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3,6-DIDEOXY-3,6-IMINO-1,2-O-ISOPROPYLIDENE-α-D-GLUCOFURANOSE AS A DIVERGENT INTERMEDIATE FOR THE SYNTHESIS OF HYDROXYLATED PYRROLIDINES: SYNTHESIS OF 1,4-DIDEOXY-1,4-IMINO-L-GULITOL, 1,4-DIDEOXY-1,4-IMINO-D-LYXITOL, 2S,3S,4R-3,4-DIHYDROXYPROLINE AND (1S,2R,8S,8aR)-1,2,8-TRIHYDROXYOCTAHYDROINDOLIZINE [8-EPI-SWAINSONINE]. X-RAY CRYSTAL STRUCTURE OF (1S,2R,8S,8aR)-1,2,8-TRIHYDROXY-5-OXO-OCTAHYDROINDOLIZINE

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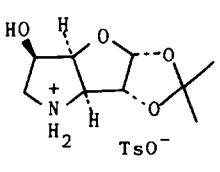
An efficient synthesis of the p-toluenesulphonate salt of 3,6-dideoxy-3,6-imino-1,2-O-isopropylidene-α-D-glucofuranose (1) from glucose is reported; the potential of (1) in making hydroxylated pyrrolidines is illustrated by the preparation of 1,4-dideoxy-1,4-imino-L-gulitol, 1,4-dideoxy-1,4-imino-D-lyxitol (a powerful α-galactosidase inhibitor), 2S,3S,4R-3,4-dihydroxyproline and (1S,2R,8S,8aR)-1,2,8-trihydroxyoctahydroindolizine [8-epi-Swainsonine]. An X-ray crystal structure of (1S,2R,8S,8aR)-1,2,8-trihydroxy-5-oxo-octahydroindolizine is reported.

This paper describes an efficient synthesis of the p-toluenesulphonate salt of 3,6-dideoxy-3,6-imino-1,2-O-isopropylidene-α-D-glucofuranose (1) in which the pyrrolidine ring is formed between C-3 and C-6 of glucose; the benzamide of (1) has been previously reported.[1] The value of (1) as a divergent intermediate for the synthesis of hydroxylated pyrrolidines is demonstrated by its conversion into the 1,4-dideoxy-1,4-imino-L-gulitol (2), the C-5 epimer of the powerful α-mannosidase inhibitor (3),[2] into the α-galactosidase inhibitor 1,4-dideoxy-1,4-imino-D-lyxitol (4), and into 2S,3S,4R-3,4-dihydroxyproline (5). The bicyclic amine (1) is also a suitable intermediate for the synthesis of bicyclic heterocyclic frameworks. Conversion of (1) into the amide of dimethylphosphonoacetic acid (17) allows the construction of the octahydroindolizine ring system by a subsequent intramolecular Wadsworth Emmons reaction onto C-1 of glucose in the lactol (19) whereas an intramolecular Wadsworth Emmons onto a ketone derived from C-2 of glucose would



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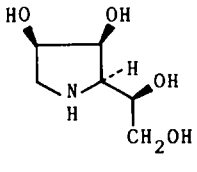

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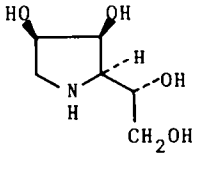

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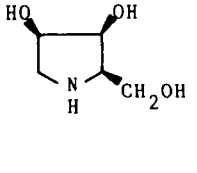

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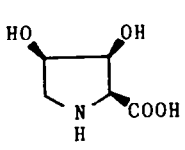

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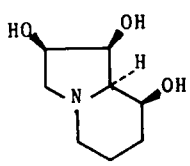

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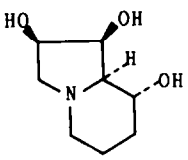

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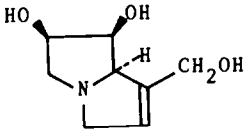
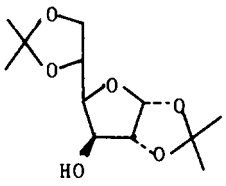


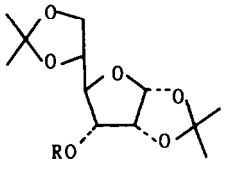
(8)

lead to the pyrrolizidine ring system. The synthesis of (1S,2R,8S,8aR)-1,2,8-trihydroxyoctahydroindolizine (6), the epimer at C-8 of swainsonine (7), is described in this paper; the use of (1) in the synthesis of necine bases such as crotanecine (8) and other highly functionalised pyrrolizidine alcohols is currently being investigated.[3] The synthesis of the p-toluenesulphonate salt of 3,6-dideoxy-3,6-imino-1,2-O-isopropylidene-α-D-glucofuranose (1) from glucose requires the introduction of azide at C-3 of glucose with retention of configuration, followed by ring closure of the nitrogen function onto C-6; this strategy for the construction of the pyrrolidine ring is well established.[4,5] The introduction of the azide with overall retention at C-3 of glucose requires a sequence involving double inversion. Diacetone glucose (9), in which only the 3-OH group of glucose is unprotected, was oxidised with pyridinium chlorochromate in the presence of powdered molecular sieve in dichloromethane and the resulting crude ketone was treated with sodium borohydride at 0°C resulting in inversion of configuration at C-3 of glucose to give diacetone allose (10) in 84% yield; the use of molecular sieve in the oxidation of (9) is crucial.[6,7] Esterification of the free hydroxyl group in (10) with trifluoromethanesulphonic anhydride formed the corresponding triflate (11) and subsequent treatment of (11) with sodium azide in dimethyl formamide at 50°C gave the 3-azido-3-deoxyglucose derivative (12) in 92% yield; the use of the triflate in this transformation gives much higher yields of (12) under much milder conditions than azide displacement of other sulphonate leaving groups.[8,9] The 5,6-O-isopropylidene protecting in (12) was selectively removed by mild acid hydrolysis to give the diol (13) in quantitative yield and reaction of the diol (13) with p-toluenesulphonyl chloride in pyridine at -10°C gave the primary tosylate (14) [89% yield]. When the tosylate (14) was hydrogenated in ethanol in the presence of palladium black, the tosylate salt (1) crystallised from the reaction mixture [77% yield]. Thus the key intermediate (1) may be formed from diacetone glucose in an overall yield of 53% on a multigram scale; it is not necessary to purify any of the intermediates in this sequence by column chromatography. However, it is essential that the crude diol (13) is washed with aqueous sodium bicarbonate solution to remove all traces of acetic acid; in an experiment where traces of acetic acid were not removed, the yield of the tosylate in the following step was much reduced and a by-product arising from displacement of the tosylate group in (14) by acetate was formed.

In the synthesis of of 1,4-dideoxy-1,4-imino-L-gulitol (2), the bicyclic amine salt (1) was first hydrolysed with aqueous trifluoroacetic acid to the corresponding lactol; most of the solvent was removed under reduced pressure and the residual trifluoroacetic acid was neutralised with aqueous sodium hydroxide. The reaction mixture was then treated with sodium borohydride and the product was isolated by loading the crude reaction mixture directly onto an acid ion exchange

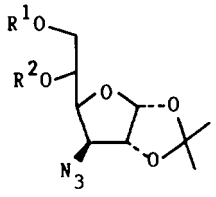


(9)



(10) R = H

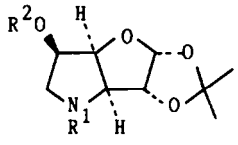
(11) R = SO_2CF_3



(12) R^1,R^2= Me_2C

(13) R^1= R^2= H

(14) R^1= Ts; R^2= H



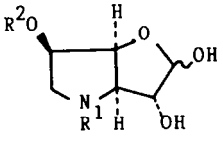
(15) R^1= Z; R^2= H

(16) R^1= Z; R^2= Bn

(17) R^1= $COCH_2PO(OMe)_2$; R^2= H

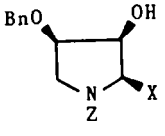
resin column and subsequently eluting the product (2) with aqueous ammonium hydroxide. In this way the iminogulitol (2), easily crystallised as the hydrochloride salt, was prepared from (1) in an overall yield of 76%. If the crude residue from the acid hydrolysis is not neutralised with sodium hydroxide prior to addition of sodium borohydride, a large of excess of sodium borohydride is necessary to effect reduction of the lactol intermediate and isolation of the iminogulitol (2) is troublesome.

