

# Access to L- and D-Iminosugar C-Glycosides from a D-*gluco*-Derived 6-Azidolactol Exploiting a Ring Isomerization/Alkylation Strategy

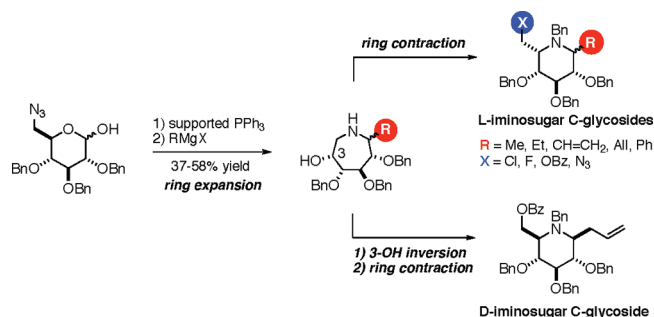
Martine Mondon,<sup>†</sup> Nathalie Fontelle,<sup>†</sup> Jérôme Désiré,<sup>†</sup> Frédéric Lecornué,<sup>†</sup> Jérôme Guillard,<sup>†</sup> Jérôme Marrot,<sup>‡</sup> and Yves Blériot<sup>\*†</sup>

*Institut de Chimie des Milieux et des Matériaux de Poitiers (IC2MP), UMR CNRS 7285, Université de Poitiers, Equipe “Chimie Organique, Bioorganique et Supramoléculaire” 4 avenue Michel Brunet, 86022 Poitiers cedex, France, and Institut Lavoisier de Versailles, UMR CNRS 8180, Université de Versailles, 45 avenue des Etats-Unis, 78035 Versailles cedex, France*

yves.bleriot@univ-poitiers.fr

Received December 20, 2011

## ABSTRACT



A flexible synthetic access to six-membered L- and D-iminosugar C-glycosides is reported starting from the easily available 6-azido-6-deoxy-2,3,4-tri-O-benzyl-D-glucopyranose precursor. This methodology involves a highly diastereoselective tandem ring enlargement/alkylation and a stereocontrolled ring contraction. It allows an efficient synthesis of iminosugar C-glycosides displaying structural diversity at both C-1 and C-6.

Iminosugars, sugar analogs in which the endocyclic oxygen has been replaced by nitrogen, constitute a major class of sugar mimetics.<sup>1</sup> Their promising therapeutic potential<sup>2</sup> is illustrated by the approval of Glyset<sup>3</sup> and Zavesca<sup>4</sup> (Figure 1) for the treatment of type II diabetes and Gaucher disease respectively. Moving the alkyl chain from the endocyclic nitrogen to the pseudoanomeric carbon leads to another class of important iminosugars, the iminosugar C-glycosides which can be seen as glycoconjugates

with a stable substituent at the C-1 position (Figure 1). Iminosugar C-glycosides are usually more potent and selective compared to the more synthetically accessible iminoalditols, an improved efficacy which can be attributed in part to a better location of the alkyl chain.<sup>5</sup> The main challenge associated with iminosugar C-glycosides is currently the design of efficient and general routes enabling introduction of structural diversity from advanced synthons to accelerate the discovery of biologically relevant molecules. Ideally such routes would require introduction of additional substituents on a late stage intermediate. Most of

<sup>†</sup> Université de Poitiers.

<sup>‡</sup> Université de Versailles.

(1) Martin, O. R.; Compain, P. *Iminosugars: From synthesis to therapeutic applications*; Wiley-VCH: Weinheim, 2007.

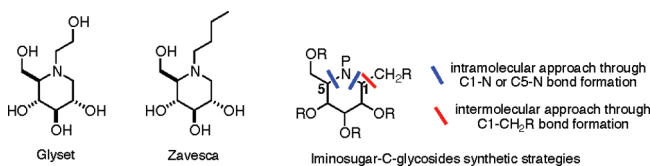
(2) (a) Horne, G.; Wilson, F. X. *Prog. Med. Chem.* **2011**, *50*, 135–176. (b) Horne, G.; Wilson, F. X.; Tinsley, J.; Williams, D. H.; Storer, R. *Drug Discov. Today* **2011**, *16*, 107–118.

