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Site-Selective Debenzylation of *C*-Allyl Iminosugars Enables Their Stereocontroled Structure Diversification at the C-2 Position

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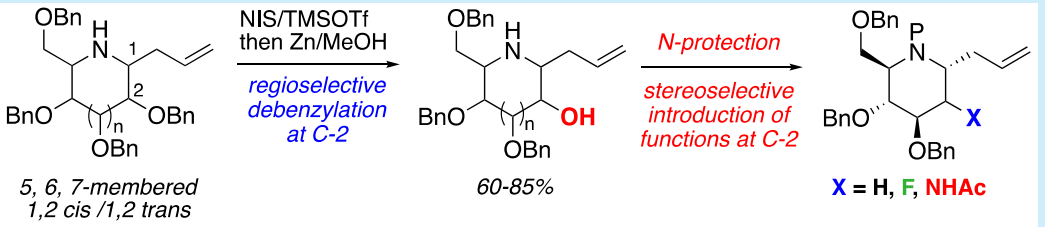
Supporting Information



ABSTRACT: A C-2 regioselective debenzylative cycloetherification/reductive elimination sequence applied to perbenzylated *C*-allyl iminosugars is described. This NIS/TMSOTf-triggered deprotection was successfully applied to five-, six-, and seven-membered *C*-allyl iminosugars including 1,2 cis and 1,2 trans stereoisomers. It allows rapid introduction of structural diversity at the key C-2 position in a stereoselective manner exploiting the anchimeric assistance of the intracyclic *N*-benzyl group, giving access to the 2-acetamido and 2-fluoro D-gluco configured *C*-allyl iminosugars and to the epimeric D-manno derivative.

Glycomimetics are gaining increased interest because they offer the possibility of emulating carbohydrate activities while circumventing their drawbacks as drug candidates. One of the current challenges associated with glycomimetics is the development of efficient methods to extend their structural diversity in order to accelerate the discovery of biologically relevant molecules.[1] *C*-Allyl iminosugars, sugar analogues in which the endocyclic oxygen has been replaced by nitrogen and that possess a stereodefined pseudoanomeric allylic appendage, have demonstrated synthetic potential as precursors of iminosugar C-glycosides, a class of potent glycosidase inhibitors.[2] They have contributed to the expansion of the chemical space of iminosugars through the generation of iminoglycoconjugates by coupling aglycons of various structures to the terminal alkene.[3,4] They have also been exploited to elaborate bicyclic natural products.[5] Their potential could be further increased if functional diversity could be rapidly introduced at the crucial C-2 position, allowing them to target other types of glycosidases and glycosyltransferases. One strategy to perform this structural modification includes a regioselective deprotection of the hydroxyl group at C-2 and its subsequent conversion into another function. Among carbohydrate protecting groups, the benzyl ether is very popular because of its ease of installation, its stability to a wide range of reaction conditions, and its removal under mild conditions.[6] A vast array of procedures have been reported for the regioselective *O*-debenzylation of highly benzylated carbohydrates. Most of them exploit either Lewis acids such as $SnCl_4$ or $TiCl_4$,[7] alanes (DIBAL, TIBAL),[8] or BCl_3[9] and usually take advantage of a functional group close to the benzyl ether to be deprotected to guide the regioselectivity.[10] It is noteworthy that the regioselective *O*-debenzylation of polybenzylated iminosugars is scarce.[11−13] In the 1990s, the group of Nicotra reported an elegant regioselective deprotection of the benzyl group at the C-2 position of *C*-allyl glucopyranosides using I_2.[14] In this transformation, the alkene is converted into a iodonium ion opened by the adjacent benzyl ether via a 5-exo-type cyclization with subsequent loss of the benzyl cation to afford an iodocycloether.[15] Its reductive elimination restores the double bond and generates a free hydroxyl group at the C-2 position, the entire process resulting in a regioselective O-2 debenzylation (Scheme 1A). Interestingly, this group also investigated the debenzylative cycloetherification of a D-gluco-configured α-*C*-allyl iminosugar with *N*-iodosuccinimide (NIS). The corresponding bicyclic iodocycloether **A** was obtained in 42% yield along with the competitive formation of the azetidinium ion **B** detected by mass spectrometry involving the *N*-benzyl group (Scheme 1B). To the best of our knowledge, iodocycloether **A** was not further processed to the reductive elimination step.[16,17] We propose that, if this C-2 regioselective O-debenzylation is successful and general in the *C*-allyl iminosugar series, it would pave the way to the introduction of structural diversity at C-2 position of this important class of iminosugars. Herein, we studied the

