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Stereospecific Access to α- and β-*N*-Glycosylamine Derivatives by a Metal Free *O*-to-*N* [3,3]-Sigmatropic Rearrangement

Debora Pratesi,[a] Stefania Mirabella,[a] Giulia Petrucci,[a] Camilla Matassini,[a] Cristina Faggi,[a] Francesca Cardona,[a] and Andrea Goti*[a]

Glycosylamine derivatives are biologically relevant compounds widespread in Nature, but the synthesis of this motif has been little addressed and its access with control of configuration at the anomeric carbon is challenging. Glycals substituted at C-3 with a carbamate group undergo, upon dehydration, a prompt allyl cyanate to isocyanate rearrangement to the isomeric *N*-glycosyl isocyanates, which can be conveniently trapped by one-pot nucleophilic addition with alcohols or amines to afford *N*-glycosyl carbamates and ureas, respectively. The rearrangement follows a [3,3]-sigmatropic pericyclic mechanism as illustrated by the stereospecificity of the reaction, with nitrogen being delivered at the anomeric position to the same face from which the oxygen at C-3 has departed. Thus, glucal and galactal give β-*N*-glycosides exclusively while allal furnishes α-*N*-glycosides. *cis*-Dihydroxylation of the synthesized unsaturated *N*-glycosides afford different 1-aminosugars with good selectivity.

Introduction

Glycosylamines (also referred to as 1-aminosugars or *N*-glycosides) and their derivatives are widespread in Nature.[1] The β-glycosylamino anomers are more common, as in *N*-linked glycopeptides and glycoproteins **1**[1] and several natural *N*-glycosides, *e.g.*, in the glycocinnamoylspermidine antibiotics **2** (Figure 1).[2] However, examples of α-glycosylamino derivatives are also known, such as in the trehalase inhibitor trehazoline **3**[3] and even in rare glycopeptides, *e.g.*, in nephritogenoside **4**, a α-*N*-glucosyl linked to a twenty-one amino acid peptide isolated from the glomerular basement membrane of normal rats which induces glomerulonephritis in experimental animals.[4]

Glycosylamines can be accessed directly from carbohydrates and amines by condensation at the anomeric position,[5] which generates imines that undergo a ring-chain tautomeric equilibrium, usually biased to give the more thermodynamically stable cyclic 1-aminosugars, *i.e.*, the β-glycosylamines for the most common glucose or galactose derivatives. For example, such a condensation reaction is involved in the initial step of the outstanding "Maillard reaction" of simple carbohydrates with amino acid residues in proteins, responsible for the browning/flavoring of food well appreciated in cuisine. As demonstrated in this complex process, the formed glycosylamines may undergo a series of transformations with partial degradation which initiate via Amadori-type rearrangements of their open-chain imine tautomers.[6]

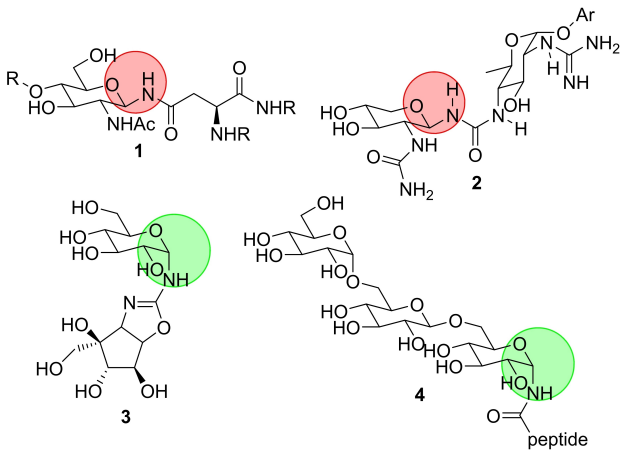

Figure 1. Representative β- (red) and α- (green) *N*-glycosylamine derivatives.

