Carbohydrate Research 435 (2016) 1–6

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

One pot oxidative dehydration - oxidation of polyhydroxyhexanal oxime to polyhydroxy oxohexanenitrile: A versatile methodology for the facile access of azasugar alkaloids☆

Sandip R. Khobare [a, b], Vikas Gajare [a], E. Vishnuvardhan Reddy [a], Rajender Datrika [a], Malavika Banda [a], Vidavalur Siddaiah [b], Sharad S. Pachore [c], Upadhya Timanna [a], Vilas H. Dahanukar [c], U.K. Syam Kumar [c, *]

[a] Technology Development Center, Custom Pharmaceutical Services, Dr. Reddy's Laboratories Ltd., Miyapur, Hyderabad 500049, India
[b] Department of Organic Chemistry, Andhra University, Visakhapatanum 530003, India
[c] Integrated Product Development, Innovation Plaza, Dr. Reddy's Laboratories Ltd., Bachupalli, Qutubullapur, R. R. Dist., 500072, Andhra Pradesh, India

ARTICLE INFO

Article history:
Received 4 July 2016
Received in revised form
5 September 2016
Accepted 6 September 2016
Available online 14 September 2016

Keywords:
Deoxynojirimycin
Miglitol
Miglustat
Alcohol oxidation & oxime dehydration
Cascade reaction
Reductive aminative cyclization

ABSTRACT

A unique oxidative dehydration-oxidation of polyhydroxy-oxime (**7**) to the corresponding ketonitrile (**8**) in one pot is reported for the first time in carbohydrate literature. Key ketonitrile intermediate (**8**) upon palladium hydroxide mediated cascade reaction afforded 1-deoxynojirimycin (DNJ) **1b** in moderate diastereoselectivity. The cascade reaction involves the conversion of nitrile to amine, heteroannulation, reduction of the imine and subsequent debenzylation to furnish the azasugars. This oxidative dehydration-oxidation and reductive heteroannulation methodology is successfully utilized for the total synthesis of 1-deoxynojirimycin (**1b**), miglitol (**2**) and miglustat (**3**).

1. Introduction

Polyhydroxylated heterocycles possessing an endocyclic nitrogen atom (azasugars or iminosugars) have long been attractive targets due to their unique biological properties, especially, for the inhibition of a variety of sugar processing enzymes [1]. Minor structural or functional modifications on these carbohydrate mimetics can have remarkable changes in their potency and specificity of inhibition [2]. Inouye et al. [3a] and latter Yagi et al. [3b] isolated azasugar based alkaloids nojirimycin **1a** and deoxynojirimycin (DNJ) **1b** in 1966 and 1976 respectively.

DNJ congeners (Fig. 1) attached with pharmacophoric groups are potentially bioactive compounds [4,5]. Miglitol (**2**, *N*-hydroxyethyldeoxynojirimycin), an azasugar based drug developed by Bayer AG, is approved for the treatment of type II (non-insulin dependent) diabetes. Deoxynojirimycin analog Miglustat (**3**, *N*-butyldeoxynojirimycin) is also an azasugar based drug invented by Acetlion and it is prescribed for the treatment of progressive neurological manifestations in adults and pediatric patients with Niemann–Pick type C disease [6]. Other prominent bioactive members of this azasugar groups are *manno*-DNJ (**4**) [7] and *galacto*-DNJ (**5**). *Manno*-DNJ (**4**) inhibits α-*L*-fucosidase, α-*D*-mannosidase and α-*D*-glucosidase activities [8] whereas *Galacto*-DNJ (**5**, AT1001) is currently under phase B clinical trials for the treatment of Fabry's disease [9].

Several elegantly designed synthetic protocols have been demonstrated in literature for the synthesis of DNJ (**1b**) and its analogs [10]. These syntheses employ stereoselective introduction of amino functionality during the endo-heterocyclization reaction with double nucleophilic displacement as key step. Intramolecular amination using azide functionality is also reported for the synthesis of DNJ (**1b**) in higher yield and good diastereoselectivity [11]. Overkleeft and co-workers developed transamination based highly stereocontrolled cascade synthesis of DNJ using enantiomerically

☆ Dedicated to Prof. H. Junjappa on the occasion of his 80th Birthday.

* Corresponding author.
E-mail address: syam_kmr@yahoo.com (U.K. Syam Kumar).

http://dx.doi.org/10.1016/j.carres.2016.09.003
0008-6215/

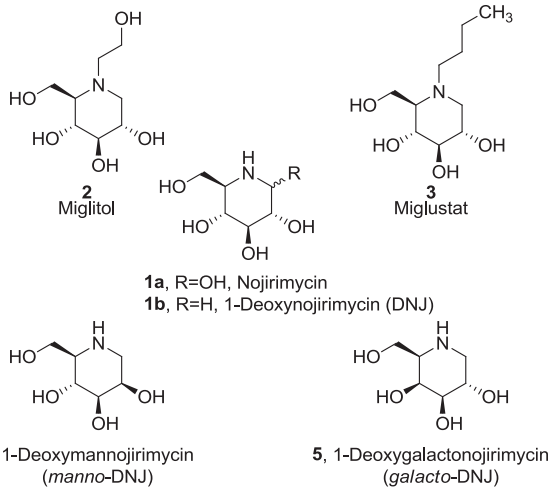


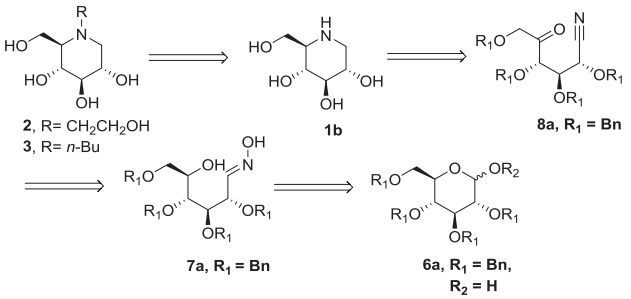
Fig. 1. Azasugar based alkaloids and their analogs.

pure cyanohydrin [12]. The ring contraction of polyhydroxy iminosugars obtained by the chemo and diastereoselective oxidation of unsaturated cyclic amines is a noteworthy approach for the synthesis of DNJ [13]. Development of new and efficient methodologies for the synthesis of DNJ and its analogs are in high demand due to their varied therapeutic properties and limited availability. As a part of our effort to develop biologically active natural and unnatural products [14], here in we describe a unique oxidative dehydration of hydroxyoxime (**7**) to ketonitrile (**8**) for the first time in carbohydrate literature and its application in the development of concise synthesis of DNJ (**1b**), miglitol (**2**) and miglustat (**3**) under cascade reaction conditions.