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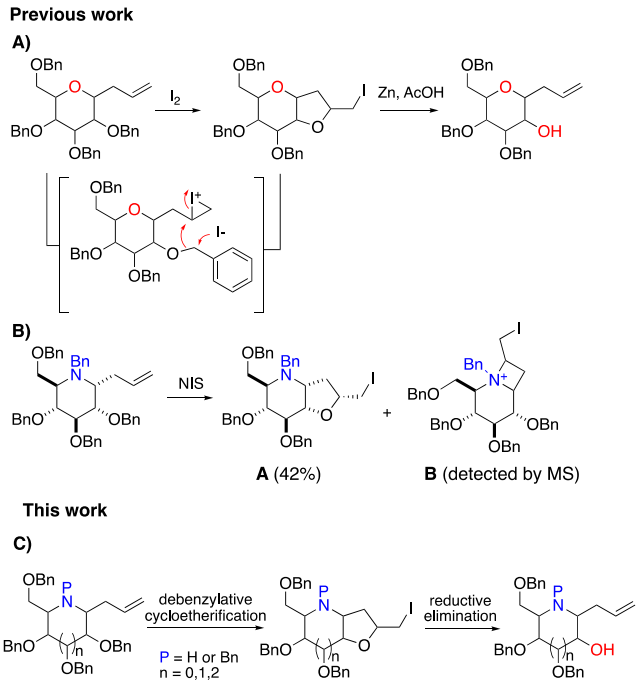
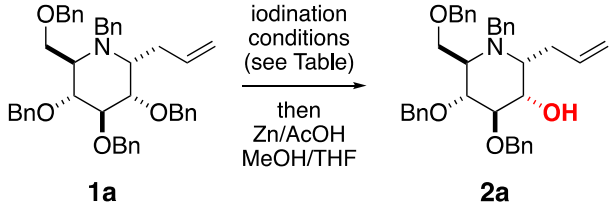
Scheme 1. State of the Art Regarding Regioselective Debenzylation of C-Allyl Glycosides and Iminosugars



relevance of this debenzylative cycloetherification/reductive elimination sequence in the context of *C*-allyl iminosugars to possibly deliver new *C*-allyl iminosugars with various configurations, ring sizes, and functional groups at C-2 (Scheme 1C).

To this end, several iodination reagents including NIS, I_2 and iodonium dicollidone perchlorate (IDCP)[18] were screened to perform the iodocycloetherification on the known D-gluco-configured *α*-C-allyl iminosugar **1a**[16] (Table 1). IDCP furnished the 2-O-deprotected iminosugar **2a** in 33% yield after reductive elimination of **A** with Zn/AcOH (entry 1). NIS proved a little bit better and provided **2a** in 41% yield (250 mg scale, entry 2), but performing the reaction on a gram scale significantly reduced the yield (20%, entry 3). Treatment of **1a** with I_2 on a milligram scale led to a similar 41% yield (entry 4), while performing the reaction on a 5 g scale increased the yield to 48% (entry 5). A procedure using a NIS/TMSOTf combination in acetonitrile[19] was also explored. Use of 2 equiv of each reagent at room temperature furnished a reasonable 48% yield of **2a** whatever the scale (entries 6 and 7). In order to evaluate the scope of this reaction, the two best conditions, namely I_2 and NIS/TMSOTf, were applied to a series of eight known and new perbenzylated *C*-allyl iminosugars **1b–i** usually obtained in five to eight steps using standard procedures.

Table 1. Debenzylative Cycloetherification/Reductive Elimination of 1a



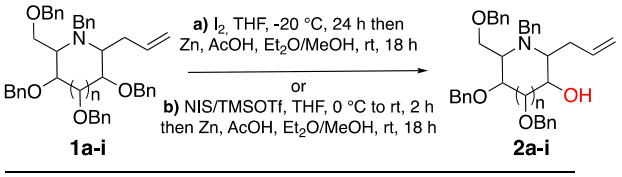
1a **2a**

entry	iodinating agent	scale	temp (°C)	yield of **2a** (%)
1	IDCP[a]	80 mg	rt	33
2	NIS[b]	250 mg	−10	41
3	NIS[b]	1.2 g	−10	20
4	I_2[c]	60 mg	−20	41
5	I_2[c]	5 g	−20	47
6	NIS/TMSOTf[d]	50 mg	0 to rt	49
7	NIS/TMSOTf[d]	2 g	0 to rt	48

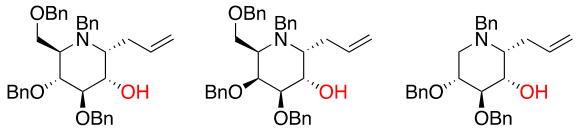
[a]IDCP (5 equiv), THF, 0 °C to rt, 4 h. [b]NIS (10 equiv), THF, −10 °C to rt, 2 h. [c]I_2 (2 equiv), THF, −20 °C, 24 h. [d]NIS (2 equiv), TMSOTf (2 equiv), CH_3CN, 0 °C to rt, 2 h.

