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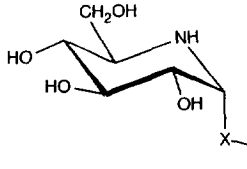
# An Efficient Synthetic Approach to Aza-*C*-glycosyl Compounds. Application to the Synthesis of an Aza-*C*-disaccharide

Olivier R. Martin,* Li Liu, and Feng Yang

Department of Chemistry, State University of New York, Binghamton, NY 13902-6016

***Summary:*** *The NIS-mediated cyclization of aminoheptenitols 5-8 (prepared in three steps from tetra-O-benzyl-D-hexopyranoses) provided 1,2,6-trideoxy-2,6-imino-l-iodoheptitol derivatives 9-12, respectively, highly stereoselectively and in high yield. The "α-D-gluco" epimer 9 was used in the synthesis of a precursor of an aza-C-disaccharide and its reaction with triethyl phosphite was investigated.*

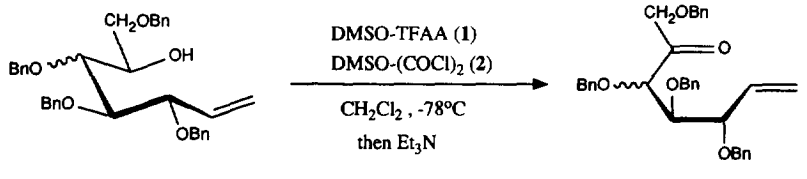
As a result of their remarkable biological activity, most prominently as glycosidase inhibitors, azasugars[1] are growing into one of the most significant class of carbohydrate mimetics. However, the lability of the O/N-acetal function[2] under hydrolytic conditions constitutes a serious limitation in azasugar chemistry and free "aza-glycosides" (i.e. compounds of type **I**) remain elusive species.[3] One possible means of generating such interesting analogs of complex glycosides consists in replacing the exocyclic oxygen atom of the O/N-acetal by a methylene group, thus forming "aza-*C*-glycosyl" compounds (i.e., compounds of type **II**). While various types of piperidine azasugars *C*-substituted at C-1 have been prepared,[4,5] only one example of an aza-*C*-analog of a complex glycoside has been reported so far, namely the aza-*C*-analog of D-Man-β-(1→6)-D-Gal.[6]




**I** X=O
**II** X=$CH_2$

As part of our continuing studies on aza-*C*-glycosyl compounds,[4,7] we found that aminoheptenitols such as **5** can be cyclized efficiently and highly stereoselectively using NIS, thus providing versatile intermediates en route to aza-*C*-analogs of complex glycosides. As an example, we describe the utilization of the α-D-*gluco* epimer **9** in the synthesis of a precursor of an aza-*C*-disaccharide. We also report the unexpected behavior of **9** on reaction with triethyl phosphite.

Oxidation of heptenitols **1**[8] and **2**,[9] readily available from tetra-*O*-benzyl D-*gluco*- and D-*galacto*-hexopyranose, respectively, afforded unsaturated hexulose derivatives **3**[5] and **4** in high yield (Scheme 1). The reduction of the oxime derived from **3** had been shown by Liu[5] to give preponderantly the corresponding D-



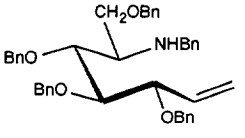
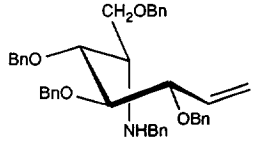
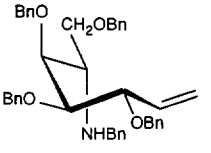
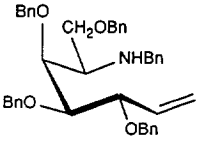

**1** (D-*gluco*)
**2** (D-*galacto*)

**Scheme 1**

**3** (L-*xylo*) (94%)
**4** (L-*lyxo*) (86%)

*gluco* aminoheptenitol; however, the separation of the resulting epimers was found to be tedious and the reported ratio of epimers difficult to reproduce. We therefore decided to investigate the introduction of nitrogen at C-6 of **1** and **2** by reductive amination as well as by other means.[7] The reaction of **3** with benzylamine/acetic acid in the presence of $NaBH_3CN$ gave D-*gluco* and L-*ido* aminoheptenitols **5**[10] and **6** in a 5:2 ratio in good yield (Table 1); a small amount of L-*altro* epimer **7** (~10%) was also isolated from the reaction mixture. All three compounds are well separable by flash chromatography on silica gel [hexane/EtOAc 9:1 containing $Et_3N$ (1%, *v/v*)]. Under the same conditions, heptulose **4** afforded L-*altro* and D-*galacto* epimers **7** and **8** in excellent yield (ratio ~2:1).

