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An efficient synthesis of 1,4-dideoxy-1,4-imino-D- and L-arabinitol and 1,4-dideoxy-1,4-imino-D- and L-xylitol from chiral aziridines

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ABSTRACT

A highly efficient method for the synthesis of 1,4-dideoxy-1,4-imino-D- and L-arabinitol (D-AB1, **1** and L-AB1, **3**) and 1,4-dideoxy-1,4-imino-D- and L-xylitol (D-DIX, **2** and L-DIX, **4**) starting from commercially available chiral aziridines was developed. The general strategy employs a sequence involving two-carbon homologation, dihydroxylation, and regioselective aziridine ring opening/intramolecular five-membered iminosugar ring formation. The facile use of recrystallization to generate pure diastereomers makes the routes more amenable to large-scale synthesis.

Iminosugars, which contain a ring-nitrogen atom instead of the endocyclic oxygen present in monosaccharides, have received great attention owing to their attractive biological activities.[1] The iminosugar, 1,4-dideoxy-1,4-imino-D-arabinitol (D-AB1, 1), was first isolated from the fruits of *Angylocalyx boutiqueanus* in 1985[2] and its diastereomer, 1,4-dideoxy-1,4-imino-D-xylitol (D-DIX, 2), was recently isolated from marine sponges.[3] D-AB1 was found to be a potent inhibitor of glycogen phosphorylase and α-glucosidases.[4–6] Glucosidase inhibitors have been utilized as therapeutic agents for the treatment of several diseases including diabetics, viral infections, cancer, and genetic disorders.[7–9] Oncogene activation has been shown to trigger aberrant glycosylation owing to an altered cascade for the expression of glycosyltransferases.[10] Moreover, the level of glycosidases is also elevated in many types of cancer cells (Fig. 1).[11]

Because of its broad spectrum of biological activities and pharmacological properties, especially anti-cancer activity[7–9] D-AB1,[12–16] as well as its three stereoisomers, 1,4-dideoxy-1,4-imino-L-arabinitol (L-AB1,[13,17–19] **3**) and 1,4-dideoxy-1,4-imino-D and L-xylitol (D-DIX,[20–22] **2** and L-DIX,[14,15,23–28] **4**) became the targets of our effort aimed at developing highly efficient synthetic strategies. Recently reported synthetic routes for the preparation of the four iminosugars follow a number of different approaches. For example, D-DIX has been synthesized starting from D-xylose through a pathway involving Vasella reductive amination followed by halocyclization/carbonylation.[22] A sequence culminating in the preparation of L-AB1 began with Garner's aldehyde and utilized Sharpless asymmetric dihydroxylation as a key step.[19] A reductive cleavage reaction of the bis-benzylidene acetal of D-mannitol was employed in an approach to the synthesis of L-DIX.[27] Pseudo-hemiketal lactams, derived from sucrose, were utilized as key intermediates in sequences culminating in the preparation of D-AB1 and L-DIX.[15] Chemo-enzymatic synthesis strategy using D-fructose-6-phosphate aldolase and L-rhamnulose-1-phosphate aldolase was adopted for the synthesis of D-AB1 and L-AB1.[29,30] SmI_2-mediated benzyloxymethylation of dibenzyltartarimide resulted in D-AB1 and L-AB1.[31] Finally, a stereoselective palladium catalyzed oxazine forming reaction of D-serine served as the key component of the synthesis of D-AB1.[16]

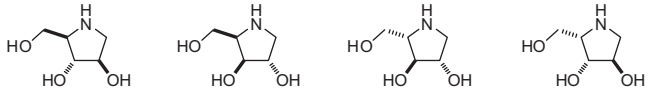

Figure 1. Structure of five-membered iminosugars.

