A new route to aminosugars from sugar nitrones: synthesis of 6-deoxynojirimycin

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Abstract: The 1,3-addition of methylmagnesium chloride to dialdose derived nitrones **3** and **7** afforded N-benzylhydroxylamines **4/5** and **8/9**, respectively, in high yields. The stereoselectivity of the addition reaction was improved by the use of trimethylsilyl triflate. The N–O bond reductive cleavages of N-benzylhydroxylamines took place in good yields and offered an easy access to N-benzylaminosugars. The potential of these aminosugars is demonstrated by the synthesis of glycosidase inhibitor 6-deoxynojirimycin **1a**. © 1997 Elsevier Science Ltd

Many naturally occurring polyhydroxylated piperidine alkaloids such as nojirimycin and congeners are endowed with a wide spectrum of biological activities and therapeutic applications in diabetes, obesity and AIDS due to their action of glycosidases inhibitors.[1] In recent years a considerable amount of work has been directed towards the synthesis of these compounds along with unnatural stereoisomers and analogues.[2,3] Most of these approaches make use of carbohydrates as chiral auxiliaries[4] or chiral building blocks.[5] The basic strategy from hexoses as chirons involves prior synthesis of a 5-aminosugar derivative and, subsequently, the formation of a nitrogen link between C-5 and C-1 of the six carbon sugar.[6] In this approach the introduction of amino functionality at C-5 of hexoses with retention of configuration is challenging. The general methods for the synthesis of 5-aminosugars involve: (i) double Walden inversion at C-5,[7] (ii) condensation of 1,2-O-isopropylidene-α-D-*xylo*-pentodialdo-1,4-furanose with benzylamine and HCN followed by reduction,[8] (iii) formation of C-5 ketoximes followed by reduction.[3]

We were particularly interested in the synthesis of 5-aminosugars and envisioned an altogether different approach as depicted in Scheme 1. If, for example, the target molecule is a (3R,4S,5R)-2,3,4,5-tetrahydroxy-6-substituted piperidine **1**, our retrosynthetic plan involves a nitrone as strategic intermediate, deriving from an appropriate sugar, in this case α-D-glucose, and the 1,3-addition of a suitable organometallic derivative to the nitrone group as the key reaction.


1   a : R = Me
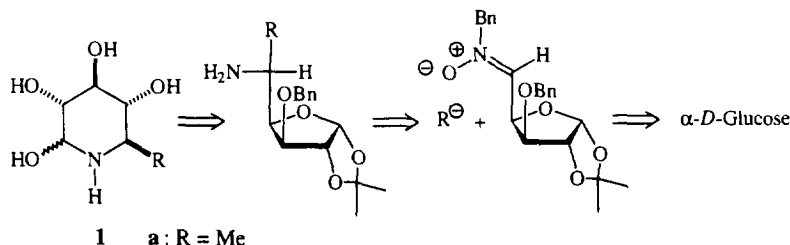
Scheme 1.

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Over the years, nitrones have been successfully applied in organic synthesis as 1,3-dipoles,[9] and a number of approaches to azasugars involving 1,3-dipolar cycloadditions has been reported.[4,10] However, the use of nitrones as electrophiles capable of reacting with different nucleophilic reagents such as Grignard[11] or other organometallic species[12] have received only limited attention, especially in carbohydrate chemistry. Such an approach has been exploited by us towards the synthesis of aminohexitols by 1,3-addition of allyl Grignard reagent to a D-glyceraldehyde derived nitrone.[13] The fact that this procedure gives an easy access to the synthesis of secondary amines prompted us to extend the approach to five carbon sugar nitrones which would lead to the synthesis of 5-aminosugars, immediate precursors of polyhydroxylated piperidines.

Results and discussion

Here we wish to show the synthetic flexibility of this method by the preparation of a series of diastereoisomeric fully protected 5,6-dideoxy-5-[(phenylmethyl)(hydroxy)amino]furanose derivatives **4,5,8** and **9** starting from 1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-*xylo*-pento-dialdose **2** and 1,2-*O*-isopropylidene-3-*O*-benzyl-α-D-*ribo*-pento-dialdose **6**, readily available from D-glucose. The usefulness of **4,5,8** and **9** is confirmed by their easy transformation into variously protected 5-amino furanoses **10–15**, and by a straightforward conversion of **5** into 6-deoxynojirimycin **1a**. 6-Deoxynojirimycins and their 1-deoxy derivatives have recently received attention both as synthetic targets and as bioactive compounds.[14]

The key step of our plan is represented by the reaction of methylmagnesium chloride (MeMgCl) with **3** and **7** (Scheme 2).[15] In a preliminary set of experiments on nitrone **3** we found that *N*-benzylhydroxylamines **4** and **5** in the ratio 39/61 and in overall 95% yield could be obtained by carrying out the reaction in THF at −30°C for 3 h using 2.5 equiv. of Grignard reagent (Table 1, entry 1). Attempts were made to improve the stereoselectivity of the addition reaction by performing the reaction in different solvents such as diethyl ether and dichloromethane[16] and under different reaction conditions (entries 2,3),[17] but, as demonstrated by the results collected in Table 1, no change in diastereoselectivity was observed.

R¹=OBn, R²=H **2**   **3**   **4**   **5**
R¹=H, R²=OBn **6**   **7**   **8**   **9**
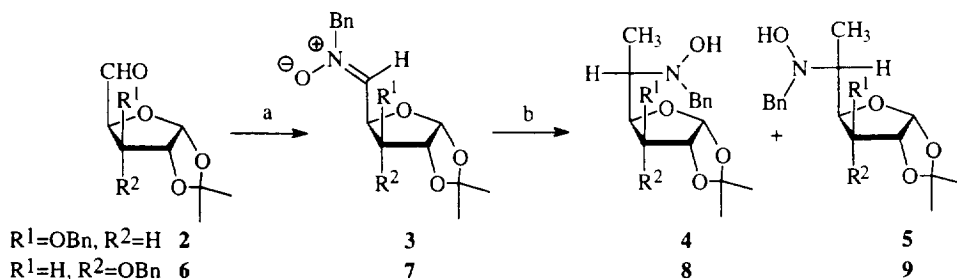
a: *N*-Benzylhydroxylamine HCl, AcONa, EtOH/H₂O, RT; b: MeMgCl

Scheme 2.