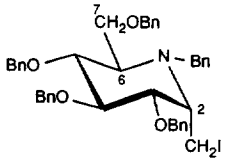
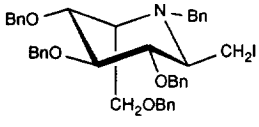
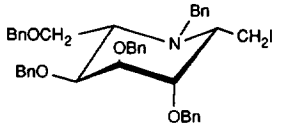
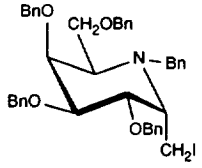
Table 1. Reductive Amination of Ketones 3 and 4[a]

| Ketone | Products, yields | | |
|---|---|---|---|
| **3** |  |  | + **7** (10%) |
| | **5** (D-*gluco*), 50% | **6** (L-*ido*), 20% | |
| **4** |  |  | |
| | **7** (L-*altro*), 59% | **8** (D-*galacto*), 31% | |

[a] Conditions: $BnNH_2$/HOAc(20 eq), $CH_3OH$, r.t., 2h, then $NaBH_3CN$ (20 eq), reflux, 4h

The cyclization of unsaturated amino- and amidoalditols related to **5-8** has been promoted usually by mercury(II) salts.[4b,5,11] However, we obtained better results in the case of **5-8** using NIS as the source of electrophile: all four aminoheptenitols underwent cyclization in high yield and with a very high degree of stereoselectivity,[12] thus providing the corresponding 1,2,6-trideoxy-2,6-imino-1-iodoheptitol derivatives **9-12** (Table 2). The NIS-promoted process is thus much more stereoselective than the mercury-mediated cyclization of related amino alkenes.[4b,11] Compounds **5**, **7**, and **8** gave the products having the anticipated 2,3-*cis* configuration, as dictated by the configuration at C-3 (allylic carbon) of the starting heptenitol.[13] The formation of the 2,3-*trans* epimer **10** from **6** (L-*ido*) is, however, exceptional: steric interactions between incipient *syn*-diaxial substituents probably destabilize the intermediate leading to the 2,3-*cis* isomer in either

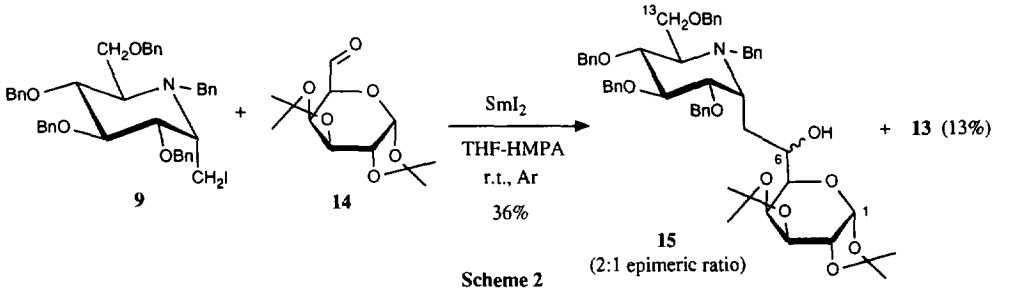
Table 2. Cyclization of Aminoheptenitols 5–8 [a]

| **5** | **6** | **7** | **8** |
|---|---|---|---|
| **Products** | | | |
|  |  |  |  |
| **9** (α-D-*gluco*), 80% | **10** (α-L-*ido*), 80% | **11** (β-L-*altro*), 90% | **12** (α-D-*galacto*), 69% |

[a] Conditions: NIS (1 equiv.), $CH_2Cl_2$, r.t., 3 h

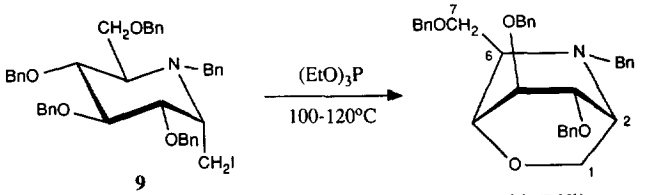
chair conformation. The stereochemistry of compounds **10-12** was established unambiguously from their NMR parameters[14] and that of **9** from the parameters of its deiodinated analog **13**.[15]