Although a significant effort has been given to devising efficient syntheses of the four iminosugars highlighted above, some of the routes developed are lengthy owing to the need for tedious protection/deprotection protocols. Herein, we describe the results

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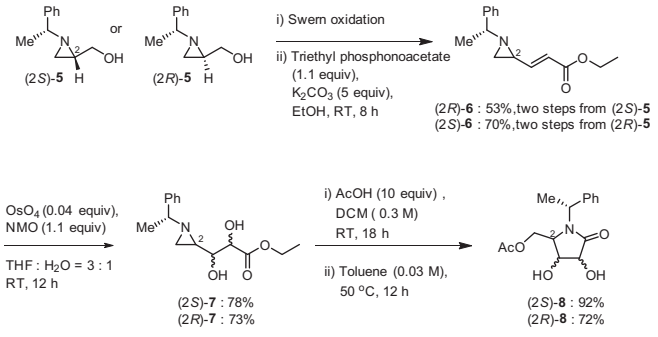
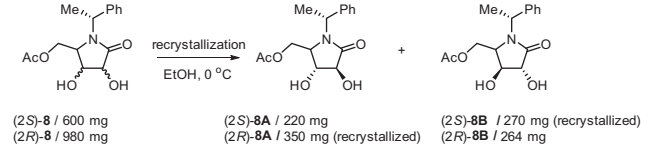
of a recent study, which has led to highly efficient and conveniently performed syntheses of the iminosugar stereoisomers D-AB1 (**1**), D-DIX (**2**), L-AB1 (**3**), and L-DIX (**4**). Each of the sequences started from a commercially and readily available chiral aziridine, and a facile recrystallization procedure was employed in each case to generate pure product.

As shown in Scheme 1, the total syntheses of diastereomerically pure D-AB1, **1** and L-AB1, **3** and D-DIX, **2** and L-DIX, **4** commenced with the commercially available 2*R*- and 2*S*-enantiomers of 1-methylbenzylaziridine-2-methanols, (2*R*)-**5** and (2*S*)-**5**, respectively. These substances were prepared from the corresponding aziridine-2-carboxylates by using $LiAlH_4$ reduction. In accord with our previous report,[32–34] independent Swern oxidations of (2*R*)-**5** and (2*S*)-**5** gave the corresponding 1-methylbenzylaziridine-2-carboxaldehydes that were then transformed to *trans*-3-aziridin-2-yl-acrylates (2*S*)-**6** and (2*R*)-**6** in 98:2 *trans*:*cis* ratios by using Horner–Wadsworth–Emmons olefination with ethyl diethylphosphonoacetate. The desired *trans*-diastereomers of each enantiomer were readily purified by using silica gel column chromatography. *Cis*-Dihydroxylation reactions of (2*S*)-**6** and (2*R*)-**6** using OsO_4 in the presence of NMO afforded diastereomers (2*S*)-**7** and (2*R*)-**7** in 77% and 73% respective yields. Based on the analysis of crude ^1H NMR spectra, diastereomeric ratios of (2*S*)-**7** and (2*R*)-**7** were 1:1.7 and 1:1, respectively. Neither diastereomer of diastereomers (2*S*)-**7** or (2*R*)-**7** were separable by employing silica gel chromatography. The C-3 bonds present in the aziridine rings of (2*S*)-**7** and (2*R*)-**7** were regioselectively cleaved by treatment with AcOH in CH_2Cl_2 to produce the corresponding acyclic acetate ester products, which then underwent lactam ring forming cyclization in the presence of AcOH at 50 °C to produce (2*S*)-**8** and (2*R*)-**8**. The diastereomeric ratios of (2*S*)-**8** and (2*R*)-**8** would be same as those of (2*S*)-**7** and (2*R*)-**7**.

The facile recrystallization of each product mixture containing (2*S*)-**8** and (2*R*)-**8** from ethanol at 0 °C afforded the individual diastereomers of (2*S*)-**8B** and (2*R*)-**8A** in a pure form as white crystalline substances (Scheme 2). This facile recrystallization could render our synthetic route more amenable to large-scale preparation of the final compounds **1**–**4**. The mother liquors from each were subjected to flash column chromatography to furnish diastereomerically pure (2*S*)-**8A** and (2*R*)-**8B**.



Scheme 1. Synthesis of the pyrrolidinones, (2*S*)-**8** and (2*R*)-**8**.



