OL | Organic Letters

Letter

Allyl Cyanate/Isocyanate Rearrangement in Glycals: Stereoselective Synthesis of 1-Amino and Diamino Sugar Derivatives

Stefania Mirabella, Giulia Petrucci, Cristina Faggi, Camilla Matassini, Francesca Cardona, and Andrea Goti*

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: The [3,3]-sigmatropic allyl cyanate/isocyanate rearrangement of glycals in the presence of *O*-, *N*-, and *C*-nucleophiles afforded β-*N*-glucosyl and galactosyl carbamates, ureas, and amides in good yields. The unsaturated products were elaborated to *N*-glycosides by dihydroxylation, to 1,3-diaminosugars by tethered aminohydroxylation, or to 1,2-diaminosugars by iteration of the sigmatropic rearrangement. This metal-free methodology represents an excellent and general method for the stereoselective synthesis of *N*-glycosides and diamino sugars with complete transmission of stereochemical information.

Pg = Protecting group

from glucal and galactal, only β-*N*-glycosides
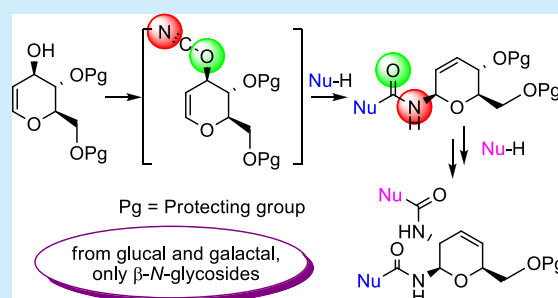
Aminosugars are widespread in Nature, possessing a variety of biological roles.[1] *N*-Glycosides (1-aminosugars and derivatives)[2] are a subclass which may serve as synthetic intermediates, besides playing a key role in *N*-linked glycoproteins involved in many recognition events or in nucleosides and antibiotics.[2b] Representative examples (Figure 1) include the *N*-acetyl-D-glucosamine asparagine moiety **1**, a key agent in cell-recognition and signal transduction,[3] glycocinnamoylspermidines **2**, broad spectrum antibacterial agents,[4] staurosporine **3**, displaying anticancer activity,[5] and trehazoline **4**, a potent and specific inhibitor of trehalase.[6]