Compound **9**,[16] a key precursor of aza-*C*-glycosyl compounds having the α-D-gluco configuration, is now accessible in four steps only (35-40% overall yield) from tetra-*O*-benzyl-D-glucopyranose. The conversion of **9** into an organometallic species followed by reaction with an *aldehydo*- or *keto*-sugar should provide a convenient and concise approach to aza-*C*-disaccharides. While this was not feasible using the alkyllithium derived from **9**, the reaction of **9** with $SmI_2$ and *aldehydo*-sugar **14** under samarium Barbier conditions[17,18] afforded the desired coupling product **15**[19] as a mixture of easily separable stereoisomers (2:1 ratio) in 36% yield [yield of isolated product based on consumed **9** (~50%)]. This product is an immediate precursor of the aza-*C*-analog of D-Glc-α-(1→6)-D-Gal; further elaboration of **15** into a free aza-*C*-disaccharide is in progress.




Scheme 2

By analogy with the corresponding pyranoid bromomethyl *C*-glycoside,[20] compound **9** was thought to constitute an excellent precursor of the phosphonate that would mimic a glycosyl phosphate. The reaction of **9** with triethyl phosphite gave, however, the unusual 1,5-anhydro-2,6-dideoxy-2,6-iminoheptitol derivative **16**[21] as the only product. Compound **16** results from the participation of the benzyloxy group at C-5 of **9** as an internal nucleophile, with concommitant debenzylation.[9] This behavior contrasts with that of the




Scheme 3

analog pyranoid substrate which undergoes exclusively the Michaelis-Arbuzov reaction under the same conditions.[20] The different outcome from **9** can be attributed to the formation of an intermediate aziridinium cation, by internal displacement of the iodine atom by nitrogen, which decreases the reactivity of the C-1 center toward the soft phosphorous nucleophile.

The oxidation/reductive amination/NIS-mediated cyclization sequence thus constitutes an efficient protocol for the conversion of heptenitols into functionalized aza-*C*-glycosyl compounds; these compounds constitute versatile precursors of novel types of carbohydrate mimetics of considerable biological significance.

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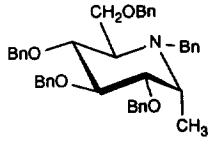
14. Selected $^1$H NMR data (360 MHz, $CDCl_3$): **10**, δ 2.53 (dt, $J_{2,3}$ 8.9, H-2), 3.18 (td, H-6), 3.48 (t, $J_{3,4}$ 8.7, H-3), 3.60 (dd, $J_{5,6}$ 5.7, H-5), 3.95 (t, $J_{4,5}$ ~8.6, H-4). **11**, δ 3.30 (m, H-6), ~3.45 (m, $J_{2,3}$ 3.5, H-2), 3.73 (dd, $J_{4,5}$ 2.8, H-4), 3.95 (dd, $J_{5,6}$ 6.5, H-5), 4.13 (dd, $J_{3,4}$ 6.6, H-3). **12** (Toluene-$d_8$, 344°K), δ ~3.2 (m, H-6), 3.48 (td, $J_{2,3}$ 3.6, H-2), 3.60 (dd, $J_{4,5}$ 2.9, H-4), 4.10 (t, $J_{5,6}$ 3.3, H-5), 4.12 (dd, $J_{3,4}$ 7.4, H-3).
15.  **13** Obtained as one of the products of the reaction of **9** with BuLi and **14**. Selected $^1$H NMR data ($CDCl_3$): δ 2.93 (ddd, H-6), 3.13 (~quintet, $J_{2,3}$ 5.2, H-2), 3.60 (dd, $J_{3,4}$ 9.5, H-3), 3.61 (t, $J_{5,6}$ 9.5, H-5), 3.76 (t, $J_{4,5}$ 9.5, H-4).
16. Selected data: $[\alpha]_D^{18}$ + 46.7° (*c* 3.6, $CHCl_3$); FAB-MS: 754 ($[M+H]^+$, 35%), 632 ($[M-BnOCH_2]^+$, 100%).
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19. Selected data (major epimer): $[\alpha]_D^{20}$ – 17.5° (*c* 1.4, $CHCl_3$); FAB-MS: 892 ($[M + Li]^+$, 100%).
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21. The long-range H-C COSY spectrum of **16** definitely established that the benzyl group at O-5 in the starting material was absent in **16**. Further evidence for the bicyclic structure of **16** was provided by the existence of long-range couplings ($^4J_{4,6}$, $^4J_{1pro\text{-}S,3}$).


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