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A nitro sugar mediated synthesis of 6-amino-1,5,6-trideoxy-1,5-imino-D-glucitol (6-amino-1,6-dideoxynojirimycin)

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ABSTRACT

6-Benzoylamino-3-*O*-benzyl-1,5,6-trideoxy-*N*-(1,1-diphenylmethyl)-1,5-imino-D-glucitol **12a** and its epimer 6-benzoylamino-3-*O*-benzyl-1,5,6-trideoxy-*N*-(1,1-diphenylmethyl)-1,5-imino-L-iditol **12b**, the protected forms of 6-amino-1,6-dideoxynojirimycin **4** and its C-5 epimer **5**, respectively, were easily prepared from diacetone-D-glucose via 6-*O*-benzoyl-3-*O*-benzyl-1,2-*O*-isopropylidene-5-*C*-nitromethyl-α-D-glucofuranose **7a** or 6-*O*-benzoyl-3-*O*-benzyl-1,2-*O*-isopropylidene-5-*C*-nitromethyl-β-L-idofuranose **7b**. 6-Amino-1,6-dideoxynojirimycin **4** (an important precursor of a wide range of glycosidase inhibitors) was easily prepared from 1,5-imino-D-glucitol **12a**.

1. Introduction

Glycobiology is an emerging research area in which glycosidases have received considerable attention on account of their involvement in a number of metabolic pathways.[1] Accordingly, the inhibition of glycosidases has become a powerful strategy for the treatment of several important diseases, such as diabetes, cancer and viral infections, including AIDS.[2] This situation has led to considerable effort in recent years aimed at understanding the structure types, action mechanisms and synthesis of glycosidase inhibitors.[3]

The most common glycosidase inhibitors are imino sugars such as the polyhydroxylated nitrogen-containing ring skeletons identical to those of sugars that mimic the enzyme. The parent iminosugar is nojirimycin **1** (Fig. 1), which can be regarded as the result of the replacement of the ring oxygen of D-glucose by a nitrogen atom. On the other hand, 1-deoxynojirimycin **2** (1-DNJ) and analogues are the compounds where the hemiacetal functionality is replaced by an aminomethylene group, a structural modification that results in an improvement in the glycosidase inhibitory activity.[4] In fact, some of the latter compounds are therapeutically useful drugs.[5]

Our strategy was first applied to the D-glucose 6-amino derivatives of 1-DNJ, for example, compounds **4** and **5**, which played an important role in glycosidase studies, not only because of their weak inhibition properties, but also because they are synthetic precursors of a wide range of glycosidase inhibitors.[6] Several methods have been described for the synthesis of 1-DNJ and its analogues.[4] However, very few syntheses of 6-amino-1-deoxynojirimycins have been reported.[7]

Nitrosugars are powerful synthetic materials that combine the synthetic potential of sugars and the chemical versatility of the nitro group; for example, for the formation of carbon–carbon bonds prior to conversion into a range of other functionalities, including reduction to an amino group.[8] In connection with our recent investigations on nitrosugars,[9] we report here the new synthesis of 6-amino-1,6-dideoxynojirimycin **4**, which is shown in Scheme 1.

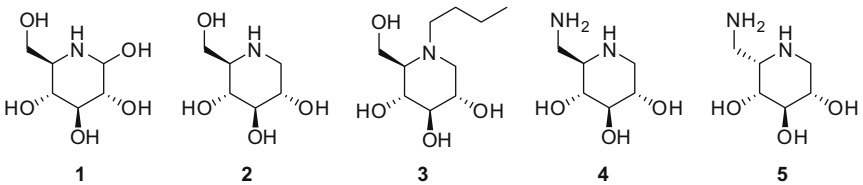

Figure 1.

