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A highly expeditious synthesis of a bicyclic iminosugar using the novel key step of $[NMM]^+[HSO_4]^-$ promoted conjugate addition and Mitsunobu reaction†

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Virendra Prasad, Dhananjay Kumar and Vinod K. Tiwari*

A simple and highly facile protocol has been developed for the stereoselective synthesis of 1-deoxy-norcastanospermine from readily available D-glucose. *N*-Methylmorpholinium hydrogen sulphate was seen for the first time as a suitable catalyst for the facile conjugate addition of an amine to a glycosyl olefinic ester. Furthermore, the key step of this strategy is the internal reductive amination of glycosyl azetidine, obtained from glycosyl β-amino alcohol under Mitsunobu reaction conditions.

Iminosugars, where the ring oxygen is replaced by nitrogen, form undoubtedly the most fascinating and attractive class of carbohydrate mimics known so far.[1] In recent years, bicyclic iminosugar ring skeletons, present in numerous alkaloids as important structural subunits, have aroused a burgeoning interest in the area of glycobiology.[1–3] Due to the well-known glucosidase[2] and the inhibitory activity of glycosyltransferase,[3] these molecules offer both new tools for studying the biological functions of oligosaccharides and a new generation of emerging carbohydrate-based therapeutics for the control of a wide range of diseases, including diabetes,[4] HIV,[5] hepatitis,[6] cancer,[5–7] Gaucher's disease[8] and viral infections.[9] The unravelling of the potential of nojirimycin and deoxynojirimycin as strong α and β-glucosidase inhibitors triggered an intensive research impetus dealing with the synthesis and evaluation of their potential to inhibit enzyme systems, which revealed castanospermine and swainsonine as potent inhibitors of glucosidase enzymes and golgi α-mannosidase II, respectively, and culminated in the approval of miglustat and miglitol for the treatment of, respectively, type-1 Gaucher's disease and type-2 diabetes mellitus (Fig. 1).[10]

Since iminosugars equipped with hydrophobic substituents are known for their increased enzyme inhibition and enhanced bioavailability,[11] the routes available for the ready installation of hydrophobic moieties are of high value. The paucity of natural materials has made total synthesis the only available avenue for the construction of these molecules for the study of their biological activities against various diseases. Although tremendous efforts have been directed towards the development of synthetic routes for iminosugars,[12] these deceptively simple looking molecules are not easy to synthesize, mainly due to the difficulty associated with the introduction of an aminomethyl group next to a stereocenter of suitably substituted carbohydrate molecules. Thus, the development of a general synthetic strategy for these iminosugars has remained sparse. Herein we report a highly convergent stereoselective synthetic route for a novel bicyclic iminosugar analogue from D-glucose.

During the course of our synthesis, we envisaged 2-(3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-ido-furanose)-1-benzyl azetidine **7** as a suitable scaffold for the stereoselective synthesis of target bicyclic iminosugar 1-deoxy-norcastanospermine (Scheme 1). Glycosyl azetidine **7** can be hydrogenated to give the target molecule **8**. The required compound **7** can in turn be synthesized by the 1,2-isopropylidene deprotection of **6**, which may be achieved from the corresponding amino alcohol, **5**, prepared from cheap and readily available D-glucose (Scheme 2).

Our synthetic strategy commenced with glycosyl olefinic ester (1*R*,2*R*,3*S*,4*R*)-ethyl-(3-*O*-benzyl-1,2-*O*-isopropylidine-1,4-pentofuranose-4-yl)-hept-5-enoate, **3**, prepared from readily available D-glucose.[13,14] The 1,4-conjugate addition of benzyl amine to **3** led to

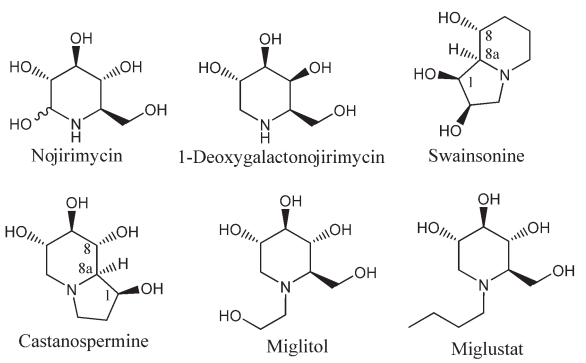
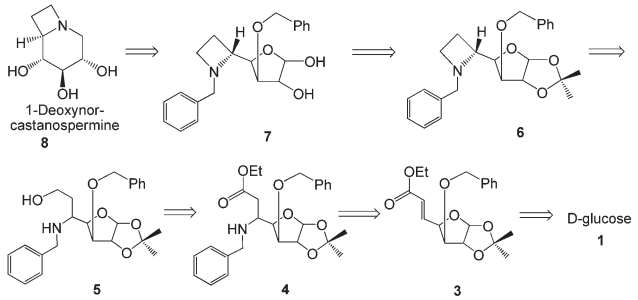


Fig. 1 Bioactive iminosugars.