On the other hand nitrones offer a further opportunity; the presence of the oxygen atom, formally carrying a net negative charge, allows a strong complexation with Lewis acids to occur. The resulting *N*-oxy-immonium species display enhanced reactivity and, in some cases, different stereochemical outcomes[18,19] in reactions with nucleophiles. In this direction we recently exploited trimethylsilyl triflate (TMSOTf) as a promoter for the coupling of nitrones with a variety of silylated nucleophiles.[20] Thus, inspired by this behaviour, we reacted nitrone **3** with TMSOTf (1 equiv.) in THF for 30 min at −10°C, then MeMgCl (2.5 equiv.) was added at −78°C and the reaction mixture was stirred at this temperature for further 1 h (entry 4). After desilylation (2 N HCl, 30 min, 0°C), neutralisation

Table 1. Reaction of nitrones **3** and **7** with MeMgCl

Entry	Nitrone	Solvent	T(°C)	t(h)	TMSOTf (equiv.)	4/5 or 8/9 ratio[a]	Yield (%)[b]
1	3	THF	-30	3	-	39/61	95
2	3	Et₂O	0	2	-	42/58	90
3	3	CH₂Cl₂	-10	2	-	38/62	92
4	3	THF	-78	1	1	13/87	93
5	7	THF	-30	1	-	36/64	91
6	7	Et₂O	-10	2.5	-	40/60	90
7	7	CH₂Cl₂	-10	1.5	-	41/59	91
8	7	THF	-78	1	1	12/88	90

[a] Ratio determined from ^{1}H NMR integrals of the crude extract. [b] Overall isolated yields.

and extraction, N-benzylhydroxylamines **4** and **5** were recovered in overall 92% yield and in the 13/87 ratio, resulting in a significant improvement of the reaction diastereoselectivity. The appreciable difference in the R_f values allowed us to separate **4** and **5** by flash-chromatography.

With success in getting **4** and **5** in pure form and excellent yield, we sought to extend the Grignard reaction to allose-derived nitrone **7** in order to observe the effect on the stereochemical outcome of the inverted configuration of C-3. Again, no effect on the ratio of N-benzylhydroxylamines **8** and **9** was observed by changing solvents or temperature (entries 5–7), while the use of TMSOTf at −78°C afforded the best stereoselectivity (entry 8). Hydroxylamines **8** and **9** were easily separated too, by flash-chromatography, in pure form.

Stereochemical proofs and assignments

On the basis of NMR spectra it is not possible to establish the relative stereochemistry of stereocentres C-4/C-5 in hydroxylamines **4** and **5**. We got indirectly the right stereochemical assignments thanks to a lucky observation: the lower R_f N-benzylhydroxylamine **5**, obtained after chromatographic separation, was found to be unstable toward air oxidation[21] and, upon storage in ether solution, a white solid settled down. A single crystal collected upon slow evaporation at room temperature of a solution in cyclohexane/chloroform was found suitable for X-ray analysis and it corresponded to nitrone **16**, whose absolute structure is reported in Figure 1. The two five membered rings fused in cis configuration (dihedral angle 63.74(1)) are puckered, with C-4 and C-14 atoms out from the average planes C-1, C-2, O-2, C-3 and C-1, C-2, O-3, O-4 of 0.568(3) and −0.409(3) Å, respectively. The structure includes five stereogenic centres: C-1 (R), C-2 (R), C-4 (R), C-3 (S) and C-5 (R). The two phenyl rings are near orthogonal (dihedral angle 85.92(9) deg). The nitrone moiety (N1,O5,C5,C7) approximately lies on the phenyl plane linked to C-7 (dihedral angle 12.27(6) deg). Co-planarity optimises charge delocalization, as evidenced by the C7–C8 distance (1.449(3) Å), and favours a weak stabilising intramolecular CH–O bond (H-9···O-5 (2.25 Å)).

Thus, the configuration of C-5 was found to be R indicating the nitrone **16** as α-D-*gluco*-isomer. As **16** derived from **5** by air oxidation without change in the stereochemistry at C-5, we can assign the α-D-*gluco* structure to hydroxylamine **5**, and, conversely, compound **4** must be a β-L-*ido*-isomer.

The assignments of the configuration to C-5 in N-benzylhydroxylamines **8** and **9** was based on NMR data. It has been reported that in the D-*allo* series, for a given epimeric pair, the vicinal coupling constant between H-4 and H-5 is constantly smaller than that of the corresponding L-*talo* isomer.[22] An analogous trend has been noticed in our case and the coupling constant $J_{4,5}$=3.1 Hz observed
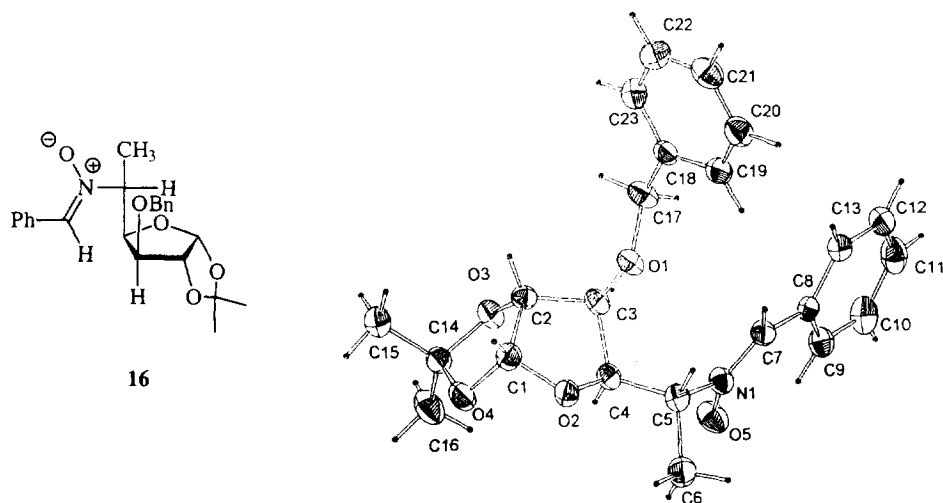
Figure 1. ORTEP Drawing of nitrone **16**. Selected interatomic lenghts (Å): O1–C3 1.423(2), O1–C17 1.431(3), O2–C1 1.406(3), O2–C4 1.436(3), O3–C2 1.419(3), O3–C14 1.432(2), O4–C1 1.403(3), O4–C14 1.421(3), O5–N1 1.289(2), N1–C7 1.289(3), N1–C5 1.496(3), C17–C18 1.498(3), H5···O1 2.52(2), C5···O1 2.864(3), H9···O5 2.25(2), C9···O5 2.872(3). Selected angles (deg): C3–O1–C17 112.9(2), C1–O2–C4 107.9(2), C2–O3–C14 108.0(2), C1–O4–C14 109.5(2), O5–N1–C7 125.2(2), O5–N1–C5 114.7(2), C7–N1–C5 120.1(2), O(4)–C(1)–O(2) 110.6(2), O(4)–C(1)–C(2) 105.4(2), C5–H···O1 101(1), C9–H9···O5 124(2). Selected torsion angles (deg): O5–N1–C7–C8 1.2(4), C5–N1–C7–C8 −178.5(2), C3–O1–C17–C18 168.5(2).
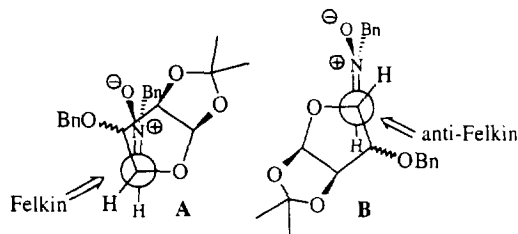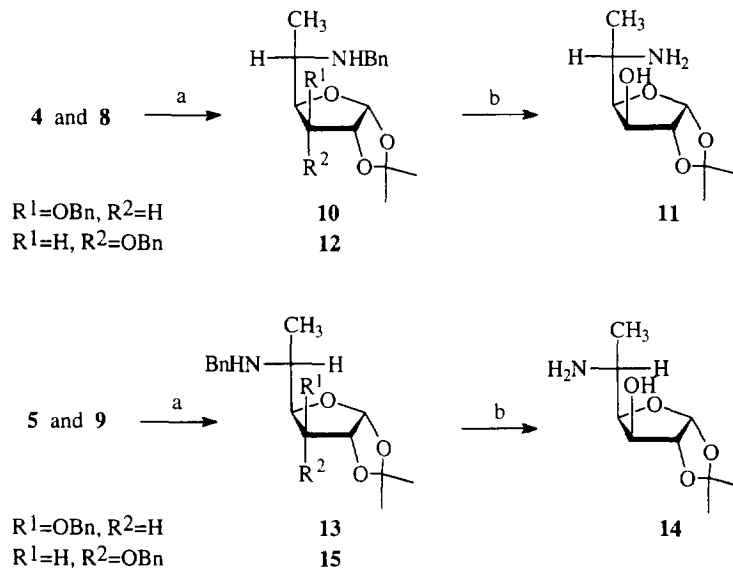