For the syntheses of 1,4-dideoxy-1,4-imino-D-lyxitol (4) and 2S,3S,4R-3,4-dihydroxyproline (5), it is necessary first to protect the amine and hydroxyl functions in (1). Treatment of the salt (1) with benzyl chloroformate gave the carbamate (15) [95% yield] which with benzyl bromide and sodium hydride gave the benzyl ether (16) [84% yield; 80% yield from (1)]. Hydrolysis of the fully protected carbamate (16) by aqueous trifluoroacetic acid removed the 1,2-O-isopropylidene protecting group to give the corresponding lactol (18) (96% yield) which with sodium periodate in aqueous ethanol underwent oxidative cleavage of the C-1 - C-2 bond of lactol (18). The resulting aldehyde was directly treated with sodium borohydride to form the protected lyxitol (20) (84% yield). Hydrogenation of (20) in acetic acid in the presence of palladium black removed both the benzyl and benzyloxycarbonyl protecting groups to give the base (4) easily crystallised as its hydrochloride. This synthesis of 1,4-dideoxy-1,4-imino-D-lyxitol (4), which is a potent inhibitor of coffee bean α-galactosidase,[10] is more convenient than the previously reported synthesis from D-mannose;[2] recently an alternative approach to the synthesis of a protected form of the imino-lyxitol (4) by osmium tetroxide oxidation of a derivative of (S)-3,4-dehydroproline has been described.[11]



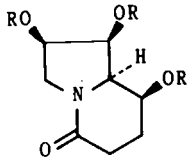
(18) R^1= Z; R^2= Bn

(19) R^1= $COCH_2PO(OMe)_2$; R^2= H



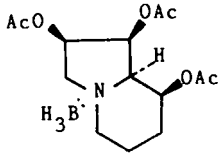
(20) X = CH_2OH

(21) X = COOH



(22) R = H

(23) R = Ac



(24)

[Ts = p-Me-$C_6H_4SO_2$; Z = $PhCH_2OCO$; Bn = $PhCH_2$; Ac = CH_3CO]

Hydrolysis of the carbamate (16) followed by oxidation of the lactol (18) first with sodium periodate and secondly with sodium chlorite in aqueous tert-butanol in the presence of an alkene[12,13] gave the protected amino acid (21) from which the benzyl and benzyloxycarbonyl protecting groups were removed by hydrogenation to give 2S,3S,4R-3,4-dihydroxyproline (5) [36% overall yield from (16)]. The racemic form of (5) has previously been prepared by osmium tetroxide oxidation of racemic 3,4-dehydroproline 2,5-dihydropyrrole-1-carboxylic acid, but no NMR data was reported;[14] the syntheses of two other dihydroxyprolines from carbohydrates have been described.[15,16]

The condensation reaction of dimethylphosphonoacetic acid with iminoglucofuranose (1) in the presence of dicyclohexylcarbodiimide gave the amide (17) in 87% yield. The isopropylidene group was removed from (17) by treatment with aqueous trifluoroacetic acid to form the corresponding lactol (19) in quantitative yield. Treatment of the N-dimethylphosphonoacetyl-3,6-dideoxy-3,6-imino-D-glucofuranose (19) with three equivalents of potassium carbonate in the presence of one equivalent of 18-crown-6[17] in dimethylformamide effected an intramolecular Wadsworth Emmons reaction[18] to give an α,β-unsaturated δ-lactam which on hydrogenation in ethanol in the presence of palladium black gave the saturated amide (22) which even after flash chromatography was contaminated with 18-crown-6. Accordingly the crude triol (22) was acetylated using acetic anhydride in pyridine at 50°C to give the pure triacetate (23) in an overall yield of 47% from (17); a pure sample of the crystalline triol (22) was obtained by treatment of the triacetate (23) with sodium methoxide in methanol. Reduction of the triacetate (23) with borane-dimethyl sulphide produced a single product (24) which had a higher R_f than the amide starting material in 70% yield; borane- dimethyl sulphide reduction of tertiary amides generally produces the corresponding tertiary amine-borane adducts.[19] The borane adduct (23), which had characteristic infra red absorbtions at 2380 and 1500 cm^{-1} (for BH and BN stretching) and a broad signal at δ -8.6 ppm in ^{11}B NMR, was stable at 0°C but slowly decomposed to the free amine at room temperature. The acetyl groups in (23) were removed by treatment with sodium methoxide in methanol; two acetyl groups were rapidly removed, but the third required heating to 50°C for two hours. The resulting borane amine complex was destroyed by treating the deacylated material with aqueous trifluoroacetic acid to give (1S,2R,8S,8aR)-1,2,8-trihydroxyoctahydroindolizine (6) in 80% yield [26% overall yield from (1)]. The strategy used in this synthesis of 8-epi-swainsonine (6) is similar to that used in the first published[20] synthesis of swainsonine (7), except that in this synthesis the 6-membered ring is formed by an intramolecular Wadsworth Emmons reaction on lactol (19) which avoids the problems encountered in the intermolecular Wittig reaction in the swainsonine synthesis.

Because of the physiological properties of swainsonine, there is interest in the synthesis and biological evaluation of stereoisomers such as (6); for example, the 8a-epimer of swainsonine has been shown to be almost as potent an inhibitor of of a human α-mannosidase as swainsonine.[21] A earlier synthesis[22] of 8-epi-swainsonine (6) by a Fujisawa group reports physical properties both of the triol (22) and of (6) which are very different from the compounds found in this work; for example, the Fujisawa group reports for (6) $[\alpha]_D^{21}$ -3.43° (c, 0.9 in MeOH) with ^{13}C NMR (CD_3OD) δ 17.9, 24.5, 44.4, 61.5, 64.3, 72.2, 75.2 and 82.1 in contrast to the data for (6) in this work of $[\alpha]_D^{20}$ -24.8° (c, 0.67 in MeOH) with ^{13}C NMR (CD_3OD) δ 20.6, 32.0, 54.2, 62.8, 67.5, 69.3, 69.9 and 74.2. Accordingly, the crystalline triol (22) was subjected to X-ray analysis and the structure was confirmed as (1S,2R,8S,8aR)-1,2,8-trihydroxy-5-oxo-octahydroindolizine (Figure), and the results previously reported[21] for the synthesis of (6) should be treated with some caution.

Recently another synthesis of (6) has been reported[23] in which the physical data for (6) are in close agreement with the properties reported in this paper.