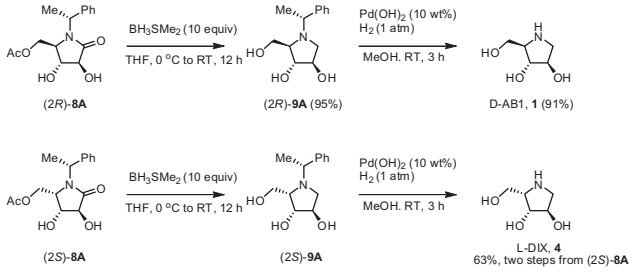
Scheme 2. Separation of the *diastereomeric* pyrrolidinones (2*S*)-**8** and (2*R*)-**8** by recrystallization.

Reductions of the amide and acetate groups in (2*S*)-**8A** and (2*R*)-**8A** were carried out using borane–dimethyl sulfide to generate the corresponding pyrrolidines (2*R*)-**9A** and (2*S*)-**9A** (Scheme 3). The (2*R*,3*R*,4*R*)-2-(hydroxymethyl)pyrrolidine-3,4-diol, (2*R*)-**9A**, generated in this manner, was subjected to silica gel chromatography (DCM:7 N ammonia in MeOH solution = 10:1) to afford pure (2*R*)-**9A** in 95% yield.

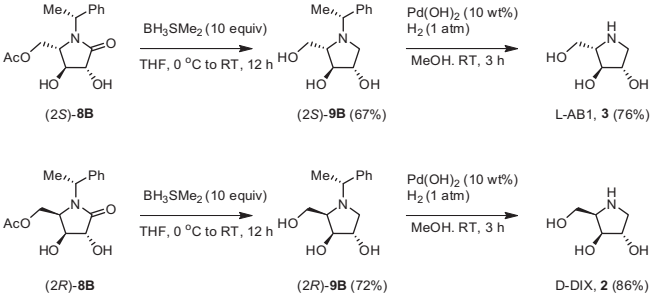
Although the crude (2*S*,3*R*,4*R*)-2-(hydroxymethyl)pyrrolidine-3,4-diol, (2*S*)-**9A** arising from the reduction reaction was also subjected to silica gel chromatography, pure (2*S*)-**9A** could not be obtained presumably because of the presence of a tight boron-(2*S*)-**9A** adduct. Therefore, the chromatographed substance was used for the ensuing hydrogenolysis step ($Pd(OH)_2$, methanol, 1 atm hydrogen in the absence of acid) to cleave the benzyl protecting group. Silica gel chromatography (DCM:MeOH:EtOH:30% NH_4OH = 5:2:2:1) of the resulting product mixture afforded pure L-DIX, **4**. It is interesting to note that the reduction conditions transform the boron-(2*S*)-**9A** complex into L-DIX, **4** which is boron free. This finding parallels the results of a previous study by Couturier et al.,[35] that showed that palladium catalyzes the methanolysis of borane–amine adducts. (2*R*)-**9A** was also subjected to the same hydrogenolysis and purification step as applied to (2*S*)-**9A** to form pure D-AB1, **1** in 91% yield.

Utilizing the same general approach employed to synthesize D-AB1, **1** and L-DIX, **4**, we have also prepared L-AB1, **3** and D-DIX, **2** from pyrrolidinones (2*S*)-**8B** and (2*R*)-**8B** (Scheme 4). It should be noted that (2*R*,3*S*,4*S*)-2-(hydroxymethyl)pyrrolidine-3,4-diol, (2*R*)-**9B** did not form boron-adducts in contrast to the (2*S*)-**9A**. As a result, both substances, (2*S*)-**9B** and (2*R*)-**9B** in scheme 4 were generated in a pure form by using silica gel chromatography.

The study described above has led to the development of a general strategy for the highly facile and efficient synthesis of iminosugar D-AB1 and three of its diastereomers. The six-step routes, beginning with commercially and readily available chiral aziridines, are comprised of steps involving a two-carbon homologation, dihydroxylation, and regioselective aziridine ring opening/intramolecular five-membered iminosugar ring formation. Moreover, the facile use of recrystallization to separate easily diastereomers



Scheme 3. Synthesis of D-AB1, **1** and L-DIX, **4**.



Scheme 4. Synthesis of L-AB1, **3** and D-DIX, **2**.

makes the approach more amenable to large-scale preparation of the target compounds.

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Supplementary data

Supplementary data (^{1}H NMR/^{13}C NMR, HRMS, optical rotation) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.040.

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