Figure 2

in **9** has been assigned to the D-*allo* configuration; consequently, the coupling constant $J_{4,5}=7.8$ Hz observed in **8** has been assigned to the L-*talo* configuration, in agreement with the literature data for related compounds.

The observed facial selectivity in favour of products **5** and **9**, both arising from nucleophilic attack to the *Re* face of the nitrone, may be rationalised assuming that conformations **A** and **B**, both in nitrone **3** and **7**, are the preferred ones (Figure 2). According to Felkin model the large substituent is perpendicular to the C=N bond. We believe that the C–O bond will adopt this position; in fact it is known that nucleophilic attack seeks the LUMO of nitrone which may be stabilised through mixing of the $\pi^*_{C=N}$ orbital with the lowest energy σ^* orbital of a substituent, generally associated with the most electronegative substituent.[23] On these grounds, **A** offers the more favourable trajectory to the incoming nucleophile and this is magnified after *O*-silylation by TMSOTf.

Synthesis of 5,6-dideoxy-5-aminosugars and 6-deoxynojirimycin

A number of reductive manipulations of *N*-benzylhydroxylamines **4**, **5**, **8** and **9** allowed us to prepare a set of variously protected aminosugars. For example, when **4**, **5**, **8** and **9** were individually reacted with Zn/Cu couple in acetic acid–water (85:15) at 70°C, *N*-benzylaminosugars **10,13** and **12,15** were

obtained in good yields (Scheme 3). This procedure represents a unique approach for the synthesis of 5,6-dideoxy-5-aminosugars in three high yielding steps from pentodialdoses **2** and **6**, which, in turn, can be easily prepared in multigram scale from D-glucose.

4 and 8 $\xrightarrow{a}$

R^1=OBn, R^2=H   **10**
R^1=H, R^2=OBn   **12**

5 and 9 $\xrightarrow{a}$

R^1=OBn, R^2=H   **13**
R^1=H, R^2=OBn   **15**

a: Zn/Cu, AcOH/H$_2$O, 70°C; b: HCOONH$_4$, 10% Pd/C, MeOH, 70°C.

Scheme 3

The 5,6-dideoxy-5-aminosugars **14** and **11** represent immediate precursors of 6-deoxynojirimycin and its C-5 epimer. Thus, deprotection of N and O benzyl groups in **10** was achieved in one step using ammonium formate and 10% Pd/C in methanol at 70°C for 40 min[24] to give 5,6-dideoxy-5-amino-1,2-O-isopropylidene-β-L-ido-furanose **11**; under the same reaction conditions, **13** gave 5,6-dideoxy-5-amino-1,2-O-isopropylidene-α-D-$gluco$-furanose **14** (Scheme 3). The removal of isopropylidene group of **14** leads to 6-deoxynojirimycin **1a**. However the deprotection step has to be conducted under mild conditions since 2-hydroxypiperidines, especially nojirimycin and congeners, are known to rapidly decompose under acidic conditions.[25] An unique procedure in these cases, however, involves trapping of the azasugar as stable bisulphite adduct.[26] Thus, reaction of **14** in SO$_2$ saturated aqueous solution at 35°C for 48 h gave 6-deoxynojirimycin as stable adduct **17**. Hydrolysis of **17** upon treatment with Amberlite IRA 400 (OH) affords 6-deoxynojirimycin **1a** as shown in Scheme 4.
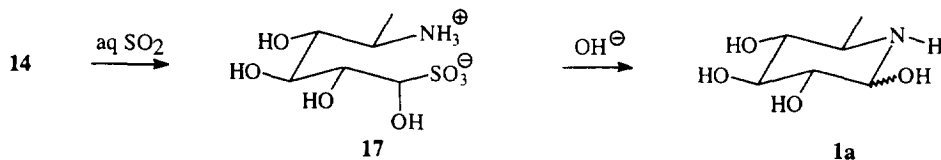
Scheme 4

In conclusion, we have demonstrated that: i) the reaction of methylmagnesium chloride with sugar derived nitrones **3** and **7** is a high yielding process; ii) the stereocontrol of the addition reaction can be improved by the use of trimethylsilyl triflate; iii) the N–O bond reductive cleavage and removal of benzyl protective groups afforded 5-aminosugars in good yield; iv) these last products may be easily converted into azasugars. The whole synthetic plan not only opens a new practical route to **1a** or its

diastereoisomeric analogues from D-glucose, but, in principle, also to any 5-substituted hydroxylated piperidine **1** by using the appropriate organometallic derivative. Work in this direction is in progress.