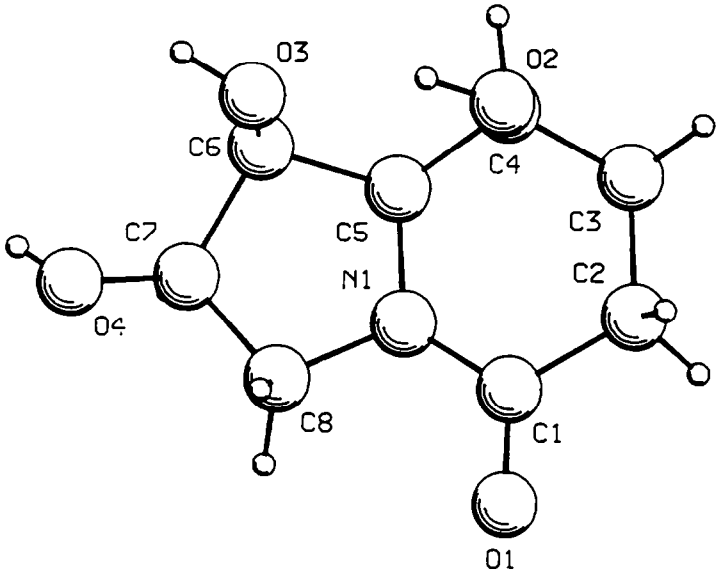


Figure. X-Ray Molecular Structure of (1S,2R,8S,8aR)-1,2,8-Trihydroxy-5-oxo-octahydroindolizine (22)with the crystallographic numbering scheme.

In summary, this paper has indicated the potential of 3,6-dideoxy-3,6-imino-1,2-O-isopropylidene-α-D-glucofuranose (1) as a chiral synthon for the synthesis of polyhydroxylated pyrrolidines; the use of a chiral unit for the synthesis of less functionalised pyrrolidines has recently been described.[24]

We are grateful for an SERC post-graduate award (to PWS) in support of this work and to Dr. C. K. Prout for his help and advice in this work.

X-Ray Crystal Structure Analysis. The crystal data for (1S,2R,8S,8aR)-1,2,8-trihydroxy-5-oxo-octahydroindolizine (22) are given in Table 1. The crystals were recrystallised from methanol. X-Ray data were collected with an Enraf-Nonius CAD4 diffractometer following the procedures recommended in the manufacturer's manual. The data were corrected for Lorentz and polarisation effects. All calculations were carried out on a VAX 11/750 computer using SHELXS-86[25] for direct methods and CRYSTALS[26] for all other calculations. Atomic scattering factors were taken from International Tables.[27] The positions of all non-hydrogen atoms were given by the SHELXS-86 direct methods routine. A difference map revealed the positions of the OH hydrogen atoms and the CH hydrogen atoms were placed geometrically. The trial structure was refined by full matrix least squares with isotropic temperature factors for the hydrogen atoms and anisotropic temperature factors for all other atoms. The Figure shows the molecular structure of (1S,2R,8S,8aR)-1,2,8-trihydroxy-5-oxo-octahydroindolizine with the crystallographic numbering scheme. The atomic coordinates have been deposited at the Cambridge Crystallographic Data Centre.

Table 1 Crystal Data for (1S,2R,8S,8aR)-1,2,8-trihydroxy-5-oxo-octahydroindolizine.

Formula	$C_8H_{13}NO_4$
Mr	187.195
crystal size/mm	0.4 x 0.3 x 0.2
crystal class	tetragonal
a/A	7.533(1)
b/A	7.533(1)
c/A	15.780(2)
$\alpha/^{o}$	90
$\beta/^{o}$	90
$\gamma/^{o}$	90
Space group	$P4_1$
Z	4
$D_c/g\ cm^{-3}$	1.389
F(000)	400
U/A^3	895.5
Radiation	CuKα
μ/cm^{-1}	9.02
$(\sin\theta/\lambda)_{max}$	0.63246
[a]Total I	1585
[b]unique I	958
$Rm/10^{-2}$	8.06
[c]n	3
$R/10^{-2}$	2.84
$Rw/10^{-2}$	3.62
[d]shift/error	0.003
[e] max/eA^{-3}	0.05
Ext para	33.5
[f]Weights	5.0, 3.9, 2.7

[a] total number of reflections measured. [b] number of unique reflections considered to be observed. [c] criterion for recognising observed reflections $I>n\sigma(I)$. [d] ratio of maximum least-squares shift to error in final refinement cycle. [e] maximum height in final difference electron density synthesis. [f]Three-term Chebychev weighting scheme[28]

Table 2. Fractional atomic coordinates and equivalent* isotropic temperature factors with e.s.d's in parenthesis for (1S,2R,8S,8aR)-1,2,8-trihydroxy-5-oxo-octahydroindolizine (atomic labelling as in Figure).

Atom	x/a	y/b	z/c	U(iso)
N(1)	-0.1820(2)	0.6890(2)	-0.0085(3)	0.0385
O(1)	-0.4550(2)	0.7631(2)	0.0350(4)	0.0566
O(2)	-0.0354(3)	0.4412(2)	0.1132(4)	0.0610
O(3)	0.1967(2)	0.6783(2)	0.0573(3)	0.0509
O(4)	0.1642(2)	1.0028(2)	-0.0272(3)	0.0556
C(1)	-0.3435(2)	0.6464(2)	0.0190(4)	0.0444
C(2)	-0.3846(3)	0.4536(3)	0.0353(4)	0.0618
C(3)	-0.2401(4)	0.3203(3)	0.0132(4)	0.0625
C(4)	-0.0559(3)	0.3985(3)	0.0248(4)	0.0535
C(5)	-0.0410(2)	0.5624(2)	-0.0309(3)	0.0421
C(6)	0.1280(2)	0.6748(3)	-0.0265(4)	0.0428
C(7)	0.0605(2)	0.8590(2)	-0.0541(4)	0.0435
C(8)	-0.1222(2)	0.8726(2)	-0.0134(4)	0.0412

* U_{eq} = (U_1, U_2, U_3) where the mean-square displacements (A^2) are along the principal axes of the thermal ellipsoid.

Table 3. Final anisotropic temperature factors with e.s.d's in parenthesis for (1S,2R,8S,8aR)-1,2,8-trihydroxy-5-oxo-octahydroindolizine (atomic labelling as in Figure).

Atom	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
N(1)	0.0409(7)	0.0376(7)	0.0388(7)	-0.0006(5)	-0.0010(5)	0.0083(5)
O(1)	0.0415(6)	0.0631(8)	0.073(1)	-0.0095(7)	0.0056(7)	0.0079(6)
O(2)	0.080(1)	0.0570(8)	0.0577(9)	0.0165(7)	-0.0165(8)	-0.0011(8)
O(3)	0.0428(7)	0.0749(9)	0.0420(8)	0.0018(6)	-0.0037(6)	0.0059(6)
O(4)	0.0565(8)	0.0653(9)	0.0550(8)	-0.0078(7)	0.0184(7)	-0.0127(6)
C(1)	0.0438(8)	0.0480(9)	0.0418(8)	-0.0007(7)	-0.0025(6)	0.0013(7)
C(2)	0.064(1)	0.054(1)	0.071(1)	0.005(1)	0.002(1)	-0.0098(9)
C(3)	0.082(2)	0.0396(9)	0.075(2)	-0.0005(9)	-0.007(1)	-0.0015(9)
C(4)	0.067(1)	0.0400(9)	0.064(1)	-0.0009(9)	-0.009(1)	0.0148(8)
C(5)	0.0497(9)	0.0424(8)	0.0405(9)	-0.0069(7)	-0.0010(6)	0.0145(7)
C(6)	0.0415(8)	0.057(1)	0.0367(8)	-0.0052(7)	0.0043(7)	0.0118(7)
C(7)	0.0488(9)	0.052(1)	0.0331(8)	-0.0005(7)	0.0051(7)	0.0020(7)
C(8)	0.0422(8)	0.0391(8)	0.0434(8)	-0.0004(7)	0.0001(7)	0.0063(6)

Table 4. Bond lengths (A) for the non-hydrogen atoms with e.s.d.'s in parenthesis (atomic labelling as in Figure) for (1S,2R,8S,8aR)-1,2,8-trihydroxy-5-oxo-octahydroindolizine.

