



Convenient strategy for the synthesis of highly functionalizable hydroxylated unsaturated azepanes

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ABSTRACT

A convenient approach to the construction of dihydroxylated unsaturated azepanes featuring a functional group (ethoxycarbonyl)methyl or (cyano)methyl at C-2 was achieved from a pent-4-enal synthon obtained in four steps from D-xylose. The key step of the sequence relied on the conjugate addition of allylamine to α,β -unsaturated ester or nitrile, prepared by Wadsworth–Emmons olefination. Subsequent RCM afforded the target unsaturated azepanes.

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Inhibition of glycosidases has been extensively studied in the last years due to the numerous biochemical roles played by these enzymes. Many natural or synthetic glycosidase inhibitors exhibit interesting therapeutic applications in the treatment of various diseases such as diabetes,¹ viral infection² including AIDS,³ Gaucher's disease,⁴ or cancer.⁵ Polyhydroxylated pyrrolidines, piperidines, and bicyclic nitrogen-heterocycles such as indolizidines or pyrrolizidines represent the most studied classes of naturally occurring carbohydrate mimics, acting as potent glycosidase inhibitors. A wide synthetic effort devoted to the preparation of these various types of iminosugars has been developed since the pioneering works in the late 1960's.⁶

More recently, polyhydroxylated azepanes have emerged as a new class of iminosugars.⁷ After a first synthetic approach by Paulsen in 1967,⁸ a set of tri- and tetra-hydroxylated azepanes exhibiting limited inhibition potencies has been prepared by Wong⁹ or Depezay.¹⁰ Addition of supplementary substituents on the 7-membered ring afforded inhibitors with micro to nanomolar affinities. Indeed, greater conformational flexibility of the 7-membered ring enables multiple favorable binding interactions in the enzyme active site.¹¹ Thus, polyhydroxylated azepanes such as **1–2** (Fig. 1) featuring an extra hydroxymethyl, carboxyl, or acetamide group have been recently prepared, and might be considered as new potential therapeutic agents.^{12–15} Only few general synthetic strate-

gies toward such functionalized polyhydroxyazepanes have been described to date. An important work in this field was developed by Blériot et al. with a method based on the versatile transformation of a key intermediate azacycloheptene **3** produced by ring-closing metathesis (Fig. 1).^{12a–d,g}

As a continuation of an ongoing program devoted to the transformation and the valorization of hemicellulose-derived pentoses,¹⁶ we wished to pave the way for a general synthetic route toward functionalized polyhydroxyazepanes, starting from dihydroxylated pent-4-enal **4**, a versatile building-block easily obtained from D-xylose. Thus, we report herein our first efforts toward the preparation of new azacycloheptenes, featuring an unprecedented functional group (ethoxycarbonyl)methyl or (cyano)methyl at the pseudo-anomeric position (Fig. 2). These compounds are precursors of imino C-glycosides, which have become an important class of iminosugars with promising biological and therapeutic properties.¹⁷

The synthetic sequence began with the preparation of the protected 2,3-dihydroxypent-4-enal **4** from D-xylose (Scheme 1). In our hands, synthesis of the benzyl-protected precursor **5a** according to a previously described procedure¹⁸ was unsatisfactory (35% overall yield). Hence, we turned to the pivaloyl protecting group. Formation of compound **5b** was easily carried out in standard conditions in a 77% overall yield (Scheme 1). Treatment of compound **5b** with activated zinc dust in a 4:1 THF/H₂O mixture under sonication^{18,19} gave pent-4-enal **4b** in 80% yield, which was used without further purification.

It is noteworthy that the same sequence could be successfully applied to L-arabinose (the C-4 epimer of D-xylose), the second

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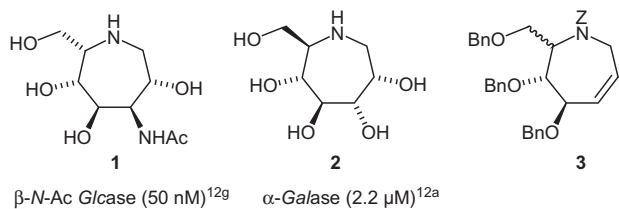


Figure 1. Structures and glycosidase inhibition potencies of polyhydroxylated azepanes previously reported.