Experimental section

NMR Spectra of CDCl$_3$ solutions were recorded with a Bruker AMX 500MHz and a Varian Gemini-300 MHz spectrometer. Chemical shifts are reported in ppm (δ) downfield to TMS. IR spectra were recorded with a Perkin–Elmer 1600 FTIR spectrophotometer. Optical rotations were measured at 25°C with a Perkin–Elmer 241 polarimeter. C,H analyses were performed on a Hosli Carbon–Hydrogen analyser. Melting points were taken on a Thomas–Hoover capillary melting point apparatus and are uncorrected. All the reactions were conducted in oven-dried glassware under dry nitrogen. TLC was carried out on Polygram Sil G/UV254 precoated plastic sheets and flash-chromatography was carried out using Kieselgel 60 (230–400 mesh) with petroleum ether (bp 40–60°C)–ethyl acetate as eluent. Dialdoses **2** and **6** were prepared according to known procedures.[27] N-Benzylhydroxylamine hydrochloride and methylmagnesium chloride (3 M THF solution) were purchased from Aldrich. Amberlite IRA 400 (OH) ion exchange resin was purchased from Sigma.

X-Ray crystallography

Crystals of **16** were grown from a solution of cyclohexane/chloroform. Crystal Data. C$_{23}$H$_{27}$NO$_5$ M=1866.7, orthorhombic, a=9.640(3), b=9.880(2), c=22.350(6) Å, V=2128.7(10) Å^3, space group P2$_1$2$_1$2$_1$ (No.19), Z=4, Dx=1.24 gcm^{-3}. Colourless flat prisms. Crystal dimensions: 0.40×0.33×0.13 mm. μ=0.087 mm^{-1}.

Data collection and processing

Diffraction intensities were collected on an Enraf–Nonius CAD-4 diffractometer at room temperature with ω scan mode (scan angle=0.9+0.35 tan θ), λ (MoKα)=0.71069 Å. Reflections measured (θ range 2.7–28, h,k,±l) 5504, unique reflections used 5110 (merging R=0.029, no absorption correction, no crystal decay).

Structure analysis and refinement

The structure was solved by direct methods which allowed the positions of all non-hydrogen atoms and refined by least-squares methods (based on F^2) using the SHELXS 86 and SHELXL 93 systems of programs.[28] All the non-hydrogen atoms were allowed to vibrate anisotropically. The hydrogen atoms were experimentally located and isotropically refined. No. of refined parameters 372, GOF on F^2=1.01, R$_1$ on F, I>2 σ (I),=0.034, wR$_2$ (on F^2, all data)=0.098. Selected bond lengths [Å], angles and torsion angles [deg] in Figure 1 (e.s.d.'s are in parentheses).[29]

Synthesis of N-benzyl nitrone 3

A mixture of 1,2-*O*-(1-methylethylidene)-3-*O*-(phenylmethyl)-α-D-*xylo*-pentodialdo-1,4-furanose **2** (0.7 g, 2.5 mmol), anhydrous sodium acetate (0.25 g, 3 mmol) and *N*-benzylhydroxylamine hydrochloride (0.5 g, 3 mmol) in ethanol/water (3:2) was stirred at room temperature for 16 h. The reaction mixture was extracted with chloroform and the collected organic layers were washed with sat. aq. NaHCO$_3$, dried over anhydrous MgSO$_4$ and evaporated to give a crude solid. Crystallisation (pet.ether/ethyl acetate 9:1) furnished nitrone **3** (0.75 g, 78%).

Mp=108°C (lit. 96°C);[30] [α]$_D^{25}$=−137.0 (c=1.0, CHCl$_3$) (lit. [α]$_D^{25}$=−135.7 (c=0.4, CHCl$_3$))[26]; R$_f$=0.28 (pet.ether/ethyl acetate 6.5:3.5); IR (nujol): ν=1612, 1496, 1456, 1372, 1210, 1163, 1133 cm^{-1}; ^{1}H NMR (300 MHz): δ=1.24 (s, 3H, CH$_3$), 1.42 (s, 3H, CH$_3$), 4.35 (d, J=11.7 Hz, 1H, OCH$_2$Ph), 4.44 (d, J=11.7 Hz, 1H, OCH$_2$Ph), 4.49 (d, J=3.3 Hz, 1H, H-3), 4.52 (d, J=3.6 Hz, 1H, H-2), 4.77 (d, J=13.6 Hz, 1H, NCH$_2$Ph), 4.84 (d, J=13.6 Hz, 1H, NCH$_2$Ph), 5.20 (dd, J=3.3/4.4 Hz, 1H, H-4), 5.88 (d, J=3.6 Hz, 1H, H-1), 6.78 (d, J=4.4 Hz, 1H, H-5), 7.05–7.36 (m, 10H, Ar-H); ^{13}C NMR (75 MHz): δ=26.3, 26.9 (CH$_3$), 69.1 (NCH$_2$Ph), 72.5 (OCH$_2$Ph), 77.9 (C-3), 82.2 (C-2), 82.7

(C-4), 104.8 (C-1), 112.1 (O–C–O), 127.3, 127.7, 128.3, 128.9, 129.5, 132.0, 137.0 (Ar), 135.9 (C-5); Anal. Calcd. for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57. Found: C, 68.86; H, 6.52.

Synthesis of N-benzyl nitrone 7

Starting from 1,2-O-(1-methylethylidene)-3-O-(phenylmethyl)-α-D-ribo-pentodialdo-1,4-furanose **6** (0.7 g, 2.5 mmol), anhydrous sodium acetate (0.25 g, 3 mmol) and N-benzylhydroxylamine hydrochloride (0.5 g, 3 mmol) in ethanol/water (3:2) at room temperature for 35 min, we got nitrone **7** (0.71 g, 74%) after crystallisation (pet.ether/ethyl acetate 9:1).

Mp=142°C; $[\alpha]_D^{25}$=−10.6 (c=0.5, CHCl₃); R_f=0.17 (pet.ether/ethyl acetate 6:4); IR (nujol): ν=1590, 1459, 1377, 1232, 1169, 1121,1028, 932, 867, 734, 700 cm⁻¹; ¹H NMR (300 MHz): δ=1.36 (s, 3H, CH₃), 1.63 (s, 3H, CH₃), 3.82 (dd, J=4.4/8.7 Hz, 1H, H-3), 4.51 (d, J=12.6 Hz, 1H, OCH₂Ph), 4.61 (dd, J=3.5/4.4 Hz, 1H, H-2), 4.62 (d, J=12.6 Hz, 1H, OCH₂Ph), 4.90 (s, 2H, NCH₂Ph), 5.25 (dd, J=6.9/8.7 Hz, 1H, H-4), 5.72 (d, J=3.5 Hz, 1H, H-1), 6.55 (d, J=8.7 Hz, 1H, H-5), 7.18–7.43 (m, 10H, Ar-H); ¹³C NMR (75 MHz): δ=26.6, 26.9 (CH₃), 70.5 (OCH₂Ph), 72.1 (NCH₂Ph), 73.0, 78.6, 79.7 (C-2, C-3, C-4), 104.0 (C-1), 113.7 (OCO), 127.8, 128.4, 129.0, 129.1, 129.4 (Ar), 134.1 (C-5). Anal. Calcd. for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57. Found: C, 69.00; H, 6.52.

