 3.94 (1H, dd, H-4, $J_{3,4}$ 2.4 Hz, $J_{4,5}$ 4.3 Hz), 3.96 (1H, dd, H-5), 4.03 (1H, dd, H-3). δ_C (D_2O): 55.7, 57.3 (2 x d, C-2, C-6), 59.3 (t, C-7), 66.2, 67.3, 69.4 (3 x d, C-3. C-4, C-5), 173.6 (s, C-1). *m/z* (NH_3, DCI): 190 ($M+H^+$, 100%), 154 (M^+-$2H_2O$, 40%).

7-O-tert-Butyldimethylsilyl-2,6-dideoxy-2,6-imino-3,4-O-isopropylidene-L-glycero-D-talo-heptitol (17). Method (i). Lithium aluminium hydride (50 mg, 1 mmol) was added to a stirred solution of the bicyclic amine (16) (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] 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 [hexane: ethyl acetate, 3:2] to give *7-O-tert-butyldimethylsilyl-2,6-dideoxy-2,6-imino-3,4-O-isopropylidene-L-glycero-D-talo-heptitol (17)* (90 mg, 54%), m.p. 112-114°C (ether-hexane), $[\alpha]_D^{20}$ +52.7° (*c*, 1.0 in $CHCl_3$), ν_{max} ($CHCl_3$): 3450 (NH) cm^{-1}; δ_H ($CDCl_3$): 0.10 (6H, s, $SiMe_2$), 0.91 (9H, s, Si^{t}Bu), 1.37 (3H, s, Me), 1.50 (3H, s, Me), 2.4 (2H, br s, OH), 2.80 (1H, ddd, H-2, $J_{1,2}$ 3.7 Hz, $J_{1',2}$ 7.4 Hz, $J_{2,3}$ 9.0 Hz), 3.02 (1H, ddd, H-6, $J_{5,6}$ 1.5 Hz, $J_{6,7}$ 4.8 Hz, $J_{6,7'}$ 6.0 Hz), 3.45 (1H, br s, OH), 3.54 (1H, dd, H-1', $J_{1,1'}$ 10.8 Hz), 3.8 (3H, m, H-1, H-7, H-7'), 3.90 (1H, dd, H-3, $J_{3,4}$ 5.0 Hz), 4.05 (1H, br s, H-5), 4.23 (1H, dd, H-4, $J_{4,5}$ 2.6 Hz). δ_C ($CDCl_3$): -5.7 (q, Si$\underline{Me}_2$), 18.0 (s, Si^{t}Bu), 25.7 (q, Si$\underline{C}Me_3$), 26.2, 28.0 (2 x q, 2 x Me), 56.1, 60.4 (2 x d, C-2, C-6), 63.6, 64.7 (2 x t, C-1, C-7), 67.5, 72.1, 76.7 (3 x d, C-3, C-4, C-5), 109.5 (s, $\underline{C}Me_2$). *m/z* (NH_3, DCI): 348 ($M+H^+$, 100%), 202

(M^+-$CH_2SiMe_2{}^tBu$, 25%). (Found: C, 55.46; H, 9.51; N, 4.03. $C_{16}H_{35}NO_5Si$ requires: C, 55.30; H, 9.57; N, 4.03%).