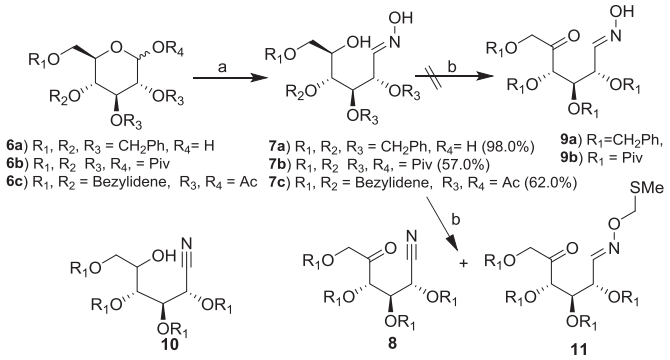
The retrosynthetic strategy employed for the synthesis of DNJ (**1b**), miglitol (**2**) and miglustat (**3**) is described in Scheme 1. *N*-Alkylation of DNJ (**1b**) with bromoethanol or *n*-butyl bromide under base assisted alkylation conditions provides miglitol (**2**) and miglustat (**3**), respectively. DNJ (**1b**) in turn could be obtained from ketonitrile **8** by a cascade reaction involving reduction of nitrile and subsequent intramolecular endo-heterocyclization under reductive amination condition. Oxidation and dehydration of hydroxy-oxime **7**, obtained from *O*-protected *D*-glucose (**6**) by reaction with hydroxylamine, provides ketonitrile **8**. The hydroxy-oxime **7** could be obtained from *O*-protected *D*-glucose **6** by reaction with hydroxylamine.

2. Results and discussion

Synthesis of miglitol (**2**) was initiated with protected *D*-glucose (**6**) as shown in Scheme 2. *D*-Glucose was subjected to tetrabenzyl (**6a**), pentapivaloyl (**6b**) and benzylidene triacetate (**6c**) protection



Scheme 1. Retrosynthetic approach.



Scheme 2. (a) $NH_2OH.HCl$, Pyridine, 25 °C, 15–18 h (b) DMSO, P_2O_5,18–20 °C or DMSO, oxalyl chloride, Et_3N, CH_2Cl_2, −65 to −70 °C, 45 min.

in excellent yields as reported in literature [15]. The *O*-protected glucose derivatives (**6a-c**) were subsequently converted to the corresponding hydroxyoximes (**7a-c**) in moderate to good yields by reacting them with hydroxyl amine hydrochloride in the presence of pyridine at ambient temperature. Oximes **7b** and **7c** were isolated after column chromatographic purification, whereas **7a** directly precipitated during the concentration of organic layer after aqueous extractive work up.

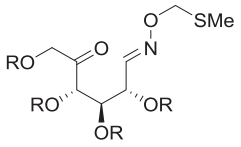
Synthesis of ketonitrile **8a** from hydroxy-oxime **7a** was originally planned in a sequential fashion with the oxidation of hydroxyl group to keto functionality as the first step followed by the dehydration of oxime to nitrile. Thus, oxidation of **7a** was attempted with different reagents and conditions as described in Table 1. The exposure of hydroxy oxime **7a** under Swern oxidation conditions (2.2 equiv. of DMSO, 1.1 equiv. of oxalyl chloride, −70 °C) provided hydroxynitrile **10a** as major product along with 1–2% of ketonitrile **8a**. No traces of expected keto oxime **9a** were observed in the reaction. Based on this observation, it was planned to further explore this unique oxidative dehydration of oxime and oxidation of secondary alcohol strategy to improve the yield of ketonitrile **8a** in a single pot operation. Considering that water liberated during the conversion of oxime to nitrile may retard further oxidation of hydroxyl group to ketone, we decided to increase the mole equivalents of DMSO and oxalyl chloride to maximize the yield of **8a**. Thus when oxidative dehydration was carried out with higher equivalents of DMSO and oxalyl chloride, the expected ketonitrile **8a** was isolated as the major product in 52% yield. Interestingly, nearly 5% of O-alkylated oxime **11a** was also observed in the reaction. Formation of **11a** is possibly due to the reaction of Pummerer adduct [16] with hydroxyl oxime **7a** (Fig. 2).

To further optimize the conversion of **7a** to ketonitrile **8a**, oxidation was performed under Albright–Onodera oxidation ($DMSO/P_2O_5$) [17] and Parikh Doering ($DMSO\text{-}Py.SO_3$) [18] conditions (Table 1). The oxidation of **7a** with $DMSO/P_2O_5$ (excess mol.

Table 1
Oxidative dehydration-oxidation of hydroxy oxime **7a-c.**

S. No.	Oxidation condition	Reactant	Ketonitrile (**8**)	Hydroxy nitrile (**10**)	Alkylated product (**11**)
1	$DMSO/COCl_2$	**7a**	52	–	5
2		**7b**	45	–	6
3		**7c**	Complex mixture		
4	$DMSO/P_2O_5$	**7a**	–	73	–
5		**7b**	40	–	–
6		**7c**	–	65	–
7	DMSO/	**7a**	48	–	10
8	$Pyridine.SO_3$	**7b**	complex mixture		

*Mentioned yields are isolated yields after chromatographic purification.