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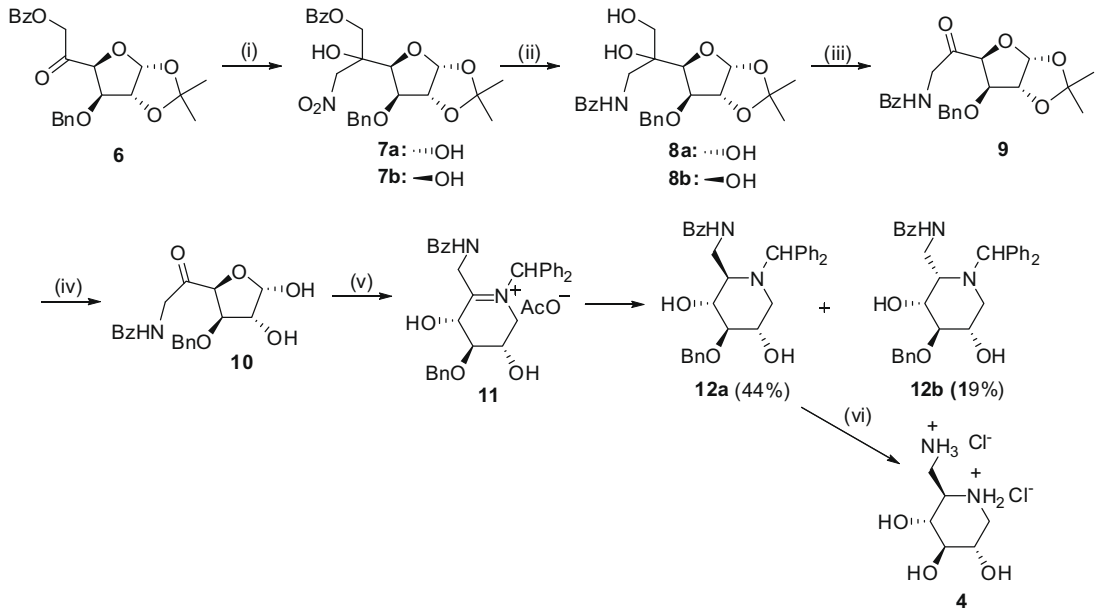


Scheme 1. Reagents and conditions: (i) KF·2H_2O, 18-crown-6 ether, CH_3NO_2, rt, 1 h (60% yield); (ii) H_2, Ni-Raney, MeOH, rt (52% yield); (iii) $NaIO_4$, CH_2Cl_2, H_2O, SiO_2, rt, 6 h (86% yield); (iv) TFA, H_2O, rt, 12 h; (v) H_2NCHPh_2, $NaCNBH_3$, AcOH, MeOH, −78 to rt (63% yield); (vi) (a) Pd/C, $HCOONH_4$, 70 °C, 1 h; (b) HCl (6 M), 50 °C, 3 d (64% yield).

2. Results and discussion

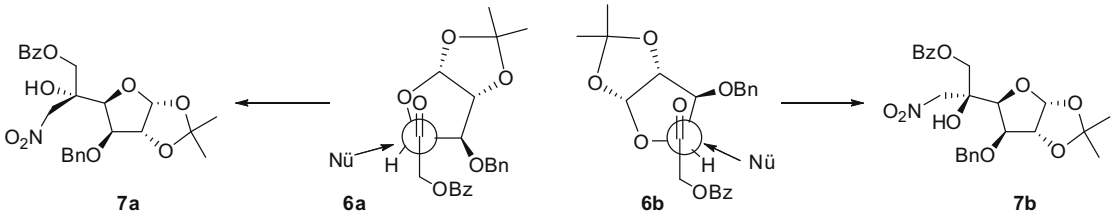
A Henry reaction of the known D-glucose derivative ketone **6**[10] with nitromethane, using KF as the base, gave a 60% yield of a 58:42 mixture of the C-5 nitromethyl-α-D-glucofuranose **7a** and the C-5 nitromethyl-β-L-idofuranose **7b**, as established by ^{1}H NMR spectroscopy. Careful chromatographic separation allowed the epimer **7a** to be isolated and its structure was established by X-ray diffraction.[11]

The ratio of **7a**:**7b** can be explained in terms of the Felkin–Ahn model (Scheme 2). Thus, the depicted attack of the nitronate anion of nitromethane onto conformer **6a** led to the major adduct **7a**. On the other hand, the alternative attack of this nitronate anion on the carbonyl group of conformer **6b**, which is less favoured than the former, provided the minor stereoisomer **7b**.