(3) Jacob, G. S. *Curr. Opin. Struct. Biol.* **1995**, *5*, 605–611.

(4) McCormack, P. L.; Goa, K. L. *Drugs* **2003**, *63*, 2427–2434.

(5) (a) Wennekes, T.; Van den Berg, R. J. B. H. N.; Boltje, T. J.; Donker-Koopman, W. E.; Kuijper, B.; van der Marel, G. A.; Strijland, A.; Verhagen, C. P.; Aerts, J. M. F. G.; Overkleeft, H. S. *Eur. J. Org. Chem.* **2010**, 1258–1283. (b) Schönemann, W.; Galienne, E.; Compain, P.; Ikeda, K.; Asano, N.; Martin, O. R. *Bioorg. Med. Chem.* **2010**, *18*, 2645–2650. (c) Weber, K. T.; Hammache, D.; Fantini, J.; Ganem, B. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 1011–1014.

the reported synthetic strategies are based either on the formation of the C1–N or C5–N bond through intramolecular reductive amination or on the late formation of the C1–CH<sub>2</sub>R bond through the use of an electrophilic iminosugar donor (Figure 1).<sup>6</sup>



**Figure 1.** Structures of Glyset and Zavesca and general strategies to access iminosugar C-glycosides.

The intermolecular approach, inspired from the synthetic strategies developed in the field of C-glycosides, appears as the best strategy for late stage diversification. It has been less explored due to the difficult generation of stable electrophilic iminosugars. Piperidinose donors have been developed by Johnson,<sup>7</sup> Vasella,<sup>8</sup> and Schmidt,<sup>9</sup> and nucleophilic addition to the endocyclic C=N bond of a six-membered iminosugar-derived cyclic imine or nitron has been reported by Davis<sup>10</sup> and Vasella<sup>11</sup> respectively. These elegant routes focus on introduction of various substituents at C-1 but usually do not allow decoration at other positions of the piperidine ring. Such modification could be of interest to increase their biological potency and/or selectivity. One exception is the SAWU strategy developed by Overkleeft which enables the synthesis of a library of iminosugar C-glycosides displaying diversity both at C-1 and at the endocyclic nitrogen.<sup>12</sup> Introduction of structural diversity at both C-1 and C-6 has not been developed despite the fact that it should give rise to novel sugar mimetics with enhanced potency through hydrophobic interaction with protein residue side chains. Our interest in the synthesis<sup>13</sup> and skeletal rearrangement<sup>14</sup> of seven-membered iminosugars prompted us to combine both

(6) Compain, P.; Chaignault, V.; Martin, O. R. *Tetrahedron: Asymmetry* **2009**, *20*, 672–711.

(7) Johnson, C. R.; Golebiowski, A.; Sundram, H.; Miller, M. W.; Dwaihy, R. L. *Tetrahedron Lett.* **1995**, *36*, 653–654.

(8) Granier, T.; Vasella, A. *Helv. Chim. Acta* **1998**, *81*, 865–880.

(9) Fuchss, T.; Streicher, H.; Schmidt, R. R. *Liebigs Ann. Recl.* **1997**, 1315–1321.

(10) (a) Maughan, M. A. T.; Davies, I. G.; Claridge, T. D. W.; Courtney, S.; Hay, P.; Davis, B. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 3788–3792. (b) Davis, B. G.; Maughan, M. A. T.; Chapman, T. M.; Villard, R.; Courtney, S. *Org. Lett.* **2002**, *4*, 103–106.

(11) Peer, A.; Vasella, A. *Helv. Chim. Acta* **1999**, *82*, 1044–1065.