11a

Fig. 2. Unexpected impurity-plausibly *via* Pummerer Rearrangement.

equiv.) conditions at 18–22 °C mostly yielded **10a**, however, when the temperature of the reaction was increased to 45–50 °C, decomposition of **10a** to a complex mixture of products was observed. Oxidation of **7a** with TEMPO/NaOCl [19] as well as Dess Martin conditions [20] was also not successful. To further study the substrate scope of this transformation, tetrapivaloyl oxime **7b** was subjected to Swern conditions to furnish the expected ketonitrile **8b** in 45% yield. However, benzylidene acetate derivative **7c** under Swern and Parikh-Doering oxidation conditions resulted in uncharacterisable complex mixture of products.

The cascade reaction involving the reduction of nitrile to primary amine followed by *in situ* endo-heterocyclization *via* reductive amination to 1-deoxynojirimycin (**1b**) was attempted with ketonitriles **8a** and **8b** as described in Scheme 3. The reduction of ketonitrile **8a** was carried out with Raney-Ni. The cascade reaction afforded tetra-*O*-benzyl DNJ (**12**) and its C5 epimer **13** with 1:1.5 diastereoselectivity in 95% yield. The diastereomers thus obtained were separated by column chromatography and major diastereoisomer was identified as *epi*-DNJ (**13**) [21,22]. In order to improve the diastereoselectivity during reductive amination reaction, different catalysts and conditions were screened. The superior result was obtained when the hydrogenation was carried out with $Pd(OH)_2/C$ in methanol-*t*BuOH under hydrogen pressure of 150–170 psi at 25–30 °C. The desired 1-deoxynojirimycin (**1b**) and its epimer (**1b'**) were obtained in 1.2:1 ratio (by HPLC). The crude product was then recrystallized from methanol to get pure DNJ (**1b**) with 99% *de* (m.p. 199 °C [23], specific optical rotation $\{[\alpha]_D^{25} = +41.64°$ (*c* 0.2, H_2O); lit. [24] $[\alpha]_D^{25} = +40.3°$ (*c* 1.47, H_2O). The spectral data of our synthetic DNJ (**1b**) was found to be in accordance with the reported literature values [25]. The ketonitrile **8b** was also subjected to reduction under the same reaction conditions, however, **12b** and **13b** were observed only in 5–10% yields. Our subsequent efforts to improve the yields under hydrogenation conditions were not successful due to the unstable nature of the substrate under the hydrogenation condition.

Further, DNJ (**1b**) was converted to miglitol (**2**) by reacting **1b** with bromoethanol in the presence of potassium carbonate in dimethyl formamide at elevated temperature, as described in Scheme 4. The obtained crude miglitol (**2**) was then purified by using Indion® 225H acidic resin followed by trituration with methanol to afford the desired product **2** in 80% yield with 99% HPLC purity. In a similar way, miglustat (**3**) was also synthesized by reacting 1-deoxynojirimycin (**1b**) with *n*-bromobutane under basic conditions, followed by purification on acidic resin.

In conclusion, a novel one pot oxidative dehydration of hydroxyl oxime to ketonitrile was developed for the first time in carbohydrate chemistry. Further application of this finding was explored towards synthesis of deoxynojirimycin (**1b**) and its analogs in moderate to good yields. The synthetic route described herein for the synthesis of imino sugars utilizes fairly inexpensive reagents and it is easy to carry out. This strategy opens a new way for the short synthesis of imino sugars and it highlights the utility of chiral ketonitriles in asymmetric synthesis. Further applications of this novel methodology for the synthesis of other biologically relevant natural products are under progress.

3. Experimental section

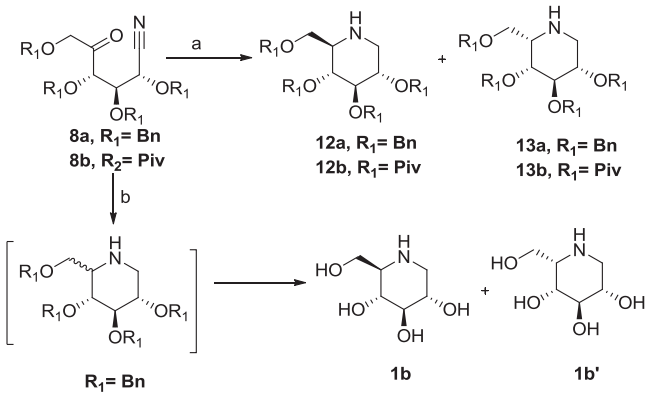
3.1. General

All reagents were used as received from commercial sources without further purification or prepared as described in the literature. Reactions were stirred using Teflon-coated magnetic stirring bars. TLC plates were visualized by ultraviolet light or by treatment with a spray of Pancaldi reagent, anisaldehyde, ninhydrine, etc. Chromatographic purification of products was carried out by flash column chromatography on silica gel (60–120 mesh, 100–200 mesh, and 230–400 mesh). Melting points were determined using a differential scanning calorimeter (DSC, Q-2000, TA) apparatus. Infrared spectra were recorded on a Perkin-Elmer 1650 Fourier transform spectrometer. NMR spectra were measured in $CDCl_3$, D_2O, DMSO-d_6 (all with TMS as internal standard) on a Varian Gemini 400 MHz FT NMR spectrometer. Chemical shifts (δ) are reported in ppm and coupling constants (J) are in Hz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. HRMS spectra were recorded on Micromass LCT Premier mass spectrometer equipped with an ESI Lockspray source for accurate mass values. Specific optical rotations were recorded on Jasco P-2000 Polarimeter.