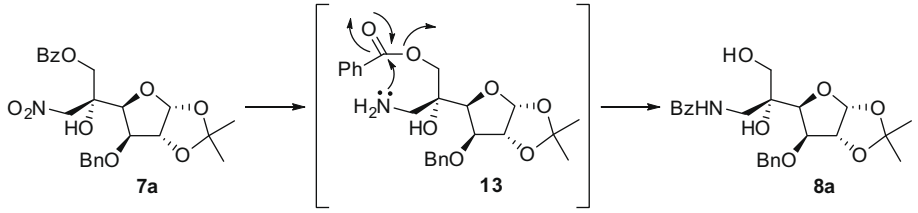
Hydrogenation of the mixture of 7**a** + **7b** at room temperature, using Raney-Ni as the catalyst, unexpectedly provided a 52% yield of a 1:1.5 mixture of the D-gluco derivative **8a** and the L-ido derivative **8b**, as established from the ^{1}H NMR spectrum of the epimeric mixture.

The formation of compound **8a** can be explained in terms of the expected reduction of the nitro group of **7a** to the amino group in compound **13** (Scheme 3), which under the reaction conditions rearranged spontaneously to **8a** as a result of an intramolecular transfer of its benzoyl group from the oxygen to the nitrogen. Compound **8b** should result from **7b** in a similar manner.

Treatment of a suspension of the mixture of **8a + 8b** and silica gel in dichloromethane with aqueous sodium periodate at room temperature resulted in an oxidative degradation of the 1,2-diole system, which gave ketone **9** in 86% yield. Compound **9** was then reacted with a mixture of trifluoroacetic acid and water in order to remove the acetonide protecting group. The resulting compound **10** was reacted with diphenylmethylamine in acidic conditions and underwent a heteroannulation process that provided the iminium



Scheme 2.



Scheme 3.

salt **11**. This compound was reacted with sodium cyanoborohydride to give an epimeric mixture of **12a + 12b**, as a result of hydrogenation the C=N bond of **11**, from which both piperidines **12a** (the thermodynamically more stable epimer) and **12b** (the thermodynamically less stable component) were isolated in 24% and 9% yields, respectively, after careful column chromatography. The structure of the minor component **12b** was established by X-ray diffraction (Fig. 2).[12]

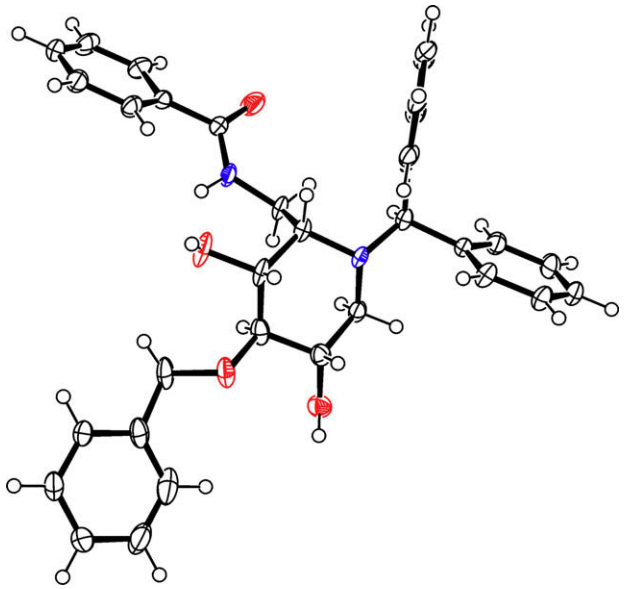


Figure 2. Molecular structure of compound **12b** in the solid state.

Finally, removal of the benzyl and benzoyl protecting groups of **12a**, by treatment with $HCOONH_4$ as a hydrogen source and Pd/C as the catalyst followed by acidic hydrolysis with HCl (6 M), furnished the known six-membered iminosugar **4** (54% yield), which was isolated as its dihydrochloride salt.

3. Conclusion

In summary, we have described a new route to 6-amino-1-dideoxynojirimycins that is shorter than the rare previous examples. Work is now in progress to optimize this synthetic approach in order to apply it to hexoses other than D-glucose and thus to gain access to novel 6-amino-1-deoxynojirimycin analogues that could show improved activity profiles.