Method (ii). Lithium borohydride (2M in THF, 0.55 ml, 1.1 mmol) was added to a stirred solution of the bicyclic amine (16) (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 (18)* (153 mg, 39 %), m.p. 110°C (dec., ether-hexane), $[\alpha]_D^{20}$ +9.8° (*c* ,1.0 in $CHCl_3$), ν_{max} ($CHCl_3$): 3450, 3230 (NH and OH), 2380 (BH_3) cm^{-1}; δ_H ($CDCl_3$): 0.16 (3H, s, Me), 0.17 (3H, s, Me), 0.93 (9H, s, Si^{t}Bu), 1.36 (3H, s, Me), 1.48 (3H, s, Me), 2.28 (1H, br s, NH), 2.94 (1H, ddd, H-2, $J_{1,2}$ 3.1 Hz, $J_{1',2}$ 7.0 Hz, $J_{2,3}$ 10.8 Hz), 3.17 (1H, ddd, H-6, $J_{5,6}$ 2.9 Hz, $J_{6,7}$ 5.9 Hz, $J_{6,7'}$ 8.8 Hz), 3.64 (1H, br s, OH), 3.81 (1H, dd, J 2.9 Hz, 11.1 Hz), 3.95 (1H, dd, J 2.4 Hz, 10.8 Hz), 4.24 (2H, m), 4.36 (1H, d, J 6.7 Hz), 4.41 (1H, dd, J 3.5 Hz, 8.0 Hz), 4.45 (1H, br s, OH), 4.50 (1H, dd, J 3.1 Hz, 10.8 Hz). δ_C ($CDCl_3$): -6.0, -5.8 (2 x q, Si<u>Me</u>$_2$), 17.0 (s, Si<u>C</u>Me$_3$), 24.8 (q, Me), 25.6 (q, C<u>Me</u>$_2$), 27.1 (q, Me), 59.4 (t), 59.7 (d, CHN), 61.5 (t), 62.6 (d, CHN), 69.3, 71.0, 74.8 (3 x d, 3 x CHO), 109.5 (s, <u>C</u>Me$_2$). *m/z* (NH_3, DCI): 360 (M^+-H, 100%), 348 (MH^+-BH_3, 98%). (Found: C, 53.81; H, 10.34; N, 3.60. $BC_{16}H_{32}NO_5Si$ requires: C, 53.18; H, 10.04; N, 3.88%). The second product was identified as *7-O-tert-butyldimethylsilyl-2,6-dideoxy-2,6-imino-3,4-O-isopropylidene-L-glycero-D-talo-heptitol (17)* (74 mg, 18%), identical in all respects to the material prepared above.

2,6-Dideoxy-2,6-imino-L-glycero-D-talo-heptitol hydrochloride [6-epi-HMJ] (7). 7-*O*-*tert*-Butyldimethylsilyl-2,6-dideoxy-2,6-imino-3,4-*O*-isopropylidene-L-*glycero*-D-*talo*-heptitol (17) (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 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 (7)*, (66 mg, 85%), a very hygroscopic solid, (R_f 0.8, EtOH : MeOH : 0.5M NH_3, 2:2:1), $[\alpha]_D^{20}$ +26.4° (*c*, 0.5 in H_2O), δ_H (D_2O): 2.63 (1H, ddd, H-2, $J_{1,2}$ 3.2 Hz, $J_{1',2}$ 5.4 Hz, $J_{2,3}$ 10.5 Hz), 2.87 (1H, dt, H-6, $J_{5,6}$ 1.5 Hz, $J_{6,7}$ 6.6 Hz), 3.45 (2H, m, H-7, H-7'), 3.51 (1H, dd, H-1', $J_{1,1'}$ 11.8 Hz), 3.57 (1H, dd, H-3, $J_{3,4}$ 3.6 Hz), 3.60 (1H, dd, H-1), 3.72 (1H, dd, H-5, $J_{4,5}$ 3.6 Hz), 3.79 (1H, t, H-4). δ_C (D_2O): 54.6, 56.0 (2 x d, C-2, C-6), 62.1 (t, C-1, C-7), 66.8, 70.1, 71.7 (3 x d, C-3, C-4, C-5). *m/z* (NH_3, DCI): 194 ($M+H^+$, 100%), 162 (M^+-CH_2OH, 25%). Repetition of this procedure with the borane adduct (18) (125 mg, 0.35 mmol) gave an identical material to that above (55 mg, 82%). The free base (7) (100 mg, 0.52 mmol) was dissolved in methanol (3 ml) and acetyl chloride (*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° (*c*, 1.0 in H_2O), ν_{max} (KBr): 3500-2500 (NH, OH) cm^{-1}; δ_H (D_2O): 3.29 (1H, ddd, H-2, $J_{1,2}$ 3.0 Hz, $J_{1',2}$ 5.0 Hz, $J_{2,3}$ 10.8 Hz), 3.48 (1H, dt, H-6, $J_{5,6}$ 1.3 Hz, $J_{6,7}$ 6.7 Hz), 3.74 (2H, d, H-7, H-7'), 3.79 (1H, dd, H-1', $J_{1,1'}$ 12.8 Hz), 3.86 (1H, dd, H-1), 3.94 (1H, dd, H-4, $J_{3,4}$ 2.9 Hz, $J_{4,5}$ 3.9 Hz), 3.98 (1H, dd, H-3), 4.00 (1H, dd, H-5). δ_C (D_2O): 56.1, 56.4 (2 x d, C-2, C-6), 58.3, 59.1 (2 x t, C-1, C-7), 63.5, 67.4, 69.4 (3 x d, C-3, C-4, C-5). *m/z* (NH_3, DCI): 194 ($M+H^+$, 100%), 162 (M^+-CH_2OH, 30%). (Found: C, 36.61; H, 7.32; N, 5.88. $C_7H_{16}NO_5Cl$ requires: C, 36.61; H, 7.02; N, 6.10%).