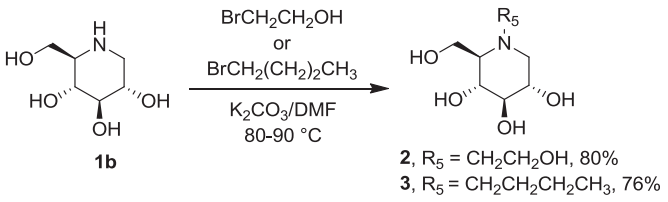
3.2. General procedure for synthesis of ***7a-c***

3.2.1. *(2S,3R,4R,5R)-2,3,4,6-tetrakis(benzyloxy)-5-hydroxyhexanal oxime **(7a)***

Hydroxylamine hydrochloride (22.2 g, 320 mmol) was added to a stirred solution of pyridine (108 mL) and 2, 3, 4, 6-tetra-*O*-benzyl-*D*-glucopyranoside (**6a**) (21.62 g, 40 mmol) and stirred for 15–18 h at ambient temperature. After completion of reaction, (monitored by TLC) the reaction mass was concentrated completely, added CH_2Cl_2 (105 mL) and filtered to remove pyridine hydrochloride salt.



Scheme 3. (a) Raney-Ni, MeOH, H_2, RT; (b) $Pd(OH)_2/C$, MeOH-*t*BuOH, MeOH.HCl, H_2.



Scheme 4. *N*-Alkylation of DNJ.

Filtrate was washed with 1N hydrochloric acid (2 × 100 mL), concentrated and co-distilled with toluene. Hexane (60 mL) was added to residue, stirred for 30 min and obtained solid was separated by filtration to afford title compound **7a** after drying (21.8 g, 98.0%); White solid; M.P 74.4 °C; IR (cm^{-1}): 3355, 3196, 3063, 3030, 2880, 1454, 1399, 1391, 1113, 1093, 1064, 920, 734, 695. ^1H NMR (400 MHz, DMSO-d_6): δ 11.13 (s, 1H, NOH), 7.38 (d, J = 7.8 Hz, 1H), 7.15–7.4 (m, 20H, ArH), 5.02 (d, J = 6.3 Hz, 1H), 4.72 (d, J = 10.8 Hz, 1H), 4.42–4.62 (m, 8H), 4.30 (t, J = 7.8, 1H), 3.99 (dd, J = 2.4, 7.8 Hz, 1H), 3.82 (m, 1H), 3.52–3.66 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 147.7, 138.7, 138.4, 138.0, 128.2, 128.09, 128.07, 127.8, 127.7, 127.6, 127.40, 127.38, 127.33, 79.4, 78.7, 77.5, 74.3, 72.9, 72.3, 71.6, 70.1, 69.3. HRMS (ESI^+) m/z calculated for $C_{34}H_{38}NO_6$ $[M+H]^+$ 556.2699, found 556.2679.

3.2.2. (2R,3R,4R,5S)-2-hydroxy-6-(hydroxyimino)hexane-1,3,4,5-tetrayl tetrakis(2,2-dimethylpropanoate) (7b)

Prepared using the similar procedure as described above and crude compound was purified by silica gel chromatography (Yield = 57.0%); White solid; ^1H NMR (400 MHz, $CDCl_3$, *E* isomer with mixture of rotamers ratio (57:43)): δ 7.62 (d, J = 11.8 Hz, 1H, NOH, exchangeable with D_2O), 7.35 (d, J = 5.8 Hz, 1H), 5.48–5.65 (m, 2H), 5.13 & 5.35 (dd, J = 2.4, 8.8 Hz, 1H), 4.13 & 4.73 (dd, J = 2.4, 12.2 Hz, 1H), 3.69–4.0 (m, 1H), 3.4 & 3.64 (dd, J = 2.9, 13.2 Hz, 1H), 2.64 & 3.14 (m, 1H, exchangeable with D_2O), 1.18–1.28 (m, 36H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 178.6, 178.5, 178.4, 177.2, 176.9, 145.6, 145.4, 70.3, 70.2, 69.6, 69.5, 69.0, 68.5, 68.3, 64.4, 59.9, 39.2, 39.15, 38.98, 38.95, 38.86, 27.2, 27.12, 27.07, 27.05, 27.04, 26.95; HRMS (ESI^+) m/z calculated for $C_{26}H_{46}NO_{10}$ $[M+H]^+$ 532.3122, found 532.3109.

3.2.3. (1R,2S)-1-((4R,5R)-5-hydroxy-2-phenyl-1,3-dioxan-4-yl)-3-(hydroxyimino)propane-2-diyl diacetate (7c)

Prepared using the similar procedure as described above and crude compound was purified by silica gel chromatography (Yield = 62.0%); ^1H NMR (400 MHz, $CDCl_3$,*E*/*Z* 3:1): δ 8.44 (s, 0.25H, NOH), 8.13 (s, 0.75H, NOH), 7.46 (m, 2H, Ar–H), 7.35 (m, 3H, Ar–H + 0.75H– C_1), 6.74 (d, J = 5.9 Hz, 0.25H–C1), 6.32 (t, J = 5.9 Hz, 0.25H–C2), 5.81 (dd, J = 5.3, 5.9 Hz, 0.75H–C2), 5.63 (dd, J = 1.5 & 5.9 Hz, 0.25H–C4), 5.5 (dd, J = 1.9 & 7.8 Hz, 0.75H–C4), 5.4 (s, 0.25H–C7), 5.39 (s, 0.75H–C7), 4.28 (dd, J = 4.8, 13.7 Hz, 1H, 6a), 3.79 (m, 1H, 6b), 3.61 (t, J = 10.2 Hz, 1H–C5), 3.55 (m, 1H–C3), 3.2 (m, 1H, OH), 2.19 (s, 3H), 1.99 (s, 2H), 1.87 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ*E*-isomer: 172.2, 169.9, 145.8, 136.9, 129.0, 128.2, 126.2, 126.0, 101.0, 80.0, 70.2, 69.4, 66.4, 60.9, 20.7, 20.6; *Z*-isomer: 172.4, 170.0, 146.5, 137.1, 101.3, 80.6, 70.5, 69.1, 61.1, 20.5; HRMS (ESI^+) m/z calculated for $C_{17}H_{22}NO_8$ $[M+H]^+$ 368.1345, found 368.1355.