Synthesis of N-benzyl hydroxylamines 4 and 5

As reference procedures we describe entries 1 and 4 of Table 1.

(Table 1, entry 1). To a stirred solution of nitrone **3** (0.67 g, 1.75 mmol) in THF (10 mL), under nitrogen atmosphere, at −30°C, was added dropwise methylmagnesium chloride (3 M in THF, 1.28 mL, 3.85 mmol). The mixture was stirred at −30°C for 3 h, then quenched with a sat aq. solution of NH₄Cl (3 mL) and filtered. The filtrate was concentrated and the residue was dissolved in diethylether (30 mL). The ethereal solution was washed with brine, dried with Na₂SO₄ and evaporated to give an oil. The ¹H NMR analysis of the crude mixture revealed the presence of two diastereoisomers **4** and **5** in the 31:69 ratio. The crude oil was subjected to flash-chromatography (pet.ether/ethyl acetate 97:3) to give first a fraction containing β-L-ido isomer **4** as an oil (0.26g, 37%), then a second fraction containing the α-D-gluco isomer **5** as an oil (0.41 g, 58%).

(Table 1, entry 4). To a stirred solution of nitrone **3** (0.2 g, 0.55 mmol) in THF (5 mL) under nitrogen at −10°C was added dropwise TMSOTf (0.12 mL, 0.60 mmol). After stirring for 10 min the mixture was cooled to −78°C and methylmagnesium chloride (0.4 mL of a 3 M solution in THF, 1.21 mmol) was added dropwise with stirring at −78°C for 90 min. Quenching was performed with 2 N HCl (2 mL) with stirring at room temperature for 30 min. After neutralisation with NaHCO₃ and extraction with ether and concentration the ¹H NMR analysis of the crude mixture revealed the presence of **4** and **5** in the 13:87 ratio. N-Benzylhydroxylamines **4** and **5** were purified as previously stated.

5,6-Dideoxy-1,2-O-(1-methylethylidene)-3-O-(phenylmethyl)-5-[(phenylmethyl)(hydroxy)amino]-β-L-idofuranose 4

Oil; R_f=0.68 (cyclohexane/ethyl acetate 7:3); $[\alpha]_D^{25}$=−49.2 (c=1.1, CHCl₃); IR (nujol): ν=3471, 2985, 2937, 1495, 1454, 1373, 1290, 1254, 1210, 1152, 1074, 1024, 738, 698 cm⁻¹; ¹H NMR (300 MHz): δ=1.33 (s, 3H, CH₃), 1.34 (d, J=6.6Hz, 3H, H-6), 1.51 (s, 3H, CH₃), 3.49 (dq, J=6.6:9.2 Hz, 1H, H-5), 3.74 (d, J=13.3 Hz, 1H, NCH₂Ph), 3.98 (d, J=13.3 Hz, 1H, NCH₂Ph), 4.10 (d, J=3.0 Hz, 1H, H-3), 4.28 (dd, J=3.0/9.2 Hz, 1H, H-4), 4.33 (bs, 1H, OH), 4.61 (d, J=3.8 Hz, 1H, H-2), 4.62 (d, J=11.8 Hz, 1H, OCH₂Ph), 4.71 (d, J=11.8 Hz, 1H, OCH₂Ph), 5.94 (d, J=3.8 Hz, 1H, H-1), 7.25–7.35 (m, 10H, Ar-H); ¹³C NMR (75 MHz): δ=8.93 (C-6), 26.1, 26.6 (CH₃), 58.8 (C-5), 60.9 (NCH₂Ph), 72.2 (OCH₂Ph), 81.6, 81.9, 82.1 (C-2, C-3, C-4), 104.6 (C-1), 111.3 (O–C–O), 127.1, 127.3, 127.6, 128.2, 128.3, 129.2, 137.8 138.2 (Ar); Anal. Calcd. for $C_{23}H_{29}NO_5$: C, 69.15; H, 7.32. Found: C, 68.92; H, 7.10.

5,6-Dideoxy-1,2-O-(1-methylethylidene)-3-O-(phenylmethyl)-5-[(phenylmethyl)(hydroxy)amino]-α-D-glucofuranose 5

Oil; R_f=0.52 (cyclohexane/ethyl acetate 7:3); $[\alpha]_D^{25}$=−39.7 (c=1.2, CHCl$_3$); IR (nujol): ν=3430, 2925, 2980, 1590, 1505, 1380, 1370, 1215, 1165, 1070, 1030 cm^{-1}; ^{1}H NMR (300 MHz): δ=1.07 (d, J=6.6Hz, 3H, H-6), 1.36(s, 3H, CH$_3$), 1.53 (s, 3H, CH$_3$), 3.45 (dq, J=6.6/9.5 Hz, 1H, H-5), 3.89 (d, J=3.0 Hz, 1H, H-3), 3.93 (d, J=13.6 Hz, 1H, NCH$_2$Ph), 4.01 (d, J=13.6 Hz, 1H, NCH$_2$Ph), 4.37 (dd, J=3.0/9.5 Hz, 1H, H-4), 4.48 (d, J=11.6 Hz, 1H, OCH$_2$Ph), 4.66 (d, J=3.9 Hz, 1H, H-2), 4.73 (d, J=11.6 Hz, 1H, OCH$_2$Ph), 4.93 (bs, 1H, OH), 6.03 (d, J=3.9 Hz, 1H, H-1), 7.33–7.36 (m, 10H, Ar-H); ^{13}C NMR (75 MHz): δ =10.0 (C-6), 26.1, 26.5 (CH$_3$), 59.2 (C-5), 60.5 (NCH$_2$Ph), 71.4 (OCH$_2$Ph), 80.7, 80.9, 82.2 (C-2, C-3, C-4), 104.9 (C-1), 111.2 (O–C–O), 126.7, 127.5, 127.7, 127.9, 128.3, 129.3, 137.1 138.4 (Ar); Anal. Calcd. for C$_{23}$H$_{29}$NO$_5$: C, 69.15; H, 7.32. Found: C, 69.03; H, 7.03.