N(1)	C(1)	1.331(2)
N(1)	C(5)	1.470(2)
N(1)	C(8)	1.457(2)
O(1)	C(1)	1.242(2)
O(2)	C(4)	1.440(3)
O(3)	C(6)	1.421(2)
O(4)	C(7)	1.401(2)
C(1)	C(2)	1.507(3)
C(2)	C(3)	1.521(4)
C(3)	C(4)	1.518(4)
C(4)	C(5)	1.520(3)
C(5)	C(6)	1.530(3)
C(6)	C(7)	1.541(3)
C(7)	C(8)	1.522(2)

Table 5. Bond angles (°) for the non-hydrogen atoms with e.s.d.'s in parenthesis (atomic labelling as in Figure) for (1S,2R,8S,8aR)-1,2,8-trihydroxy-5-oxo-octahydroindolizine.

C(5)	N(1)	C(1)	125.6(1)
C(8)	N(1)	C(1)	121.9(1)
C(8)	N(1)	C(5)	112.3(1)
O(1)	C(1)	N(1)	120.9(2)
C(2)	C(1)	N(1)	118.4(2)
C(2)	C(1)	O(1)	120.6(2)
C(3)	C(2)	C(1)	116.8(2)
C(4)	C(3)	C(2)	111.7(2)
C(3)	C(4)	O(2)	107.5(2)
C(5)	C(4)	O(2)	111.7(2)
C(5)	C(4)	C(3)	108.3(2)
C(4)	C(5)	N(1)	109.5(2)
C(6)	C(5)	N(1)	103.4(1)
C(6)	C(5)	C(4)	119.0(2)
C(5)	C(6)	O(3)	110.8(2)
C(7)	C(6)	O(3)	111.5(2)
C(7)	C(6)	O(5)	102.2(1)
C(6)	C(7)	O(4)	115.3(2)
C(8)	C(7)	O(4)	109.0(1)
C(8)	C(7)	C(6)	103.8(1)
C(7)	C(8)	N(1)	103.8(1)

Experimental

M.p.s were recorded on a Kofler block. Infra red spectra were recorded on a Perkin-Elmer 297 spectrophotometer. ^{1}H NMR spectra were run at 300 MHz on a Bruker WH 300 spectrometer (500 MHz on a Bruker AM 500 spectrometer); ^{13}C NMR spectra were recorded on a Bruker AM 250 (62.9 MHz) or a Bruker AM 500 (125.0 MHz) spectrometer. All NMR spectra were obtained using deuteriochloroform as solvent unless otherwise stated; for ^{13}C NMR spectra in D_2O, 1,4-dioxane (δ 67.6) was used as the internal

standard. Mass spectra were recorded on VG Micromass ZAB 1F or MM 30F spectrometers; in order to obtain satisfactory mass spectra for these highly polar compounds, it was necessary to use DCI or FAB techniques. Microanalyses were performed by the microanalytical services of the Dyson Perrins Laboratory or of the Chemistry Department of Manchester University. TLC was performed on glass plates coated with silica gel Blend 41, and compounds were visualised with a spray of 5% v/v sulphuric acid in ethanol or a solution of 5% dodecamolybdophosphoric acid in ethanol. Flash chromatography was carried out using Merck Kieselgel 60, 230-400 mesh. Tetrahydrofuran was distilled from a solution dried with sodium in the presence of benzophenone under dry nitrogen. Dimethylphosphonoacetic acid was prepared by alkaline hydrolysis of trimethylphosphonoacetate as previously reported.[29] Diacetone glucose was obtained from Sigma Chemical Company and was used without purification.

1,2;5,6-Di-O-isopropylidene-α-D-allofuranose (10). Pyridinium chlorochromate (25.8 g, 0.12 mol) and powdered molecular sieve (30 g) were added to diacetone glucose (6) (15.67 g, 0.06 mol) in dry dichloromethane (100 ml) and the mixture was stirred at room temperature for 3 h. The resulting suspension was diluted with ether (100 ml), triturated and filtered through a silica plug (eluted with ether). The solvent was removed from filtrate to give the crude ketone which was not isolated, but dissolved in a mixture of ethanol (90 ml) and water (10 ml) and cooled to 0°C. Sodium borohydride (6 g, 0.16 mol) was added and the solution stirred for 1 h. Addition of an excess of ammonium chloride destroyed unreacted borohydride and the resulting solution was concentrated. The crude material was dissolved in chloroform (200 ml) and washed with water (2 x 100 ml), dried (sodium sulphate) and concentrated to give 1,2;5,6-di-O-isopropylidene-α-D-allofuranose (10), (12.37 g, 84%), m.p. 72-74°C (lit.[30] 77-78°C), which could be used for the next stage without any further purification.

3-Azido-3-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (13). 1,2;5,6-Di-O-isopropylidene-α-D-allofuranose (10) (11.04 g, 42.5 mmol) was dissolved in dry dichloromethane (150 ml) containing pyridine (6.9 ml, 2 equivs) and the solution cooled to -30°C under an atmosphere of nitrogen. Trifluoromethanesulphonic anhydride (14.38 g, 1.2 equivs) was added dropwise over 10 min and the suspension stirred for a further 30 min. The reaction was quenched by addition of methanol (5 ml) and the clear solution obtained was allowed to warm to room temperature. The solution was washed with water (2 x 100 ml), dried and evaporated to a pale yellow syrup of crude 1,2;5,6-di-O-isopropylidene-3-O-trifluoromethanesulphonyl-α-D-allofuranose (11) which was not purified but dissolved in dimethylformamide (100 ml) and stirred at 50°C for 8 h with sodium azide (5.5 g, 2 equiv). The solvent was evaporated and the residue partitioned between chloroform (100 ml) and water (100 ml). The organic layer was dried and concentrated to a syrup containing 3-azido-3-deoxy-1,2;5,6-di-O-isopropylidene-α-D-glucofuranose (12) (11.12 g, 92%). A small quantity was purified by flash chromatography to give (12), a colourless oil, $[\alpha]_D^{20}$ -41.8° (*c*, 4.3 in $CHCl_3$) [lit.[8] $[\alpha]_D^{20}$ -41.5° (*c*, 2.0 in $CHCl_3$)]. ν_{max} 2120 cm^{-1}. ^1H NMR δ 5.90 (1H, d, H-1); 4.60 (1H, d, H-2); 4.25 (1H, m, H-5); 4.15 (2H, m, H-6,6');3.95 (1H, dd, H-4); 1.50, 1.45, 1.35, 1.30 (12H, 4s, CH_3C). *m/z* 286 (M + H+). The remaining (12) was dissolved in methanol : acetic acid : water (50 ml, 40 ml, 60 ml) and heated at 50°C for 12 h. The solvent was removed and the residue partitioned between chloroform (200 ml) and saturated aqueous sodium bicarbonate solution (200 ml). The organic layer was dried and evaporated and the resulting product filtered through a silica plug (eluted with ether) to give 3-azido-3-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (13) (9.55 g, 100%) as a colourless syrup

which crystallised. m.p. 86-87°C, (lit.[1] 84-85°C). $[\alpha]_D^{20}$ -32.3° (c, 0.95 in $CHCl_3$) [lit.[1] $[\alpha]_D^{20}$ -30° (c, 1.0 in $CHCl_3$)]. ν_{max} 3540-3320, 2100 cm^{-1}. ^1H NMR δ 5.90 (1H, d, H-1); 4.65 (1H, d, H-2); 4.25-3.75 (5H, m, H-3,4,5,6,6'); 2.65 (1H, br d, OH); 2.20 (1H, br s, OH); 1.55, 1.40 (6H, 2s, CH_3C). m/z : 263 ($M + NH_4^+$), 220 (100%). (Found C, 44.5; H, 6.4; N, 17.0. $C_9H_{15}N_3O_5$ requires C, 44.1; H, 6.1; N, 17.1%).