3.3. General procedure for oxidation of 7a-c with DMSO/Oxalyl chloride

To a solution of freshly distilled oxalyl chloride (9.26 mL, 0.1029 mol) in dry CH_2Cl_2 (130.0 mL) was added dry DMSO (14.6 mL, 0.205 mol) under nitrogen atmosphere at −65 to −70 °C and stirred for 30 min. Solution of **7a** (13.0 g, 0.023 mol) in CH_2Cl_2 (65.0 mL) was added over 30–45 min and stirred for 45 min at same temperature. Triethylamine (42.4 mL, 0.30 mol) was added drop wise over 30–40 min at −65 °C to −70 °C. The turbid mixture was slowly warmed to 0 °C and diluted with water (130 mL). Organic layer was separated and distilled under vacuum to get crude compound which was purified by column chromatography to afford **8a** (6.5 g, 52% yield) as yellow to colorless oil.

3.4. General procedure for oxidation of 7a-c with DMSO-Py.SO_3

To a solution of **7a** (0.5 g, 0.9 mmol) in CH_2Cl_2 (5.0 mL) was added *N, N*-diisopropylamine (1.09 mL, 6.0 mmol) at 0–5 °C under nitrogen atmosphere. The solution of pyridine sulphur trioxide (0.57 g, 3.0 mmol) in DMSO (1.5 mL) was slowly added to the reaction mass at 0–5 °C and stirred for 60–90 min at the same temperature. After completion of reaction (monitored by TLC), reaction mixture was concentrated under vacuum. Water (50 mL) was added to the residue and extracted with MTBE (2 × 50 mL). Combined organic layer was washed with 1N HCl followed by brine solution and concentrated under vacuum to afford crude ketonitrile which was purified by flash chromatography to yield **8a** (0.22 g, 45.0% yield); Colorless liquid; IR (film) cm^{-1}: 3030, 2925, 1735, 1455, 1217, 1091, 698 (No sharp peak for nitrile observed) [26]; ^1H NMR (400 MHz, $CDCl_3$): δ 7.17–7.37 (m, 20 ArH), 4.78 (d, J = 11.2 Hz, 1H, $PhCH_2$), 4.61 (d, J = 11.2 Hz, 2H, $PhCH_2$), 4.54 (d, J = 9.8 Hz, 1H, $PhCH_2$), 4.49–4.52 (m, 3H), 4.39 (d, J = 3.4 Hz, 1H), 4.37 (d, J = 4.0 Hz, 1H), 4.36 (d, J = 3.4 Hz, 1H), 4.1–4.23 (m, 3H);^{13}C NMR (100 MHz, $CDCl_3$): 206.8, 137.0, 136.6, 136.2, 135.2, 128.7, 128.6, 128.57, 128.48, 128.3, 127.95, 127.93, 116.3, 82.1, 79.0, 77.3, 77.0, 76.7, 75.1, 74.8, 74.4, 73.3, 73.1, 68.3; HRMS (ESI^+) m/z calculated for $C_{34}H_{34}NO_5$ $[M+H]^+$ 536.2437, found 536.2427.

3.5. General procedure for DMSO/P_2O_5 oxidation of 7a-c

Phosphorous pentoxide (0.8 g, 5.64 mmol) was added in three lots to dry DMSO (2.5 mL) at 18–22 °C under nitrogen atmosphere and stirred for 20 min. A solution of **7b** (0.5 g, 0.94 mmol) in DMSO (2.0 mL) was added to the reaction mixture at 25–30 °C and stirring was maintained until TLC showed no unreacted starting material left out. Reaction mixture was quenched with ice water (50 mL) and extracted with MTBE (2 × 50 mL). Combined organic layers were washed with brine solution and concentrated under vacuum to get crude product which was purified by column chromatography to yield **8b** (0.19 g, 40.0%); Solid; IR (film) cm^{-1}: 2979, 1744, 1483, 1123, 1034; ^1H NMR (400 MHz, $CDCl_3$): δ 5.66–5.72 (m, 2H), 5.6 (d, J = 2.9 Hz, 1H), 4.69 (dd, J = 17.1, 9.3 Hz, 2H), 1.33 (s, 9H), 1.25 (s, 9H), 1.22 (s, 9H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): 196.8, 177.3. 177.1, 176.5, 175.7, 113.9, 73.4, 68.1, 66.3, 59.1, 39.0, 38.92, 38.88, 38.7, 27.1, 26.95, 26.87, 26.8. HRMS (ESI^+) m/z calculated for $C_{26}H_{42}NO_9$ $[M+H]^+$ 512.2860, found 512.2853.

3.6. General procedure for synthesis of tetrabenzyl DNJ (12)

To a solution of ketonitrile **8a** (1.0 g, 1.9 mmol) in MeOH (20 mL) was added Raney Nickel (0.5 g, wet) and the mixture was hydrogenated at 150–170 psi hydrogen pressure at ambient temperature for 24 h. The suspension was filtered through celite and washed with methanol. The filtrate was concentrated under vacuum to afford crude tetrabenzyl DNJ (**12**) and its C5 epimer (**13**) in 4:6 ratio and 95% yield. Both isomers were separated by column chromatography to afford **12** (0.29 g, 30%) and its C5 epimer **13** (0.39 g, 40%).