Several synthetic efforts have been devoted to accessing diverse *N*-glycosides (amides, ureas, heterocycles), in view of
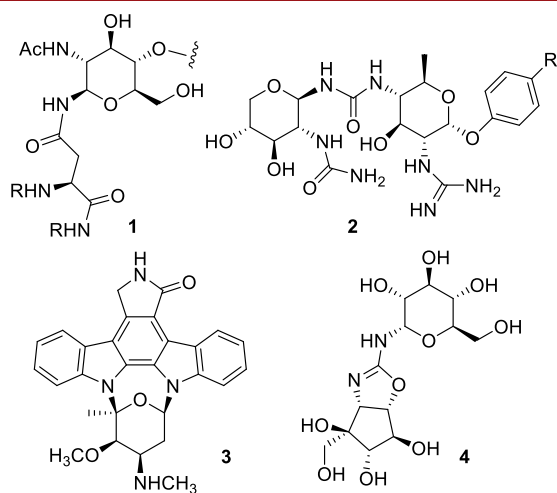
their potential for medicinal chemistry.[7,8] However, compared to *O*- and *C*-glycosides, efficient and stereoselective syntheses of *N*-glycosides are less investigated and remain challenging.[1d−f,9] Major issues are formation of anomeric mixtures and configurational stability. Selectivity for a single anomer is an important target and represents a substantial synthetic challenge. Synthesis of 2- and 3-aminosugars and challenging 1,2(or 3)-diaminosugar backbones, such as in compounds **1**−**3**, is also of paramount importance,[1] and new versatile methods for achieving this task are desired.
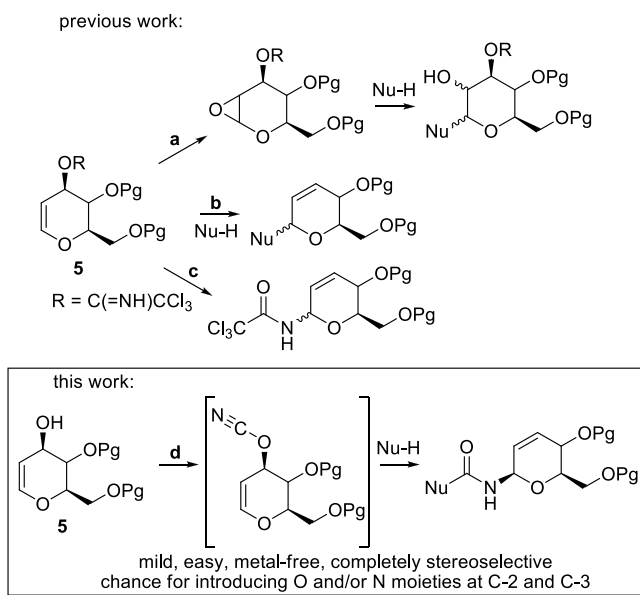
We tackled this topic following our interest in iminosugar glycomimetics,[10] recently extended to aminosugars.[11] A straightforward way for introducing a nitrogen atom onto a carbohydrate backbone involves the use of unsaturated sugar derivatives. Glycals (1,2-deoxyanhydro carbohydrates, **5**) are readily accessible from inexpensive sources and serve as useful precursors for the synthesis of 1-aminosugars.[12] Appropriate strategies rely on epoxidation of glycals followed by regioselective epoxide opening with an *N*-nucleophile (Scheme 1, route a)[13] and related approaches.[14,12] Alternatively, introduction of the nitrogen moiety at C-1 with a concomitant double bond shift has been pursued through Ferrier rearrangement (Scheme 1, route b). However, this approach met with limited success and required peculiar *N*-nucleophiles and use of catalysts, affording mostly moderate yields of α/β anomeric mixtures.[15] The *O*-allyl

Figure 1. Examples of natural *N*-glycosides.
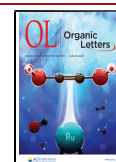
Scheme 1. Known Procedures for the Synthesis of *N*-Glycosides from Glycals and the Strategy Reported Herein Based on the Allyl Cyanate/Isocyanate Rearrangement

versatility of the resulting isocyanates. Absence of applications to glycals for accessing glycosyl isocyanates is surprising and suggested that the envisioned rearrangement might be challenging. Ichikawa reported the synthesis of *N*-glycosyl isocyanates, generated however by oxidation of the corresponding isonitriles, obtained in turn from glycosyl azides.[24] An additional pro of the envisaged rearrangement rests in the opportunity to manipulate the shifted C=C double bond for installing other oxygen and/or nitrogen functionalities.

In this paper, we report our results on the application of the allyl cyanate/isocyanate rearrangement to glycals to give *N*-glycosides (Scheme 1, route d) and diaminosugar derivatives.

In order to synthesize allyl carbamates of simple D-glycals, 4,6-*O*-protected D-glucal **5a** and D-galactal **5b**[25] were reacted with trichloroacetyl isocyanate followed by potassium carbonate to give **6a** and **6b** in quantitative yield (Scheme 2). Their

Scheme 2. Synthesis of the D-Glucal Carbamate 6a and the D-Galactal Carbamate 6b and the Expected Rearrangement to Yield the *N*-Glycosides 9