4. Experimental

Melting points were determined using a Kofler Thermogerate apparatus and are uncorrected. Specific rotations were recorded on a JASCO DIP-370 optical polarimeter. Infrared spectra were recorded on an MIDAC Prospect-IR spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Bruker DPX-250 apparatus. Mass spectra were obtained on a Hewlett Packard 5988A mass spectrometer. Elemental analyses were obtained from the Elemental Analysis Service at the University of Santiago de Compostela. Thin layer chromatography (TLC) was performed using Merck GF-254 type 60 silica gel and ethyl acetate/hexane mixtures as eluants; the TLC spots were visualized with Hanessian mixture. Column chromatography was carried out using Merck type 9385 silica gel. Solvents were purified as per Ref. 13. Solutions of extracts in organic solvents were dried with anhydrous sodium sulfate.

4.1. 6-*O*-Benzoyl-3-*O*-benzyl-1,2-*O*-isopropylidene-5-*C*-nitromethyl-α-D-glucofuranose 7a and 6-*O*-benzoyl-3-*O*-benzyl-1,2-*O*-isopropylidene-5-*C*-nitromethyl-β-L-idofuranose 7b

$KF{\cdot}2H_2O$ (0.46 g, 4.90 mmol) and 18-crown-6 ether (0.82 g, 3.10 mmol) were added to a solution of ketone **6** (1.19 g (2.90 mmol) in nitromethane (18 mL) and the resulting suspension was stirred at room temperature for 1 h. The reaction mixture was added to a mixture of ice/water (50 mL) and extracted with ethyl acetate (3 × 80 mL). The organic layers were then dried with anhydrous sodium sulfate, filtered and evaporated to give a residue, which was purified by flash column chromatography (ethyl acetate/hexane 1:3) to give 6-*O*-benzoyl-3-*O*-benzyl-1,2-*O*-isopropylidene-5-*C*-nitromethyl-α-D-glucofuranose **7a** (0.47 g, 34%) and 6-*O*-benzoyl-3-*O*-benzyl-1,2-*O*-isopropylidene-5-*C*-nitromethyl-β-L-idofuranose **7b** (0.36 g, 26%) as solids, which were crystallized from a mixture of ethyl acetate and hexane.

Compound **7a**: mp: 102–106 °C (ethyl acetate/hexane). $[\alpha]_D^{22} = -75.6$ (*c* 1.00, $CHCl_3$). IR (NaCl, *ν*, cm^{-1}): 3454 (OH); 2854–3064 ($C_{Ar}H$); 1722 (CO); 1554, 1375 (NO_2). ^1H NMR (250 MHz, $CDCl_3$) *δ* 1.32 (s, 3H, CH_3); 1.46 (s, 3H, CH_3); 4.30 (d, 1H, $J_{3,4}$ = 3.35 Hz, H-3); 4.38 (d, 1H, $J_{4,3}$ = 3.35 Hz, H-4); 4.42–4.47 (m, 2H, CH_2NO_2); 4.54–4.60 (m, 2H, H-6 + H-6′); 4.66 (d, 1H, $J_{2,1}$ = 3.65 Hz, H-2); 4.73 (d, 1H, *J* = 11.87 Hz, CHPh); 4.80 (s, 1H, OH); 4.91 (d, 1H, *J* = 11.87 Hz, CHPh); 6.02 (d, 1H, $J_{1,2}$ = 3.65 Hz, H-1); 7.31–7.61 (m, 8H, 8 × HPh); 7.98–8.01 (m, 2H, 2 × HPh). ^{13}C NMR (62.8 MHz, $CDCl_3$) *δ* 26.17 (CH_3); 26.56 (CH_3); 65.34 (CH_2); 72.40 (CH_2); 73.05 (CH_2); 77.62 (CH); 77.76 (C); 81.38 (CH); 82.99 (CH); 104.53 (CH); 112.19 (C); 128.21 (2 × $C_{Ar}H$); 128.45 (2 × $C_{Ar}H$); 128.67 ($C_{Ar}H$); 128.79 (2 × Ar $C_{Ar}H$); 129.06 (C_{Ar}); 129.54 (2 × $C_{Ar}H$); 133.39 ($C_{Ar}H$); 135.47 (C_{Ar}); 165.64 (CO). MS (CI) *m*/*z* 474 [$(M+H)^+$, 1]; 105 (38); 91 [$(PhCH_2)^+$, 81], 28 (100).

