A norbornyl route to azasugars: a new synthesis of deoxynojirimycin analogues

Goverdhan Mehta* and Narinder Mohal

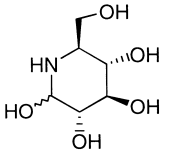
Department of Organic Chemistry, Indian Institute of Science, Bangalore 560 012, India

Abstract

A new synthesis of deoxynojirimycin (DNJ) analogues (galacto- and altrose configuration) has been achieved through a functionalized cyclopentene derivative crafted from the norbornyl system, employing double reductive amination as the key step. The new DNJ analogues have been evaluated against various glycosidases and found to be moderate to strong inhibitors.

Keywords: azasugars; glycosidase inhibitors; osmylation; reductive amination.

Natural and unnatural polyhydroxylated piperidines have aroused the widespread attention of organic chemists in recent years due to their very promising biological activity profile and synthetically challenging structural features present in them.[1] These polyhydroxylated piperidines generically termed as iminosugars ('azasugars'), closely resemble monosaccharides in terms of their shape and structure; they competitively inhibit glycosidases, enzymes responsible for the cleavage of glycosidic bonds. In azasugars, the ring oxygen is replaced by nitrogen, which can be protonated under physiological pH, thus mimicking the glycopyranosyl cation. Inhibition of glycosidases is projected to be useful in the treatment of carbohydrate related metabolic disorders and holds promise for the development of drugs for the treatment of cancer, diabetes, HIV and viral infections.[2] A large number of naturally occurring azasugars and their synthetically designed analogues are known, and nojirimycin **1**, 1-deoxynojirimycin **2**[1a] (DNJ), amidine **3**[3a] and deoxyfuconojirimycin **4**[3b] are typical examples, all of which have been found to inhibit carbohydrate processing enzymes.



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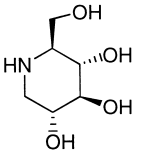

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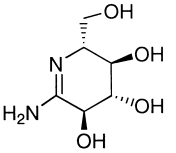

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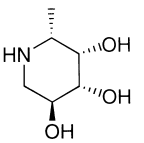

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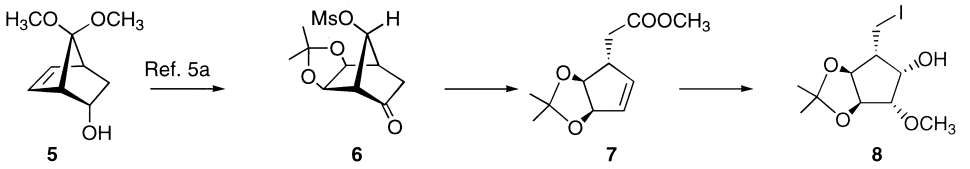
* Corresponding author. E-mail: gm@orgchem.iisc.ernet.in

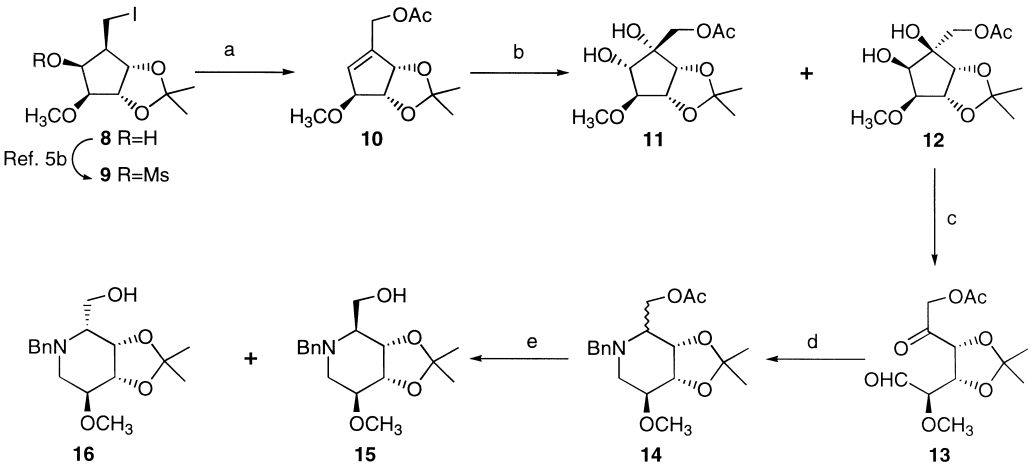
A wide range of synthetic strategies have been devised to access polyhydroxylated piperidines.[1,3,4] Prominent among these, which are also of general applicability, are the restructuring or elaboration of chiral pool derived precursors (carbohydrates, amino acids, *myo*-inositol, tartaric acid etc.),[1a,3,4] chemoenzymatic[4b,c] and microbial (hydroxylated aromatics) approaches,[4d] Diels–Alder[4e] and hetero-Diels–Alder[4f] cycloaddition based routes, and aza-Achmatowicz reaction (furan reorganization).[4g,h] Herein, we report a new synthesis of deoxynojirimycin analogues originating from a bicyclo[2.2.1]heptane (norbornyl) system.

