Imino Glycals in Synthesis: Preparation of Novel Deoxymannojirimycin Analogues

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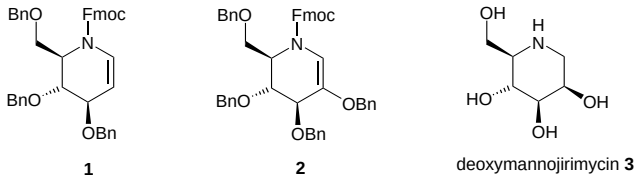
Abstract: The synthesis of imino glucal **2** from tetra-*O*-benzyl-D-glucopyranose in 7 steps is described. This imino sugar building block is converted into conformationally constrained deoxymannojirimycin analogue (+)-**9** by means of a stereocontrolled cyclopropanation followed by a two step deprotection sequence. Regioselective fission of the cyclopropane ring prior to deprotection provides access to related analogue (+)-**11**.

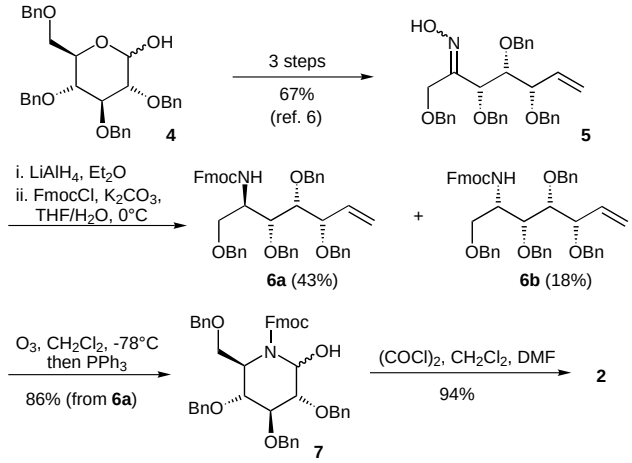
Key words: carbohydrates, piperidines, stereoselective synthesis, imino glycals, glycosidases

Glycals, carbohydrates incorporating a double bond between C-1 and C-2, have proven to be useful building blocks in organic chemistry especially in the context of oligosaccharide synthesis.[1] By analogy, we reasoned that imino glycals, glycals in which the ring oxygen atom is replaced by nitrogen, might prove to be useful synthetic intermediates, as the alkene double bond would be expected to undergo a variety of addition, cycloaddition and metal catalysed cross-coupling reactions. In this way, we envisaged that a variety of novel imino sugars could be assembled, enabling us to probe further the binding specificity of the glycosidase family of enzymes.[2] Very recently, we described our first studies relating to the synthesis and chemistry of imino glycals, wherein we reported the preparation of imino glucal **1** from tri-*O*-benzyl-D-glucal, and used it to prepare the naturally occurring imino sugar, (+)-fagomine.[3,4] In this Letter, we report the synthesis of related imino glucal **2**, bearing a benzyloxy group at C-2, and describe stereocontrolled cyclopropanation reactions of this system. Further synthetic manipulations provide novel analogues of the naturally occuring imino sugar, deoxymannojirimycin **3**.[5]



Figure

Tetra-*O*-benzyl-D-glucopyranose **4** was converted into oxime **5** in three steps essentially by the published method (Scheme 1).[6,7] Reduction of this oxime with lithium aluminium hydride furnished the primary amine, which was immediately transformed into **6** by protection with the base labile Fmoc group. The oxime reduction occurred with modest selectivity in favour of the required (6*R*)-diastereomer (**6a**:**6b**; *ca* 2.4:1 as judged by ^{1}H NMR spectroscopy).[8] Separation of (6*R*)-**6a** from the unwanted minor diastereomer (6*S*)-**6b** was accomplished by MPLC using a Merck Lobar Lichroprep Si60 column. Ozonolysis of **6a** followed by treatment with triphenylphosphine provided **7**, which underwent elimination to glucal **2** in excellent yield upon treatment with oxalyl chloride. Overall, this sequence provides imino glucal **2** in 7 steps from tetra-*O*-benzyl-D-glucopyranose in 23% overall yield.