Synthesis of N-*benzyl hydroxylamines 8 and 9*

Adopting the same experimental procedure described for the synthesis of **4** and **5**, hydroxylamines **8** and **9** were synthesized starting from nitrone **7** and isolated by flash-chromatography using pet.ether/ethylacetate 9.7:0.3.

5,6-Dideoxy-1,2-O-(1-methylethylidene)-3-O-(phenylmethyl-5-[(phenylmethyl)(hydroxy)amino]-β-L-talofuranose 8

Mp=81–3°C; R_f=0.55 (cyclohexane/ethyl acetate 7:3); $[\alpha]_D^{25}$=+50.0 (c=2.1, CHCl$_3$); IR (nujol): ν=3465, 3030, 2983, 2933, 1496, 1454, 1376, 1217, 1096, 1024, 742, 700 cm^{-1}; ^{1}H NMR (500 MHz): δ=1.24 (d, J=6.3 Hz, 3H, H-6), 1.37(s, 3H, CH$_3$), 1.60 (s, 3H, CH$_3$), 2.80 (dq, J=6.3/7.8 Hz, 1H, H-5), 3.74 (d, J=13.2 Hz, 1H, NCH$_2$Ph), 3.80 (dd, J=4.2/8.7 Hz, 1H, H-3), 4.01 (d, J=13.2 Hz, 1H, NCH$_2$Ph), 4.14 (dd, J=7.8/8.7 Hz, 1H, H-4), 4.55 (dd, J=3.7/4.2 Hz, 1H, H-2), 4.58 (d, J=11.2 Hz, 1H, OCH$_2$Ph), 4.80 (d, J=11.2 Hz, 1H, OCH$_2$Ph), 5.18 (bs, 1H, OH), 5.72 (d, J=3.7 Hz, 1H, H-1), 7.32–7.36 (m, 10H, Ar-H); ^{13}C NMR (125 MHz): δ=9.5 (C-6), 26.9, 27.1 (CH$_3$), 59.9 (C-5), 63.2 (NCH$_2$Ph), 72.7 (OCH$_2$Ph), 77.6, 81.1, 81.8 (C-2, C-3, C-4), 104.4 (C-1), 113.0 (O–C–O), 127.3–138.0 (Ar); Anal. Calcd. for C$_{23}$H$_{29}$NO$_5$: C, 69.15; H, 7.32. Found: C, 69.05; H, 7.59.

5,6-Dideoxy-1,2-O-(1-methylethylidene)-3-O-(phenylmethyl)-5-[(phenylmethyl)(hydroxy)amino]-α-D-allofuranose 9

Mp 151–3°C (dec.); R_f=0.45 (cyclohexane/ethyl acetate 7:3); $[\alpha]_D^{25}$=+32.7 (c=2.3, CHCl$_3$); IR (nujol): ν=3456, 1496, 1454, 1372, 1307, 1216, 1167, 1102, 1023, 933, 880, 739, 699 cm^{-1}; ^{1}H NMR (500 MHz): δ=1.26 (d, J=6.8 Hz, 3H, H-6), 1.38(s, 3H, CH$_3$), 1.61 (s, 3H, CH$_3$), 3.13 (dq, J=3.1/6.8 Hz, 1H, H-5), 3.69 (d, J=13.2 Hz, 1H, NCH$_2$Ph), 3.96 (dd, J=4.4/8.9 Hz, 1H, H-3), 4.00 (d, J=13.2 Hz, 1H, NCH$_2$Ph), 4.19 (dd, J=3.1/8.9 Hz, 1H, H-4), 4.47 (d, J=11.6 Hz, 1H, OCH$_2$Ph), 4.58 (dd, J=3.7/4.1 Hz, 1H, H-2), 4.70 (d, J=11.6 Hz, 1H, OCH$_2$Ph), 5.18 (bs, 1H, OH), 5.74 (d, J=3.7 Hz, 1H, H-1), 7.30–7.38 (m, 10H, Ar-H); ^{13}C NMR (125 MHz): δ=9.3 (C-6), 26.9, 27.0 (CH$_3$), 59.2 (C-5), 60.7 (NCH$_2$Ph), 72.4 (OCH$_2$Ph), 77.4, 77.9, 81.7 (C-2, C-3, C-4), 104.1 (C-1), 113.2 (O–C–O), 127.4–138.5 (Ar); Anal. Calcd. for C$_{23}$H$_{29}$NO$_5$: C, 69.15; H, 7.32. Found: C, 69.28; H, 7.23.

5,6-Dideoxy-1,2-O-(1-methylethylidene)-3-O-(phenylmethyl)-5-[(phenylmethyl)amino]-β-L-idofuranose 10

Zinc dust (0.29 g, 4.5 mmol) was added to a solution of copper(II) acetate (0.015 g) in glacial acetic acid (1 mL) under nitrogen; the mixture was stirred at room temperature for 15 min until the colour disappeared. *N*-Benzylhydroxylamine **4** (0.3 g, 0.75 mmol) in glacial acetic acid (0.7 mL) and water (0.3 mL) was successively added, the reaction mixture was heated at 70°C for 1 h and then cooled to room temperature. The sodium salt of EDTA (0.1 g) was added, the mixture was stirred for 10 min and then made alkaline to mpH 10 by addition of 3 N NaOH. The resulting solution was extracted with chloroform, the combined organic layer was washed with brine, dried over MgSO$_4$ and evaporated to

give an oil. Purification by flash-chromatography (pet.ether/ethyl acetate 9:1) gave **10** (0.22 g, 77%) as a colourless oil.

Oil; R_f=0.60 (pet.ether/ethyl acetate 7:3); $[\alpha]_D^{25}$=-52.8 (c=1.3, CHCl$_3$); IR (nujol): v=3311, 3028, 2932, 1603, 1496, 1454, 1373, 1314, 1214, 1164, 1075, 1025, 887, 861, 738, 698 cm^{-1}; ^{1}H NMR (300 MHz): δ=1.31 (d, J=6.3 Hz, 3H, H-6), 1.37 (s, 3H, CH$_3$), 1.48 (bs, 1H, NH), 1.54 (s, 3H, CH$_3$), 3.23 (dq, J=6.3:9.0 Hz, 1H, H-5), 3.72 (d, J=12.9 Hz, 1H, NCH$_2$Ph), 3.92 (d, J=12.9 Hz, 1H, NCH$_2$Ph), 3.97 (dd, J=3.0/9.0 Hz, 1H, H-4), 4.11 (d, J=3.0 Hz, 1H, H-3), 4.55 (d, J=11.6 Hz, 1H, OCH$_2$Ph), 4.68 (d, J=3.9 Hz, 1H, H-2), 4.76 (d, J=11.6 Hz, 1H, OCH$_2$Ph), 5.98 (d, J=3.9 Hz, 1H, H-1), 7.20–7.40 (m, 10H, Ar-H); ^{13}C NMR (75 MHz): δ=17.83 (C-6), 26.2, 26.8 (CH$_3$), 50.7 (C-5), 51.0 (NCH$_2$Ph), 71.7 (OCH$_2$Ph), 81.5, 81.8, 84.5 (C-2, C-3, C-4), 104.7 (C-1), 111.3 (O–C–O), 126.7, 127.8, 127.9, 128.2, 128.4, 137.3, 140.6 (Ar); Anal. Calcd. for C$_{23}$H$_{29}$NO$_4$: C, 72.03; H, 7.62. Found: C, 71.80; H, 7.61.