The iodine-mediated debenzylative cycloetherification followed by reductive elimination was first applied to the panel of *C*-allyl iminosugars (Scheme 2). The 1,2-cis D-galacto **1b**,[20] D-xylo **1c**,[21] and L-ido **1d**[22] configured piperidines prepared according to literature procedures furnished the expected 2-hydroxy iminosugars **2b–d** albeit in modest yield (2–25%) compared to **1a**. Because the I_2-mediated debenzylation also works with the 1,2-trans *C*-allyl glucoside,[14] the 1,2-trans piperidines **1e** and **1f** and azepane **1g** were prepared (see the SI) and tested. Unfortunately, the corresponding 2-hydroxy derivatives **2e–g** could not be isolated when using these reaction conditions. A similar result was obtained with the

Scheme 2. Regioselective Deprotection of Perbenzylated C-Allyl Iminosugars 1a–i



1a-i **2a-i**

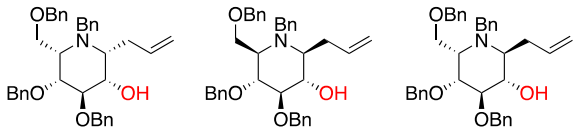


2a **2b** **2c**

cond. a: 48%
cond. b: 49%

cond. a: 25%
cond. b: 25%

cond. a: 2%
cond. b: 25%

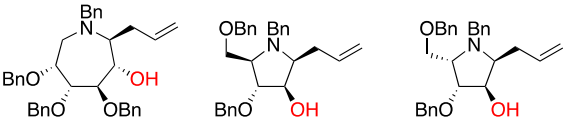


2d **2e** **2f**

cond. a: 0%
cond. b: 21%

cond. a: 0%
cond. b: 27%

cond. a: 0%
cond. b: 43%



2g **2h** **2i**

cond. a: 0%
cond. b: 30%

cond. a: 0%
cond. b: 23%

cond. a: 0%
cond. b: 27%

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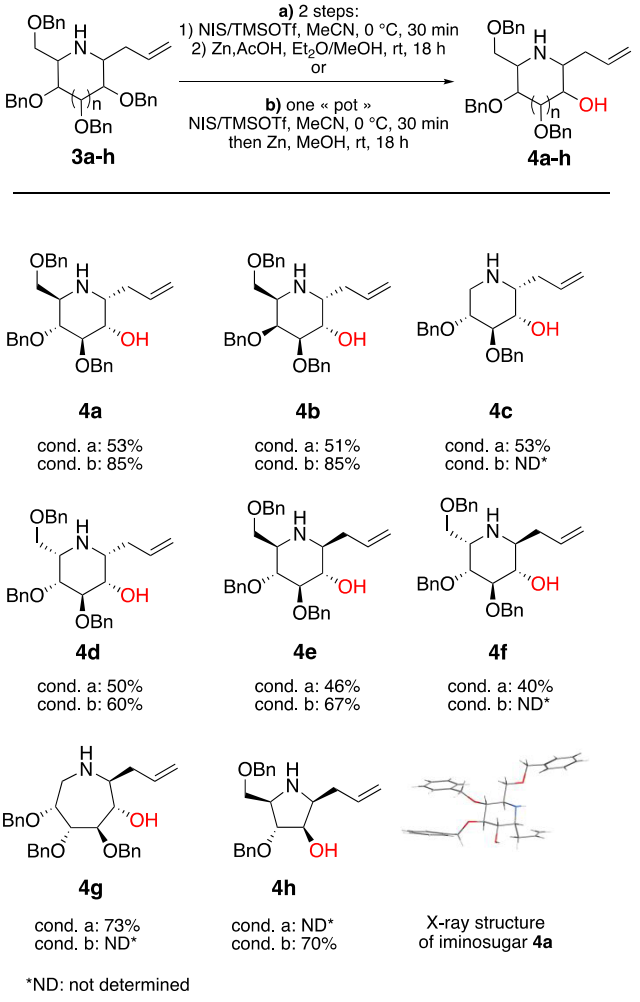
known[23] *C*-allyl pyrrolidines **1h** and **1i**, while the corresponding C-allyl furanosides have been reported to undergo efficient cycloetherification.[24] Overall, this debenzylation method appeared disappointing both in terms of yield and scope. Interestingly, during the iodination step, all of the starting *C*-allyl iminosugars **1a−i** were fully consumed according to TLC monitoring, but significant (20−30%) amounts were recovered after Zn/AcOH treatment. This result can be linked to the competititve formation of a transient azetidinium ion intermediate **B** arising from trapping of the iodonium ion by the *N*-benzyl group (Scheme 1) that reverses to the starting *C*-allyl iminosugar **1a** after Zn/AcOH treatment. This phenomenon is probably operative in all cases to a different degree. Accordingly, we expected that using the more acidic NIS/TMSOTf conditions could minimize this competing reaction through deactivation the *N*-benzyl group. When applied to the perbenzylated *C*-allyl iminosugars **1b−i**, these conditions furnished the expected C-2 deprotected derivatives **2b−i** in slightly higher (21−43%) yields. Although this second method proved general, the observed yields do not compete with the ones reported for the regioselective deprotection of *C*-allyl glycosides, pointing to the detrimental influence of the *N*-benzyl group in this transformation.