2-Azido-7-O-tert-butyldimethylsilyl-2-deoxy-3,4-O-isopropylidene-D-talo-6-heptulosono-1,5-lactone (19). The alcohol (13) (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 (19),* (1.53 g, 74%), m.p. 120-122°C (ether), $[\alpha]_D^{20}$ +5.4° (*c*, 1.0 in $CHCl_3$), ν_{max} ($CHCl_3$): 2123 (N_3), 1780 (C=O), 1743 (C=O) cm^{-1}; δ_H ($CDCl_3$): 0.10 (3H, s, Me), 0.12 (3H, s, Me), 0.93 (9H, s, ^tBu), 1.35 (3H, s, Me), 1.48 (3H, s, Me), 3.80 (1H, d, H-2, $J_{2,3}$ 2.8 Hz), 4.64 (1H, d, H-7, $J_{7,7'}$ 19.9 Hz), 4.72 (1H, d, H-5, $J_{4,5}$ 1.4 Hz), 4.74 (1H, d, H-7'), 4.90 (2H, m, H-3, H-4). δ_C ($CDCl_3$): -5.8, -5.7 (2 x q, $SiMe_2$), 18.2 (s, CMe_3), 24.0, 25.5 (2 x q, 2 x Me), 25.6 (q, CMe_3), 59.5 (d, C-2), 68.8 (t, C-7), 74.1, 75.1 (2 x d, C-3, C-4), 80.2 (d, C-5), 111.7 (s, CMe_2), 165.7 (s, C-1), 202.1 (s, C-6). *m/z* (NH_3, DCI): 403 ($M+NH_4^+$, 100%), 358 (MH^+-N_2, 75%). (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%).

Bicyclic Imine (20). Triethyl phosphite (1.3 M in THF, 2.4 ml, 3.1 mmol) was added, under nitrogen, to a stirred solution of the ketone (19) (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 (20),* (477 mg, 89%), a colourless oil, $[\alpha]_D^{20}$ +98.3° (*c*, 1.0 in $CHCl_3$), ν_{max} (film): 1780 (C=O), 1650 (C=N) cm^{-1}; OH ($CDCl_3$): 0.11 (3H, s, Me), 0.13 (3H, s, Me), 0.94 (9H, s, Si^tBu), 1.33 (3H, s, Me), 1.35 (3H, s Me), 4.43 (1H, d, H-7, $J_{7,7'}$ 14.9 Hz), 4.56 (1H, d, H-7'), 4.64 (1H, dd, H-3, $J_{2,3}$ 2.5 Hz, $J_{3,4}$ 6.9 Hz), 4.72 (1H, dd, H-4, $J_{4,5}$ 4.1 Hz), 5.22 (1H, d, H-2), 5.52 (1H, d, H-5). δ_C ($CDCl_3$): -5.8, -5.6 (2 x q, $SiMe_2$), 18.1 (s, $SiCMe_3$), 24.6, 25.2 (2 x q, 2 x Me), 25.6 (q, CMe_3), 62.3 (d, C-2), 65.2 (t, C-7). 71.6, 73.0, 74.2 (3 x d, C-3, C-4, C-5). 168.1 (s. C-6), 177.5 (s, C-1). *m/z* (NH_3, DCI): 342 ($M+H^+$, 100%), 284 ($MH^+-CH_3COCH_3$, 30%). (Found: C, 56.39; H, 8.02; N, 4.05. $C_{16}H_{27}NO_5Si$ requires: C, 56.28; H, 7.97; N, 4.10%).