5,6-Dideoxy-1,2-O-(1-methylethylidene)-3-O-(phenylmethyl)-5-[(phenylmethyl)amino]-α-D-glucofuranose 13

The reaction of N-benzylhydroxylamine **5** (0.3 g, 0.75 mmol) with Zn/Cu couple under the same conditions reported for **4**, gave N-benzylamine **13** (0.23 g, 80%) as a thick oil. R_f=0.38 (pet.ether/ethyl acetate 7:3); $[\alpha]_D^{25}$=-10.3 (c=1.3, CHCl$_3$); IR (nujol): v=3329, 3029, 2927, 1603, 1454, 1378, 1314, 1215, 1166, 1076, 859, 738, 699 cm^{-1}; ^{1}H NMR (300 MHz): δ=1.01 (d, J=6.3 Hz, 3H, H-6), 1.34 (s, 3H, CH$_3$), 1.50 (s, 3H, CH$_3$), 1.95 (bs, 1H, NH), 3.21 (dq, J=6.3/9.1 Hz, 1H, H-5), 3.74 (d, J=12.6 Hz, 1H, NCH$_2$Ph), 3.89 (d, J=12.6 Hz, 1H, NCH$_2$Ph), 3.91 (d, J=3.1 Hz, 1H, H-3), 4.03 (dd, J=3.1/9.1 Hz, 1H, H-4), 4.48 (d, J=11.8 Hz, 1H, OCH$_2$Ph), 4.65 (d, J=3.9 Hz, 1H, H-2), 4.71 (d, J=11.8 Hz, 1H, OCH$_2$Ph), 5.95 (d, J=3.9 Hz, 1H, H-1), 7.20–7.40 (m, 10H, Ar-H); ^{13}C NMR (75 MHz): δ=15.4 (C-6), 26.0, 26.4 (CH$_3$), 51.1 (C-5), 51.5 (NCH$_2$Ph), 71.4 (OCH$_2$Ph), 81.3, 81.5, 84.0 (C-2, C-3, C-4), 104.5 (C-1), 111.2 (O–C–O), 126.4, 127.5, 127.7, 127.9, 128.0, 128.1, 136.9, 140.2 (Ar); Anal. Calcd. for C$_{23}$H$_{29}$NO$_4$: C, 72.03; H, 7.62. Found: C, 71.88; H, 7.51.

5,6-Dideoxy-1,2-O-(1-methylethylidene)-3-O-(phenylmethyl)-5-[(phenylmethyl)amino]-β-L-talofuranose 12

The reaction of N-benzylhydroxylamine **8** (0.3 g, 0.75 mmol) with Zn/Cu couple under the same conditions reported for **4**, gave N-benzylamine **12** (0.20 g, 75%) as an oil. R_f=0.38 (pet.ether/ethyl acetate 7:3); $[\alpha]_D^{25}$=$+25.13$ (c=0.3, CHCl$_3$); IR (nujol): v=3442, 2933, 1680, 1666, 1497, 1440, 1414, 1391, 1255, 1102, 1063, 1024, 663 cm^{-1}; ^{1}H NMR (300 MHz): δ=1.08 (d, J=6.6 Hz, 3H, H-6), 1.35 (s, 3H, CH$_3$), 1.59 (s, 3H, CH$_3$), 1.84 (bs, 1H, NH), 2.99 (dq, J=4.0/6.6 Hz, 1H, H-5), 3.71 (d, J=13.2 Hz, 1H, NCH$_2$Ph), 3.85 (dd, J=4.0/8.6 Hz, 1H, H-4), 3.87 (d, J=13.2 Hz, 1H, NCH$_2$Ph), 4.10 (dd, J=4.2/8.6 Hz, 1H, H-3), 4.53 (d, J=11.7 Hz, 1H, OCH$_2$Ph), 4.56 (dd, J=3.7/4.2 Hz, 1H, H-2), 4.76 (d, J=11.7 Hz, 1H, OCH$_2$Ph), 5.69 (d, J=3.7 Hz, 1H, H-1), 7.19–7.38 (m, 10H, Ar-H); ^{13}C NMR (75 MHz): δ=15.5 (C-6), 26.7, 26.9 (CH$_3$), 51.1 (C-5), 52.7 (NCH$_2$Ph), 71.9 (OCH$_2$Ph), 77.7, 78.3, 80.8 (C-2, C-3, C-4), 104.0 (C-1), 112.8 (O–C–O), 126.8, 127.9, 128.1, 128.2, 128.3, 128.4, 137.6, 140.6 (Ar); Anal. Calcd. for C$_{23}$H$_{29}$NO$_4$: C, 72.03; H, 7.62. Found: C, 71.91; H, 7.72.

5,6-Dideoxy-1,2-O-(1-methylethylidene)-3-O-(phenylmethyl)-5-[(phenylmethyl)amino]-α-D-allofuranose 15

The reaction of N-benzylhydroxylamine **9** (0.3 g, 0.75 mmol) with Zn/Cu couple under the same conditions reported for **4**, gave N-benzylamine **15** (0.22g, 78%) as an oil. R_f=0.30 (pet.ether/ethyl acetate 7:3); $[\alpha]_D^{25}$=$+115.6$ (c=0.5, CHCl$_3$); IR (nujol): v=3332, 1604, 1495, 1455, 1377, 1307, 1215, 1100, 1023, 932, 874, 734 cm^{-1}; ^{1}H NMR (300 MHz): δ=1.20 (d, J=6.6 Hz, 3H, H-6), 1.35 (s, 3H, CH$_3$), 1.58 (s, 3H, CH$_3$), 1.66 (bs, 1H, NH), 2.79 (dq, J=2.9/6.6 Hz, 1H, H-5), 3.59 (d, J=12.9 Hz, 1H, NCH$_2$Ph), 3.88 (d, J=12.9 Hz, 1H, NCH$_2$Ph), 3.94–4.01 (m, 2H, H-3, H-4), 4.49 (d, J=11.7 Hz, 1H, OCH$_2$Ph), 4.55 (dd, J=3.6/3.9 Hz, 1H, H-2), 4.70 (d, J=11.7 Hz, 1H, OCH$_2$Ph), 5.68 (d, J=3.6 Hz, 1H, H-1), 7.22–7.39 (m, 10H, Ar-H); ^{13}C NMR (75 MHz): δ=16.9 (C-6), 26.6, 26.9 (CH$_3$), 50.8 (C-5), 52.1 (NCH$_2$Ph), 72.1 (OCH$_2$Ph), 77.8, 78.1, 82.3 (C-2, C-3, C-4), 104.0 (C-1), 112.8 (O–C–O),