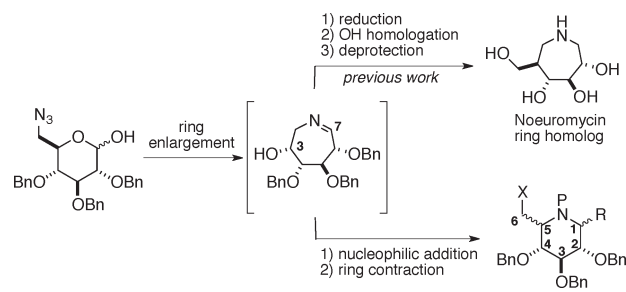
(12) Timmer, M. S. M.; Risseuw, M. D. P.; Verdoes, M.; Filippov, D. V.; Plaisier, J. R.; Van der Marel, G. A.; Overkleeft, H. S.; Van Boom, J. H. *Tetrahedron: Asymmetry* **2005**, *16*, 177–185.

(13) (a) Marcelo, F.; He, Y.; Yuzwa, S. A.; Nieto, L.; Jiménez-Barbero, J.; Sollogoub, M.; Vocadlo, D. J.; Davies, G. J.; Blériot, Y. *J. Am. Chem. Soc.* **2009**, *131*, 5390–5392. (b) Li, H.; Liu, T.; Zhang, Y.; Favre, S.; Bello, C.; Vogel, P.; Butters, T. D.; Oikonomakos, N. G.; Marrot, J.; Blériot, Y. *ChemBioChem* **2008**, *9*, 253–260. (c) Li, H.; Blériot, Y.; Chantreau, C.; Mallet, J.-M.; Sollogoub, M.; Zhang, Y.; Rodriguez-García, E.; Vogel, P.; Jiménez-Barbero, J.; Sinay, P. *Org. Biomol. Chem.* **2004**, *2*, 1492–1499.

(14) Liu, T.; Zhang, Y.; Blériot, Y. *Synlett* **2007**, 905–908.

aspects to develop a new powerful strategy toward piperidine iminosugar C-glycosides based on the alkylation of a seven-membered electrophilic iminosugar and its subsequent ring isomerization. This approach should allow tuning of the substituents at C-1 and C-6. We have previously disclosed the synthesis of seven-membered iminosugar homologues of glycosidase inhibitor noeuromycin starting from a sugar-based azidolactol **1** and exploiting a Staudinger/aza-Wittig ring expansion.<sup>15</sup> Since this transformation proceeds by a two-step reduction, trapping of the intermediate seven-membered imine by an organometallic species instead of hydride should allow selective functionalization at the C-7 position. Subsequent azepane ring isomerization through 3-OH group activation should provide the corresponding six-membered iminosugar C-glycosides displaying structural diversity at C-6 (Scheme 1).

**Scheme 1.** New Strategy Developed Herein to Access Iminosugar C-Glycosides



Initial attempts using triphenylphosphine and starting from azidolactol **1**, easily available from methyl glucopyranoside,<sup>16</sup> failed to furnish the pure imine **2** in good yield. More encouraging results were obtained by switching to the polymer-bound triphenylphosphine. After optimization of the reaction conditions, a major product was isolated in 62% yield and assigned to the bicyclic N,O-acetal **3**<sup>17</sup> by NMR (signals at 5.06 and 88.7 ppm in the <sup>1</sup>H and <sup>13</sup>C NMR spectra respectively for the hemiaminal moiety). It results from the trapping of the transient seven-membered imine **2** by the free 3-OH group (Scheme 2). This electrophilic bicycle can be seen as a stable form of **2** allowing introduction of hydrophobic groups at C-7 through organometallic addition. The reactivity of N,O-acetals with organometallics is well-documented<sup>18</sup> but has

(15) Li, H.; Zhang, Y.; Vogel, P.; Sinay, P.; Blériot, Y. *Chem. Commun.* **2007**, 183–185.

