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A concise synthesis of 2,5-dideoxy-2,5-imino-D-mannitol (DMDP) and HomoDMDP from L-xylose

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Abstract—A short and practical procedure for the preparation of C-2 substituted polyhydroxypyrrolidines is described. The C-2 substituent is introduced by a stereoselective addition of a Grignard reagent to a 2,3,5-protected aldofuranose and the cyclization to the pyrrolidine ring system is performed through a bis-mesylation/double nucleophilic displacement sequence. The efficiency of the methodology was demonstrated by its application to the synthesis of HomoDMDP and DMDP.

Naturally occurring polyhydroxypyrrolidines such as DMDP (2,5-dideoxy-2,5-imino-D-mannitol) **1** and the related analogues **2** and **3** (Fig. 1) display potent biological activities including anti-HIV effect,[1] tumour growth inhibition[2] or antifeedant properties against pest insects.[3] These nitrogen-containing sugar analogues are known to interfere with glycoprocessing enzymes (glycosidases or glycosyltransferases) by mimicking the natural glycoside substrate.[4] In this regard, DMDP is a powerful α- and β-glucosidase inhibitor displaying K_i's in the micromolar range and homoDMDP **2** inhibits specifically α-glucosidases.[5] Compound **3** (6-deoxy-homoDMDP) has less pronounced glycosidase inhibitory potencies but was found to inhibit potently chitin synthase ($K_i = 38$ μM), an obligate and specific fungal glycosyl transferase.[6]

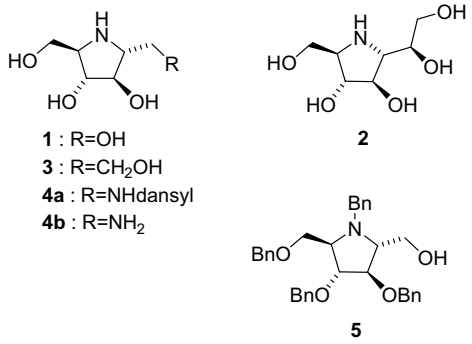

Figure 1. Structures of iminosugars **1**–**5**.

It was found recently that O-alkylated as well as N-alkylated derivatives of DMDP featuring a hydrophobic substituent at C-2 (such as **4a**), display unprecedented K_i's in the nanomolar range towards β-glucosidases.[7] The synthesis of these derivatives is usually performed starting from **1** itself or from the corresponding amine **4b**.[5,8] A new library of O-alkylated DMDP analogues might also be obtained from a partially protected analogue such as **5** (Fig. 1). Hence, in view of the biological potential of DMDP, HomoDMDP and their derivatives, efficient approaches are still needed. We report herein a new synthesis of the key compounds **1**, **2** or **5** that involves the stereoselective addition of vinylmagnesium bromide to a suitably protected L-xylose derivative, followed by a bis-mesylation/double nucleophilic displacement sequence.

In a previous work we have applied with success a practical route to iminosugars, starting from benzylglycosylamines, via the nucleophilic addition of an organometallic species and subsequent cyclization with methanesulfonylchloride (Scheme 1, X = NBn).[9,10] However, in this case, the addition is *syn* selective and affords, starting from benzyl-L-xylofuranosylamine, a D-*gluco* configurated iminosugar **B** as the main product. Due to the high selectivities observed with vinylmagnesium bromide or other organometallics, this synthetic

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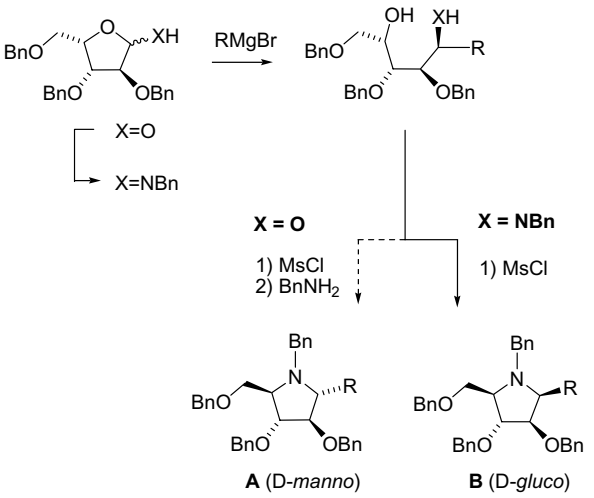


Scheme 1. Strategies for the synthesis of five-membered iminosugars.

route is not applicable to compounds like **1** or **2** which would result from the minor *anti* isomer.