7-O-tert-Butyldimethylsilyl-2,6-dideoxy-2,6-imino-3,4-O-isopropylidene-D-glycero-D-talo-heptitol (21). Lithium borohydride (2M in THF, 0.6 ml, 1.2 mmol) was added, under nitrogen, to a stirred solution of the imine (20) (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 1 h and stirred for an additional 4 h before quenching with saturated aqueous ammonium chloride (0.3 ml). The solution was evaporated to dryness and the residue was purified by flash chromatography (gradient elution; hexane:ethyl acetate, 1:1 to 0:1) to give two products; the first (R_f 0.3, ethyl acetate) was *7-O-tert-butyldimethylsilyl-2,6-dideoxy-2,6-imino-3,4-O-isopropylidene-L-glycero-D-talo-heptitol (17)* (3 mg, 2%), identical in all respects to the material prepared above. The second compound was identified as *7-O-tert-butyldimethylsilyl-2,6-dideoxy-2,6-imino-3,4-O-isopropylidene-D-glycero-D-talo-heptitol (21),* (85 mg, 46%), m.p. 165-166°C (ethyl acetate-ether), $[\alpha]_D^{20}$ -28.5° (*c*, 1.0 in $CHCl_3$), ν_{max} ($CHCl_3$): 3450 (OH) cm^{-1}, δ_H ($CDCl_3$): 0.09 (6H, s, $SiMe_2$), 0.91 (9H, s, Si^tBu), 1.37 (3H, s, Me), 1.52 (3H, s, Me), 2.1-2.5 (3H, br s, NH and 2 x OH, D_2O exchange), 2.66 (1H, dt, J 4.2 Hz, J 8.9 Hz), 3.30 (1H, ddd, J 3.5 Hz, J 5.0 Hz, J 9.7 Hz), 3.51 (1H, t, J 10.1 Hz), 3.66 (1H, d, J 10.1 Hz), 3.67 (1H, t, J 9.2 Hz), 3.75 (1H, dd, J 7.3 Hz, J 9.2

Hz), 3.97 (2H, m), 4.03 (1H, dd, J 5.0 Hz, J 6.0 Hz). δ_C ($CDCl_3$): -5.8 (q, $SiMe_2$), 25.7 (q, $SiC\underline{Me}_3$), 26.0, 27.0 (2 x q, 2 x Me), 52.8, 54.0 (2 x d, C-2, C-6), 60.5, 62.7 (2 x t, C-1, C-7), 71.0, 74.4, 79.3 (3 x d, C-3, C-4, C-5), 109.0 (s, $\underline{C}Me_2$). *m/z* (NH_3, DCI): 348 ($M+H^+$, 100%), 316 (M^+-CH_2OH, 15%), 202 ($M^+-CH_2OSiMe_2{}^tBu$, 40%).(Found: C, 55.56; H, 10.01; N, 3.99. $C_{16}H_{35}NO_5Si$ require : C, 55.30: H, 9.57; N 4.03%).

2,6-Dideoxy-2,6-imino-D-glycero-D-talo-heptitol [α-Homomannojirimycin] (6). The protected iminoheptitol (21) (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° (*c*, 0.55 in H_2O); δ_H (D_2O): 2.62 (1H, m, H-6), 3.02 (1H, ddd, H-2, $J_{2,3}$ 2.6 Hz, $J_{1,2}$ 7.5 Hz, $J_{1',2}$ 9.2 Hz), 3.4-3.6 (6H, m), 3.81 (1H, t, H-3, $J_{3,4}$ 2.6 Hz). δ_C (D_2O): 56.2, 59.0 (2 x d, C-2, C-6), 59.6, 61.3 (2 x t, C-1, C-7), 68.9, 69.4, 72.2 (3 x d, C-3, C-4, C-5). *m/z* (NH_3, DCI): 194 ($M+H^+$, 100%), 162 (MH^+-CH_3OH, 15%).

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References

[1] Fairbanks, A. J., Carpenter, N. C., Fleet, G. W. J., Ramsden, N. G., Cenci de Bello, I., Winchester, B. G., Al-Daher, S. S., and Nagahashi, G., *Tetrahedron*, 1992, **48**, 3365

[2] Winchester, B., and Fleet, G. W. J., *Glycobiology*, 1992, **2**, 199; G. Legler, *Adv. Carbohydr. Chem. Bichem.*, 1990, **48**, 319.

[3] Kite, G. C., Fellows, L. E., Fleet, G. W. J., Liu, P. S.. Scofield, A. M., and Smith, N. G., *Tetrahedron Lett.*, 1988, **29**, 6483.

[4] Kite, G. C., Fellows, L. E., Lees, D. C., Kitchen, D., and Monteith, G. B., *Biochem. Syst. Ecol.*, 1991, **19**, 441; Kite, G.C., Horn, J. M., Romeo, J. T. Fellows, L. E.. Lees, D. C. Scofield, A. M., and Smith, N. G., *Phytochemistry*, 1990, **29**, 103.