Scheme 1

With imino glucal **2** in hand, we have begun to explore its reactivity. In the first instance, we chose to examine methods for the cyclopropanation of this system. This transformation was readily accomplished using excess diiodomethane and diethyl zinc (Scheme 2).[9] The reaction was highly stereoselective and only one diastereomer could be detected in the crude reaction mixture by ^{1}H NMR spectroscopy. Further treatment of the resultant cyclopropane with morpholine provided secondary amine **8** in 64% yield over the two steps. The stereochemical outcome of the reaction was established on the basis of nOe measurements performed on **8**.[10,11] To account for the observed stereoselectivity, we suggest that imino glucal **2** adopts a half-chair conformation in which the substituents at C-4 and C-5 adopt *pseudo* equatorial orientations. Carbenoid addition *anti* to the OBn substituent at C-3 accounts for the formation of the observed diastereomer.

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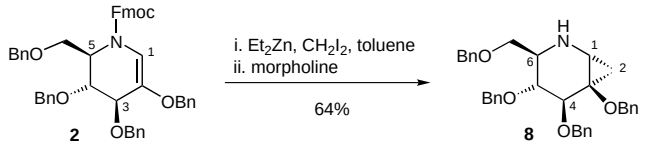
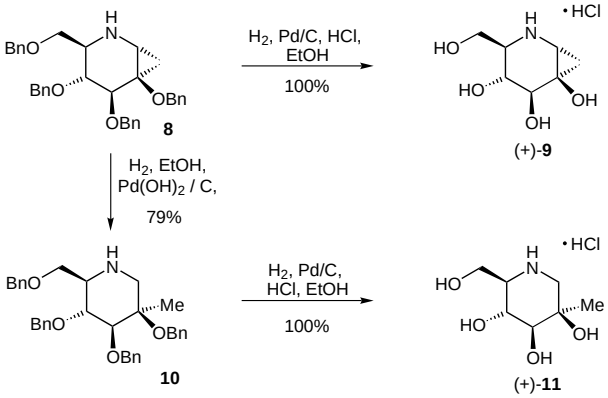
Other methods of cyclopropanation were also briefly examined {$CHCl_3$, NaOH, $BnNEt_3Cl$; $PhHgCCl_3$, DME, 85 °C; N_2CHCO_2Et, CH_2Cl_2, Cu powder or $Rh_2(OAc)_4$} although these proved to be ineffective.



Scheme 2

From an examination of the vicinal coupling constants of piperidine **8** ($J_{4,5}$ = 5.8 Hz), we conclude that the cyclopropane ring fusion forces the piperidine out of the traditional chair conformation.[12] Consequently, we felt that it would be of interest to deprotect this material and compare its enzyme inhibitory activity against that of the naturally occurring imino sugar, deoxymannojirimycin **3** which does not possess this conformational constraint. Initially, we attempted to effect debenzylation using trimethylsilyl iodide as we were concerned that catalytic hydrogenation might result in fission of the cyclopropane ring. However, whilst exhaustive debenzylation to (+)-**9** could be accomplished using TMSI, we were unable to obtain it in a satisfactorily pure state. Despite our initial reservations, catalytic hydrogenation using palladium on carbon proved to be very effective method for debenzylation provided the reaction was performed in the presence of hydrochloric acid. In this way, conformationally constrained deoxymannojirimycin analogue (+)-**9** could be isolated in quantitative yield as its hydrochloride salt.[11] Interestingly, using palladium hydroxide on carbon in the absence of acid, it was possible to regioselectively cleave the cyclopropane ring between C-1 and C-2 without concomitant debenzylation. The resultant piperidine **10** appears to adopt a chair conformation as indicated by the large vicinal coupling constants for H-4 (J = 10.4 and 9.2 Hz). Further hydrogenation of **10** using Pd/C as catalyst under acidic conditions yielded deoxymannojirimycin analogue (+)-**11** in quantitative yield.[11]

Imino sugars (+)-**9** and (+)-**11** display weaker inhibitory activity against α-mannosidase (from jackbean) at pH 5 than deoxymannojirimycin **3** itself {(+)-**9** (K_i = 1.5 mM); (+)-**11** (K_i = 5.1 mM); **3** (K_i = 0.06 mM {lit values: K_i = 68 μM at pH 5.5; K_i = 400 μM at pH 4.5[13]}).[14] Further work to explore the utility of imino glucals **1** and **2** is ongoing and will be disclosed in due course.



Scheme 3

Acknowledgement

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(6) Liu, P.S. *J. Org. Chem.* **1987**, *52*, 4717. We found it more convenient to use TPAP/NMO for the oxidation step rather than DCC/DMSO as originally reported.