Compound **7b**: mp: 109–111 °C (ethyl acetate/hexane). $[\alpha]_D^{22} = -38.0$ (*c* 1.90, $CHCl_3$). IR (NaCl, ν_{max}, cm^{-1}): 3454 (OH); 2854–3089 ($C_{Ar}H$); 1722 (CO); 1554, 1375 (NO_2). ^1H NMR (250 MHz, $CDCl_3$) *δ* 1.33 (s, 3H, CH_3); 1.45 (s, 3H, CH_3); 4.27 (d, 1H, $J_{3,4}$ = 3.35 Hz, H-3); 4.31 (s, 1H, OH); 4.39 (1H, d, $J_{4,3}$ = 3.35 Hz, H-4); 4.49–4.64 (m, 5H, H-6 + H-6′ + CH_2NO_2 + CHPh); 4.69 (d, 1H, $J_{2,1}$ = 3.35 Hz, H-2); 4.74 (d, 1H, *J* = 11.8 Hz, CHPh); 6.01 (d, 1H, $J_{1,2}$ = 3.35 Hz, H-1); 7.33–7.60 (m, 8H, 8 × H-Ph); 7.96–8.01 (m, 2H, 2 × H-Ph). ^{13}C NMR (62.8 MHz, $CDCl_3$) *δ* 26.60 (CH_3); 27.09 (CH_3); 65.90 (CH_2); 72.52 (CH_2); 73.90 (C); 78.96 (CH_2); 79.20 (CH); 81.80 (CH); 82.70 (CH); 104.90 (CH); 112.70 (C); 128.90 (4 × $C_{Ar}H$); 129.20 (2 × $C_{Ar}H$); 129.30 (2 × $C_{Ar}H$); 129.80 (C_{Ar}); 130.02 ($C_{Ar}H$); 133.70 ($C_{Ar}H$); 136.02 (C_{Ar}); 166.05 (CO). MS (CI) *m*/*z* 105 (38); 91 [$(PhCH_2)^+$, 86], 61 (100); 28 (87).

4.2. 5-*C*-[(Benzoylamino)methyl]-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-idofuranose 8a and 5-*C*-[(benzoylamino)methyl]-3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-glucofuranose 8b

Raney-Ni (7.5 mL, 1 g/10 mL) was added to a deoxygenated solution of a 1:1 mixture of **7a** + **7b** (0.5 g, 1.05 mmol) in methanol (50 mL) and the resulting suspension was stirred at room temperature under a hydrogen atmosphere (*P* = 1 atm) for 15 h. The mixture was then filtered through Celite®, which was washed with methanol (50 mL), and the filtrate was evaporated to dryness. The residue was purified by flash column chromatography (ethyl acetate/hexane 2:1) to give 0.24 g (52%) of a 1:1.5 mixture of the epimers 5-*C*-[(benzoylamino)methyl]-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose **8a** and 5-*C*-[(benzoylamino)-methyl]-3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-idofuranose **8b**. IR (NaCl, ν_{max}, cm^{-1}): 3378 (OH); 3064–2878 ($C_{Ar}H$); 1640 (CO). ^1H NMR (250 MHz, $CDCl_3$) *δ* 1.32 (s, 3H, CH_{3a}); 1.34 (s, 3H, CH_{3b});