Relevant synthetic glycosylamines have been achieved for addressing biological and medicinal issues[1d,7] and for applications in enantioselective synthesis as chiral auxiliaries.[8]

As opposed to simple glycosylamines, their protected carbonyl derivatives (amides, carbamates, ureas) appear to be stable, not only to subsequent transformations, but also from the point of view of configurational stability. In order to access anomerically pure α- and β-glycosylamine derivatives it is then of paramount importance to utilize procedures that allow to install configurationally stable nitrogen functional groups directly and with a high degree of stereocontrol at the anomeric

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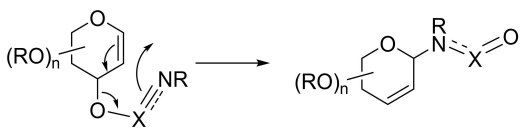
position. Albeit the synthesis of *N*-glycosides has been much less investigated with respect to *O*- and *C*-glycosides, substantial work has been devoted to this aim,[5,9] but most procedures afforded anomeric mixtures. Therefore, the development of new methodologies able to produce anomerically pure *N*-glycosides is still desirable and challenging. Several methods have been established which allow to access β-glycosylamine derivatives stereoselectively,[10] while only few procedures for obtaining α-anomers have been reported. Bernardi conceived a traceless Staudinger ligation for generating α-*N*-glycosylamides by intramolecularly trapping the intermediate from α-glucosyl azides.[11] Nicolaou developed simple procedures for synthesizing either α- or β-glycosylamine derivatives with high selectivity employing the Burgess reagent.[12] Glycals,[13] readily accessible from inexpensive carbohydrates, have also been used as suitable substrates for installing a nitrogen substituent at the anomeric position.[9c,14] Reddy reported a successful aza-Ferrier rearrangement to give C-1 amidation of glucals, but with modest α-selectivity (1:1 to 3:1).[15] Nguyen found that a Pd-catalyzed rearrangement allows to access *N*-glycosyl trichloroacetamides with high α- or β-selectivity, depending on the ligand used.[16,17] Successively, the same group has reported the synthesis of α-glycosyl ureas from simple glycosyl trichloroacetimidates by means of a highly α-selective (up to 11:1) Ni-catalyzed 1,3-rearrangement to intermediate *N*-glycosyl trichloroacetamides.[18]

In this connection, we envisaged that a thermal, metal-free [3,3]-sigmatropic rearrangement occurring via a pericyclic mechanism would allow to generate stereospecifically β- or α-*N*-glycosylamine derivatives starting from the appropriate glycal precursor, according to its configuration at C-3. A conceptually similar strategy has proven successful in the stereoselective synthesis of *C*-glycosides utilizing Claisen rearrangements and has been applied extensively by Fairbanks and co-workers.[19] In order to achieve our aim, a [3-3]-rearrangement suitable to transform allyl alcohol derivatives into allyl amine ones was necessary (Scheme 1).

Three thermal processes have been reported for accomplishing a *O*-to-*N* allyl [3,3]-sigmatropic rearrangement:[20] i) the Ichikawa cyanate to isocyanate (R = lone pair, X=C, C≡N);[21] ii) the Overman trichloroacetimidate to acetamide (R=H, X=C–CCl_3);[22] and iii) the Mapp phosphorimidate to phosphoramidate (R = protecting group, X=P(OR′)$_2$) one.[23,24] The first two processes have been seldom applied for the synthesis of aminosugars from unsaturated carbohydrates,[25,26] but never for accessing glycosylamines,[27] despite the broad variety of glycals available. We were particularly attracted by the Ichikawa rearrangement for the following reasons: ready access to the required stable and manageable carbamate precursors, occurrence of the spontaneous sigmatropic rearrangement at low temperature due to the instability of allyl cyanates with respect to their allyl isocyanate isomers,[28] versatility of the resulting isocyanates for accessing several functional groups by reacting with different nucleophiles. Moreover, both α- and β-glycosyl isocyanates, obtained as intermediates for the synthesis of glycosyl ureas by oxidation of the corresponding isocyanides, have been shown to be configurationally stable.[29] Therefore, if accessed stereospecifically by the proposed [3,3]-sigmatropic rearrangement, they are expected to furnish *N*-glycosyl derivatives with complete α- or β-selectivity.