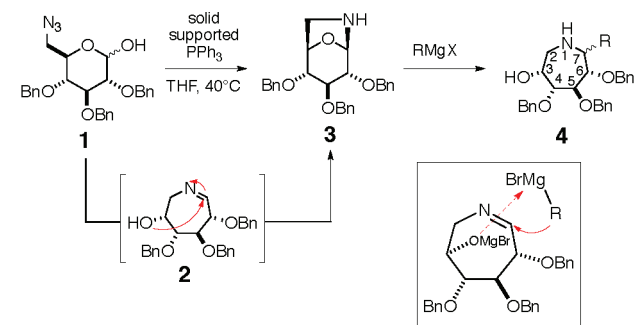
(16) (a) Kobertz, W. R.; Bertozzi, C. R.; Bednarski, M. D. *J. Org. Chem.* **1996**, *61*, 1894–1897. (b) Chakraborty, T. K.; Ghosh, S.; Jayaprakash, S.; Sharma, J. A. R. P.; Ravikanth, V.; Diwan, P. V.; Nagaraj, R.; Kunwar, A. C. *J. Org. Chem.* **2000**, *65*, 6441–6457.

(17) Similar bicyclic [5,6] N,O-acetals derived from sugars have been reported: (a) Lafont, D.; Wollny, A.; Boullanger, P. *Carbohydr. Res.* **1998**, *310*, 9–16. (b) Beacham, A. R.; Smelt, K. H.; Biggadike, K.; Britten, C. J.; Hackett, L.; Winchester, B. G.; Nash, R. J.; Griffiths, R. C.; Fleet, G. W. *J. Tetrahedron Lett.* **1998**, *39*, 151–154. (c) Fuentes, J.; Gasch, C.; Olano, D.; Pradera, M. A.; Repetto, G.; Sayago, F. *J. Tetrahedron: Asymmetry* **2002**, *13*, 1743–1753.

(18) (a) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407–1438. (b) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895–1946. (c) Steinig, A. G.; Spero, D. M. *Org. Prep. Proc. Int.* **2000**, *32*, 205–234.

been unexplored with [5,6] bicyclic systems.<sup>19</sup> The one-pot Staudinger/aza-Wittig/alkylation of **1** was thus studied screening various conditions and organometallics to generate the corresponding C-7 alkyl azepanes **4** (Scheme 2).

**Scheme 2.** Synthesis of C-7 Alkyl Azepanes **4a–4e**



Entry	R	yield (%)	C-7 <i>R/S</i> ratio	$^3J_{6,7}$ (Hz)
<b>1</b>	All	<b>4a</b> 58	< 5:95	8.5
<b>2</b>	Me	<b>4b</b> 37	>95:5	0
<b>3</b>	Et	<b>4c</b> 49	>95:5	0
<b>4</b>	CH=CH <sub>2</sub>	<b>4d</b> 38	67:33	0: 8.4
<b>5</b>	Ph	<b>4e</b> 35	<5:95	9.5

Initial experiments, to optimize the reaction conditions, were performed using allylmagnesium bromide as a nucleophile as it gave the best yield for this transformation. In a typical procedure, **1** was treated with solid-supported PPh<sub>3</sub> at 40 °C in THF overnight and the solution was filtered through a Celite plug. The crude solution was concentrated and engaged in the next alkylation step involving organomagnesium reagents. Reverse addition of a crude solution of **3** in THF into an excess of Grignard reagent (10 equiv) in THF, and running the reaction at rt, gave the best conversion.<sup>20</sup> Allyl azepane **4a** was obtained in 58% yield and as a single diastereomer after SiO<sub>2</sub> flash column chromatography. Its structure was ascertained by typical NMR data. The <sup>13</sup>C NMR spectrum in CDCl<sub>3</sub> displayed five CH signals at 85.5, 82.4, 78.6, 70.0, and 60.5 ppm (C-7), one CH= signal at 135.8 ppm and one CH<sub>2</sub>= signal at 117.9 ppm. The <sup>1</sup>H NMR spectrum in CDCl<sub>3</sub> showed a signal at 2.93 ppm for the C-7 proton. Other Grignard reagents, namely, methyl, ethyl, vinyl, and phenyl magnesium halides, were also reacted leading to the corresponding C-7 alkyl azepanes **4b–4e** in moderate yields (35–49% yield over two steps) and excellent diastereoselectivities (> 95%) except for the vinyl derivative (34%). The configuration of the C-7 stereogenic center for each new azepane was determined by NMR. While the methyl, ethyl, vinyl azepanes **4b–d** displayed a coupling