126.8, 127.9, 128.1, 128.2, 128.3, 128.4, 137.8, 140.8 (Ar); Anal. Calcd. for $C_{23}H_{29}NO_4$: C, 72.03; H, 7.62. Found: C, 72.0; H, 7.62.

5-Amino-5,6-dideoxy-1,2-O-(1-methylethylidene)-β-L-idofuranose 11

N-Benzylamine 10 (0.26 g, 0.68 mmol) in dry methanol (7 mL) was refluxed for 45 min in the presence of 10% Pd/C (0.52 g) and ammonium formate (0.3 g, 4.74 mmol). The reaction mixture was filtered through celite, the residue was washed with methanol and the solvent was evaporated to give an oil. Flash-chromatography on basic alumina using chloroform/methanol 9:1 gave amine 11 (0.107 g, 78%) as a white solid.

Mp=123–125°C (lit[8] 128°C); R_f=0.44 (chloroform/methanol 8:2); $[\alpha]_D^{25}$=–20.0 (c=2.4, CHCl$_3$); IR (nujol): n=3359, 3294, 2935, 1606, 1457, 1377, 1296, 1254, 1218, 1167, 1117, 1074, 1016, 885, 861, 794, 633 cm^{-1}; ^{1}H NMR (300 MHz): δ=1.32 (s, 3H, CH$_3$), 1.34 (d, J=6.8 Hz, 3H, H-6), 1.48 (s, 3H, CH$_3$), 3.76 (dq, J=3.7/6.8 Hz, 1H, H-5), 3.95 (dd, J=2.6/3.7 Hz, 1H, H-4), 4.1–4.4 (broad m, 3H, OH, NH$_2$), 4.37 (d, J=2.6 Hz, 1H, H-3), 4.52 (d, J=3.6 Hz, 1H, H-2), 5.99 (d, J=3.6 Hz, 1H, H-1); ^{13}C NMR (75 MHz): d=17.1 (C-6), 23.0, 26.6 (CH$_3$), 46.7 (C-5), 75.3, 80.5, 85.3 (C-2, C-3, C-4), 104.7 (C-1), 111.3 (O–C–O); Anal. Calcd. for $C_9H_{17}NO_4$: C, 53.19; H, 8.43. Found: C, 53.48; H, 8.80.

5-Amino-5,6-dideoxy-1,2-O-(1-methylethylidene)-α-D-glucofuranose 14

N-Benzylamine 13 (0.24 g, 0.67 mmol), under the same experimental conditions reported for the synthesis of 11, gave amine 14 (0.11 g, 80%) as a thick oil, after flash-chromatography on basic alumina. R_f=0.28 (chloroform/methanol 8:2); $[\alpha]_D^{25}$=+14.5 (c=0.1, CHCl$_3$); IR (nujol): ν=3750–3200, 2933, 1636, 1455, 1375, 1214, 1166, 1074, 1017, 859, 774, 648 cm^{-1}; ^{1}H NMR (500 MHz): δ=1.28 (s, 3H, CH$_3$), 1.31 (d, J=6.4 Hz, 3H, H-6), 1.45 (s, 3H, CH$_3$), 3.36 (dq, J=1.4/6.4 Hz, 1H, H-5), 3.98 (dd, J=1.2/1.4 Hz, 1H, H-4), 4.2–4.4 (broad m, 3H, OH, NH$_2$), 4.22 (d, J=1.2 Hz, 1H, H-3), 4.44 (d, J=3.2 Hz, 1H, H-2), 5.93 (d, J=3.2 Hz, 1H, H-1); ^{13}C NMR (75 MHz): δ=23.5 (C-6), 26.4, 27.1 (CH$_3$), 47.4 (C-5), 77.2, 80.7, 86.0 (C-2, C-3, C-4), 105.2 (C-1), 111.7 (O–C–O); Anal. Calcd. for $C_9H_{17}NO_4$: C, 53.19; H, 8.43. Found: C, 52.78; H, 8.83.

6-Deoxynojirimycin, bisulphite adduct 17

A solution of 5-amino-5,6-dideoxy-1,2-O-(1-methylethylidene)-α-D-glucofuranose 14 (0.2 g, 0.98 mmol) in water (2.5 mL), saturated with SO$_2$, was stirred at 35°C for 48 h until complete disappearance of 14 on TLC (silica gel, nBuOH saturated with water). After addition of methanol (10 mL), the reaction mixture was again saturated with SO$_2$ and cooled. The residue obtained was filtered, washed with methanol (5 mL) and dried under vacuum to give bisulphite adduct 17 (0.14 g, 58%) as a white solid.[31]

Mp=148–150°C (dec.); R_f=0.23 (ethanol/water 8:2); $[\alpha]_D^{25}$=–20.0 (c=0.4, water, 72 h); IR (nujol): ν=3320, 3120, 2920, 2860, 1640, 1590, 1530, 1460, 1210, 1180, 1060, 1040 cm^{-1}; Anal. Calcd. for $C_6H_{15}NO_7S$: C, 29.38; H, 6.12; N, 5.70; S, 13.06. Found: C, 29.56; H, 6.22; N, 5.83; S, 13.58.

6-Deoxynojirimycin 1a

A suspension of 16 (0.08 g, 0.33 mmol) in water (1 mL) was treated with Amberlite IRA-400 (OH form, 4 mL) for 5 min. The mixture was placed on a column of the same resin (10 mL) and eluted with water (40 mL). Lyophilization of the solution afforded yellow crystals of 1a (0.042 g, 82%). Mp=103–105°C (dec.); $[\alpha]_D^{25}$=–20.5 (c=0.2, water, 42 h); IR (nujol): ν=3600–3000 broad, 3300, 1590, 1440, 1370, 1080 cm^{-1}; Anal. Calcd. for $C_6H_{13}NO_4$: C, 44.16; H, 8.03; N, 8.58. Found: C, 44.56; H, 7.58; N, 8.52.

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