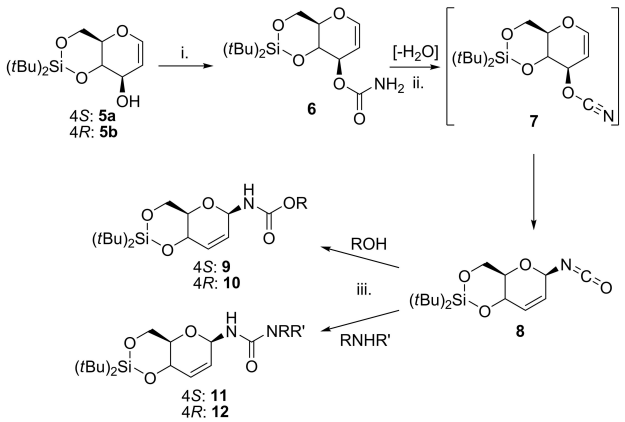
In a preliminary communication we have reported the successful obtainment of β-*N*-glycosyl carbamates and ureas by applying this concept to proper glucal and galactal precursors.[30,31] In the current report, besides reporting full details and the dihydroxylation of selected products to give rare 1-aminocarbohydrates, we demonstrate the feasibility of the process for accessing α-*N*-glycosyl derivatives with complete stereoselectivity starting from an allal precursor, thus giving strong support to the pericyclic mechanism of these reactions.



Scheme 1. The key [3,3]-sigmatropic process conceived for the synthesis of α- and β-glycosylamine derivatives.

Results and Discussion

As reported in our preliminary communication,[30] the process was initially studied with the readily available D-glucal **5a**[32] (Scheme 2). The most appropriate precursors of the allyl cyanates **7** required for the rearrangement are the carbamates **6**, which are obtained quantitatively from the corresponding glycals **5**[32] by reacting with trichloroacetyl isocyanate followed by basic treatment.[33] The key and critical step of the allyl cyanate to isocyanate rearrangement consists in the dehydration of carbamates to the corresponding allyl cyanates, which is often tricky and is probably the reason that hampered a more



Scheme 2. The whole process for the synthesis of glycosylamine derivatives from glycals **5** via carbamates **6** and their allyl cyanate-to isocyanate [3,3]-sigmatropic rearrangement. Reaction conditions: i. $Cl_3CCONCO$, CH_2Cl_2, 35 min, 0 °C to rt, then K_2CO_3, MeOH, 3 h, 0 °C to rt; ii. TFAA (2 equiv), NEt_3 (6 equiv), THF, 0 °C, 35 min, then ROH or RNHR′ (3 equiv). The alcohols and amines used as nucleophiles are detailed in Scheme 3.

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extensive use of this useful process in organic synthesis.[34] The two procedures more successful for accomplishing this dehydration employed Appel type conditions (CBr_4, PPh_3, NEt_3, CH_2Cl_2) and trifluoroacetic anhydride (or trifluoromethanesulfonic anhydride) with a tertiary amine.[21,34] While the former procedure was unsatisfactory in our case for generating isocyanates **8** and led to extensive decomposition and formation of complex reaction mixtures, the latter one proved to afford the elusive cyanates **7**[28] successfully. As usual, these intermediates rearranged immediately to the isomeric isocyanates **8**, in turn trapped conveniently in a one-pot process with *O*- or *N*-nucleophiles to furnish glycosyl carbamates **9** and **10** and ureas **11** and **12** (Scheme 2). After extensive optimization, the reaction conditions reported in Scheme 2 were selected for the three steps (formation of carbamate, dehydration to allyl cyanate which undergoes spontaneous rearrangement to allyl isocyanate, addition of nucleophile to transform the isocyanate to stable glycosyl carbamates or ureas).