3-Azido-3-deoxy-1,2-O-isopropylidene-6-O-p-toluenesulphonyl-α-D-glucofuranose (14). 3-Azido-3-deoxy-1,2-O-isopropylidene-α-D-glucofuranose (13) (5.1 g, 20.8 mmol) was dissolved in dry pyridine (60 ml) and p-toluenesulphonyl chloride (4.16 g, 21.8 mmol) was added, with stirring at -10°C. The solution was kept at this temperature for 24 h. The bulk of the pyridine was removed, and the solution was diluted with dichloromethane (100 ml) and washed successively with hydrochloric acid (2M aq, 100 ml), water (100 ml) and aqueous saturated sodium bicarbonate solution (100 ml). The organic layer was dried and evaporated to a syrup which was filtered through a silica plug (eluted with ether) to give 3-azido-3-deoxy-1,2-O-isopropylidene-6-O-p-toluenesulphonyl-α-D-glucofuranose (14), (7.42 g, 89%), as a syrup, $[\alpha]_D^{20}$ -9.0° (c, 4.7 in $CHCl_3$). ν_{max} 3600, 2120, 1360, 1180 cm^{-1}. ^1H NMR δ 7.80, 7.30 (4H, 2d, ArH); 5.80 (1H, d, H-1); 4.60 (1H, d, H-2); 4.3-4.0 (5H, m, H-3,4,5,6,6'); 3.1 (1H, br s, OH); 2.45 (3H, s, CH_3Ar); 1.40, 1.30 (6H, 2s, CH_3C). m/z : 417 ($M + NH_4^+$). (Found C, 48.5; H, 5.3; N, 10.4. $C_{16}H_{21}N_3O_7S$ requires C 48.1; H, 5.3; N, 10.5%).

3,6-Dideoxy-3,6-imino-1,2-O-isopropylidene-α-D-glucofuranose p-toluenesulphonate (1). 3-Azido-3-deoxy-1,2-O-isopropylidene-6-O-p-toluenesulphonyl-α-D-glucofuranose (14) (7.42 g, 18.6 mmol) was dissolved in ethanol (80 ml) and hydrogenated in the presence of palladium black (0.28 g). After a few minutes the title compound (1) began to crystallise from the reaction mixture. After 24 h, the crystallised material was re-dissolved by addition of water (100 ml) and the catalyst was removed by filtration. The solvent was evaporated and recrystallisation of the residue from hot ethanol gave 3,6-dideoxy-3,6-imino-1,2-O-isopropylidene-α-D-glucofuranose p-toluenesulphonate (1), (5.31 g, 77% yield; 53% yield from diacetone glucose), white needles, m.p 187-188°C. $[\alpha]_D^{20}$ +28.1° (c, 0.83 in H_2O). ^1H NMR (D_2O) δ 7.5, 7.2 (4H, 2d, ArH); 6.0 (1H, d, H-1, $J_{1,2}$ 3.8 Hz); 4.97 (1H, d, H-2); 4.81 (1H, t, H-4); 4.37 (1H, ddd, H-5); 4.18 (1H, d, H-3, $J_{3,4}$ 3.9 Hz); 3.35 (1H, dd, H-6, $J_{6,6'}$ 11.7 Hz, $J_{5,6}$ 6.6 Hz); 3.03 (1H, dd, H-6', $J_{5,6'}$ 8.5 Hz); 2.23 (3H, s, CH_3Ar); 1.37, 1.22 (6H, 2s, CH_3C). ^{13}C NMR (D_2O) δ 20.26 (q, CH_3Ar); 25.46, 25.81 (2q, CH_3C); 47.83 (t, C-6); 65.21 (d, C-3); 69.21 (d, C-5); 81.74, 82.56 (2d, C-2,4); 106.29 (d, C-1); 113.96 (s, CH_3C); 125.20 (d), 129.29 (d), 139.35 (s), 142.29 (s) (ArC). m/z (FAB, Ar+) : 202 ($M + H^+$, 100%) (Found C, 51.4; H, 6.2; N, 3.7. $C_{16}H_{23}NO_6S$ requires C, 51.5; H, 6.2; N, 3.8%).

1,4-Dideoxy-1,4-imino-L-gulitol Hydrochloride (3). 3,6-Dideoxy-3,6-imino-1,2-O-isopropylidene-α-D-glucofuranose p-toluenesulphonate (1) (0.2 g, 0.54 mmol) was dissolved in 50% aqueous trifluoroacetic acid (4 ml) and warmed to 50°C for 1 h. [The reaction could be monitored by NMR if D_2O was used by observing the disappearance of the two isopropylidene singlets (δ 1.5, 1.3) and appearance of the singlet of acetone (δ 2.05)]. The solvent was removed and several co-distillations with toluene ensured removal of virtually all traces of TFA. The resulting syrup was dissolved in 50% aqueous ethanol, neutralised with aqueous sodium hydroxide (2M) and then treated with sodium borohydride (25 mg, excess). After 15 min, the reaction was quenched with ammonium chloride and the reaction mixture concentrated to a volume of 2 ml. This solution was loaded directly onto an acid ion exchange column (Dowex 50W-XH, H^+ form). The inorganic impurities were washed away with distilled water and then the amine (3) was eluted from the column with aqueous

ammonium hydroxide (0.5 M). After freeze drying, the free amine (3) was obtained (69 mg, 76%) as a colourless syrup. Neutralisation of the amine with dilute aqueous hydrochloric acid and further freeze drying gave crystalline 1,4-dideoxy-1,4-imino-L-gulitol hydrochloride (3), m.p. 170-173°C. $[\alpha]_D^{20}$ +7.1° (c, 0.48 in H_2O). ν_{max} (KBr) : 3392, 2961, 2741, 2579, 2497, 2424, 2364, 2041, 1910, 1601, 1478, 1450, 1397, 1377, 1288, 1231 cm^{-1}. ^1H NMR (D_2O) δ 4.35 (1H, dt, H-2, $J_{2,3}$ 4.0 Hz, $J_{1,2}$ 8.3 Hz); 4.13 (1H, t, H-3); 3.98 (1H, m, H-5); 3.62 (1H, dd, H-6, $J_{6,6'}$ 12.2 Hz); 3.45 (3H, m, H-1,4,6'); 3.01 (1H, dd, H-1', $J_{1,1'}$ 12.0 Hz). ^{13}C NMR (D_2O) δ 47.48 (t, C-1); 63.97 (t and d, C-4 and C-6); 69.07, 70.68, 71.32 (3d, C-2, C-3 and C-5). m/z: 164 ($M + H^+$, 100%) (Found C, 35.99; H, 7.07; N, 6.66. $C_6H_{14}NO_4Cl$ requires C, 36.09; H, 7.02; N, 7.02%).