to *N*-allyl rearrangements (cyanate/isocyanate[16] or Overman[17]), reliable methods for introducing nitrogen moieties on allyl alcohol skeletons with high degree of stereochemical control, might serve the purpose. These methods are largely neglected in synthesis; particularly, the allyl cyanate/isocyanate rearrangement has been used in limited examples of elegant syntheses mainly by Ichikawa following his reliable procedure for generating the required cyanate functionality[16a,18] and more recently by Stecko's and Carreaux's groups.[19] Although glycals and other unsaturated sugars are readily affordable, applications of these methodologies to carbohydrates are rare. Only Ichikawa and co-workers have studied the allyl cyanate/isocyanate rearrangement with unsaturated sugars, however focusing on 2- or 3-hexenopyranosides for the synthesis of 2- and 4-amino-sugars, respectively.[20] Donohoe and co-workers also synthesized 2-aminosugars applying the related Overman rearrangement to 2-hexenopyranosides derived from Ferrier reaction of glycals.[21]
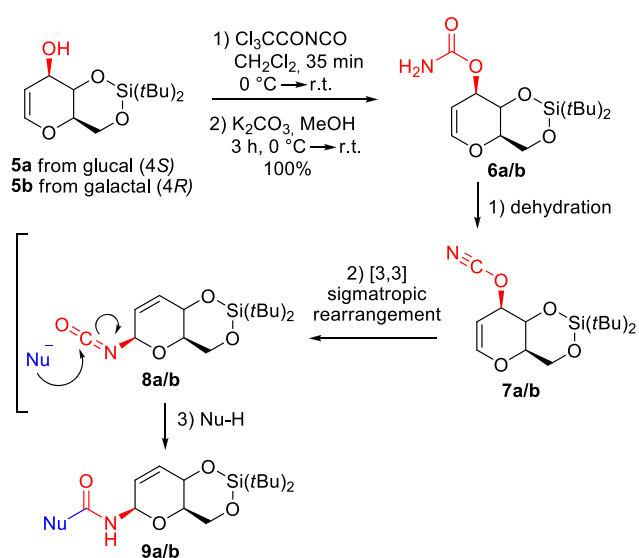
Pd(II)-catalyzed rearrangements of glycal imidates to yield α- and β-*N*-glycosyl trichloroacetimidates (Scheme 1, route c)[22] or *N*-heterocyclic glycosides[23] have been reported. However, no example of a thermal Overman or cyanate/isocyanate rearrangement on glycals has been described, despite the value of *N*-glycosides. The latter rearrangement is particularly attracting, in view of several advantages, including use of manageable carbamate precursors, much milder rearrangement under metal-free conditions, high degree of stereocontrol, and

transformation to the desired products involves three steps,[16] which are usually performed in one-pot. Initial dehydration of the carbamate to the corresponding elusive cyanate **7**[26] is followed by spontaneous [3,3]-sigmatropic rearrangement to the isocyanate **8**, which is conveniently trapped with a nucleophile to afford the final products **9**.

The D-glucal carbamate **6a** was selected for studying the process and optimizing the reaction conditions. As anticipated, however, the rearrangement proved troublesome. All attempts employing the standard Appel's conditions for dehydration (CBr₄, PPh₃, NEt₃ in CH₂Cl₂, entries 1 and 2, Table 1) were

Table 1. Reaction Conditions of the Three-Step Reaction of Scheme 2 with 6a and Benzyl Alcohol As Nucleophile

	step 1		step 2		
entry	reagents	temp °C, time	BnOH (equiv)	temp (°C), time (h)	yield of **10a** (%)
1	CBr₄, PPh₃, NEt₃,CH₂Cl₂	0, 6 h	1	rt, 16	complex mixture
2	CBr₄, PPh₃, NEt₃,CH₂Cl₂	0, 10 h	1	0, 3	complex mixture
3	TFAA, NEt₃, THF	−20, 35 min			no reaction
4	TFAA, NEt₃, THF	0, 35 min	6	−20, 3	80
5	TFAA, NEt₃, THF	0, 35 min	6	0, 3	92
6	TFAA, NEt₃, THF	0, 35 min	3	0, 3	92

unsuccessful. Addition of BnOH as nucleophile either at rt or 0 °C after consumption of the starting material resulted in a complex mixture of products from which isolation of **10a** was impossible, providing a hint for the dearth of reports of this rearrangement on glycals. Early formation (TLC) of the complex mixture after addition of the dehydrating reagents suggested that carbamates **6** are sensitive to these conditions, possibly due to competitive Ferrier type processes. Then, use of trifluoroacetic anhydride (TFAA) as the dehydrating agent, according to recent work by Stecko,[19] was investigated. No reaction was obtained by treatment of **6a** with TFAA (2 equiv) and NEt₃ (3 equiv) in THF at −20 °C (entry 3, Table 1), but raising the temperature to 0 °C led to its complete and clean conversion (entries 4−6). Optimal conditions resulted by using 3 equiv of BnOH at 0 °C for 3 h and afforded the desired benzyl carbamate **10a** in 92% yield (entry 6).