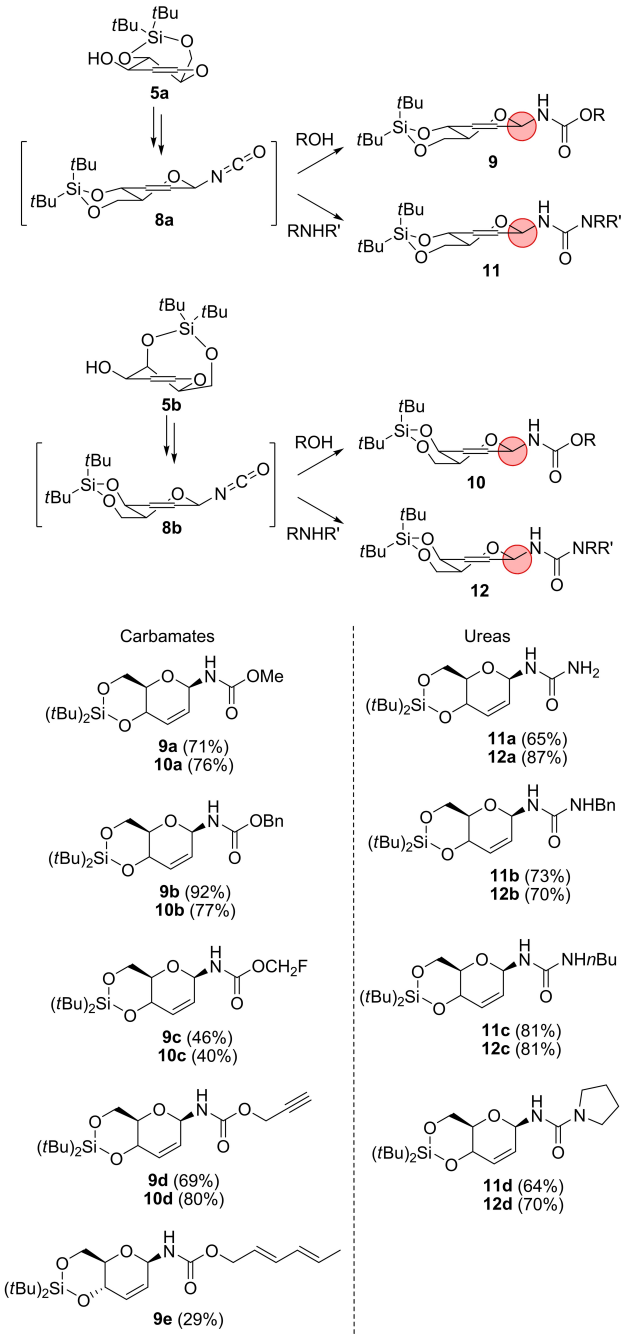
As anticipated, the process furnished the β-*N*-glycosylamine derivatives exclusively either starting from D-glucal **5a** or D-galactal **5b**, affording respectively the glycosyl carbamates **9** and **10** with alcohols as nucleophiles and the glycosyl ureas **11** and **12** with amines (Scheme 3). All compounds were obtained with satisfactory yields for a 3-step sequence, except than for bulkier nucleophiles which furnished the desired glycosylamine derivatives in more moderate amount. It is worth noting that carbamates **9**, **10a–c**, bearing groups broadly utilized for protecting amines and suitable to be removed under various conditions such as Moc, Cbz and Fmoc, are easily accessible.

Formation of β-*N*-glycosides was proved by an X-ray structural determination of compound **10b** (Figure 2). Moreover, this assignment was confirmed by structural studies (vide infra) of 1-aminosugars obtained by dihydroxylation of **9a** and **10a** (nOe experiments) and **11b** (X-ray crystallography determination).

The observed complete β-selectivity in the formation of glycosylamines **9–12** from glucal **5a** and galactal **5b** is consistent with a synchronous pericyclic mechanism for the rearrangement with the cyanate migrating from C-3 to C-1 of the carbohydrate at the upper face. However, considering the higher stability and easier formation of 1-aminocarbonyl derivatives of glucose and galactose, an alternative stepwise process could not be completely ruled out. In order to prove the pericyclic mechanism and, more importantly, to demonstrate that the α-*N*-glycosyl anomers are equally easily and stereosepecifically accessible, a glycal possessing the opposite configuration at C-3 was necessary. Suitably protected D-allal **13** was then synthesized starting from commercial glucose diacetonide and inverting the configuration at C-3 utilizing a slight modification of the reported procedure.[19,35] The optimal reaction conditions identified for the glucal carbamate **6a** worked equally well with the allal carbamate **14**, as testified by the preparation of α-*N*-glycosyl carbamates **17** and ureas **18** in good yields (Scheme 4).

According to our expectation, only the α-anomers were formed from allal **13**. Indeed, products **17a–c** and **18a–c** showed ^{1}H NMR spectra very similar to those of their anomers **9** and **11**, except that for the hydrogen at the anomeric carbon which experienced an upfield shift of ca. 0.1–0.3 ppm. Final proof for the α-anomeric configuration was provided by an X-ray structural determination of compound **18a** (Figure 3).

Thus, the accessibility of both α- and β-*N*-glycosylamine derivatives with complete control of stereoselectivity through the allyl cyanate to isocyanate rearrangement has been demonstrated, provided a thoughtful choice of the glycal precursor. At the same time, this result is a strong evidence for the hypothesized pericyclic mechanism of the rearrangement,



Scheme 3. Synthesis of β-*N*-glycosyl carbamates **9–10** and ureas **11–12** from D-glucal **5a** and D-galactal **5b**.