Looking for alternative *N*-protecting groups, it has been shown that benzyl carbamate is not suitable because it cyclizes onto the iodonium species leading to bicyclic products.[25] Furthermore, installation of a deactivating $COCF_3$ group on the ring nitrogen gave complex mixtures under various iodocycloetherification conditions. These data forced us to apply the NIS/TMSOTf-mediated debenzylative cycloetherification/reductive elimination sequence directly on the NH-free *C*-allyl iminosugars **3a−h** that are easily prepared following literature procedures (see the SI) (Scheme 3). Satisfyingly, the deprotection was also regioselective and general in this case, affording the corresponding 2-hydroxy compounds **4a−h** in improved 40−73% yield, the structure of **4a** being confirmed by X-ray crystallography. The good 73% yield observed for the deprotection of azepane **3g** compared to polyhydroxylated pyrrolidines and piperidines can be tentatively explained by the higher ring flexibility of this seven-membered iminosugar,[26] which reduces the entropic penalty to pay to form the intermediate bicyclic iodocycloether.

In order to improve the overall yield of this transformation, as the Zn-mediated reductive elimination step requires a protic solvent, we postulated that simple addition of MeOH and Zn to the reaction mixture resulting from the cycloetherification step might also achieve the reductive elimination. This one-pot procedure would avoid the use of AcOH and the workup of the sensitive iodocycloether that probably account for the moderate yield obtained so far for the two-step procedure. Indeed, this procedure applied to *C*-allyl iminosugars **3a**,**b**, **3d**,**e**, and **3h** significantly increased the overall yield of this deprotection, providing the α-D-gluco- and α-D-galacto-configured piperidines **4a** and **4b** in 85% yield. With these 2-hydroxy-*C*-allyl iminosugars in hand, we then explored the introduction of structural diversity at C-2 position focusing on the α-D-gluco-configured iminosugar **2a** (Scheme 4) that was now obtained in good yield from **4a**. Fluorine is becoming more and more important in glycochemistry because of its inherent properties,[27] and an increasing number of iminosugars incorporating fluorine atoms have been reported, leading sometimes to improved glycosidase inhibition properties.[28] Introduction of fluorine was examined using DAST,[29] affording

Scheme 3. Regioselective Deprotection of Per-*O*-benzylated C-Allyl Iminosugars 3a−h and Crystallographic Structure of Iminosugar 4a



the corresponding D-gluco-configured 2-fluoropiperidine **5a** (47%) with retention of configuration at C-2, thanks to the anchimeric assistance of the *N*-benzyl group. The related fluorinated pyrrolidine **5b** (21%) resulting from attack at the methine carbon of the transient fused pyrrolidine−aziridinium ion intermediate was also isolated. Introduction of an acetamido group at C-2 position was studied next. It is of significant interest as it would constitute an entry to unprecedented 2-acetamido *C*-allyl D-iminosugars, useful precursors to access iminoglycoconjugates GlcNAc mimetics that might demonstrate high biological potential as hexosaminidase inhibitors.[30−34] Preliminary data showed the product resulting from azidation (diphenyl phosphoryl azide (dppa), PPh_3, DIAD) rapidly decomposed, probably via 1,3 dipolar adducts, as previously observed in the case of the pyranose counterpart.[35] Therefore, iminosugar **2a** was converted into its 2-azido derivative, and the crude mixture was rapidly treated with $Zn/Ac_2O/AcOH$[36] to afford the separable D-gluco-configured five- and six-membered acetamido *C*-allyl iminosugars **6b** (23%) and **6a** (23%). In parallel, the free secondary OH in **2a** was also deoxygenated via xanthate ester formation followed by treatment with tributyltin hydride and AIBN[38] to afford the α-*C*-allyl fagomine derivative[37] **7** in 44% yield over two steps. Finally, the free 2-OH in **2a** was exploited to invert