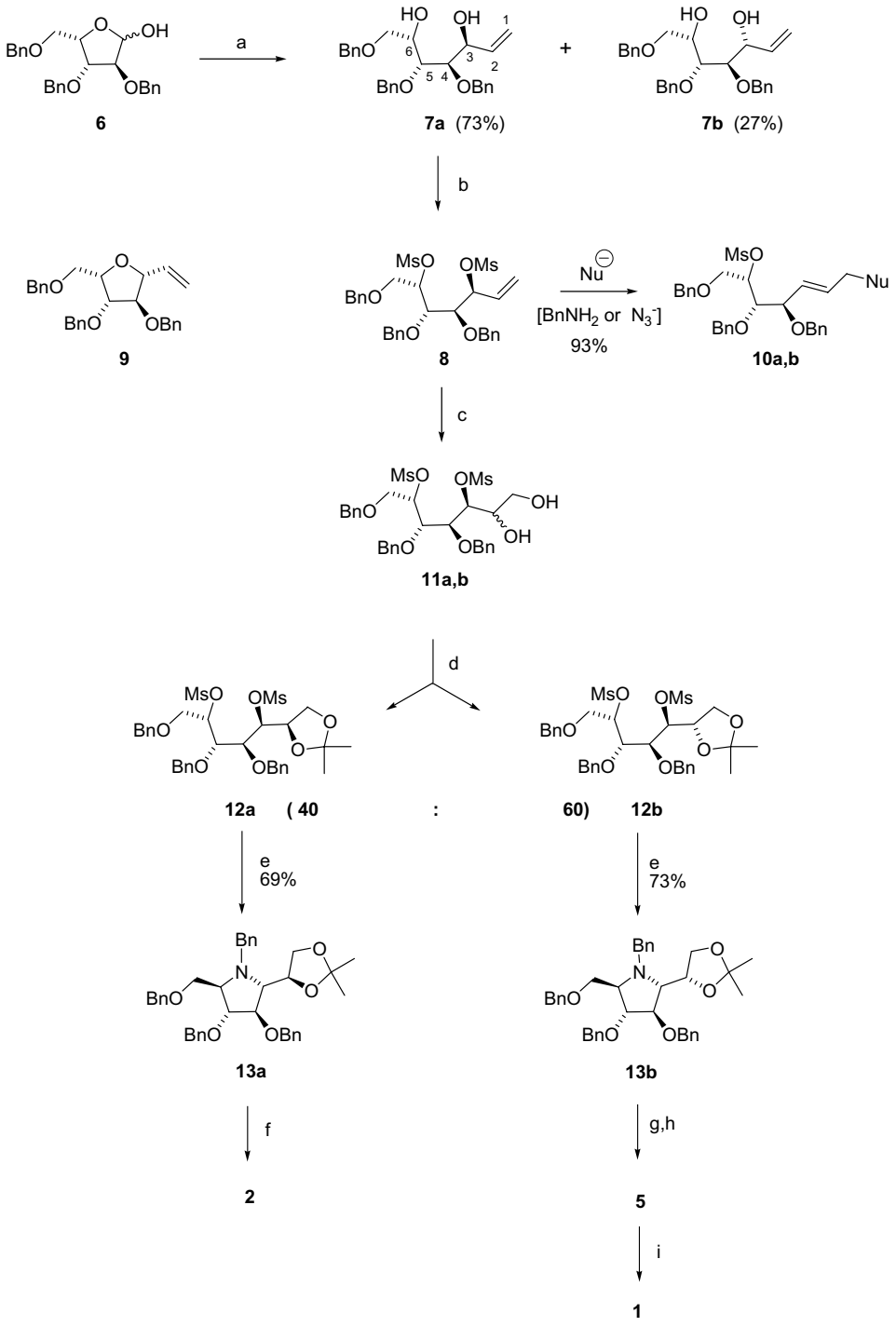
It is well known that the addition of organometallics to aldoses follows the same *syn* selectivity.[11,12] However, only few attempts to prepare iminosugars by this chain elongation strategy have been described.[2a] Interestingly, the major stereoisomer obtained in this case would afford a D-*manno* iminosugar **A** (Scheme 1, X = O) after introduction of nitrogen with concomitant inversion of configuration at both the free hydroxyl groups.