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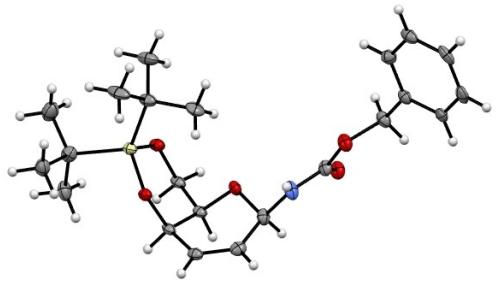
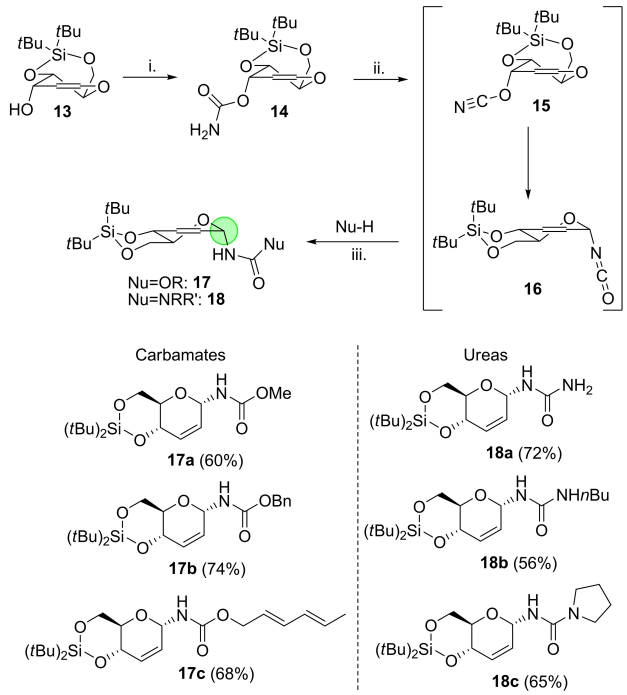


Figure 2. X-ray crystal structure of **10b** (ellipsoid contour at 40% probability).



Scheme 4. Application of the key [3,3]-sigmatropic process to D-allal **13** for the synthesis of α-*N*-glycosyl carbamates **17** and ureas **18**. Reaction conditions: i. $Cl_3CCONCO$, CH_2Cl_2, 35 min, 0 °C to rt, then K_2CO_3, MeOH, 3 h, 0 °C to rt; ii. TFAA (2 equiv), NEt_3 (6 equiv), THF, 0 °C, 1 h, then ROH or RNHR' (6 equiv).

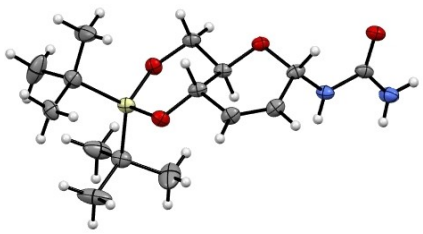


Figure 3. X-ray crystal structure of **18a** (ellipsoid contour at 40% probability).

occurring in a concerted fashion through **TS-β** for glucal and galactal and **TS-α** for allal (Figure 4).

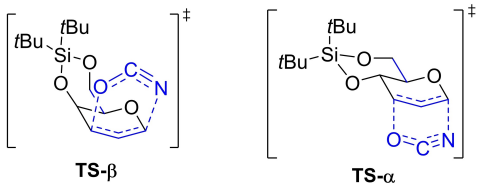
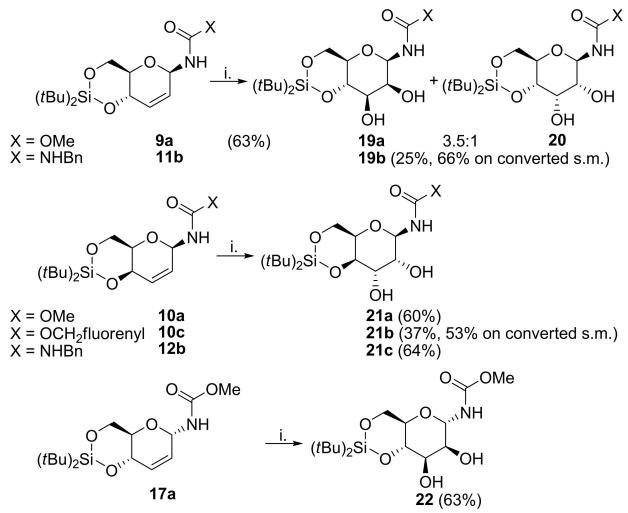