Recently we have developed a fragmentation reaction-based strategy to extract a highly functionalized and stereochemically well defined cyclopentene derivative **8** from the readily available norbornyl derivative **5** through the intermediacy of **6** and **7**, respectively, Scheme 1.[5] Cyclopentane derivative **8** has now been further restructured to DNJ analogues[6] employing double reductive amination as the key step.



Scheme 1.

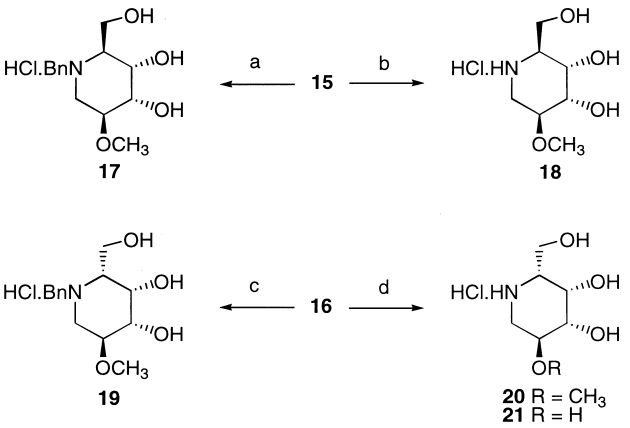
The free hydroxyl group in the iodocyclopentane **8** was transformed to a leaving group through mesylation to furnish the mesylate **9**. Acetolysis of **9** led to elimination followed by allylic displacement to furnish acetoxycyclopentene **10**, in which the olefinic moiety was well positioned for further manipulation. OsO_4-mediated catalytic dihydroxylation of **10** proceeded in a stereoselective manner to give **11**[7] and **12**[7] (10:90), Scheme 2. While diastereomers **11** and **12** were separated and characterized, it was not considered necessary for the next step. Sodium periodate-induced glycol cleavage in **11** and **12** furnished the labile keto-aldehyde **13** which was as such subjected to double-reductive amination in the $NaCNBH_3$–$BnNH_2$ milieu to furnish **14** as a



Scheme 2. Reagents and conditions: (a) NaOAc, DMF, 105°C, 6 h, 77%; (b) OsO_4, NMMO (50% aq. sol.), Me_2CO: H_2O (4:1), 48 h, 86%; (c) $NaIO_4$ (1.3 equiv.), DCM, 0°C; (d) $BnNH_2$, AcOH, $NaCNBH_3$, 20 h, –10°C→rt, 30% for two steps; (e) KOH, MeOH, 2 h, 90%

mixture of two diastereomers (1:2). Base mediated hydrolysis of the acetate group in **14** and chromatographic separation of the diastereomers led to **15**[7] and **16**,[7] which were fully characterized as having the altrose and galactose stereochemical disposition,[6] respectively, on the basis of incisive NMR (COSY, NOE) studies (Scheme 2).

In independent deprotection sequences, **15** and **16** were transformed to the hydrochlorides of *N*-benzyl DNJ derivatives **17** and **19**, respectively, Scheme 3. In a similar manner, hydrochlorides of *altro*-deoxynojirimycin methyl ether **18**[6] and galactostatin methyl ether **20** were obtained from **15** and **16**, respectively, and duly characterized.[7]



Scheme 3. Reagents and conditions: (a) 2.5% HCl: Et_2O (1:1), 18 h, >90%; (b) H_2, Pd/C (10%), EtOH, 18 h, 60%; 2.5% HCl: Et_2O (1:1), 95%; (c) same as (a), 90%; (d) same as (b), quantitative

Table 1
Inhibition constants[a,b] ($\mathbf{K_i}$) in μm

Enzyme	compound			
	17	**18**	**19**	**20**
α-glucosidase (*yeast*)	*[c]	NI[d]	784	NI
β-glucosidase (*sweet almonds*)	*	NI	NI	NI
α-galactosidase (*green coffee beans*)	*	27	233	1.76
β-galactosidase (*E. Coli*)	NI	NI	NI	NI

[a]Each 200 μL assay contained indicated enzyme 0.1-0.5U/mL, inhibitor **17-20** in water (2-3 mM) and nitrophenyl glycosides (2-2.5 mM) in appropriate buffer at optimal temp and pH of each enzyme. [b] Inhibition constants were determined using Dixon plots of inhibition data. [c] 10-25% inhibition was observed at higher conc. (above 800 μM) of inhibitor. [d] No inhibition is observed up to 1mM conc. of inhibitor.

Compounds **17**–**20** were assayed for their glycosidase inhibition activity (Table 1). All measurements were carried out with the corresponding nitrophenyl glycoside substrates in aqueous buffer at appropriate pH. Galactostatin methyl ether **20** was found to be a selective and potent inhibitor of α-galactosidase and there was no inhibition observed for α- and β-glucosidases and β-galactosidase. It was notable that inhibitory activity of **20** was approximately 1000 fold less than of the natural product galactostatin **21**.[6] When **20** was compared with its benzyl derivative **19**, a marked decline in inhibitory activity as well as selectivity was observed and the latter was only a moderate inhibitor of α-galactosidase, and a weak inhibitor of α-glucosidase. Interestingly, **18** (C_2-epimer of **20**) was also found to be a selective inhibitor of α-galactosidase whereas its benzyl derivative was found to be essentially ineffective towards glycosidase inhibition.