N-Benzyloxycarbonyl-3,6-dideoxy-3,6-imino-1,2-O-isopropylidene-α-D-glucofuranose (15). Benzyl chloroformate (2 ml, 8.94 mmol) was added to a vigorously stirred suspension of 3,6-dideoxy-3,6-imino-1,2-O-isopropylidene-α-D-glucofuranose (1) (2 g, 5.36 mmol) partitioned between ether (30 ml) and saturated aqueous sodium bicarbonate solution (12 ml) at 0°C. After 1 h, the two layers were separated and the organic layer dried and concentrated to a syrup. Purification of the residue by flash chromatography (ethyl acetate : hexane, 1:1) afforded N-benzyloxycarbonyl-3,6-dideoxy-3,6-imino-1,2-O-isopropylidene-α-D-glucofuranose (15), (1.7 g, 95%), as a colourless syrup. $[\alpha]_D^{20}$ -28.2° (c, 0.44 in $CHCl_3$). ν_{max} 3500-3300, 1700 cm^{-1}. ^1H NMR δ 7.45-7.30 (5H, m, ArH); 5.87 (1H, d, H-1, $J_{1,2}$ 3.3 Hz); 5.13-4.31 (5H, m); 4.1, 3.94, 3.05 (3H, m, H-3,6,6'); 2.5 (1H, br s, OH); 1.52, 1.33 (6H, 2s, CH_3C). m/z : 353 ($M + NH_4^+$, 100%), 336 (Found C, 60.9; H, 6.7; N, 4.3. $C_{17}H_{21}NO_6$ requires C, 60.9; H, 6.3; N, 4.2%).

N-Benzyloxycarbonyl-5-O-benzyl-3,6-dideoxy-3,6-imino-1,2-O-isopropylidene-α-D-glucofuranose (16). N-Benzyloxycarbonyl-3,6-dideoxy-3,6-imino-1,2-O-isopropylidene-α-D-glucofuranose (15) (1.7 g, 5.1 mmol) in dry tetrahydrofuran (10 ml) was added to a stirred suspension of sodium hydride (50% dispersion in oil, pre-washed with hexane, 0.25 g, 1.1 equiv) in tetrahydrofuran (10 ml) at 0°C. Benzyl bromide (0.66 ml, 5.5 mmol) and tetrabutylammonium iodide (0.2 g) were added to the suspension and the reaction mixture was refluxed for 1 h. The solvent was removed and the residue partitioned between chloroform (50 ml) and water (50 ml). The organic layer was dried and concentrated to a syrup. Purification by flash chromatography (ethyl acetate : hexane, 1:3) gave N-benzyloxycarbonyl-5-O-benzyl-3,6-dideoxy-3,6-imino-1,2-O-isopropylidene-α-D-glucofuranose (16), (1.82 g, 84%), as a clear syrup. $[\alpha]_D^{20}$ -25.2° (c, 0.79 in $CHCl_3$). ν_{max} 1680 cm^{-1}. ^1H NMR δ 7.3-7.2 (10H, m, ArH); 5.95 (1H, d, H-1); 5.15-4.1 (7H, m); 3.9-3.15 (3H, m, H-3,6,6'); 1.45, 1.25 (6H, 2s, CH_3C). m/z : 443 ($M + NH_4^+$), 426, 368 (100%) (Found C, 68.2; H, 6.4; N, 3.5. $C_{24}H_{27}NO_6$ requires C, 67.8; H, 6.4; N, 3.3%).

N-Benzyloxycarbonyl-5-O-benzyl-3,6-dideoxy-3,6-imino-D-glucofuranose (18). N-Benzyloxycarbonyl-5-O-benzyl-3,6-dideoxy-3,6-imino-1,2-O-isopropylidene-α-D-glucofuranose (16) (1.82 g, 4.28 mmol) was dissolved in 50% aqueous trifluoroacetic acid (10 ml) and stored at room temperature for 4 h. The solvent was removed and the residue purified by flash chromatography (ethyl acetate : hexane, 1:1) to give N-benzyloxycarbonyl-5-O-benzyl-3,6-dideoxy-3,6-imino-D-glucofuranose (18), (1.58 g, 96%), as a hygroscopic syrup, $[\alpha]_D^{20}$ -16.7° (c, 0.76 in $CHCl_3$). ν_{max} 3500-3300, 1680 cm^{-1}. ^1H NMR δ 7.4-7.25 (10H, m, ArH); 5.55-5.41 (8H, m); 3.9, 3.8, 3.3 (3H, m, H-3,6,6'). m/z : 403 ($M + NH_4^+$), 386, 368, 91 (100%) (Found C, 65.1; H, 6.0; N, 3.65. $C_{21}H_{23}NO_6$ requires C, 65.4; H, 6.0; N, 3.64%).

N-Benzyloxycarbonyl-2-O-benzyl-1,4-dideoxy-1,4-imino-D-lyxitol (20). N-Benzyloxycarbonyl-5-O-benzyl-3,6-dideoxy-3,6-imino-D-glucofuranose (18) (1.4 g, 3.64 mmol) was dissolved in 50% aqueous ethanol (25 ml) and stirred at room temperature for 1 h with sodium periodate (0.86 g, 1.1 equivs). Sodium borohydride (75 mg, 0.5 molar equivs) was added and the stirring continued for 15 min. Excess ammonium chloride was added to consume unreacted borohydride and the mixture concentrated to a syrup, which was partitioned between chloroform (50 ml) and water (50 ml). The organic layer was dried and evaporated to a syrup. Purification of the residue by flash chromatography (ethyl acetate : hexane, 1:1) gave N-benzyloxycarbonyl-2-O-benzyl-1,4-dideoxy-1,4-imino-D-lyxitol (20), (1.09 g, 84%), as a clear syrup, $[\alpha]_D^{20}$ -50.5° (c, 0.37 in $CHCl_3$). ν_{max} 3420-3300, 1680 cm^{-1}. ^1H NMR δ 7.4-7.25 (10H, m, ArH); 5.15-3.90 (9H, m); 3.75, 3.60 (2H, 2m, H-1,1'). m/z: 358 ($M + H^+$).

1,4-Dideoxy-1,4-imino-D-lyxitol Hydrochloride (4). N-Benzyloxycarbonyl-2-O-benzyl-1,4-dideoxy-1,4-imino-D-lyxitol (20) (1.09 g, 3.05 mmol) was dissolved in glacial acetic acid (10 ml) and hydrogenated in the presence of palladium black (0.1 g) for 24 h. The catalyst was filtered and the solvent evaporated. Purification of the residue by ion exchange chromatography (Sigma CG 120, H^+ form, eluted with aqueous ammonia, then freeze dried) afforded the free base (4); an aqueous solution of (4) was titrated to pH 4 with dilute hydrochloric acid solution and freeze dried to produce 1,4-dideoxy-1,4-imino-D-lyxitol hydrochloride (4), (0.34 g, 66%), m.p. 159-161°C. $[\alpha]_D^{20}$ +19.8° (c, 0.45 in H_2O). ^1H NMR (D_2O) δ 4.31 (1H, dt, H-2, $J_{2,3}$ 4.1 Hz); 4.17 (1H, t, H-3, $J_{3,4}$ 4.1 Hz); 3.81 (1H, dd, H-5, $J_{4,5}$ 5.0 Hz); 3.72 (1H, dd, H-5', $J_{5,5'}$ 12.1 Hz, $J_{4,5'}$ 8.4 Hz); 3.56 (1H, m, H-4); 3.36 (1H, dd, H-1, $J_{1,2}$ 7.3 Hz); 3.03 (1H, dd, H-1', $J_{1,1'}$ 12.2 Hz, $J_{1',2}$ 7.3 Hz). ^{13}C NMR (D_2O) δ 70.70, 70.55 (2d, C-2,3); 63.22 (d, C-4); 58.38 (t, C-5); 47.87 (t, C-1). m/z: 134 ($M + H^+$, 100%), 102 (Found C, 35.4; H, 7.1; N, 8.0; Cl, 20.7. $C_5H_{12}NO_3Cl$ requires C, 35.4; H, 7.1; N, 8.26; Cl, 20.9%).