[5] Rhinehart, B. L., Robinson, K. M., Liu, P. S., Payne, A. J. Wheatley, M. E., Wagner, S. R., *J. Pharmacol. Exp. Ther.*, 1987, **241**, 915.

[6] Kaushal, G. P.. Pan, Y. T., Tropea, J., Mitchell, M., Liu, P., Elbein, A. D., *J. Biol. Chem.*,1988, **263**, 17278; Kaushal, G. P., Pastuszak, I., Hatanaka, K., and Elbein, A. D, *J. Biol. Chem.*, 1990, **265**, 16271.

[7] Salleh, H. M., and Honek, J. F., FEBS Lett., 1990, **262**, 359.

[8] Fuhrmann, U., Bause, E., Legler, G., and Ploegh, H., *Nature*, 1984, **307**, 755.

[9] Evans, S. V., Fellows, L. E., Fleet, G. W. J., and Shing, T. K. M., *Phytochemistry*, 1985, **24**, 1953

[10] Winchester, B., Barker, C., Baines, S., Jacob, G. S., Namgoong, S. K., and Fleet, G., *Biochem. J.*, 1990, **265**, 277.

[11] Winchester, B. G., Cenci di Bello, I., Richardson, A. C., Nash, R. J., Fellows, L. E., Ramsden, N. G., and Fleet, G., *Biochem. J.*, 1990, **269**, 227.

[12] Anzeveno, P. B., Creemer, L. J., Daniel, J. K., King, C. H. R., and Liu, P. S., *J. Org. Chem.*, 1989, **54**, 2539; Liu, P. S., *J. Org. Chem*, **52**, 4717.

[13] Fleet, G. W. J., Namgoong, S. K., Barker, C., Baines, S., Jacob, G. S., and Winchester, B., *Tetrahedron Lett.*, 1989, **30**, 4439.

[14] Aoyagi, S., Fujimaki, S., and Kibayashi, C., *J. Chem. Soc., Chem. Commun.*, **1990**, 1457.

[15] Straub, A., Effenberger, F., and Fischer, P., *J. Org. Chem.*, 1990, **55**, 3926.

[16] Bruce, I., Fleet, G. W. J., Cenci Di Bello, I., and Winchester, B., *Tetrahedron Lett.*, 1989, **30**, 7257.

[17] Beacham, A. R., Bruce, I., Choi, S., Doherty, O., Fairbanks, A. J., Fleet, G. W. J., Skead, B. M., Peach, J. M., Saunders, J., and Watkin, D. J., *Tetrahedron: Asymm.*, 1991, **2**, 883.

[18] Fleet, G. W. J., Bruce, I., Girdhar, A., Haraldsson, M., Peach, J. M., and Watkin, D. J., *Tetrahedron*, 1990, **46**, 19.

[19] Myerscough, P. M., Fairbanks, A. J., Jones, A. H., Choi, S.-S., Fleet, G. W. J., Al-Daher, S. S., Cenci di Bello, I., and Winchester, B., preceding paper

[20] Bashyal, B. P., Chow, H.-F., and Fleet, G. W. J., *Tetrahedron Lett.*, 1986, **27**, 3205; Dho, J. C., Fleet, G. W. J., Peach, J. M., Prout, K., and Smith, P. W., *Tetrahedron Lett.*, 1986, **27**, 3203; Bashyal, B. P., Chow, H.-F., Fellows, L. E., and Fleet, G. W. J., *Tetrahedron*, 1987, **43**, 415; Bashyal, B. P., Chow, H.-F., and Fleet, G. W. J., *Tetrahedron*, 1987, **43**, 423; Fleet, G. W. J., and Witty, D. R., *Tetrahedron Asymm.*, 1990, **1**, 119 and references cited therein.

[21] Takeuchi, H., Yanigada, S., Ozaki, T., Hagiwara, S., and Eguchi, S., *J. Org. Chem.*, 1989, **54**, 431; Eguchi, S., and Takeuchi, H., *J. Chem. Soc., Chem. Commun.*, **1989**, 602.

[22] Al-Daher, S. S., Fleet, G., Namgoong, S. K., and Winchester, B., *Biochem. J.*, 1989, **258**, 613.