Gratified by this result, we addressed the scope of the process with both D-glucal and D-galactal carbamates **6a** and **6b**. Several *O*-, *N*-, and *C*-nucleophiles were used to yield *N*-glucosyl and *N*-galactosyl carbamates, ureas, and amides **a** and **b**, respectively (Table 2). Alcohols gave carbamates **10−13**, several of which display common amino protecting groups at the anomeric amine, such as benzyloxy, methoxy, and fluorenylmethoxy carbonyl (Cbz, Moc, and Fmoc, entries 1−3) suitable to be removed under different conditions.[9a] Ammonia and primary and secondary amines gave the corresponding ureas **14−17** (entries 5−8). Most of the nucleophiles afforded the desired *N*-glycosides in good to excellent yields, considering the challenging three-step transformation. The yield dropped with bulky nucleophiles, as in case of the fluorenylmethyl alcohol. Addition of MeMgBr as a model *C*-nucleophile also gave the expected amides in more moderate yields (entry 9). In the reaction from **6b** an unexpected product, characterized by NMR and MS as an aminal derived from a double addition and trapped as its trifluoroacetic ester (see the SI), was also isolated besides the desired acetamide **18b**.

All products **10−18a/b** were obtained as single isomers, assumed to be the *β*-anomers in consideration of the concerted mechanism of the [3,3]-sigmatropic rearrangement through the cyclic TS **19** occurring with complete 1,3-chirality transfer (Scheme 3).[16,26,27] However, formation of the *α*-anomer which

Scheme 3. TS Involved in the Rearrangement
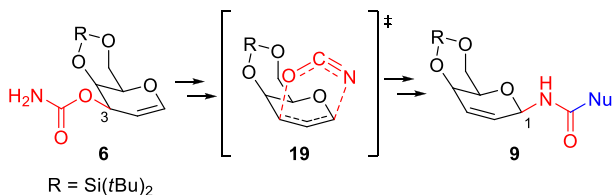
may experience anomeric effect[2b,9a,28] consequent to a different mechanism, e.g., a Ferrier-type, could not be ruled out. Then, single crystals of products **18a** from D-gluco and **10b** from D-galacto series were subjected to X-ray structural determination (SI), which confirmed the *N*-glycosides *β*-configuration.

We have then proved the feasibility and generality of the desired process, which works satisfactorily in both gluco and galacto series under mild conditions without the use of metal mediators, affording *β*-*N*-glycosides in good yields and with complete stereocontrol.

In order to illustrate the potential of this methodology for accessing a variety of rare carbohydrate derivatives, such as those of allose or gulose, which constitute the backbone of important biologically active substances and are not economically

Table 2. Nucleophiles and Reaction Products of the Cyanate/Isocyanate Rearrangement from D-Glucal and D-Galactal Carbamates 6a and 6b

entry	nucleophile	products gluco series (**a**): from D-glucal **6a** galacto series (**b**): from D-galactal **6b**
1	BnOH	 **10a** (92%) **10b** (77%)
2	MeOH	 **11a** (71%) **11b** (76%)
3		 **12a** (46%) **12b** (40%)
4		 **13a** (69%) **13b** (80%)
5	NH₄OH	 **14a** (65%) **14b** (87%)
6	BnNH₂	 **15a** (73%) **15b** (70%)
7	*n*BuNH₂	 **16a** (81%) **16b** (81%)
8		 **17a** (64%) **17b** (70%)
9	MeMgBr	 **18a** (57%) **18b** (34%) (+ 35%[a])

[a]Yield of the double addition product (see text and SI).

accessible from natural sources,[29] we aimed to elaborate the obtained unsaturated products into amino and diamino carbohydrates. Dihydroxylation to *N*-glycosides was demonstrated with the reaction of the D-galacto carbamate **11b** under Upjohn conditions,[30] which afforded the single gulose derivative **20** derived from selective attack of OsO$_4$ to the α-face (Scheme 4). Final desilylation of **20** with TBAHF in THF gave the β-*N*-guloside **21** in 87% yield.