Compound 12: Colorless liquid; ^1H NMR (400 MHz, $CDCl_3$): δ 7.18–7.37 (m, 20H, Ar–H), 4.9 (d, J = 11.3 Hz, 1H), 4.8 (t, J = 10.3 Hz, 2H), 4.64 (dd, J = 4.9 & 11.8 Hz, 2H), 4.4 (m, 3H), 3.65 (dd, J = 2.5 & 6.3 Hz, 1H), 3.3–3.57 (m, 3H), 3.22 (dd, J = 4.7, 12.2 Hz, 2H), 2.7 (ddd, J = 2.9, 6.3, 9.2 Hz, 1H), 2.47 (dd, J = 10.3, 12.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.8, 138.4, 138.3, 137.9, 128.35, 128.32, 128.30, 127.96, 127.89, 127.81, 127.7, 127.6, 127.5, 87.3, 80.5, 80.0, 75.6, 75.1, 73.3, 72.7, 70.2, 59.7, 48.0. HRMS (CI) calcd for $C_{34}H_{38}NO_4$ $(M+H)^+$ 524.2801, found 524.2794.

Compound 13 (C5 epimer of tetrabenzylated DNJ):

^1H NMR (400 MHz, $CDCl_3$) δ 7.2–7.36 (m, 20H, Ar–H), 4.51–4.64

(m, 8H, 4 × CH_2, Bn), 3.54–3.71 (m, 4H), 3.39–3.48 (m, 2H), 3.0 (dd, J = 3.9, 13.2 Hz, 1H), 2.9 (m, 1H).

3.7. General procedure for synthesis of DNJ (1b)

A solution of **8a** (2.0 g, 3.73 mmol) in MeOH: *t*-BuOH (4:1) (40 mL) was treated with $Pd(OH)_2$ (20 wt % Pd, dry basis on carbon, 400 mg) and the mixture was hydrogenated at ambient temperature for 6–8 h at 150–170 psi hydrogen pressure. The suspension was filtered through celite, washed with methanol and the filtrate was concentrated under vacuum. Methanolic HCl was added to the residue, stirred for 30 min and concentrated under vacuum and again hydrogenated for 48–72 h at 90–100 psi using $Pd(OH)_2$/C (20 wt % Pd dry basis on carbon, 400 mg) and methanol (40 mL). The suspension was filtered through celite and washed with methanol. The combined filtrate was concentrated in vaccuum, passed through acidic resin and eluted with water followed by 5% aq. ammonia. The ammonical fractions were concentrated completely under vacuo and residue was crystallized from methanol to afford the desired product **1b** as white solid (219 mg, 35%, overall yield 19% from **6a**).

White solid; $[\alpha]_D^{25}$ = +41.64° (*c* 0.2, H_2O). M.P. = 199.04 °C, IR, cm^{-1}: 3349, 2894, 2699, 1408, 1373, 1105, 992, 838, 625; ^{1}H NMR (400 MHz D_2O): δ 3.82 (dd, J = 1.9 Hz, 1.8 Hz, 1H-6a), 3.61 (dd, J = 6.2, 11.6 Hz, 1H-6b), 3.46 (dt, J = 5.2, 9.8 Hz, 1H-2), 3.3 (t, J = 9.0 Hz, 1H-3), 3.2 (t, J = 9.4 Hz, 1H-4), 3.1 (dd, J = 5.1, 12.3 Hz, 1H-1a), 2.53 (ddd, J = 3.0, 6.4, 9.3 Hz, 1H-5), 2.44 (dd, J = 10.8, 12.2 Hz, 1H-1b); ^{13}C NMR (100 MHz, D_2O): δ 81.1, 74.3, 73.7, 64.1, 63.3, 51.4, HRMS (ESI^+) m/z calculated for $C_6H_{14}NO_4$ $[M+H]^+$ 164.0923, found 164.0918.

3.8. Procedure for synthesis of miglitol (2)

To a suspension of **1b** (0.1 g, 0.61 mmol) and potassium carbonate (0.34 g, 2.4 mmol) in DMF (1.0 mL) was added bromoethanol (0.30 g, 2.4 mmol) and stirred at 90–100 °C for 4–5 h. After completion of the reaction, reaction mass pH was adjusted to acidic (pH ~5) using acetic acid. Reaction mass was next passed through acidic resin and subsequently treated with 1–5% aqueous ammonia solution. Aqueous ammonical solution was concentrated completely to get crude miglitol **(2)** which was re-crystallized using methanol to afford white solid (0.1 g, 80%).

White solid; $[\alpha]_D^{20}$: −7.95° (*c* 0.56, H_2O); M.P. = 145.17 °C. IR (thin film) cm^{-1}: 3365, 3280, 2922, 1545, 1429, 1304, 1075, 1033; ^{1}H NMR (400 MHz, D_2O): δ 3.9 (dd, J = 2.5,13.5 Hz, 1H), 3.79 (dd, J = 3.4, 12.9 Hz, 1H), 3.7 (td, J = 2, 6.4 Hz, 2H), 3.49 (ddd, J = 4.9, 3.4, 4.4 Hz, 1H), 3.22–3.32 (m, 2H), 3.05 (dd, J = 4.9, 11.3 Hz, 1H), 2.90 (dt, J = 6.8, 14.2 Hz, 1H), 2.68 (dt, J = 6.8, 14.2 Hz, 1H), 2.29 (m, 2H); ^{13}C NMR (100 MHz, D_2O): δ 81.1, 72.7, 71.5, 68.4, 60.7, 60.4, 58.9, 55.6; HRMS: calculated for $C_8H_{18}NO_5$ $[M+H]^+$ 208.1185, found 208.1194.