1.47 (s, 3H, CH_{3a}); 1.49 (s, 3H, CH_{3b}); 3.09 (dd, 1H, J = 4.39 Hz, J = 13.99 Hz, $CHNHBz_a$); 3.25 (br s, 1H, OH_b); 3.33 (br s, 1H, OH_a); 3.46 (d, 2H, J = 11.80 Hz, CH_2OH_a); 3.56 (dd, 1H, J = 4.39 Hz, J = 13.99 Hz, $CHNHBz_b$); 3.66 (d, 2H, J = 11.80 Hz, CH_2OH_b); 4.01 (dd, 2H, J = 8.58 Hz, J = 13.99 Hz, 2 × $CHNHBz_{(a+b)}$); 4.23 (d, 2H, $J_{3,4}$ = 3.029, 2 × $H_{3(a+b)}$); 4.23 (d, 2H, $J_{4,3}$ = 3.029, 2 × $H_{4(a+b)}$); 4.35 (s, 2H, 2 × $OH_{(a+b)}$); 4.49–4.75 (m, 6H, 2 × $CH_2Ph_{(a+b)}$ + 2 × $H_{2(a+b)}$); 5.99 (d, 1H, J_{12} = 3.84 Hz, H_{1a}); 6.03 (d, 1H, $J_{1,2}$ = 3.84 Hz, H_{1b}); 6.82–6.89 (m, 2H, 2 × $NHBz_{(a+b)}$); 7.27–7.79 (m, 16H, 16 × H-$Ph_{(a+b)}$); 7.75–7.79 (m, 4H, 4 × H-$Ph_{(a+b)}$). ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 25.87 (CH_{3a}); 25.94 (CH_{3b}); 26.34 (CH_{3a}); 26.36 (CH_{3b}); 43.33 (C_a); 43.37 (C_b); 63.12 (CH_{2a}); 63.75 (CH_{2b}); 71.69 (CH_{2a}); 71.86 (CH_{2b}); 74.91 (CH_{2a}); 75.19 (CH_{2b}); 78.85 (CH_a); 78.95 (CH_b); 81.10 (CH_a); 81.32 (CH_b); 82.80 (CH_a); 83.23 (CH_b); 103.98 (CH_a); 104.29 (CH_b); 111.51 (C_a); 111.53 (C_b); 126.86, 127.89, 127.95, 128.10, 128.20, 128.37, 128.44, 131.40, 131.46 (20 × $C_{Ar}H$); 133.22 ($C_{Ar\text{-}a}$); 133.45 ($C_{Ar\text{-}b}$); 135.63 ($C_{Ar\text{-}a}$); 136.05 ($C_{Ar\text{-}b}$); 168.80 (CO_a); 169.25 (CO_b). MS (CI) m/z 444 [$(M+H)^+$, 100]; 443 [$(M)^+$, 5]; 442 [$(M-H)^+$, 13]; 386 (63); 91 [$(PhCH_2)^+$, 70].

4.3. 6-Benzoylamino-3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-xylo-hexofuran-5-one 9

A solution of a 1:1.5 mixture of the epimers **8a** + **8b** (0.23 g, 0.53 mmol) in dichloromethane (4 mL) was added to a suspension of silica gel (1.30 g), dichoromethane (2 mL) and a solution of $NaIO_4$ (0.23 g, 1.07 mmol) in H_2O (1.80 mL). The resulting mixture was stirred at room temperature for 6 h. The reaction mixture was filtered through Celite®, which was washed with dichloromethane (25 mL), and the filtrate was evaporated to dryness. The residue was purified by flash column chromatography (ethyl acetate/hexane 1:2) to give 6-benzoylamine-3-*O*-benzyl-6-deoxy-1,2-*O*-isopropylidene-α-D-xylo-hexofuran-5-one **9** (0.19 g, 86%) as an oil. $[\alpha]_D^{22} = -94.8$ (c 1.20, $CHCl_3$). IR (NaCl, ν_{max}, cm^{-1}): 3063–2871 ($C_{Ar}H$); 1735 (CO); 1659 (CO). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.33 (s, 3H, CH_3); 1.48 (s, 3H, CH_3); 4.33 (d, 1H, $J_{3,4}$ = 3.51 Hz, H-3); 4.46 (d, 1H, J = 11.72 Hz, CHPh); 4.57–4.62 (m, 4H, CH_2NHBz + CHPh + H-4); 4.81 (d, 1H, $J_{2,1}$ = 3.51 Hz, H-2); 6.11 (d, 1H, $J_{1,2}$ = 3.51 Hz, H-1); 6.83–6.86 (m, 1H, NHBz); 7.17–7.31 (m, 5H, 5 × H-Ph); 7.42–7.54 (m, 3H, 3 × H-Ph); 7.79–7.82 (m, 2H, 2 × H-Ph). ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 26.14 (CH_3); 26.77 (CH_3); 49.03 (CH_2); 72.33 (CH_2); 81.55 (CH); 83.48 (CH); 84.57 (CH); 105.96 (CH); 112.43 (C); 126.94 (2 × $C_{Ar}H$); 127.39 (2 × $C_{Ar}H$); 127.95 ($C_{Ar}H$); 128.37 (4 × $C_{Ar}H$); 131.47 ($C_{Ar}H$); 133.82 (C_{Ar}); 136.46 (C_{Ar}); 166.95 (CO); 203.76 (CO). MS (CI) m/z 412 [$(M+H)^+$, 100]; 354 (20); 91 [$(PhCH_2)^+$, 87].