Scheme 4. Synthesis of *N*-Guloside 21 by *cis*-Dihydroxylation of Hexenopyranoside 11b and of 1,3-Diaminoallose 25 by Tethered Aminohydroxylation of Hexenopyranoside 24
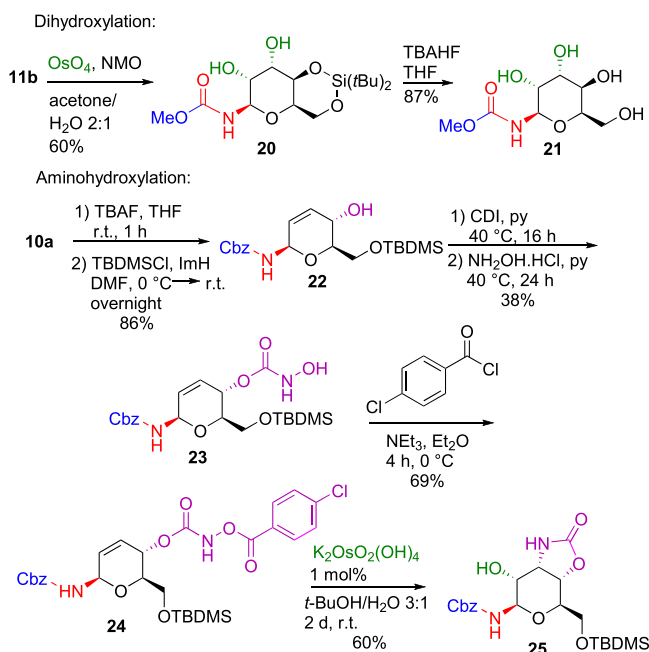

Access to 1,3-diaminosugars was secured via an osmium-catalyzed tethered *syn*-aminohydroxylation (TA)[31] of 2-hexenopyranosides, extending the methodology on glycals reported recently by us for the synthesis of 2-aminosugars.[11] Toward this goal, a sequential deprotection of the hydroxy groups of **10a** followed by selective protection of the primary alcohol gave **22** in 86% yield (Scheme 4). Conversion of the free OH to the suitable *p*-chlorobenzoyloxy carbamate **24** for the key Os-catalyzed TA was achieved as reported.[11] Reaction of **24** with 1 mol % K$_2$OsO$_2$(OH)$_4$ in *t*BuOH/water 3:1 for 2 d gave the isoxazolidinone **25**, a protected 1,3-diamino allose, in a satisfactory 60% yield. The reaction occurred with complete *cis*-stereoselectivity and afforded exclusively the diastereoisomer with the installed functionalities at C-2 and C-3 *trans* to the anomeric substituent, as attested by a large diaxial H-1/H-2 coupling constant in the ¹H NMR spectrum, in agreement with the proposed mechanism through a key *N*-imido osmium TS. The accomplishment of the TA reaction from **24** is noteworthy, considering our previously experienced failure of the same reaction from a related D-gluco derivative bearing an α-OMe at C-1.[11]

Having proved the access to 1,3-diaminosugars by TA, we envisaged that iteration of the cyanate/isocyanate rearrangement would furnish complementary alternative for introduction of a second amino group at C-2 of the carbohydrate. This opportunity arises since products **10−18** of the one-pot rearrangement/nucleophilic addition process contain a pro-

tected allyl alcohol. Iteration of the process would allow to access 1,2-diaminosugars leaving another double bond suited for further elaboration. The allylic alcohol **22** was converted as before to the carbamate **26** in 82% yield. The one-pot dehydration/rearrangement was performed as usual and the resulting isocyanate trapped in situ using MeOH as the nucleophile, affording the orthogonally protected 1,2-diamino sugar **27** in 51% yield with complete transmission of the α-configuration (Scheme 5). The