In short, we have devised a new synthesis of DNJ derivatives **17**–**20** from the cyclopentanoid building block **7**. Our results of enzymatic assays reveal that *N*- and *O*-substituents have significant consequence on the glycosidase activity and selectivity.

Acknowledgements

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7. All new compounds reported here were racemic and gave satisfactory spectral data (^{1}H and ^{13}C NMR, IR, Mass). Selected spectral data (^{1}H NMR and ^{13}C NMR) **15** δ_H (300 MHz, $CDCl_3$): 7.32–7.28 (5H, m, Ar-H), 4.18 (1H, dd,

$J = 2.7$, 6.0 Hz), 4.08 (1H, dd, $J = 4.8$, 6.0 Hz), 4.03 (1H, $\frac{1}{2}$ABq, $J = 13.2$ Hz), 3.78 (1H, $\frac{1}{2}$ABq, $J = 13.2$ Hz), 3.66 (1H, dd, $J = 4.2$, 10 Hz), 3.54–3.45 (3H, series of m), 3.35 (3H, s), 3.15–3.10 (1H, m), 2.76 (1H, dd, $J = 3.3$, 13.5 Hz), 2.62 (1H, dd, $J = 7.8$, 13.5 Hz), 1.56 (3H, s), 1.36 (3H, s); δ_C (75 MHz, $CDCl_3$): 138.72, 128.88 (2C), 128.51 (2C), 127.42, 108.1, 76.43, 75.51, 75.01, 60.76, 60.46, 59.37, 57.20, 45.26, 28.06, 25.51. **16** δ_H (300 MHz, $CDCl_3$): 7.34–7.26 (5H, m, Ar-H), 4.31 (1H, dd, $J = 2.2$, 6.0 Hz), 4.14 (1H, dd as t, $J = 6.0$ Hz), 4.12–4.10 (2H, m), 3.99–3.89 (2H, series of m), 3.50–3.42 (1H, m), 3.42–3.38 (1H, m), 3.40 (3H, s), 3.0 (1H, dd, $J = 4.5$, 11.7 Hz), 2.68 (1H, m), 1.91 (1H, dd, $J = 10.8$, 11.7 Hz), 1.57 (3H, s), 1.38 (3H, s); δ_C (75 MHz, $CDCl_3$): 137.73 (C), 129.14 (CH, 2C), 128.35 (CH, 2C), 127.24 (C), 109.45 (C), 79.38 (CH), 78.96 (CH), 77.63 (CH), 61.71 (CH_2), 60.63 (CH), 57.86 (CH_3), 56.69 (CH_2) 51.69 (CH_2), 28.28 (CH_3), 26.26 (CH_3). **17** δ_H (300 MHz, D_2O): 7.41 (5H, br. s), 4.26-3.98 (6H, series of m), 3.55 (1H, br. s), 3.4-3.08 (3H, series of m), 3.16 (3H, s); δ_C (100 MHz, D_2O): 132.84 (2C), 131.55, 130.57 (2C), 129.36, 76.23, 67.43, 65.96, 64.62, 63.68, 58.31, 55.81, 49.07. **18** δ_H (300 MHz, D_2O): 4.0 (1H, dd as t, $J = 3.6$ Hz), 3.82 (1H, dt, $J = 3.6$, 12.3 Hz), 3.70–3.65 (3H, series of m), 3.38–3.34 (1H, m), 3.29 (3H, s), 3.25–3.12 (2H, series of m); δ_C (100 MHz, D_2O): 76.22 (CH), 67.40 (CH), 64.49 (CH), 59.00 (CH_2), 57.67 (CH_3), 56.37 (CH), 41.36 (CH_2). **19** δ_H (300 MHz, D_2O): 7.51 (5H, br. s), 4.26 (2H, m), 4.19–4.17 (3H, m), 3.68–3.60 (2H, m), 3.54 (1H, br. s), 3.43 (1H, dd, $J = 4.5$, 12.3 Hz), 3.30 (3H, s), 2.76 (1H, dd, $J = 10.5$, 12 Hz), δ_C (100 MHz, D_2O): 132.85 (2C), 131.64, 130.57 (2C), 129.45, 74.91, 72.75, 70.78, 65.92, 59.68, 59.44, 58.27, 50.63. **20**: δ_H (300 MHz, D_2O): 4.02–3.99 (m, 1H), 3.75–3.50 (5H, series of m), 3.34 (3H, s), 3.27–3.23 (1H, m), 2.70–2.62 (1H, t like m); δ_C (100 MHz, D_2O): 74.93 (CH), 72.56 (CH), 67.40 (CH), 60.53 (CH), 59.60 (CH_2), 58.85 (CH_3), 44.24 (CH_2).