constant  $J_{6,7}$  close to 0 Hz indicative of a 6,7 *cis* relative configuration and an *R* configuration for the C-7 carbon, the phenyl and allyl derivatives **4a** and **4e** displayed a large  $J_{6,7}$  (8.5 and 9.5 Hz respectively) in agreement with a 6,7 *trans* relative configuration and a *S* configuration for C-7.<sup>21</sup> The 6,7 *cis* relative configuration for **4b–d** could be explained by a mechanism involving an intramolecular delivery of the nucleophile in an early transition state (Scheme 2). The rationale for the 3,7 *trans* configuration of **4a** and **4e** remains unclear. One notable aspect of this strategy is that it allows a fast access to 7-C-alkyl-3,4,5,6-tetrahydroazepanes, which have been scarcely reported,<sup>22</sup> and could display potent glycosidase inhibition and a pharmacological chaperone profile.<sup>23</sup> Polyhydroxylated azepanes are useful synthons for generating polysubstituted piperidines through ring isomerization.<sup>24</sup> This process is triggered by activation of the free 3-OH group and displacement by the endocyclic nitrogen which leads to a transient fused piperidine-aziridinium intermediate. Its regioselective opening by the released nucleophile at the methylene carbon leads to a six-membered azacycle, while attack at the methine carbon gives the corresponding azepane with retention of configuration at C-3. Applied to the C-alkyl azepanes, this transformation, which requires an electron-rich nitrogen, should furnish the six-membered iminosugar C-glycosides displaying structural diversity at C-6 brought by the incoming nucleophile. Azepane **4a** was chosen as a representative model of the C-alkyl azepanes synthesized. Its N-benylation under mild basic conditions afforded hydroxyazepane **5** (53% yield over 3 steps from azidolactol **1**) which was then submitted to different OH group activation conditions (Scheme 3) to introduce several functionalities at C-6 during the ring isomerization process. Mesylation (MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>) of **5** furnished the chlorinated six-membered iminosugar-C-glycoside **6a** (72%). Mitsunobu conditions (PPh<sub>3</sub>, DEAD, *p*NO<sub>2</sub>PhCOOH) applied to **5** yielded the corresponding piperidine **6b** in satisfactory yield (67%) along with some azepane **7b** (21%).<sup>25</sup> Piperidine **6a** displays a typical  $J_{5,6}$  value (5.7 Hz) for a *cis* relative configuration between H-5 and H-6 which is in agreement with a double displacement mechanism during the skeletal rearrangement. Furthermore, the observed  $J_{2,3}$  value (9.7 Hz) confirms the *trans* relative configuration for

(21) Configuration of the C-7 carbon of azepane **4a** was further confirmed after its ring contraction leading to classical coupling constants associated with a piperidine motif. It allowed deduction of the C-7 configuration of azepanes **4b–e**.

(22) (a) Otero, J. M.; Estévez, A. M.; Soengas, R. Q.; Estévez, J. C.; Nash, R. J.; Fleet, G. W. J.; Estévez, R. J. *Tetrahedron: Asymmetry* **2008**, *19*, 2443–2446. (b) Tite, T.; Tsimilaza, A.; Lallemand, M.-C.; Tillequin, F.; Leproux, P.; Libot, F.; Husson, H.-P. *Eur. J. Org. Chem.* **2006**, 863–868.