4.4. 6-Benzoylamino-3-*O*-benzyl-6-deoxy-α-D-xylo-hexofuran-5-one 10

Compound **9** (0.640 g, 1.55 mmol) was dissolved in a mixture (1:1) of trifluoroacetic acid and H_2O (28 mL) and the resulting solution was stirred at room temperature for 12 h. The reaction was evaporated to dryness and coevaporated with toluene (2 × 1.5 mL) to give a yellow residue of 6-benzoylamine-3-*O*-benzyl-6-deoxy-α-D-xylo-hexofuran-5-one **10**, which was used in the next step without further purification.

4.5. 6-Benzoylamino-3-*O*-benzyl-1,5,6-trideoxy-*N*-(1,1-diphenylmethyl)-1,5-imino-D-glucitol 12a and 6-benzoylamine-3-*O*-benzyl-1,5,6-trideoxy-*N*-(1,1-diphenylmethyl)-1,5-imino-L-iditol 12b

A solution of compound **10** (570 mg) in methanol (11 mL) was added dropwise to a solution of diphenylmethylamine (1.22 mL, 1.24 mmol) and acetic acid (0.07 mL, 1.24 mmol) in methanol (11 mL) at −78 °C. The resulting reaction mixture was stirred at −78 °C for 30 min and sodium cyanoborohydride (0.2 g, 3.12 mmol) was then added in three portions over 45 min. The mixture was stirred for 2 h at −78 °C, allowed to warm up to room temperature and then stirred for 22 h. Saturated aqueous sodium bicarbonate (50 mL) was added and the mixture was extracted with dichloromethane (3 × 50 mL). The organic layers were dried with anhydrous sodium sulfate, filtered, evaporated in vacuo and the resulting residue was purified by flash column chromatography (ethyl acetate/hexane 1:2 to 1:1) to give 6-benzoylamine-3-*O*-benzyl-1,5,6-trideoxy-*N*-(1,1-diphenylmethyl)-1,5-imino-D-glucitol **12a** (0.35 g, 44%) as an amorphous solid and 6-benzoylamine-3-*O*-benzyl-1,5,6-trideoxy-*N*-(1,1-diphenylmethyl)-1,5-imino-L-iditol **12b** (0.15 g, 19%) as a yellow solid, which was crystallized from a mixture of ethyl acetate and hexane.

Compound **12a**: $[\alpha]_D^{22} = -1.3$ (c 0.50, $CHCl_3$). IR (NaCl, ν_{max}, cm^{-1}): 3365 (OH); 3063–2871 ($C_{Ar}H$); 1659 (CO). ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.91 (dd, 1H, $J_{1,1'}$ = 11.52 Hz; $J_{1,2}$ = 10.15 Hz, H-1); 2.14 (br s, 2H, 2 × OH); 2.63–2.69 (m, 1H, H-5); 3.01 (dd, 1H, $J_{1',1}$ = 11.52 Hz; $J_{1',2}$ = 4.39 Hz, H-1′); 3.15 (t, 1H, $J_{3,4}$ = 8.50 Hz, H-3); 3.55 (t, 1H, $J_{4,3}$ = 8.50 Hz, H-4); 3.64–3.77 (m, 2H, H-6 + H-6′); 4.33–4.43 (m, 1H, H-2); 4.72 (d, 1H, J = 11.52 Hz, CHPh); 4.95 (d, 1H, J = 11.52 Hz, CHPh); 5.42 (s, 1H, $CHPh_2$); 6.56–6.61 (m, 1H, NHBz); 7.16–7.53 (m, 20H, 20 × H-Ph). ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 36.95 (CH_2); 51.05 (CH_2); 62.17 (CH); 64.77 (CH); 69.28 (CH); 71.32 (CH); 74.57 (CH_2); 85.38 (CH); 126.72, 126.99, 127.04, 127.38, 127.60, 127.68, 127.89, 128.19, 128.36, 128.41, 129.96, 131.64 (20 × $C_{Ar}H$); 133.48 (C_{Ar}); 137.05 (C_{Ar}); 138.43 (C_{Ar}); 141.39 (C_{Ar}); 168.80 (CO). MS (CI) m/z 523 [$(M+H)^+$, 25]; 388 [$(M-CH_2NHBz)^+$, 37]; 167 (100); 91 [$(PhCH_2)^+$, 49].