To demonstrate the efficiency of this methodology, we initially examined its application to the synthesis of homoDMDP (Scheme 2). Accordingly, we performed the addition of vinylmagnesium bromide to 2,3,5-tri-*O*-benzyl-L-xylose **6**. When the Grignard reagent was slowly added to a solution of the aldose **6**[9] in THF at room temperature, a mixture of the two possible stereoisomers was obtained in a 28% de in favour of the *syn* adduct **7a** (HPLC determination) and 90% isolated yield (**7a** + **7b**). These results are analogous to those obtained by Boschetti et al. in the enantiomeric series.[12] Interestingly, adducts **7a**,**b** could be easily separated by standard flash chromatography on silica gel (eluent, $CHCl_3/Et_2O$: 7/3, v/v). The ^1H and ^{13}C NMR data of **7a** and **7b** were identical to those described for the enantiomers and the optical rotations that we measured were in good agreement with the reported values: we found $[\alpha]_D^{20}$ −6.1 for the major isomer **7a** (lit. $[\alpha]_D^{20}$ +6.7 for the enantiomer)[12] and $[\alpha]_D^{20}$ +17.7 for the minor **7b** (lit. $[\alpha]_D^{20}$ −14.3 for the enantiomer). When the reaction was performed at 0 °C, an increase in stereoselectivity was observed (de = 46% as determined by HPLC, 83% overall yield). Interestingly, when the reaction was performed at room temperature in the presence of $ZnBr_2$ the selectivity was markedly improved in favour of the expected *syn* isomer (70% de), as already observed in the D-series.[12] Nevertheless, in this case, only 70% conversion was obtained after 6 days of reaction (40% isolated yield), hampering the use of these reaction conditions at a preparative scale.

The transformation of the major stereoisomer **7a** into the targeted iminosugars required three distinct steps: (i) activation of the free hydroxyl substituents at C-3 and C-6 by a leaving group, (ii) amination with benzylamine via a sequential nucleophilic displacement at both positions, (iii) bis-hydroxylation of the double bond. Activation of the 3-OH and the 6-OH was performed by standard esterification of **7a** with an excess of methanesulfonyl chloride in the presence of triethylamine at 0 °C. Under these conditions, the transformation occurred efficiently and bis-mesylate **8** was obtained in 91% yield after purification by silica gel chromatography ($CHCl_3/Et_2O$/petroleum ether: 5/3/2, v/v). Attempts to introduce a more efficient leaving group failed. Reaction of **7a** with chloromethanesulfonyl chloride[13] afforded *C*-vinyl furanosid **9** as the main product (43%) after spontaneous cyclization of the intermediate 6-OMs monoprotected ester. Such cycloetherification process has been observed frequently as an unexpected side reaction with triflates derived from 1,4-diols and even exploited for the synthesis of a series of *C*-vinyl furanosides.[14]