(23) Orwig, S. D.; Tan, Y. L.; Grimster, N. P.; Yu, Z.; Powers, E. T.; Kelly, J. W.; Lieberman, R. L. *Biochemistry* **2011**, *50*, 10647–10657.

(24) (a) Poitout, L.; Le Merrer, Y.; Depezay, J.-C. *Tetrahedron Lett.* **1996**, *37*, 1613–1616. (b) Bagal, S. K.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Russell, A. J.; Scott, P. M.; Thompson, J. E. *Org. Lett.* **2010**, *12*, 136–139.

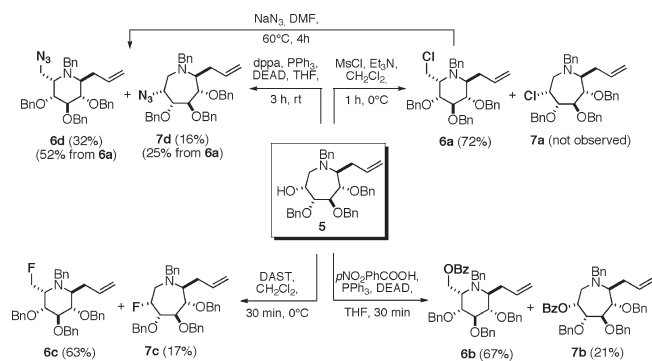
(25) In all cases azepanes **7a–d** proved to be less polar than the corresponding piperidines **6a–6d** and were isolated first by column chromatography. Their structures were unambiguously established through extensive NMR analysis.

(19) Addition of organomagnesium reagents to a related [5,6] bicyclic amina has been disclosed in a tandem ring enlargement/alkylation strategy to afford 3-aminoazepane derivatives: Cutri, S.; Bonin, M.; Micouin, L.; Husson, H.-P.; Chiaroni, A. *J. Org. Chem.* **2003**, *68*, 2645–2651.

(20) Organomagnesium halide normal addition or use of diethyl ether as solvent gave a lower yield and diastereomeric excess.

the C-6/C-7 carbons of azepane **4a**. Introduction of the more biologically relevant fluorine atom which has been considered as an isostere of an OH group<sup>26</sup> was then investigated. Skeletal rearrangement of cyclic  $\beta$ -aminoalcohols with concomitant introduction of fluorine has been extensively explored to rapidly access fluorinated piperidines and pyrrolidines of interest.<sup>27</sup> Among the various fluorinating agents, *N,N*-diethylaminosulfur trifluoride (DAST) appears as the most effective reagent to perform such reactions. When reacted with hydroxyazepane **5**, the expected fluoropiperidine **6c** (63%) was obtained as the major product with some minor azepane **7c** (17%). Finally, introduction of an azido group was investigated as it can rapidly generate compound libraries through click chemistry or reductive amination/peptide coupling starting from the corresponding amine. Treatment of **5** with diphenylphosphoryl azide (dppa)<sup>28</sup> yielded the expected azidopiperidine **6d** in modest yield (32%) along with some azidoazepane **7d** (16%). Piperidine **6d** was alternatively obtained (52%) from **6a** by azide displacement of the chlorine atom (Scheme 3).

**Scheme 3.** Ring Isomerization of Azepane **5**



L-Iminosugars are attracting increased interest from the synthetic community because, while being usually less potent glycosidase inhibitors than their D-counterparts, they demonstrate unexpected biological activities including pharmacological chaperone behavior.<sup>29</sup> In this context, **6a–d** constitute valuable precursors of new L-iminosugar C-glycosides. It can be argued that the approach developed herein is only limited to L-iminosugar C-glycosides and misses the most studied D-iminosugar C-glycosides. During the skeletal rearrangement which operates with overall retention of configuration, the L-identity of the six-membered iminosugar C-glycosides **6a–d** is imposed by the R configuration of the free 3-OH group in the azepane

(26) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308–319.