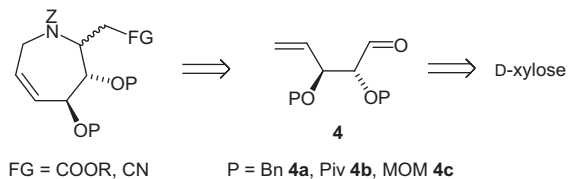
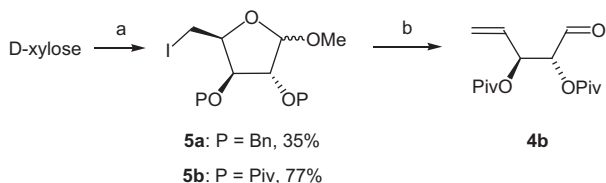


Figure 2. Retrosynthetic scheme toward the target molecules.

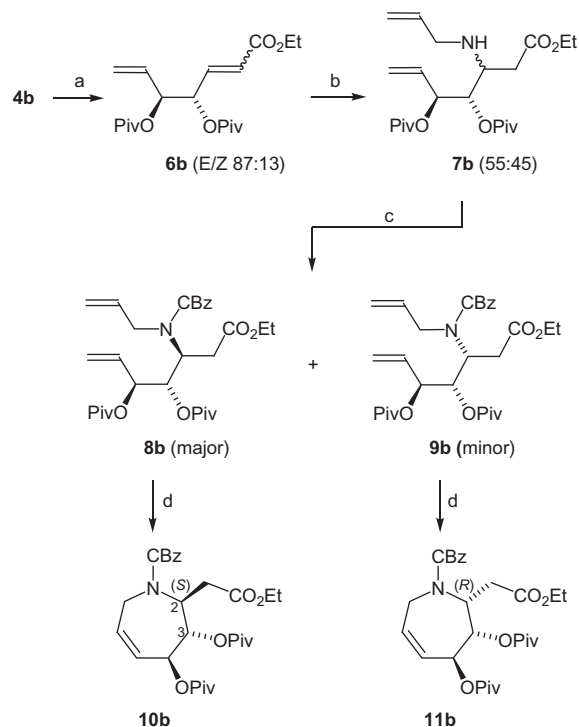
main pentose in the structure of wheat straw and bran hemicelluloses, and to a mixture of both pentoses, yielding **4b** in comparable yields.

First attempts were conducted to prepare the azacycloheptene featuring a (ethoxycarbonyl)methyl group as the functional group. To this aim, aldehyde **4b** was first subjected to a Wadsworth–Emmons olefination with triethyl phosphonoacetate.²⁰ The reaction was effected at room temperature and yielded efficiently the expected α,β -unsaturated diene **6b** in a 87:13 *E/Z* ratio (Scheme 2). Then, aza-Michael addition was carried out under very mild conditions by stirring **6b** with neat allylamine for 16 h at rt, which afforded adducts **7b** in 66% yield (55/45 mixture of diastereomers). Interestingly, in our work, the lack of stereoselectivity might be considered as an opportunity, a source of diastereochemical diversity, to obtain both diastereomers and, after purification and cyclization, epimeric azepanes. It has to be noticed that such an aza-Michael addition was recently reported on analogous substrates,²¹ using more restricting conditions with substituted homochiral lithium benzylamides as nucleophiles. This reaction was applied to the synthesis of polyhydroxylated pyrrolidine,²² piperidine,²³ and pyrrolizidine²⁴ scaffolds.