3.9. Procedure for synthesis of miglustat (3)

To a suspension of **1b** (0.1 g, 0.61 mmol) and potassium carbonate (0.34 g, 2.4 mmol) in DMF (1.0 mL) was added 1-bromobutane (0.2 g, 2.4 mmol) and stirred at 80–90 °C for 24 h. Reaction mass pH was adjusted to acidic side with acetic acid and subsequently passed through acidic resin followed by treatment with 1–5% aqueous ammonia solution. Aqueous ammonical solution was concentrated completely to get miglustat (**3**) (0.108 g, 76%); ^{1}H NMR (400 MHz, D_2O): δ 3.95 (d, J = 2.2 Hz, 2H), 3.64 (dd, J = 3.8, 9.7 Hz, 1H), 3.50 (t, J = 9.5 Hz, 1H), 3.36 (t, J = 9.6 Hz, 1H), 3.28 (m, 1H), 2.9–3.06 (m, 2H), 2.7–2.8 (m, 2H), 1.54–1.64 (m, 2H), 1.3–1.39 (m, 2H), 0.91 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, D_2O): δ 80.0, 71.5, 70.4, 68.0, 58.6, 57.0, 55.0, 27.6, 22.5, 15.8; Mass $(M+H)^+$ 220.20.

Acknowledgments

The authors would like to thank analytical department, Dr. Reddy's Laboratories Ltd. for providing the analytical support. (IPDO-DRL IPM No.:00433)

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.carres.2016.09.003.

References

[1] (a) S. Aoyagi, S. Fujimaki, C. Kibayashi, J. Chem. Soc. Chem. Commun. (1990) 1457;
(b) P.J. Card, W.D. Hitz, J. Org. Chem. 50 (1985) 891;
(c) A. Dondoni, P.P. Giovannini, D. Perrone, J. Org. Chem. 67 (2002) 7203;
(d) M.L. Sinnott, Chem. Rev. 90 (1990) 1171;
(e) A.E. Stutz, Angew. Chem. Int. Ed. Engl. 35 (1996) 1926;
(f) T.D. Heightman, A.T. Vasella, Angew. Chem. Int. Ed. Engl. 38 (1999) 750.
[2] A. Daher, G. Fleet, S.K. Namgoong, B. Winchester, Biochem. J. 258 (1989) 613.
[3] (a) S. Inouye, T. Tsuruoka, T. Niida, J. Antibiot. 19 (1966) 288;
(b) M. Yagi, T. Kouno, Y. Aoyagi, H. Murai, The structure of moranoline-a piperidine alkaloid from Morus species, Nippon. Nogeikagaku Kaishi 50 (1976) 571.
[4] (a) W. Meutermans, G. Thanh Le, B. Becker, Chem. Med. Chem. 1 (2006) 1164;
(b) J.L. Dunne, P.V. Murphy, Curr. Org. Synth. 3 (2006) 403;
(c) R. Hirschmann, K.C. Nicolaou, S. Pietranico, J. Salvino, E.M. Leahy, P.A. Sprengeler, G. Furst, A.B. Smith III, C.D. Strader, M.A. Cascieri, M.R. Candelore, C. Donaldson, W. Vale, L. Maechler, J. Am. Chem. Soc. 114 (1992) 9217;
(d) R. Hirschmann, K.C. Nicolaou, S. Pietranico, E.M. Leahy, J. Salvino, B. Arison, M.A. Cichy, P.G. Spoors, W.C. Shakepseare, P.A. Sprengler, P. Hamley, A.B. Smith, T. Reisine, K. Raynor, L. Maechler, C. Donaldson, W. Vale, R.M. Freidinger, M.R. Cascieri, C.D. Strader, J. Am. Chem. Soc. 115 (1993) 12550.
[5] For examples of solid phase synthesis of prospecting libraries using pyranoside derivatives, see: (a) T. Unberg, C. Kallus, T. Opatz, S. Henke, W. Schmidt, H. Kunz, Angew. Chem. Int. Ed. 37 (1998) 2503–2505;
(b) M.J. Sofia, R. Hunter, T.Y. Chan, A. Vaughan, R. Dulina, H.M. Wang, D. Gange, J. Org. Chem. 63 (1998) 2802–2803;
(c) R. Jain, M. Kamau, C. Wang, R. Ippolito, H. Wang, R. Dulina, J. Anderson, D. Gange, M. Sofia, Bioorg. Med. Chem. Lett. 13 (2003) 2185–2189;
(d) T. Opatz, C. Kallus, T. Wunberg, H. Kunz, Tetrahedron 60 (2004) 8613–8626.
[6] B.G. Winchester, Tetrahedron Asymmetry 20 (2009) 645–651.
[7] For isolation see L.E. Fellows, E.A. Bell, D.G. Lynn, F. Pilkiewicz, I. Miura, K. Nakanishi, J. Chem. Soc. Chem. Commun. (1979) 977–978.
[8] U. Fuhrmann, E. Bause, G. Legler, H. Ploegh, Nature 307 (1984) 755–758.
[9] (a) J.-Q. Fan, S. Ishii, N. Asano, Y. Suzuki, Nat. Med. 5 (1999) 112–115;
(b) See: http://www.clinicaltrials.gov/ct/gui/show/NCT00231036.
[10] (a) G.N. Wang, G. Reinkensmeier, S.W. Zhang, J. Zhou, L.R. Zhang, L.H. Zhang, T.D. Butters, X.S. Ye, J. Med. Chem. 52 (2009) 3146–3149;
(b) N. Wang, L.H. Zhang, X.S. Ye, Org. Biomol. Chem. 8 (2010) 2639–2649;
(c) C.Y. Yu, M.H. Huang, Org. Lett. 8 (2006) 3021–3024;
(d) X.G. Hu, B. Bartholomew, R.J. Nash, F.X. Wilson, G.W.J. Fleet, S. Nakagawa, A. Kato, Y.M. Jia, R. van Well, C.Y. Yu, Org. Lett. 12 (2010) 2562–2565;
(e) C.H. Vonderosten, A.J. Sinskey, C.F. Barbas, R.L. Pederson, Y.F. Wang, C.H. Wong, J. Am. Chem. Soc. 111 (1989) 3924–3927;
(f) Morwenna S.M. Pearson, Monique Mathé-Allainmat, Valérie Fargeas, Jacques Lebreton, Eur. J. Org. Chem. (2005) 2159;
(g) B.L. Stocker, E.M. Dangerfield, A.L. Win-Mason, G.W. Haslett, M.S.M. Timmer, Eur. J. Org. Chem. (2010) 1615;
(h) S.R. Kallam, R. Datrika, S.R. Khobare, V.S. Gajare, N. Rajana, H. Rama Mohan, J. Moses Babu, V. Siddaiah, T.V. Pratap, Tetrahedron Lett. 57 (2016) 1351;
(i) T. Wennekes, B. Lang, M. Leeman, A.G. van der Marel, E. Smits, M. Weber, J. Wiltenburg, M. Wolberg, J. Aerts, H. Overkleeft, Org. Process Res. Dev. 12 (2008) 414.
[11] B.G. Davis, M.A.T. Maughan, T.M. Chapman, R. Villard, S. Courtney, Org. Lett. 4 (2002) 103.
[12] A.M.C.H. Van den Nieuwendijk, M. Ruben, S.E. Engelsma, M.D.P. Risseeuw, J.B. Richard, H.N. van den Berg, R.G. Boot, J.M. Aerts, J. Brussee, G.A. van der Marel, H.S. Overkleeft, Org. Lett. 12 (17) (2010) 3957.
[13] S.K. Bagal, S.G. Davies, J.A. Lee, P.M. Roberts, P.M. Scott, J.E. Thomson, J. Org. Chem. 75 (2010) 8133.
[14] (a) V.S. Gajare, S.R. Khobare, R. Datrika, K. Srinivas Reddy, N. Rajana, K. Sarvesh, B.V. Rao, Tetrahedron Lett. 56 (2015) 6659;
(b) V.S. Gajare, S.R. Khobare, R. Datrika, K. Srinivas Reddy, N. Rajana, B.B. Babu, B.V. Rao, U.K. Syam Kumar, Tetrahedron Lett. 57 (2016) 1486;
(c) V.S. Gajare, S.R. Khobare, R. Datrika, K. Srinivas Reddy, N. Rajana, U.K. Syam