(2S,3S,4R)-3,4-Dihydroxyproline (4). N-Benzyloxycarbonyl-5-O-benzyl-3,6-dideoxy-3,6-imino-D-glucofuranose (16) (0.57 g, 1.49 mmol) was dissolved in ethanol : water (3:1, 32 ml) and stirred at room temperature with sodium periodate (1.24 g, 5.8 mmol). After 2 h, the solution was filtered and concentrated and the residue partitioned between water (10 ml) and chloroform (10 ml). The chloroform layer was dried and concentrated to a syrup. The crude syrup was dissolved in tert-butyl alcohol (20 ml) containing cyclohexene (1.4 ml, 13.8 mmol). A solution of sodium chlorite (1.3 g, 14.4 mmol) and potassium dihydrophosphate (1.4 g, 10.3 mmol) in water (7 ml) was added with vigorous stirring and the solution became yellow in appearance. After 12 h the colour had disappeared and the solvent was removed. The residue was partitioned between water (5 ml) and ethyl acetate (20 ml) and the organic extract was dried and concentrated to a syrup. The crude syrup was dissolved in glacial acetic acid (10 ml) and stirred under hydrogen with palladium black catalyst (50 mg) for 24 h. The catalyst was filtered and the solvent evaporated. Purification of the residue by ion exchange chromatography (Aldrich 50X 8-100, H^+ form, eluted with aqueous pyridine) gave (2S,3S,4R)-3,4-dihydroxyproline (4), (0.08 g, 36% over 3 steps), as white crystals, m.p. decomposes above 220°C. $[\alpha]_D^{20}$ -56.8° (c, 0.16 in H_2O). ν_{max} (KBr) 3460, 3160, 3080, 2980, 2940, 1625, 1420 cm^{-1}. ^1H NMR (D_2O) δ 4.29 (2H, m, H-3,4); 3.96 (1H, d, H-2, $J_{2,3}$ 3.9 Hz); 3.35 (1H, dd, H-5, $J_{4,5}$ 7.5 Hz); 3.07 (1H, dd, H-5', $J_{5,5'}$ 11.4 Hz, $J_{4,5'}$ 8.8 Hz). ^{13}C NMR (D_2O) δ 47.62 (t, C-5); 65.36 (d, C-2); 71.36, 71.65 (2d, C-3,4); 171.20 (s, C-1). m/z: 165 ($M + NH_4^+$), 148 ($M + H^+$, 100%), 102, 84, 68 (Found C, 40.78; H, 6.67; N, 9.52. $C_5H_9NO_4$ requires C, 40.82; H, 6.12; N, 9.71%)

N-Dimethylphosphonoacetyl-3,6-dideoxy-3,6-imino-1,2-O-isopropylidene-α-D-glucofuranose (17). A solution of 3,6-dideoxy-3,6-imino-1,2-O-isopropylidene-α-D-glucofuranose p-toluenesulphonate (1) (2 g, 5.36 mmol) in dimethyl formamide (10 ml) was neutralised with triethylamine (1.12 ml, 1.5 equivs) and added to a solution of dimethylphosphonoacetic acid (1.35 g, 1.5 equivs) and N,N'-dicyclohexylcarbodiimide (1.66 g, 1.5 equivs) in dimethyl formamide (10 ml) at 0°C. The solution was allowed to warm to room temperature and stirred for 8 h. The dicyclohexylurea produced by the reaction was removed by filtration and the solution concentrated to a syrup. Purification by flash chromatography (10% ethanol in chloroform) gave N-dimethylphosphonoacetyl-3,6-dideoxy-3,6-imino-1,2-O-isopropylidene-α-D-glucofuranose (17), (1.63 g, 87%), m.p. 123-124°C, $[\alpha]_D^{20}$ -40.6° (c, 0.34 in MeOH). ν_{max} 3400 (br), 1640 cm^{-1}. ^1H NMR δ 5.9 (1H, d, H-1); 4.9-3.1 (7H, m); 3.8 (6H, 2m, CH_3O); 3.0 (2H, d, CH_2P); 1.5, 1.3 (6H, 2s, CH_3C). m/z : 369 ($M + NH_4^+$), 308 (100%) (Found C, 44.6; H, 6.5; N, 3.8; P, 8.6. $C_{13}H_{22}NO_8P$ requires C, 44.4; H, 6.3; N, 4.0; P, 8.8%).

N-Dimethylphosphonoacetyl-3,6-dideoxy-3,6-imino-D-glucose (19). N-Dimethylphosphonoacetyl-3,6-dideoxy-3,6-imino-1,2-O-isopropylidene-α-D-glucofuranose (17) (1 g, 2.8 mmol) was dissolved in 50% aqueous trifluoroacetic acid (10 ml) and stirred at 50°C for 1 h. The solvent was removed and purification by flash chromatography (20% methanol in chloroform) gave N-dimethylphosphonoacetyl-3,6-dideoxy-3,6-imino-D-glucose (19), (0.88 g, 100%), as a foam, $[\alpha]_D^{20}$ -49.1° (c, 0.4 in EtOH). ν_{max} 3500-3200, 1630 cm^{-1}. ^1H NMR (D_2O) δ 5.2 (1H, m, H-1); 4.2-3.2 (6H, m); 3.6 (6H, 2m, CH_3O); 3.1 (2H, d, CH_2P). m/z : 312 ($M + H^+$).

(1S,2R,8S,8aR)-1,2,8-tri-O-Acetyl-5-oxo-octahydroindolizine (23). N-Dimethylphosphonoacetyl-3,6-dideoxy-3,6-imino-D-glucose (19) (0.55 g, 1.78 mmol) was stirred at 70°C for 12 h with potassium carbonate (0.74 g, 3 equivs) and 18-crown-6 (0.47 g, 1 equiv) in dimethyl formamide (12 ml). The progress of this cyclisation was difficult to monitor since both the lactol (19) and the lactam had very similar R_f values (0.25 in 20% methanol in chloroform). The product was, however, strongly u.v. active in contrast to the starting lactol (19), so it was possible to follow the progress of the reaction by t.l.c.; after several experiments, it was established that the reaction was complete after 12 h. The solution was cooled, filtered through celite, concentrated and purified by flash chromatography (20% methanol in chloroform) to give the cyclised α,β-unsaturated δ-lactam contaminated with 18-crown-6 [ν_{max} 3400 (br), 1660, 1590 cm^{-1}. ^1H NMR (D_2O) δ 6.68 (1H, dd, H-7, $J_{6,7}$ 9.8 Hz, $J_{7,8}$ 6.0 Hz); 5.90 (1H, d, H-6); 4.49 (1H, dd, H-1, $J_{1,2}$ 4.0 Hz); 4.43 (1H, dd, H-8, $J_{8,8a}$ 3.5 Hz); 4.20 (1H, dt, H-2, $J_{2,3}$ 6.9 Hz); 3.75 (1H, m, H-8a); 3.64 (1H, ddd, H-3, $J_{3,3'}$ 12.2 Hz, $J_{3,8a}$ 1.0 Hz); 3.29 (1H, ddd, H-3', $J_{3',8a}$ 1.3 Hz). m/z : 282 (18 crown 6 + NH_4^+, 100%), 186 ($M + H^+$)]. The crude unsaturated lactam was dissolved in ethanol (8 ml) and hydrogenated in the presence of palladium black (40 mg). The progress of the reaction was monitored by the disappearance of u.v activity on t.l.c as the saturated and unsaturated amides had identical R_f values (0.25 in 20% methanol in chloroform). After 1 h, no starting material remained. The catalyst was removed by filtration and the solvent evaporated. Purification by flash chromatography gave the saturated amide (1S,2R,8S,8aR)-1,2,8-trihydroxy-5-oxo-octahydroindolizine (22) contaminated with 18-crown-6. [A pure sample of (22) was prepared by de-acetylation of the triacetate (23) using sodium methoxide in methanol at 50°C, $[\alpha]_D^{20}$ -2.0° (c, 0.66 in MeOH) [lit.[22] $[\alpha]_D^{25}$ +44.0° (MeOH)]. ^1H NMR (D_2O) δ 3.72 (1H, dt, H-8); 3.68 (1H, t, H-1); 3.56 (1H, dt, H-2); 3.00 (1H, m, H-8a); 2.92 (1H, dd, H-3, $J_{3,3'}$ 12.0 Hz); 2.59 (1H, ddd, H-3'); 1.63 (2H, m, H-6,6'); 1.2 (2H, m, H-7,7'). m/z : 188 ($M + H^+$,