Scheme 5. Iterative Allyl Cyanate/Isocyanate Rearrangement to Yield the 1,2-Diamino Sugar 27
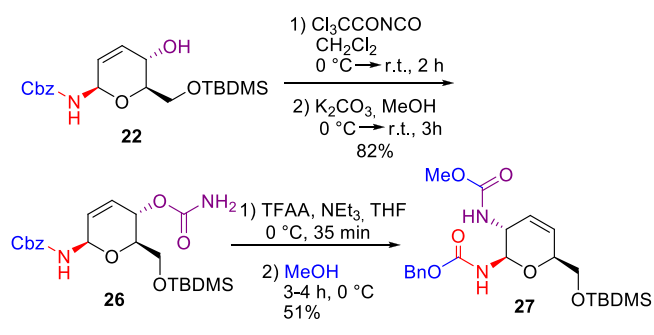
trans relationship of the two aminocarbonyl groups in **27** was assigned on the basis of the large H-1/H-2 coupling constant (8.5 Hz) in the ¹H NMR spectrum.[32] It is worthy of note that compound **27** possesses the same stereochemical 1,2-diamino pattern of *N*-glycosides **1** in Figure 1.

In conclusion, we proved the viability of the [3,3]-sigmatropic allyl cyanate/isocyanate rearrangement with glycals to give a straightforward access to various functionalized β-*N*-glycosides with complete chirality transfer by reaction with several *O*-, *N*- and *C*-nucleophiles. The resulting hexenopyranosides were elaborated to 1-amino and 1,3-diaminosugars by *cis*-dihydroxylation and tethered aminohydroxylation, respectively. 1,2-Diamino unsaturated sugars were also obtained by double allyl cyanate/isocyanate rearrangement. The variety of glycals available and all possible elaboration of the rearranged products make this simple and mild method widely applicable in principle to the synthesis of constitutionally and configurationally diversified aminosugars.

Further studies are ongoing in our laboratory to extend this methodology to other carbohydrate derivatives and to address the scope of the multiple rearrangement for the conversion of chiral polyols to polyamines.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03438.

> Experimental procedures, characterization data, and NMR spectra for all new compounds; X-ray crystallographic data for compounds **10b** and **18a** (PDF)

Accession Codes

CCDC 1986263−1986264 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.

■ AUTHOR INFORMATION

Corresponding Author

    Andrea Goti − *Dipartimento di Chimica "Ugo Schiff", Università di Firenze, 50019 Sesto Fiorentino, FI, Italy;* ⊙ orcid.org/0000-0002-1081-533X; Email: andrea.goti@unifi.it

Authors

    Stefania Mirabella − *Dipartimento di Chimica "Ugo Schiff", Università di Firenze, 50019 Sesto Fiorentino, FI, Italy*

    Giulia Petrucci − *Dipartimento di Chimica "Ugo Schiff", Università di Firenze, 50019 Sesto Fiorentino, FI, Italy*

    Cristina Faggi − *Dipartimento di Chimica "Ugo Schiff", Università di Firenze, 50019 Sesto Fiorentino, FI, Italy;* ⊙ orcid.org/0000-0002-2448-6354

    Camilla Matassini − *Dipartimento di Chimica "Ugo Schiff", Università di Firenze, 50019 Sesto Fiorentino, FI, Italy;* ⊙ orcid.org/0000-0002-8336-383X

    Francesca Cardona − *Dipartimento di Chimica "Ugo Schiff", Università di Firenze, 50019 Sesto Fiorentino, FI, Italy;* ⊙ orcid.org/0000-0002-6766-4624

Complete contact information is available at:
https://pubs.acs.org/10.1021/acs.orglett.0c03438

Notes

The authors declare no competing financial interest.