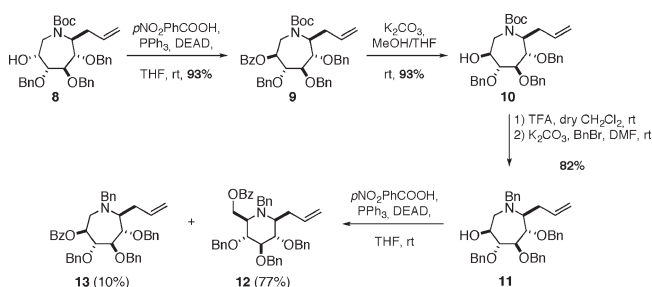
(27) (a) Deschamps, I.; Gomez Pardo, D.; Cossy, J. *Synlett* **2007**, 263–267. (b) Ferret, H.; Deschamps, I.; Gomez Pardo, D.; Van Hijfte, L.; Cossy, J. *ARKIVOC* **2010**, *8*, 126–159.

(28) Lal, B.; Pramanik, B. N.; Manhas, M. S.; Bose, A. K. *Tetrahedron Lett.* **1977**, *18*, 1977–1980.

(29) (a) D'Alonzo, D.; Guaragna, A.; Palumbo, G. *Curr. Med. Chem.* **2009**, *16*, 473–505. (b) Jenkinson, S. F.; Fleet, G. W. J.; Nash, R. J.; Koike, Y.; Adachi, I.; Yoshihara, A.; Morimoto, K.; Izumori, K.; Kato, A. *Org. Lett.* **2011**, *13*, 4064–4067.

precursor **5**. Accordingly, inversion of the 3-OH group in azepane **4** should pave the way to D-iminosugar C-glycosides via the same sequence. It requires preliminary deactivation of the endocyclic nitrogen to avoid its anchimeric assistance and the subsequent ring isomerization. To this end, **1** was converted into the N-Boc hydroxyazepane **8** (48% over 3 steps). Uneventful inversion of the free OH group under Mitsunobu conditions (PPh<sub>3</sub>, DEAD, *p*NO<sub>2</sub>PhCOOH) to afford azepane **9** followed by ester hydrolysis yielded the diastereomeric and crystalline hydroxyazepane **10** (86% yield over two steps) whose crystal structure was solved (see Supporting Information) firmly confirming the 3-OH group inversion and the C-7 allyl group configuration. Removal of the Boc protecting group with TFA followed by N-benylation under mild basic conditions furnished the N-benzyl azepane **11** (82% yield over two steps) which upon treatment under Mitsunobu conditions (*p*NO<sub>2</sub>PhCOOH, DEAD, PPh<sub>3</sub>) yielded the protected piperidine D-iminosugar C-glycoside **12** (77% yield) along with some azepane **13** (10%) (Scheme 4).

**Scheme 4.** Synthesis of D-Iminosugar C-Glycoside **12**



In conclusion, we have developed a flexible strategy to access both L- and D-iminosugar-C-glycosides from a common and easily available precursor, the 6-azido-6-deoxy-2,3,4-tri-*O*-benzyl-D-glucopyranose **1**. Our approach is based on the generation of an electrophilic [5,6] bicyclic N, O-acetal **3** and exploits the ability of  $\beta$ -hydroxyazepanes to undergo skeletal rearrangement. This methodology is powerful as it allows introduction of additional structural diversity at C-6 leading to fluoro-, chloro-, and azidopiperidines. This work highlights the synthetic potential of polyhydroxylated azepanes. Such an approach appears general and should, in principle, be applicable to other glycosides. Work in this direction is in progress.

**Acknowledgment.** N.F. thanks the CNRS and Région Poitou-Charentes for a PhD grant.

**Supporting Information Available.** Experimental procedures, characterization data, copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra, and crystallographic information file (for structure CCDC 857995). This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.