100%) (Found C, 51.33; H, 7.15; N, 7.89. $C_8H_{13}NO_4$ requires C, 51.34; H, 6.95; N, 7.49%)].

The crude saturated amide (22) was dissolved in pyridine (2 ml) containing acetic anhydride (1 ml). The solution was heated to 50°C for 4 h, when t.l.c (ethyl acetate : acetone, 3:1) showed a single product (R_f 0.3). The solvent was removed and purification of the residue by flash chromatography (ethyl acetate : acetone, 3:1) gave (1S,2R,8S,8aR)-1,2,8-tri-O-acetyl-5-oxo-octahydroindolizine (23), (0.26 g, 47% over three steps). m.p. 127-128°C (lit.[23] 126-127°C). $[\alpha]_D^{20}$ -17.2° (c, 0.25 in $CHCl_3$) [lit.[23] $[\alpha]_D^{21}$ -21.8° (c 0.9, $CHCl_3$)]. ν_{max} 1740, 1640, 1235 cm^{-1}. ^1H NMR δ 5.56 (1H, t, H-1); 5.39 (1H, dt, H-8); 5.30 (1H, dt, H-2); 3.98 (1H, dd, H-8a); 3.82 (1H, dd, H-3); 3.71 (1H, dd, H-3'); 2.32 (2H, m, H-6,6'); 2.01 (2H, m, H-7,7'); 2.08, 2.07, 2.05 (9H, 3s, CH_3CO). ^{13}C NMR δ 20.50 (2q), 21.04 (q, $\underline{C}H_3CO$); 26.24 (t, C-7); 27.04 (t, C-6); 46.78 (t, C-3); 60.00 (d, C-8a); 64.70, 69.06, 71.60 (t, C-1,2,8); 168.02 (s, C-5); 169.61 (s), 169.73 (2s, $CH_3\underline{C}O$). m/z (ACE, NH_3): 314 ($M + H^+$, 100%) (Found C, 53.52; H, 6.13; N, 4.27. $C_{14}H_{19}NO_7$ requires C, 53.67; H, 6.07; N, 4.47%).

(1S,2R,8S,8aR)-1,2,8-Tri-O-acetyl-octahydroindolizine borane adduct (24). (1S,2R,8S,8aR)-1,2,8-Tri-O-acetyl-5-oxo-octahydroindolizine (23) (0.18 g, 0.58 mmol) was dissolved in dry tetrahydrofuran (15 ml) and borane dimethyl sulphide complex (0.3 ml) added at room temperature under a stream of dry nitrogen. After 1 h, the reaction was carefully quenched with water (10 ml) and extracted with chloroform (3 x 20 ml). The organic extracts were combined, dried and evaporated. Purification by flash chromatography (ethyl acetate : hexane, 2:3) gave (1S,2R,8S,8aR)-1,2,8-tri-O-acetyl-octahydroindolizine borane adduct (24), (0.12 g, 70%), m.p. 131-135°C. $[\alpha]_D^{20}$ -22.3° (c, 0.22 in $CHCl_3$). ν_{max} 2380, 1735, 1500 cm^{-1}. ^1H NMR δ 5.85 (1H, t, H-1); 5.58 (1H, dt, H-2); 5.32 (1H, m, H-8); 3.72 (1H, dd, H-8a); 3.60 (1H, dd, H-3); 3.35 (1H, dd, H-3'); 3.22 (2H, m, H-5); 2.05 (9H, 3s, CH_3CO); 1.9-1.7 (4H, m, H-6,6',7,7'). ^{13}C NMR δ 17.22 (t, C-6); 20.42 (2q), 21.05 (q, $\underline{C}H_3CO$); 26.30 (t, C-7); 56.83 (t), 63.91 (t, C-3,5); 65.43 (d, C-8a); 66.32 (d), 68.91 (d), 70.30 (d, C-1,2,8); 168.77 (s), 169.29 (2s, $CH_3\underline{C}O$). ^{11}B NMR δ -8.6 (br s). m/z (CI, NH_3): 300 ($M + H^+-BH_3$), 273, 231 (100%). (FD) 313. (Found C, 53.71; H, 7.88; N, 4.75. $C_{14}H_{21}NO_6BH_3$ requires C, 53.67; H, 7.67; N, 4.48%).

(1S,2R,8S,8aR)-1,2,8-Trihydroxy-octahydroindolizine (6). (1S,2R,8S,8aR)-1,2,8-Tri-O-acetyl-octahydroindolizine borane adduct (24) (50 mg, 0.16 mmol) was dissolved in methanol (5 ml) and stirred at 50°C for 2 h with a trace of sodium methoxide. The solution was evaporated to dryness and the residue dissolved in 50% aqueous trifluoroacetic acid (2 ml). After 5 min, the solvent was evaporated. Subsequent purification of the residue by ion exchange chromatography (Sigma CG 400, OH^- form, then Aldrich 50X 8-100, H^+ form elute with aqueous ammonia) and removal of the solvent by freeze drying afforded (1S,2R,8S,8aR)-1,2,8-trihydroxy-octahydroindolizine (6), (22 mg, 80%), $[\alpha]_D^{20}$ -25.0° (c, 0.1 in MeOH) [lit.[23] $[\alpha]_D^{21}$ -24.8° (c, 0.67 in MeOH). ^1H NMR (D_2O) δ 4.1 (2H, m, H-1,2); 4.05 (1H, dt, H-8); 2.9 (1H, dt, H-5); 2.8 (1H, dd, H-3); 2.3 (1H, dd, H-3'); 1.95 (1H, dd, H-8a); 1.9 (1H, dt, H-5'); 1.7-1.3 (4H, m, H-6,6',7,7'). ^{13}C NMR (CD_3OD) δ 20.6 (t, C-7); 32.0 (t, C-6); 54.2, 62.8 (2t, C-3,5); 67.5 (d, C-8a); 69.3, 69.9, 74.2 (3d, C-1,2,8) [lit.[23] 20.68, 32.08, 54.27, 62.98, 67.53, 69.40, 69.96, 74.29].

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