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A Short and Convenient Synthesis of 1-Deoxymannojirimycin and *N*-Oxy Analogues from D-Fructose

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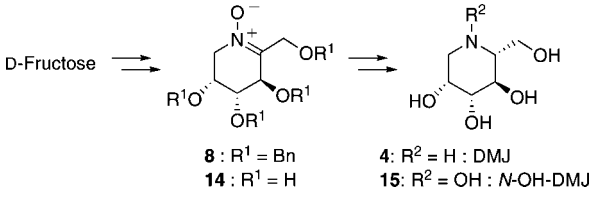

Ketonitrone **8** was prepared from D-fructose as an inexpensive starting material and was used in a stereoselective synthesis of 1-deoxymannojirimycin (DMJ, **4**), of its previously unknown *N*-hydroxy analogue **15**, and of the polyhydroxylated ketonitrone **14**. The latter were assayed as potential glycosidase inhibitors on a panel of 13 selected purified enzymes. Disappointingly, the polyhydroxylated nitrone **14** inhibited none of these enzymes. However, *N*-hydroxy-DMJ (**15**) exhibited a moderate and non-selective activity toward the snail β-mannosidase EC 3.2.1.25.

Iminosugars (or iminocyclitols) constitute the most important class of glycoprocessing enzyme modulators.[1] It is known that their bioactivity originates in their ability to mimic the oxocarbenium-type transition state of these enzymes.[1,2] As the inhibition of glycoprocessing enzymes finds potential applications in the development of antiviral,[3] anticancer,[4] and metabolic disorder[5] therapies, iminosugars have attracted much attention among synthetic and medicinal chemists. In particular, polyhydroxylated piperidines[6] such as 1-deoxynojirimycin (DNJ, **1**) have demonstrated potent biological activities.[7] Intense research in this area culminated in the approval of miglustat (*N*-butyldeoxynojirimycin, **2**) and miglitol (*N*-hydroxyethyl-deoxynojirimycin, **3**), prescribed for the treatment of, respectively, type-1 Gaucher's disease and type-2 diabetes mellitus (Figure 1).[1a]

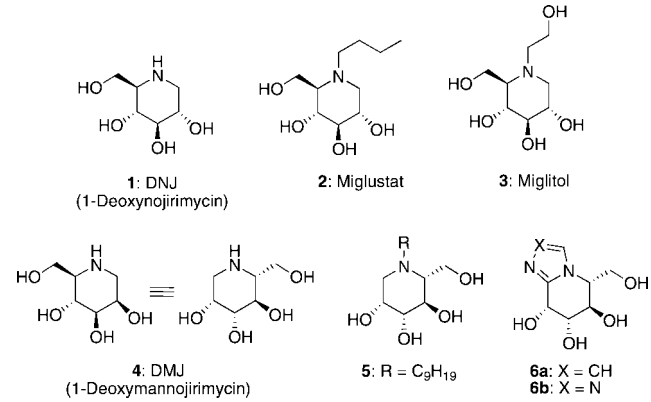

FIGURE 1. Bioactive piperidinic iminosugars.

1-Deoxymannojirimycin (DMJ, **4**, Figure 1) is a DNJ congener, exhibiting the *manno* configuration. DMJ selectively inhibits jack bean α-mannosidase (EC 3.2.1.24, IC_{50} 150 μM)[8] and Golgi α-mannosidase II (EC 3.2.1.114, IC_{50} 400 μM).[9] It also was proven to block the conversion of high mannose to complex oligosaccharides in cells[10] and to improve the anticancer activity of cisplatin against head and neck carcinoma (IMC-3 cells, 64% enhancement of the IC_{50} of cisplatin at 10 μg/mL).[11] Its *N*-nonyl analogue **5** is active against hepatitis B virus (Hep G2 2.215 cells);[12] bicyclic derivatives **6a** and **6b** are also potential anticancer agents as potent inhibitors of jack bean α-mannosidase (EC 3.2.1.24, IC_{50} 0.12 μg/mL for **6a** and IC_{50} 13 μg/mL for **6b**) and snail β-mannosidases (EC 3.2.1.25, IC_{50} 0.023 μg/mL for **6a** and IC_{50} 0.078 μg/mL for **6b**).[13,14]

As a result of the promising applications of DMJ derivatives as therapeutic agents, the synthesis and biological evaluation of new analogues is a field of interest.