(7) All new compounds have been fully characterised using standard spectroscopic and analytical techniques.

(8) We have been unable to reproduce the higher levels of diastereocontrol (d.r. 6:1) reported for the reduction of oxime **5** in ref. 6.

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(10) Selected nOe data for **8**. Enhancement of H-1 (9.7%), H-4 (7.0%) and H-6 (9.9%) from H-2/H-2'; of H-2/H-2' (1.4%) and H-6 (2.4%) from H-4; Thus, the cyclopropane (H-2, H-2'), H-4 and H-6 reside on the α-face of the piperidine ring.

(11) *Selected physical and spectroscopic data:*
8: $[\alpha]_D^{20}$ -6.8 (*c* 1.2, $CHCl_3$); ν_{max} 3334, 3027, 2852, 1450, 1265, 1096 cm^{-1}; δ_H (400 MHz; $CDCl_3$) 7.33-7.24 (20H, m, Ar*H*), 4.85 (1H, d, *J* 11.6, OC*H*HPh), 4.74-4.69 (3H, m, 3 × OC*H*HPh), 4.55-4.46 (4H, m, 4 × OC*H*HPh), 4.06 (1H, d, $J_{4,5}$ 5.8, H-4), 3.60 (3H, m, H-5, 2 × H-7), 2.89 (1H, m, H-6), 2.83 (1H, dd, *J* 5.9, 7.8, H-1), 1.82 (1H, br s, N*H*), 1.10-1.06 (2H, m, 2 × H-2); Found: MH^+ (ESI), 536.2794. $C_{35}H_{38}NO_4$ requires 536.2801.
9·HCl: $[\alpha]_D^{20}$+22.1 (*c* 0.95, H_2O); ν_{max} 3339, 2950, 2832, 1024 cm^{-1}; δ_H (400 MHz; CD_3OD) 4.03 (1H, d, $J_{4,5}$ 3.2, H-4), 4.00 (1H, dd, $J_{7',7}$ 12.4, $J_{7',6}$ 9.1, H-7'), 3.83 (1H, m, H-5), 3.75 (1H, dd, $J_{7,6}$ 3.6, $J_{7,7'}$ 12.4, H-7), 3.17 (1H, m, H-6), 2.79 (1H, dd, $J_{1,2'}$ 4.7, $J_{1,2}$ 9.1, H-1), 1.55 (1H, dd, $J_{2',1}$ 4.7, $J_{2',2}$ 7.7, H-2'), 1.28 (1H, dd, $J_{2,2'}$ 7.7, $J_{2,1}$ 9.1, H-2); δ_C (100 MHz; CD_3OD)

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69.1 (C-5), 68.8 (C-4), 59.5 (C-6), 59.0 (C-7), 53.1 (C-3), 33.3 (C-1), 16.6 (C-2); Found: C, 36.60; H, 7.09; N, 5.71. $C_7H_{14}ClNO_4{\cdot}H_2O$ requires C, 36.61; H, 7.02; N, 6.10%. **11·HCl**: $[\alpha]_D^{20}$+3.1 (*c* 0.64, H_2O); ν_{max} 3339, 2950, 1050 cm^{-1}; δ_H (400 MHz; CD_3OD) 3.99 (1H, dd, $J_{6',5}$ 3.4, $J_{6',6}$ 11.8, H-6'), 3.76 (1H, dd, $J_{6,5}$ 7.3, $J_{6,6'}$ 11.8, H-6), 3.71 (1H, dd, *J* 10.4, 9.2, H-4), 3.30 (1H, m, H-3), 3.13 (1H, d, *J* 13.0, H-1), 3.06 (1H, d, *J* 13.0, H-1'), 3.07-2.99 (1H, m, H-5), 1.31 (3H, s, C*H*$_3$); δ_C (100 MHz; CD_3OD) 77.9 (C-3), 70.7 (C-2), 68.8 (C-4), 62.6 (C-5), 60.0 (C-6), 53.4 (C-1), 23.2 (*C*H_3); Found: MH^+ (ESI), 178.1081. $C_7H_{16}NO_4$ requires 178.1079.

(12) It is unclear whether **8** (and **9**) prefer to adopt half-chair or boat conformations. Conformer distribution calculations conducted using MacSpartan Pro® (MMFF force field) indicate that both are energetically accessible.

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