Compound **12b**: mp: 128–130 °C (ethyl acetate/hexane). $[\alpha]_D^{22} = +10.2$ (c 2.42, $CHCl_3$). IR (NaCl, ν_{max}, cm^{-1}): 3355 (OH); 3084–2855 ($C_{Ar}H$); 1640 (CO). ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.56 (dd, 1H, $J_{1,1'}$ = 11.52 Hz; $J_{1,2}$ = 10.15 Hz, H-1); 2.86–3.22 (m, 4H, 2 × OH + H-1′ + H-5); 3.52 (t, 1H, $J_{3,4}$ = 8.50 Hz, H-3); 3.61–4.02 (m, 4H, H-2 + H-4 + H-6 + H-6′); 4.78 (d, 1H, J = 11.52 Hz, CHPh); 4.90 (d, 1H, J = 11.52 Hz, CHPh); 4.95 (s, 1H, $CHPh_2$); 6.80–6.84 (m, 1H, NHBz); 7.13–7.65 (m, 20H, 20 × H-Ph). ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 35.07 (CH_2); 48.97 (CH_2); 57.83 (CH); 70.16 (CH); 70.32 (CH); 72.05 (CH); 74.58 (CH_2); 83.54 (CH); 126.82, 127.15, 127.28, 127.36, 127.42, 127.84, 127.90, 128.45, 128.63, 128.73, 131.64 (20 × $C_{Ar}H$); 134.33 (C_{Ar}); 138.52 (C_{Ar}); 141.39 (C_{Ar}); 142.67 (C_{Ar}); 167.40 (CO). MS (CI) m/z 523 [$(M+H)^+$, 99]; 388 [$(M-CH_2NHBz)^+$, 100]; 167 (85); 91 [$(PhCH_2)^+$, 68].

4.6. 6-Amino-1,5,6-trideoxy-1,5-imino-D-glucitol dihydrochloride 4

Pd/C (10%) (185 mg) and $HCOONH_4$ (60 mg, 0.95 mmol) were added to a deoxygenated solution of compound **12a** (70.5 mg, 0.134 mmol) in methanol (4 mL) and the resulting suspension was stirred at 70 °C under an argon atmosphere for 1 h. The reaction mixture was filtered through Celite®, which was washed with methanol (10 mL). The filtrate was concentrated to dryness and the residue dissolved in H_2O (10 mL) and washed with dichloromethane (3 × 10 mL). The aqueous solution was evaporated to dryness, dissolved in aqueous HCl (6 M, 3 mL), stirred for 3 d at 50 °C and evaporated. The residue was dissolved in methanol and ethyl ether was added to give a white solid, which was filtered off and identified as 6-amino-1,5,6-trideoxy-1,5-imino-D-glucitol dihydrochloride **4** (17 mg, 54%). mp 187–188 °C (methanol/ethyl ether). $[\alpha]_D^{22} = +11.5$ (c 0.12, H_2O). IR (NaCl, ν_{max}, cm^{-1}): 3425 (OH). ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.92 (dd, 1H, $J_{1,1'}$ = 11.52 Hz; $J_{1,2}$ = 12.11 Hz, H-1); 4.25–4.49 (m, 6H, H-1′ + H-3 + H-4 + H-5 + H-6 + H-6′); 4.60–4.78 (m, 1H, H-2). ^{13}C NMR (62.8 MHz, $CDCl_3$) δ 40.82 (CH_2); 47.97 (CH_2); 57.14 (CH); 68.18 (CH); 72.60 (CH);

76.95 (CH). HRMS: Calculated for $C_6H_{15}N_2O_3$ $(M+H)^+$ 163.1083; found 163.1095.

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