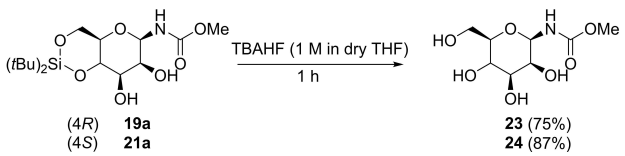
Figure 4. Transition states involved in the rearrangement from glucal and galactal (**TS-β**) and from allal (**TS-α**).

The products obtained by the methodology described are 2-hexenopyranosides, amenable to be transformed into a variety of carbohydrate derivatives via appropriate functionalization at the double bond.[36] The simplest and most straightforward one rests in a *cis*-dihydroxylation, leading to 1-amino-sugars. The stereoselectivity of this addition is expected to be dictated by steric requirements. Representative unsaturated carbohydrates deriving from the different glycals, *i.e.*, methyl carbamates **9a**, **10a** and **17a**, fluorenylmethyl carbamate **10c**, and benzyl ureas **11b** and **12b**, have been subjected to Os-catalyzed *cis*-dihydroxylation under Upjohn conditions (Scheme 5).[37]

The 2-hexenopyranosides **9a** and **11b** deriving from D-glucal and **17a** deriving from D-allal furnished the 1-amino-sugars with D-manno configuration **19a–c** and **22**, respectively.



Scheme 5. *cis*-Dihydroxylation of *N*-(2-hexenopyranos-1-yl) carbamates **9**, **10** and **17** and ureas **11** and **12** deriving from glucal, galactal and allal. Reaction conditions: i. *N*-methylmorpholine *N*-oxide (2 equiv), OsO_4 (0.04 equiv), acetone/water 2:1, rt, 7 d.



Scheme 6. Deprotection of methylcarbamates **19a** and **21a**.

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While the α-*N*-glycosyl carbamate **17a** showed a high preference for osmylation at the β-face, its β-anomer **9a** showed only a moderate preference for a β-attack, affording a 3.5:1 mixture of D-mannosylamine **19a** and D-allosylamine **20**. With bulkier substituents at C-1 the addition was more sluggish. The Fmoc amine **9c** reacted only to a very little extent, while the urea **11b** gave only the manno configured product **19b**, but conversion was modest. The β-*N*-galactosylamines **10a**, **10c** and **12b** also showed a high preference for addition, but at the opposite α-face, yielding exclusively the D-gulosylamines **21a–c**.

The observed facial stereoselectivities can be rationalized according to the preferred half-chair conformations depicted in Figure 5(a).[33b] When substituents at the vicinal C-1 and C-4 are *cis*, the addition occurs from the opposite face with complete stereoselectivity. Thus, compounds **10a**, **10c** and **12b** underwent only dihydroxylation from the bottom face and **17a** exclusively from the top face. When the substituents at C-1 and C-4 are *trans*, higher competition between the two attacks occurs leading to a lower face selectivity, as observed for **9a**. The structural assignment to 1-aminosugar derivatives **19–22** was based on ^{1}H NMR and NOESY spectra. For example, the H at C-3 in the β-*N*-mannosyl methylcarbamate **19a** resonates as a dd with coupling constants $J = 9.2$ and 2.4 Hz, which are consistent with an axial-axial and an equatorial-axial relationship with the vicinal protons, resulting from a *cis*-dihydroxylation occurred at the β-face (Figure 5b). Similarly, the coupling constant $J = 9.2$ Hz observed for the proton at the anomeric position of β-*N*-gulosyl carbamate **21a** attests the axial-axial relationship with H at C-2 arising from dihydroxylation at the α-face. Accordingly, the H at the anomeric carbon of **19a** showed strong nOe relationships with the axial protons at C-3 and C-5, while the one of **21a** correlates only with the proton at C-5 (Figure 5c). These experiments confirm also the previous assignments made for the rearrangement reactions. The observed selectivities of the *cis*-dihydroxylation reactions are in agreement with results reported for dihydroxylation of related unsaturated carbohydrates,[36,38] except that for the β-*N*-glucosyl derivatives **9a** and **11b**. Indeed, for related *O*-glycosides a high selectivity for the formation of allo derivatives has been reported.[39] Final confirmation of our assignment with formation of manno derivatives rests on an X-ray structural determination of compound **19b** (Figure 6).