■ REFERENCES

(1) (a) Horton, D.; Wander, J. D. In *The Carbohydrates*; Pigman, W., Horton, D., Eds.; Academic Press: New York, 1980;, Vol. *1B*, pp 643−760. (b) Banaszek, A.; Mlynarski, J. Recent advances in the chemistry of bioactive 3-deoxy-ulosonic acids. In *Studies in Natural Products Chemistry*; Atta-ur-Rahman, Ed.; Elsevier, Amsterdam; 2005; Vol. *30*, p 419−482. (c) Gilbert, D. N. Aminoglycosides. In *Principles and Practice of Infectious Diseases*, 6th ed.; Mandell, G. L., Bennett, J. E., Dolin, R., Eds.; Churchill Livingstone: New York, 2005; pp 328−356. For selected reviews on the synthesis of aminosugars, see: (d) Witczak, Z. J.; Bielski, R. Recent Examples of Novel Synthetic Approaches to Diverse Amino Sugars. *Carbohydr. Chem.* **2016**, *42*, 344−367. (e) Pfrengle, F.; Reissig, H.-U. Amino Sugars and their Mimetics via 1,2-Oxazines. *Chem. Soc. Rev.* **2010**, *39*, 549−557. (f) Skarbek, K.; Milewska, M. J. Biosynthetic and Synthetic Access to Amino Sugars. *Carbohydr. Res.* **2016**, *434*, 44−71.

(2) (a) Dwek, R. A. Glycobiology: Toward Understanding the Function of Sugars. *Chem. Rev.* **1996**, *96*, 683−720. (b) Nicolas, C.; Martin, O. R. A Practical Approach to Dideoxy-1,4- and 1,5-Iminopentitols from Protected Sugar Hemiacetals. *Molecules* **2018**, *23*, 1612−1641.

(3) Liu, L.; Bennett, C. S.; Wong, C.-H. Advances in Glycoprotein Synthesis. *Chem. Commun.* **2006**, 21−33.

(4) Dobashi, K.; Nagaoka, K.; Watanabe, Y.; Nishida, M.; Hamada, M.; Naganawa, H.; Takita, T.; Takeuchi, T.; Umezawa, H. Glycocinnasperimicin D, a New Member of Glycocinnamoylspermidine Antibiotic. *J. Antibiot.* **1985**, *38*, 1166−1170.

(5) Bruno, S.; Ardelt, B.; Skierski, J. S.; Traganos, F.; Darzynkiewicz, Z. Different Effects of Staurosporine, an Inhibitor of Protein Kinases, on the Cell Cycle and Chromatin Structure of Normal and Leukemic Lymphocytes. *Cancer Res.* **1992**, *52*, 470−473.

(6) (a) Ando, O.; Kifune, M.; Nakajima, M. Effects of Trehazolin, a Potent Trehalase Inhibitor, on Bombyx mori and Plant Pathogenic Fungi. *Biosci., Biotechnol., Biochem.* **1995**, *59*, 711−712. (b) Kobayashi, Y. Chemistry and Biology of Trehazolins. *Carbohydr. Res.* **1999**, *315*, 3−

15. (c) Matassini, C.; Parmeggiani, C.; Cardona, F. New Frontiers on Human Safe Insecticides and Fungicides: An Opinion on Trehalase Inhibitors. *Molecules* **2020**, *25*, 3013.

(7) Weerapana, E.; Imperiali, B. Asparagine-Linked Protein Glycosylation: from Eukaryotic to Prokaryotic Systems. *Glycobiology* **2006**, *16*, 91R−101R.

(8) (a) McKay, M. J.; Nguyen, H. M. Recent developments in glycosyl urea synthesis. *Carbohydr. Res.* **2014**, *385*, 18−44. (b) Norris, P. Pyranose N-Glycosyl Amines: Emerging Targets with Diverse Biological Potential. *Curr. Top. Med. Chem.* **2008**, *8*, 101−113.

(9) For recent notable synthetic approaches, see: (a) Nielsen, M. M.; Mała, P.; Baldursson, E. P.; Pedersen, C. M. Self-Promoted and Stereospecific Formation of *N*-Glycosides. *Chem. Sci.* **2019**, *10*, 5299−5307. (b) Zheng, J.; Urkalan, K. B.; Herzon, S. B. Direct Synthesis of *β-N*-Glycosides by the Reductive Glycosylation of Azides with Protected and Native Carbohydrate Donors. *Angew. Chem., Int. Ed.* **2013**, *52*, 6068−6071.