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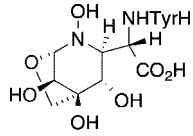


7: SB-219383

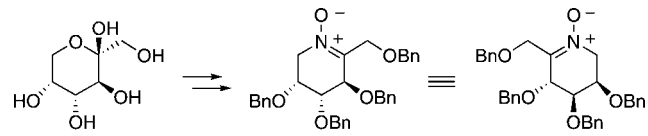
FIGURE 2. Structure of SB-219383, a selective inhibitor of bacterial tyrosyl tRNA synthetase.

In the course of our work on the synthesis and uses of carbohydrate-derived nitrones,[15] it appeared that these intermediates could give access not only to a variety of iminosugars but also to their *N*-hydroxy derivatives, as soon as a method was available for deprotecting alkoxy groups without affecting N—O bonds.[16] Strikingly, while a few polyhydroxylated piperidine *N*-oxides have been previously studied,[17] the potential of polyhydroxylated nitrones or *N*-hydroxy piperidines as glycosidase or glycosyltranferase inhibitors remains largely unknown. To the best of our knowledge, the only *N*-hydroxypiperidine for which biological activity has been reported is SB-219383 (**7**, Figure 2), a natural product extracted from *Micromonospora* sp. The latter was developped by GlaxoSmith-Kline as a potent and selective inhibitor of bacterial tyrosyl tRNA synthetase.[18]

In this note, we describe the synthesis of a carbohydrate-derived six-membered-ring ketonitrone (from D-fructose) and its stereoselective transformation to DMJ and *N*-hydroxy DMJ.

A number of polyfunctionalized five-membered-ring cyclic nitrones have been prepared from carbohydrates and tartaric acid derivatives, mostly in the groups of Goti and Brandi.[19] Such intermediates have been used in a variety of reactions including addition of organometallics,[20] 1,3-cycloaddition,[21] or SmI_2-induced reductive coupling.[22] In contrast, six-membered-ring endocyclic nitrones are scarce in the literature,[23] and most of them were reported to be unstable.[24] Probably for this reason, such nitrones have been used in synthesis without isolation.[25]

SCHEME 1



We considered the use of D-fructose as a cheap and readily available starting ketose to access the six-membered-ring ketonitrone **8** and derivatives exhibiting the *manno* configuration (Scheme 1).[26]

1,3,4,5-Tetra-*O*-benzyl β-D-fructopyranose **9** was first prepared using the method of Chittenden[27] with slight modifications.[28] An *O*-protected oxime functionality was next introduced at the anomeric position by treating compound **9** with *O*-*tert*-butyldiphenylsilylhydroxylamine,[29] in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate and with azeotropic elimination of water.[30] Then, adapting the method proposed by Tamura for the synthesis of carbohydrate-derived cyclic aldonitrones, the primary alcohol was mesylated to produce the oximes **10a** and **10b** in 86% yield (for the two steps) as a mixture of diastereomers, *E*(**10a**):*Z*(**10b**) = 60:40.[31] Nitrone cyclization was then induced by fluoride attack at the silyl protecting group of the oxime. In this case, the use of silica-supported tetrabutylammonium fluoride[32] was found advantageous when compared to tetrabutylammonium triphenyl-difluorosilicate (TBAT)[33] or other fluoride sources, conciliating good yields and easy isolation of the polar nitrone **8**. However, only the *E* isomer **10a** cyclized to the corresponding nitrone, while the *Z* isomer **10b** was transformed quantitatively to the corresponding deprotected oxime **11**. Attempts to isomerize **11** and transform it into the nitrone **8** were not met with success.[34]

Nitrone **8** was next reduced stereoselectively as shown in Scheme 3. First, its hydrogenation over 10% Pd/C afforded

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(31) The configuration of each isomer was assigned from nOe experiments (see Supporting Information) and their ratio was determined from ^{1}H NMR spectra.