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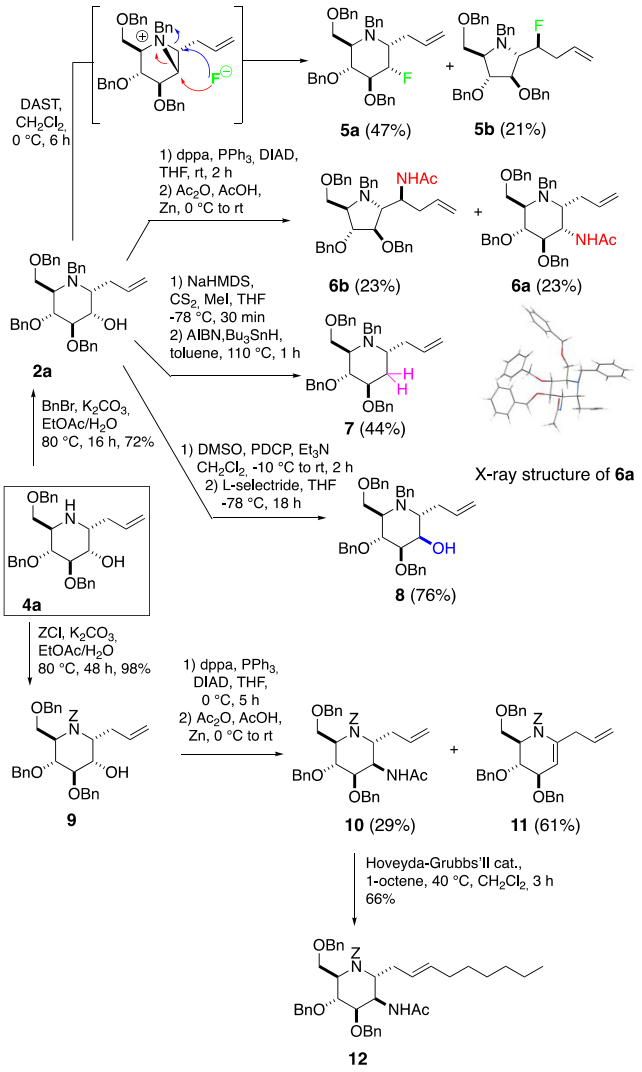
Scheme 4. Synthesis of 2-Acetamido, 2-Deoxy, 2-Fluoro, and 2-Epimeric α-C-Allyl Iminosugars



the stereochemistry at C-2 and access the epimeric D-manno-configured α-C-allyl iminosugar **8**. Oxidation of **2a** with phenyl dichlorophosphate (PDCP)[39] followed by reduction with L-Selectride produced the piperidine **8** in 70% yield. To avoid ring contraction during the substitution step associated with the *N*-benzyl group, piperidine **4a** was protected as its benzyl carbamate **9**. Its azide displacement with dppa, PPh_3, and DIAD followed by reduction with Zn in the presence of Ac_2O furnished a separable mixture of the D-manno-configured 2-acetamidopiperidine **10** (29%) and of the iminoglycal **11** (61%). Compound **10** constitutes a useful precursor to access D-ManNAc-configured iminoglycoconjugates, and its cross-metathesis with 1-octene using Hoveyda–Grubbs II catalyst in CH_2Cl_2 uneventfully furnished the corresponding olefin **12** (Scheme 4).

In conclusion, we have developed a regioselective C-2 debenzylative cycloetherification[40] that has been applied to a range of five-, six-, and seven-membered perbenzylated C-allyl iminosugars. This reaction has paved the way to the stereoselective introduction of functional groups at the C-2 position allowing the synthesis of unprecedented 2-fluoro and 2-acetamido-C-allyl iminosugars. These synthons should be useful for accessing new iminosugars of biological interest through conjugation and deprotection.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01712.

Experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for compounds **1**–**12** (PDF)

Accession Codes

CCDC 1908031–1908032 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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