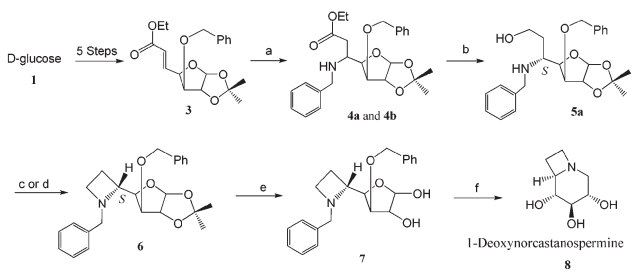
Department of Chemistry, Faculty of Science, Banaras Hindu University, Varanasi-221005, India. E-mail: tiwari_chem@yahoo.co.in; vtiwari@ucdavis.edu; Fax: 91-542-2368174; Tel: 91-542-6702466

† Electronic supplementary information (ESI) available: ^1H and ^{13}C NMR spectra of all new compounds. See DOI: 10.1039/c3ra23467c



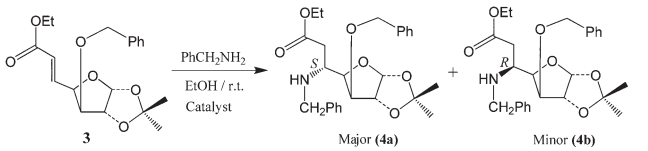
Scheme 1 Retrosynthetic analysis of 1-deoxy-norcastanospermine.

(1*R*,2*R*,3*S*,4*R*)-ethyl-(3-*O*-benzyl-5-benzylamino-5,6-dideoxy-1,2-*O*-isopropylidene)-α-D-gluco- and β-L-ido-heptofuranuronate (**4a** and **4b**) as a diastereomeric mixture in good yield. A variety of promising catalysts such as $InCl_3$, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), starch, $Y(NO_3)_3{\cdot}6H_2O$[15] and ionic liquids[16] were screened to identify a suitable activator for a high diastereoselective addition with a reduced reaction span (Table 1). Unfortunately, $InCl_3$, DBU, DABCO, starch and $Y(NO_3)_3{\cdot}6H_2O$ failed to bring a significant improvement to the diastereoselectivity of the conjugate addition as well as to shorten the reaction time. However, the conjugate addition carried out in the presence of an ionic liquid, *e.g. N*-methylmorpholinium hydrogen sulphate, $[NMM]^+[HSO_4]^-$, and *N*-methylmorpholinium methyl sulphonate, $[NMM]^+[CH_3SO_3]^-$, is notable as the reaction time is now reduced to 15–20 min. The predominant diastereoselectivity observed in this addition was merely because of the alkene–arene π stacking effect as previously elaborated on the basis of the Felkin–Anh like transition state model.[13] The configuration at the newly formed stereogenic centre C-5 in compound **4** was determined after the lithium aluminium hydride reduction of the individual major/minor isomers to the corresponding alcohols, where J = 8.7 Hz (*threo*-) was calculated for alcohols reduced from major isomers, while J = 5.7 Hz (*erythro*-) from minor isomers and thus the relative configurations were assigned as '*S*' and '*R*' for the major (**4a**) and minor isomers (**4b**), respectively.[14e] The reduction of glycosyl β-amino ester **4a** with



Scheme 2 Synthesis of 1-deoxy-norcastanospermine. Reaction conditions: (a) benzyl amine, EtOH, $[NMM]^+[HSO_4]^-$, rt., 15 min, 95% (ratio 80 : 20), major isomer (**4a**) isolated in pure form using flash column chromatography; (b) $LiAlH_4$, THF, rt., 3 h, 96%; (c) PPh_3, DIAD, $PhI(OAc)_2$, THF, rt., 10 h, 72%; (d) PPh_3 and DIAD (each 1.5 equiv.), THF, rt., 12 h, 70% (e) TFA–H_2O (3 : 2), rt., 12 h, 90%; (f) 10% Pd/C, H_2, 80 psi, MeOH, 12 h, 60%.

Table 1 Optimization of the 1,4-conjugate addition of benzyl amine to glycosyl olefinic ester **3**



Entry	Catalyst used	Time[a]	Yield[b] (%)	Diastereomer ratio (major/minor)[c]
1	—	40 h	85	78 : 22
2	$InCl_3$ (5 mmol%)	12 h	90	75 : 25
3	DBU	20 h	85	74 : 26
4	DABCO	20 h	85	77 : 23
5	Starch	30 h	70	76 : 24
6	$Y(NO_3)_3{\cdot}6H_2O$	18 h	91	80 : 20
7	$Y(NO_3)_3{\cdot}6H_2O$, solvent free	25 h	85	77 : 23
8	$[NMM]^+[CH_3SO_3]^-$	20 min	95	80 : 20
9	$[NMM]^+[HSO_4]^-$	15 min	95	80 : 20

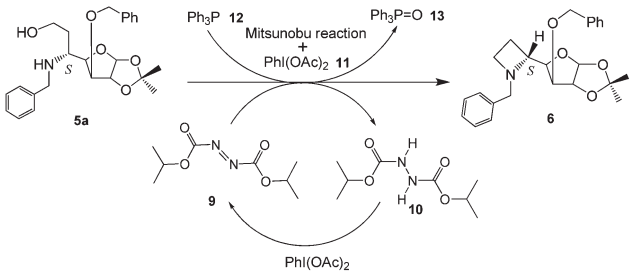
[a] Time required. [b] Isolated yield. [c] Determined by ^{1}HNMR.