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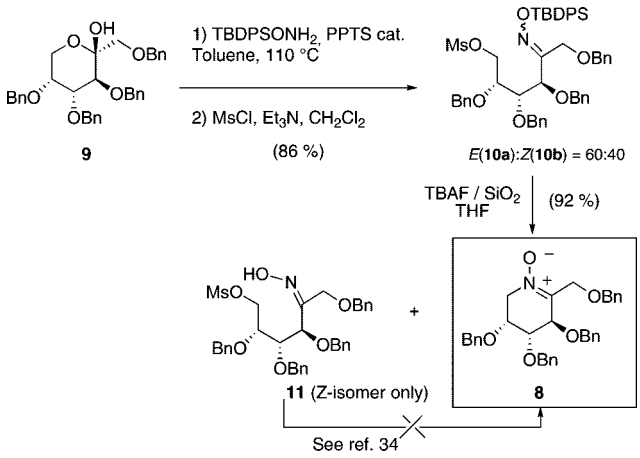
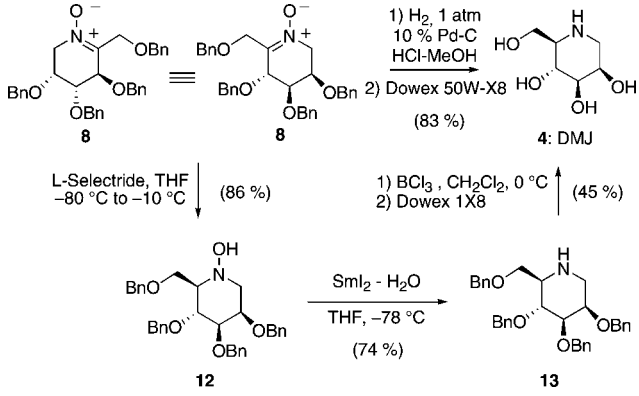
SCHEME 2



SCHEME 3



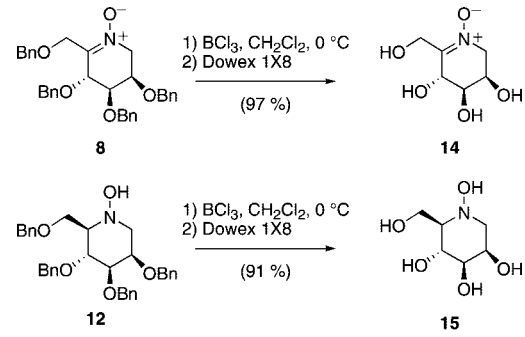
directly DMJ (**4**) in a satisfactory 83% yield and as a single diastereomer. Then, hydride reduction of **8** was investigated to access the *N*-hydroxy derivative of **4**.[35] While treatment with $NaBH_4$ (MeOH, 0 °C) yielded a 90:10 mixture of diastereomers (82% yield), the use of L-selectride as reducing agent furnished the single diastereomer **12** in 86% yield. The configuration of **12** was confirmed by its two-step transformation into DMJ (**4**): SmI_2-mediated reduction of the hydroxylamine[36] afforded 2,3,4,6-tetra-*O*-benzyl-DMJ (**13**),[37] which was next converted to **4**[38] upon treatment with BCl_3 in dichloromethane. Additionally, the *N*-hydroxypiperidine **12** was found to crystallize as colorless prismatic monocrystals, of which X-ray analysis confirmed the *R* configuration at the newly created stereogenic center.[39] Interestingly, X-ray analysis also showed equatorial orientation of the *N*-OH group in **12** in the solid state. The stereochemical outcome of both hydrogenation and hydride reduction of nitrone **8** results from axial attack of the reagents onto the *si* face of the favored half-chair conformer of nitrone **8** (exhibiting most of the substituents in pseudoequatorial orientation).

TABLE 1. Evaluation of Compounds 14 and 15 as Potential Inhibitors of Glycosidases[a]

enzymes	compound **14**	compound **15**
α-glucosidase rice EC 3.2.1.20	none	19%
β-glucosidase almonds EC 3.2.1.21	none	32%
β-mannosidase snail EC 3.2.1.25	none	43%
β-xylosidase *Aspergillus niger* EC 3.2.1.37	none	37%

[a] % Inhibition at [inhibitor] = 1 mM.