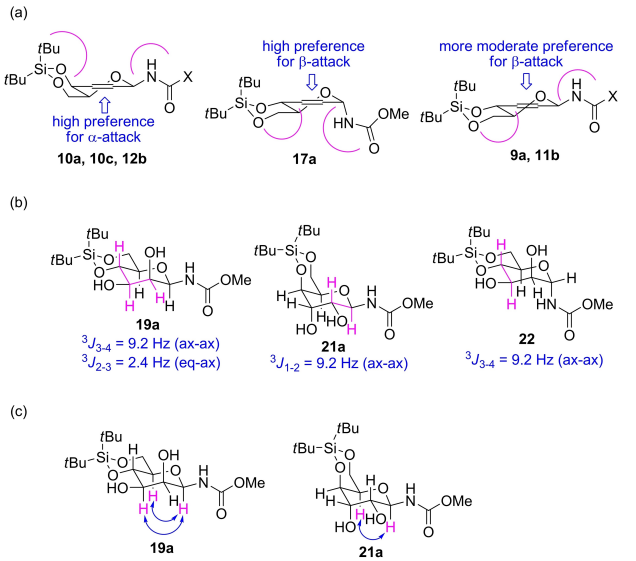

Figure 5. (a) Rationalization for the facial selectivity observed for 2-hexenopyranosides derived from galactal (**10** and **12**), allal (**17**) and glucal (**9** and **11**). (b) Selected coupling constants for the assignment of face selectivity of the *cis*-dihydroxylation. (c) Observed nOe interactions useful for assignment of configuration of manno (**19a**) and gulo (**21a**) derivatives.

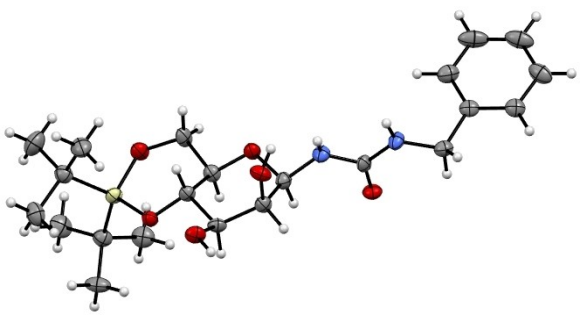

Figure 6. X-ray crystal structure of **19b** (ellipsoid contour at 40% probability).

Access to *N*-glycosyl derivatives was proved by final deprotection of mannoside **19a** and guloside **21a**. Desilylation of the di(*tert*-butyl)silylene group was conveniently achieved by treatment with tributylammonium fluoride (TBAHF) generated in situ from tributylamine and HF as reported[40] and furnished the β-*N*-mannosyl methylcarbamate **23** and the β-*N*-gulosyl methylcarbamate **24** in good yield (Scheme 6).

Conclusion

The allyl cyanate to isocyanate rearrangement has been applied to glycals substituted at C-3 with a carbamate group, which underwent the desired dehydration on treatment with trifluoroacetic anhydride. The dehydration was followed by immediate [3,3]-sigmatropic rearrangement of cyanates to the isomeric *N*-glycosyl isocyanates, which were conveniently trapped by one-pot nucleophilic addition with alcohols or amines to afford *N*-glycosyl carbamates and ureas, respectively. The *N*-glycosyl derivatives were obtained with complete anomeric selectivity, affording α- or β-linked amines depending on the configuration at C-3 of the carbohydrate. Thus, glucal and galactal gave β-*N*-glycosides exclusively while allal furnished α-*N*-glycosides. Representative synthesized unsaturated *N*-glycosides were subjected to Upjohn *cis*-dihydroxylation to afford different 1-aminosugars, mostly with good selectivity. The unsaturated *N*-glycosides deriving from the rearrangement are versatile intermediates, amenable to be converted into a variety of products by proper interconversion at the double bond. For example, access to 1,2- and 1,3-diaminosugar derivatives by iteration of the rearrangement and Os-catalyzed tethered aminohydroxylation,[41] respectively, has already been

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demonstrated.[30] Further studies are ongoing in our labs in order to extend their synthetic application.