Kumar, V. Siddaiah, Tetrahedron Lett. 56 (2015) 2207;
(d) V.S. Gajare, S.R. Khobare, N. Rajana, B. Malavika, B.V. Rao, U.K. Syam Kumar, Tetrahedron Lett. 56 (2015) 3743;
(e) M.V. Madhubabu, R. Shankar, S. Satish, More, M.V.B. Rao, U.K. Syam Kumar, A. Raghunadh, RSC Adv. 6 (2016) 36599.
[15] (a) X. Li, Z. Li, P. Zhang, H. Chen, S. Ikegami, Synth. Commun. 37 (2007) 2195–2202;
(b) D.P. Larson, C.H. Heathcock, J. Org. Chem. 61 (1996) 5208–5209;
(c) Hui, Y.; Yang, Z.; Liu, J.; Xie, H.; Zhang. J; Teng, J. US2008/0275225A1.
[16] (a) T. Numata, S. Oae, Tetrahedron Lett. 18 (1977) 1337;
(b) S. Raghavan, R.K. Chiluveru, S.S. Ganapathy, J. Org. Chem. 81 (2016) 4252–4261.
[17] (a) J.D. Albright, L. Goldman, J. Am. Chem. Soc. 87 (1965) 4214;
(b) K. Onodera, S. Hirano, N. Kashimura, J. Am. Chem. Soc. 87 (1965) 4651.
[18] J.R. Parikh, W. Doering, E. von, J. Am. Chem. Soc. 89 (1967) 5505.
[19] (a) R.A. Sheldon, I.W.C.E. Arends, Adv. Synth. Catal. 346 (2004) 1051;
(b) A.E.J. de Nooy, A.C. Besemer, H. van Bekkum, Synthesis (1996) 1153.
[20] (a) D.B. Dess, J.C. Martin, J. Org. Chem. 48 (1983) 4155;
(b) D.B. Dess, J.C. Martin, J. Am. Chem. Soc. 113 (1991) 7277;
(c) S.D. Meyer, S.L. Schreiber, J. Org. Chem. 59 (1994) 7549.
[21] P. Compain, C. Decroocq, J. Iehl, M. Holler, D. Hazelard, T. Mena Barragán, C. Ortiz Mellet, J.F. Nierengarten, Angew. Chem. 122 (2010) 5889. *Angew. Chem. Int. Ed.* 2010, 49, 5753.
[22] T. Wennekes, A.J. Meijer, A.K. Groen, R.G. Boot, J.E. Groener, M. van Eijk, R. Ottenhoff, N. Bijl, K. Ghauharali, H. Song, T.J. O'Shea, H. Liu, N. Yew, D. Copeland, R.J. van den Berg, G.A. van der Marel, H.S. Overkleeft, J.M. Aerts, J. Med. Chem. 53 (2010) 689–698.
[23] R.R. Carlos, M. Lopes, C. Lopes, Synthesis 4 (1999) 571.
[24] C. Kuriyama, O. Kamiyama, K. Ikeda, F. Sanae, A. Kato, I. Adachi, T. Imahori, H. Takahata, T. Okamoto, N. Asano, Bioorg. Med. Chem. 16 (2008) 7330–7336.
[25] Z.X. Zhang, B.L. Wu, B. Wang, T.H. Li, P.F. Zhang, L.N. Guo, W.J. Wang, W. Zhao, P.G. Wang, Tetrahedron Lett. 52 (2011) 3802.
[26] Philipp Ermert, A. Vasella, Helv. Chim. Acta 74 (1991) 2043.