SCHEME 4



Finally, nitrone **8** and *N*-hydroxypiperidine **12** were deprotected using BCl_3, affording the novel *N*-oxy iminosugars **14** and **15** in excellent yields of 97% and 91%, respectively (Scheme 4).[16] These two compounds were assayed against a panel of 13 purified glycosidases.[40] Unfortunately, nitrone **14** was inactive against all of the classical glycosidases.[41] In contrast, the *N*-hydroxypiperidine **15** exhibited a weak inhibition (43% inhibition at [inhibitor] = 1 mM) of the snail β-mannosidase (EC 3.2.1.25; see Table 1). It also inhibited a α-glucosidase from rice (EC 3.2.1.20, 19% inhibition at 1 mM), a β-glucosidase from almonds (EC 3.2.1.21, 32% inhibition at 1 mM), and a β-xylosidase from A*spergillus niger* (EC 3.2.1.37, 37% inhibition at 1 mM). Thus, it can be concluded that **14** and **15** do not compete favorably with DMJ (**4**) in terms of bioactivity toward these enzymes.

In conclusion, nitrone **8** has been readily prepared from D-fructose and proved, as did its debenzylated derivative **14**, to be stable at room temperature. The transformation of nitrone **8** into either 1-deoxymannojirimycin (**4**) or its *N*-hydroxy derivative **15** by highly stereoselective reduction and BCl_3-promoted debenzylation is also presented. The novel polyhydroxylated *N*-hydroxypiperidine **15**, related to the well-recognized glycosidase inhibitor 1-deoxymannojirimycin, exhibits weak inhibition of β-mannosidase. We are currently exploring the utility of nitrone **8** in organic synthesis and of **14** as a water-soluble radical trap.[42]

Experimental Section

(3*R*,4*R*,5*R*)-3,4,5-Tris(benzyloxy)-6-(benzyloxymethyl)-2,3,4,5-tetrahydropyridine 1-Oxide (8). To a solution of mesylates **10** (6.71 g, 7.69 mmol) in distilled THF (250 mL) was added, at 0 °C,

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(42) For recent work on cyclic nitrones as radical traps, see: Han, Y.; Tuccio, B.; Lauricella, R.; Rockenbauer, A.; Zweier, J. L.; Villamena, F. A. *J. Org. Chem.* **2008**, *73*, 2533, and references therein.

TBAF on silica gel (15.40 g, 15.40 mmol). The reaction was stirred at room temperature during 14 h. The mixture was filtered, and the solid was washed with THF. The filtrate was concentrated under vacuum. Purification of the obtained residue by chromatography over silica gel (pentane/AcOEt/MeOH 3:1:0 to 0:8:1) afforded pure nitrone **8** (2.32 g, 55%) as a yellow oil and oxime **11** (1.80 g, 37%) as a pale yellow oil. Nitrone **8**: $[\alpha]^{20}_D = -60.0$ (*c* 1.00, $CHCl_3$); MS (ESI) *m*/*z* 538 $[M + H]^+$; IR ν (neat, cm^{-1}) 3414 (br), 3062 (m), 3033 (m), 2919 (m), 2865 (m), 1599 (m), 1456 (s), 1202 (s), 1112 (s), 1055 (s); ^1H NMR (300 MHz, $CDCl_3$) δ 3.79−3.81 (m, 1H), 3.87−3.97 (m, 1H), 4.05−4.17 (m, 2H), 4.40−4.72 (m, 12H), 7.09−7.13 (m, 2H), 7.23−7.36 (m, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 58.4, 66.7, 70.9, 71.8, 72.2, 72.6, 72.8, 73.5, 73.6, 127.9−128.7, 137.5, 137.6, 137.9, 144.5. Anal. Calcd for $C_{34}H_{35}NO_5$: C, 75.96; H, 6.57; N, 2.61. Found: C, 75.71; H, 6.60; N, 2.74.