The formation of the pyrrolidine ring from bis-mesylate **8** was envisioned by reaction with benzylamine. Such a transformation has already been performed in the literature and proved effective with primary mesylates.[15] Only few examples of such ring formation are described, which involve two secondary activated hydroxyl groups.[16] In this latter case, long time reaction and high temperature are required to allow the substitution to take place. Surprisingly, on reaction with benzylamine at 50 °C, bis-mesylate **8a** was readily converted to a more polar product which was isolated in 76% yields after chromatography on silica gel (eluent: AcOEt). The so-obtained monomesylate **10a**, the structure of which was ascertained by spectroscopic and analytical data, arose from a more favourable S_N2' process as outlined in Scheme 2. The same reaction was observed when **8** was reacted with sodium azide affording **10b**. Interestingly, this unexpected reaction could be exploited for the synthesis of 7-membered-ring iminosugars. Nevertheless, to circumvent this side reaction, osmylation of the double bond was performed before the nucleophilic displacement. Thus, the reaction of bismesylate **8** with OsO_4 in the presence of NMO according to well-experimented procedures[17] gave a mixture of the two possible diols **11a**,**b** (89% yield, 20% de), which could be resolved by chromatography (Et_2O/petroleum ether: 1/1, v/v) after transformation to the corresponding acetonides **12a**,**b**. The configuration of the newly formed stereocentre was established after transformation of **12a** to the known HomoDMDP **2**, which features the (1′*S*) configuration at the corresponding position.[18] At this stage of our project, no attempts were undertaken in order to improve the stereoselectivity of the bis-hydroxylation procedure.

The nucleophilic displacement of acetonide **12a** with benzylamine required some optimization. When the reaction was performed in a sealed tube at 135 °C with a slight excess of benzylamine according to the recommended procedure,[16b] partial conversion was observed



Scheme 2. Reactions and conditions: (a) vinylMgBr, THF, 0 °C, 91%; (b) MsCl, NEt_3, CH_2Cl_2, 91%; (c) OsO_4, NMO, acetone/water, 80%; (d) acetone, TsOH, 89%; (e) $BnNH_2$, 120 °C; (f) 80% HCOOH then H_2, $Pd(OH)_2/C$, 70%; (g) 5% TFA in CH_2Cl_2, 100%; (h) $NaIO_4$ in EtOH/water, then $NaBH_4$, 66%; (i) $HCOONH_4$, 10% Pd/C, MeOH, reflux, 67%.

and pyrrolidine **13a** was isolated in an unsatisfactory 30% yield. Same results were obtained when the reaction was conducted under microwave irradiation. Nevertheless, the best results were obtained when **12a** was reacted under argon with a large excess of freshly distilled benzylamine at 120 °C. Complete conversion occurred after 24 h and the protected iminosugar **13a** was isolated in a pure form after silica gel chromatography (Et_2O/petroleum ether: 2/8, v/v) in 69% yield. Standard deprotection procedures (80% formic acid, then H_2–Pd/C) afforded HomoDMDP **2** in 70% yield (2 steps) after ion-exchange chromatography (Dowex 50WX-8, elution with 0.8 M NH_4OH). Spectral data as well as optical rotation of **2** ($[\alpha]_D^{20}$ +32.0) were in agreement with the reported values ($[\alpha]_D^{20}$ +25.6).[18]

DMDP **1** was prepared starting from acetonide **12b**. Cyclization with benzylamine gave the protected iminosugar **13b** (61% yield), which was converted to the partially protected DMDP derivative **4**[19] by the following

reaction sequence: deprotection of the acetonide with 5% TFA in CH_2Cl_2, treatment with sodium periodate and subsequent reduction of the aldehyde with sodium borohydride (66% overall yield). Debenzylation of **4** was performed by hydrogen transfer with ammonium formate in the presence of 10% Pd/C in refluxing methanol, affording the title compound **1** in 67% yield.

In conclusion, a new method has been developed for the preparation of iminosugars, which involves the stereoselective addition of a Grignard to a 2,3,5-protected aldofuranose, followed by a bis-mesylation/double nucleophilic displacement sequence. Our synthesis of HomoDMDP (7 steps) compares favourably in terms of length with the one reported in literature (12 steps). Further investigations on synthetic applications of this methodology are currently underway in our laboratory.

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Supplementary data

^1H and ^{13}C NMR spectra for compounds **1**, **2**, **5**, **7**, **8**, **12**, **13** are provided. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.01.125.

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