$LiAlH_4$ in anhydrous THF resulted in glycosyl β-amino alcohol **5a** in 96% quantitative yield.

Access to esters and their related compounds by the reaction of alcohols and carboxylic acids through Mitsunobu reaction conditions is well known. Following a similar chemistry, the DEAD–PPh_3 induced intramolecular cyclization of **5** was carried out in anhydrous THF to afford 2-(3-*O*-benzyl-1,2-*O*-isopropylidene-β-L-ido-furanose)-1-benzyl azetidine **6**. Diethyl azodicarboxylate (DEAD) is known to be toxic, shock sensitive and thermally unstable, thus the exploration of another azo reagent such as diisopropyl azodicarboxylate (DIAD) may be a more feasible approach because it is less expensive, easy to handle and has previously been proved to allow a wider range of nucleophiles.[17]

DIAD–PPh_3 mediated intramolecular cyclization of compound **5a** was very effective but required an excess amount of reagent to afford the product in a significantly high yield. Developing a strategy which could reduce the quantity of DIAD required in the reaction would be of vital importance to expedite the overall synthetic protocol for the scale-up synthesis. Employing diacetoxyiodobenzene (DIB) to oxidize 1,2-dicarbisopropoxyhydrazine back to DIAD during the intramolecular cyclization of **5a** was studied, as DIB has emerged as an efficient oxidant for metal free oxidations in organic transformations.[18] To test the feasibility of this strategy, the intramolecular cyclization reaction of glycosyl β-amino alcohol **5a** was performed under various conditions. The desired azetidine **6** was formed in good yield using the initial conditions of 0.2 equiv. of DIAD in combination with 1.5 equiv. of DIB and PPh_3 each. Eventually, the optimal conditions were determined to be 1.0 equiv. of **5a** and 1.2 and 1.5 equiv. of both DIB and PPh_3, respectively, after conducting a set of reactions (Table 2, entry 6). Since the involved alcohol is of a primary nature, the inversion of configuration under Mitsunobu reaction conditions using PPh_3–DIAD is feasible, hence intramolecular cyclization afforded glycosyl azetidine **6** in good yield. The 1,2-isopropylidene deprotection of glycosyl azetidine **6** was carried out using TFA–

Table 2 Cycle of catalytic intramolecular cyclization of glycosyl β-amino alcohol **5a**



Entry	Amino alcohol (equiv.)	Ph_3P (equiv.)	DEAD (equiv.)	DIAD (equiv.)	DIB	Yield (%)
1	1.0	1.2	1.2	—	—	68
2	1.0	1.5	1.5	—	—	70
3	1.0	1.5	0.1	—	2.0	72
4	1.0	1.2	—	1.2	—	70
5	1.0	1.5	—	1.5	—	73
6	1.0	1.2	—	0.2	1.5	72

H_2O (3 : 2) at room temperature and the diol **7** thus obtained was subjected to debenzylation by treatment with 10% palladium on charcoal under a hydrogen atmosphere in methanol. The resultant product after removal of the benzyl groups was found to be unstable and quickly slipped into intramolecular cyclization after *in situ* formation to deliver the desired final bicyclic iminosugar 1-deoxy-norcastanospermine **8** in 60% yield (Scheme 2). All the synthesized molecules, such as the glycosyl amino esters, glycosyl β-amino alcohol, glycosyl azetidine and 1-deoxy-norcastanospermine, were purified by flash column chromatography (SiO_2) and characterized by spectroscopic techniques (IR, ^1H NMR, ^{13}C NMR) and elemental analysis.

In conclusion, a novel, simple and facile protocol has been developed for the stereoselective synthesis of the bicyclic iminosugar analogue 1-deoxy-norcastanospermine from readily available D-glucose. The key step of our strategy is the internal reductive amination of novel glycosyl azetidine, achieved from glycosyl β-amino alcohol under Mitsunobu reaction conditions with the aid of a modified reduction and recycling of DIAD through a hypervalent iodine reagent. In addition, this method reports other attractive features like the development of an ionic liquid catalyzed and highly facile conjugate addition to reduce the reaction time. This protocol may be useful to develop other bicyclic iminosugars with potential chemotherapeutic properties.

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