(2*R*,3*R*,4*R*,5*R*)-3,4,5-Tris(benzyloxy)-2-(benzyloxymethyl)piperidin-1-ol (12). To a solution of nitrone **8** (50 mg, 0.09 mmol) in distilled THF (1 mL) was added L-selectride (1 M solution in THF, 0.186 mL, 0.18 mmol) was added at −80 °C. The reaction mixture was stirred at −80 °C during 2.5 h and then for 7 h at −10 °C. An aqueous saturated solution of NH_4Cl (0.5 mL) was added. The aqueous layer was extracted three times with Et_2O. The organic phase was stirred with an aqueous saturated solution of KHF_2 (2 mL) during 1 h. The aqueous layer was extracted three times with Et_2O. The organic phase was washed with brine, dried over $MgSO_4$, and concentrated. Purification of the residue by chromatography on silica gel (pentane/AcOEt 3:1 to 0:1) afforded pure, colorless crystals of *N*-hydroxypiperidine **12** (43 mg, 86%): mp 78−80 °C; $[\alpha]^{20}_D = +1.9$ (*c* 1.00; $CHCl_3$); MS (ESI) *m*/*z* 540 $[M + H]^+$; IR ν (CH_2Cl_2, cm^{-1}) 3393 (m), 3026 (m), 2857 (m), 1494 (m), 1449 (s), 1351 (m), 1115 (s), 1095 (s); ^1H NMR (400 MHz, CD_3OD) δ ppm 2.43 (br d, J = 9.4 Hz, 1H), 2.50 (d, J = 11.9 Hz, 1H), 3.52 (dd, J = 3.3, 9.6 Hz, 1H), 3.59 (dd, J = 3.4, 12.0 Hz, 1H), 3.79 (dd, J = 2.6, 10.2 Hz, 1H), 3.92−3.94 (m, 2H), 4.11 (t, J = 9.6 Hz, 1H), 4.44 (d, J = 11.8 Hz, 1H), 4.49−4.69 (m, 5H), 4.75 (d, J = 12.0 Hz, 1H), 4.84 (d, J = 10.6 Hz, 1H), 7.16−7.42 (m, 20H); ^{13}C NMR (75 MHz, CD_3OD) δ ppm 59.5, 67.3, 72.4, 72.5, 72.8, 72.9, 74.5, 76.2, 76.3, 84.3, 128.5−129.5, 139.8, 139.9, 140.1. Anal. Calcd for $C_{34}H_{37}NO_5$: C, 75.68; H, 6.92; N, 2.60. Found: C, 75.90; H, 7.03; N, 2.68.

(2*R*,3*R*,4*R*,5*R*)-2-(Hydroxymethyl)piperidine-1,3,4,5-tetraol (15). To a stirred solution of hydroxylamine **12** (105 mg, 0.19 mmol) in CH_2Cl_2 (8 mL) cooled to 0 °C, under argon, was added a solution of BCl_3 (2.30 mL, 2.30 mmol) in hexane. The solution was stirred at 0 °C during 20 h then MeOH (2 mL) was added dropwise. The reaction mixture was concentrated under vacuum. MeOH (4 mL) was added, and then mixture was concentrated under vacuum. This operation was repeated six times. The crude product was dissolved in H_2O (4 mL) and stirred with DOWEX 1X8 (OH^- form) until pH 6. After filtration, the filtrate was concentrated under vacuum to give **15** (31 mg, 91%) as a pale oil. $[\alpha]^{20}_D = -47.5$ (*c* 0.44; H_2O); MS (ESI) *m*/*z* 180 $[M + H]^+$; IR ν (KBr, cm^{-1}) 3405 (br, s), 2955 (m), 2842 (m), 1640 (m), 1402 (m), 1333 (m), 1254 (w), 1098 (s), 1064 (s); ^1H NMR (400 MHz, D_2O) δ 2.45 (br s, 1H), 2.89 (d, J = 11.2 Hz, 1H), 3.47 (dd, J = 2.4, 11.9 Hz, 1H), 3.58 (dd, J = 3.6, 9.7 Hz, 1H), 3.74−3.80 (m, 1H), 3.88 (dd, J = 3.3, 12.1 Hz, 1H), 4.03 (dd, J = 2.3, 12.1 Hz, 1H), 4.07−4.10 (m, 1H); ^{13}C NMR (75 MHz, D_2O) δ 58.4, 61.1, 66.9, 67.4, 71.4, 73.8; HRMS (ESI) calcd for $C_6H_{13}N_1Na_1O_5$ *m*/*z* = 202.06859 $[M + Na^+]$; found *m*/*z* = 202.06843.

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Note Added after ASAP Publication. Figure 2 was incorrect in the version published ASAP January 16, 2009; the correct version was published January 23, 2009.

Supporting Information Available: Experimental procedures, compounds characterization data, and copies of ^1H NMR and ^{13}C NMR for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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