Separation of diastereomers was carried out after protection as *N*-benzyloxycarbonyl derivatives **8b** and **9b**.²⁵ Final ring-closing metathesis with both pure diastereomers to obtain the targeted 7-membered ring compounds proved somewhat sluggish and complete conversion required 72 h of stirring in toluene at 90 °C. Addition of DMSO as scavenger for the ruthenium catalyst and purification by silica gel chromatography afforded β -aminoesters **10b** and **11b** in excellent 83–84% yields.²⁶ The configuration of



Scheme 1. Synthesis of **4b**. Reagents and conditions: (a) (i) MeOH, HCl (cat.), 12 h then CaCO₃, rt, quant.; (ii) TsCl (1 equiv), pyridine, rt, 48 h; (iii) benzyltrichloroacetimidate, triflic acid, dioxane, rt, (40% for the two steps) or Piv-Cl (3 equiv), pyridine, rt, (87% for the 2 steps); (iv) NaI (2 equiv), dimethoxyethane, 48 h, 90 °C, 87% for **5a**, 88% for **5b**; (b) activated Zn dust (10 equiv), THF/H₂O 4:1, 40 °C, sonication, 80%.



Scheme 2. Synthesis of unsaturated azepanes **10b** and **11b**. Reagents and conditions: (a) (EtO)₂PO-CH₂-COOEt (1 equiv), Et₃N (2.1 equiv), LiCl (4 equiv), rt, 5 h, 83%; (b) allylamine (12 equiv), rt, 3 days, 66%; (c) CBz-Cl (2.1 equiv), NaHCO₃ (19 equiv), EtOAc/H₂O 1:1, 0 °C 1 h then rt 12 h, 90% (mixture of diastereomers); (d) Grubbs's I catalyst (15 mol %), toluene, 90 °C, 3 days, 83% for **10b**, 84% for **11b**.

the new stereocenter was deduced from NMR analysis of the cyclized compound **10b** derived from the major diastereomer **8b** by comparison of the characteristic $J_{2,3}$ coupling constant ($J_{2,3} = 8.8$ Hz for both rotamers) indicating a *trans*-configuration as described in the literature for analogous heterocycles ($J_{\text{trans}} = 8.8\text{--}9.4$ Hz) and unambiguously confirmed by X-ray crystallography.^{12a}

A similar sequence was then applied to the synthesis of a nitrile-functionalized azepane. Reaction of **4b** with diethyl cyanomethylphosphonate was efficiently carried out under the conditions stated above to give α,β -unsaturated nitrile **12b** in a 90% yield and a 87:13 *E/Z* ratio. Reaction of **12b** with allylamine afforded the expected Michael adduct **13b** with an unsatisfactory 54% yield in the best conditions (allylamine 4 equiv, methanol, 35 °C), due to the formation of decomposition products.

Altering the protecting groups of the pent-4-enal **4** from pivaloyl **4b** to methoxymethyl (MOM) **4c** permitted to improve this conjugate addition. Hence, the MOM-protected α,β -unsaturated nitrile **12c** was easily obtained in a 68% yield and a 89:11 *E/Z* ratio from the known aldehyde **4c**,²⁷ by condensation with cyanomethylphosphonate. Reaction of **12c** with an excess of allylamine (4 equiv) in methanol at 35 °C afforded the desired β -aminonitrile **13c** in acceptable 76% yield and a 64:36 ratio of diastereomers (de 28%). Again, separation of diastereomers was carried out after protection as *N*-benzyloxycarbonyl derivatives **14c** and **15c**. Terminal RCM was then performed on Cbz-protected compounds to afford target cyanoazaheptenes **16c** and **17c** in 60–80% yields (Scheme 3). The stereochemistry at C-2 for the diastereomers **16c** and **17c** was assigned by analogy with the preceding reaction onto the conjugated ester function.²⁸

In conclusion, we have developed a convenient synthetic sequence affording highly functionalizable dihydroxylated unsaturated azepanes featuring (ethoxycarbonyl)methyl or

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