Experimental Section

General methods: Commercial reagents were used as received. All reactions were carried out under magnetic stirring and monitored by TLC on 0.25 mm silica gel plates (Merck F254). Column chromatographies were carried out on Silica Gel 60 (32–63 μm) or on silica gel (230–400 mesh, Merck). Yields refer to spectroscopically and analytically pure compounds unless otherwise stated. Melting points were obtained with a Stuart Scientific melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 200 MHz, a Varian Mercury 400 MHz or on a Varian INOVA 400 MHz instrument at 25 °C. Chemical shifts are reported relative to $CDCl_3$ (^{13}C: δ = 77.0 ppm). Integrals are in accordance with assignments, coupling constants are given in Hz. For detailed peak assignments, 2D spectra were carried out (COSY, HSQC, NOESY, and NOE as necessary). IR spectra were recorded with a BX FTIR Perkin-Elmer system spectrophotometer and with an IRAffinity-1S Shimadzu spectrophotometer. ESI-MS spectra were recorded with a Thermo Scientific™ LCQ fleet ion trap mass spectrometer. Elemental analyses were performed with a Thermoscientific FlashSmart Elemental Analyzer CHNS/O or with a Thermo Finnigan FLASH EA 1112 CHN/S analyzer. Optical rotation measurements were performed on a JASCO DIP-370 polarimeter.

Crystallographic analyses: For compounds **10b** and **19b** collections were carried out with a Goniometer Oxford Diffraction KM4 Xcalibur2 at 100 °K. Cu/Kα radiation (40 mA/−40KV), monochromated by an Oxford Diffraction Enhance ULTRA assembly, and an Oxford Diffraction Excalibur PX Ultra CCD were used for cells parameters determination and data collection. The integrated intensities, measured using the ω scan mode, were corrected for Lorentz and polarization effects.[42] Direct methods of SIR2004[43] were used in solving the structures and the refinements were performed using the full-matrix least squares on F^2 provided, within WinGX v.2013.3 routine,[44] by SHELXL2014.[45] Multi-scan symmetry-related measurement was used as experimental absorption correction type. For compound **18a** single crystals were mounted in a loop and intensity data collected at 100 °K with a Bruker Apex-II CCD diffractometer, using a Cu–Kα (λ = 1.54184 Å) radiation. Data were collected with the Bruker APEX2 program, integrated and reduced with the Bruker SAINT software. The integrated intensities, measured using the ϕ and ω scan mode, were corrected for Lorentz and polarization effects. The substantial redundancy in data allows empirical absorption corrections to be applied using SADABS-2016/2 (Bruker AXS area detector scaling and absorption correction).[46] Structures were solved by direct methods of SIR2019[2] and refined using the full-matrix least squares on F2 provided by SHELXL-2014/6[4]. The non-hydrogen atoms were refined anisotropically whereas hydrogen atoms as isotropic.

Deposition Numbers 1986264 (for **10b**), 2182614 (for **18a**), and 2183859 (for **19b**) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

General Procedure I: Allyl cyanate/isocyanate rearrangement[30]

A solution of D-glucal carbamate **6a** or D-galactal carbamate **6b** or D-allal carbamate **14** (1 equiv) and NEt_3 (6 equiv) in dry THF (10 mL/mmol) was cooled at 0 °C and TFAA (2 equiv) was added. After complete disappearance of the starting material (35–60 min) revealed by a TLC control, the dry nucleophile (3–6 equiv) was added. The solution was stirred for 2–3 h at 0 °C and then quenched by addition of a saturated aqueous solution of NH_4Cl. The aqueous layer was extracted with ethyl acetate (3 × 5 mL) and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography affording the rearranged compound.

General Procedure II: Dihydroxylation reactions

The compounds **9a**, **10a**, **10c**, **11b**, **12b**, **17a** obtained from procedure I were dissolved in acetone/water 2:1 (30 mL/mmol), and *N*-methylmorpholine *N*-oxide (2 equiv) and a catalytic amount of osmium tetroxide (up to 10 mol%) were added. The solution was stirred at room temperature for 4–7 days, then quenched by stirring at 0 °C for 30 min with a saturated solution of sodium bisulfite. The aqueous layer was extracted with ethyl acetate (3 × 20 mL) and the combined organic solution was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude material was purified by flash chromatography affording the corresponding dihydroxylated product.

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Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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