(10) For representative examples, see: (a) Brandi, A.; Cardona, F.; Cicchi, S.; Cordero, F. M.; Goti, A. Stereocontrolled Cyclic Nitrone Cycloaddition Strategy for the Synthesis of Pyrrolizidine and Indolizidine Alkaloids. *Chem. - Eur. J.* **2009**, *15*, 7808−7821. (b) Mirabella, S.; D'Adamio, G.; Matassini, C.; Goti, A.; Delgado, S.; Gimeno, A.; Robina, I.; Moreno-Vargas, A. J.; Šesták, S.; Jiménez-Barbero, J.; Cardona, F. Mechanistic Insight into the Binding of Multivalent Pyrrolidines to α-Mannosidases. *Chem. - Eur. J.* **2017**, *23*, 14585−14596. (c) Mirabella, S.; Fibbi, G.; Matassini, C.; Faggi, C.; Goti, A.; Cardona, F. Accessing 2-Substituted Piperidine Iminosugars by Organometallic Addition/Intramolecular Reductive Amination: Aldehyde vs. Nitrone Route. *Org. Biomol. Chem.* **2017**, *15*, 9121−9126. (d) Clemente, F.; Matassini, C.; Faggi, C.; Giachetti, S.; Cresti, C.; Morrone, A.; Paoli, P.; Goti, A.; Martínez-Bailén, M.; Cardona, F. Glucocerebrosidase (GCase) activity modulation by 2-alkyl trihydroxypiperidines: Inhibition and pharmacological chaperoning. *Bioorg. Chem.* **2020**, *98*, 103740. (e) Matassini, C.; Warren, J.; Wang, B.; Goti, A.; Cardona, F.; Morrone, A.; Bols, M. Imino- and Azasugar Protonation Inside Human Acid *β*-Glucosidase, the Enzyme that is Defective in Gaucher Disease. *Angew. Chem., Int. Ed.* **2020**, *59*, 10466−10469.

(11) Mirabella, S.; Cardona, F.; Goti, A. Osmium-Catalyzed Tethered Aminohydroxylation of Glycals: A Stereodirected Access to 2-and 3-Aminosugars. *Org. Lett.* **2015**, *17*, 728−731.

(12) Mirabella, S.; Cardona, F.; Goti, A. From Glycals to Aminosugars: a Challenging Test for New Stereoselective Aminohydroxylation and Related Methodologies. *Org. Biomol. Chem.* **2016**, *14*, 5186−5204.

(13) Halcomb, R. L.; Danishefsky, S. J. On the Direct Epoxidation of Glycals: Application of a Reiterative Strategy for the Synthesis of *β*-Linked Oligosaccharides. *J. Am. Chem. Soc.* **1989**, *111*, 6661−6666.

(14) Meyerhoefer, T. J.; Kershaw, S.; Caliendo, N.; Eltayeb, S.; Hanawa-Romero, E.; Bykovskaya, P.; Huang, V.; Marzabadi, C. H.; De Castro, M. A. Practical Synthesis of Various 2-Deoxy-*N*-glycosides by Using d-Glucal. *Eur. J. Org. Chem.* **2015**, *2015*, 2457−2462.

(15) (a) Ferrier, R. J.; Zubkov, O. A. Transformation of Glycals into 2,3-Unsaturated Glycosyl Derivatives. *Org. React.* **2003**, *62*, 569−736. (b) Gómez, A. M.; Lobo, F.; Uriel, C.; López, J. C. Recent Developments in the Ferrier Rearrangement. *Eur. J. Org. Chem.* **2013**, *2013*, 7221−7262.

(16) (a) Ichikawa, Y. Evolution, Development and Personal Experience in Studies of the Allyl Cyanate-to-Isocyanate Rearrangement. *Synlett* **2007**, *2007*, 2927−2936. (b) Nocquet, P.-A.; Henrion, S.; Macé, A.; Carboni, B.; Villalgordo, J. M.; Carreaux, F. The Allyl Cyanate/Isocyanate Rearrangement: An Efficient Tool for the Stereocontrolled Formation of Allylic C−N Bonds. *Eur. J. Org. Chem.* **2017**, *2017*, 1295−1307.

(17) (a) Overman, L. E.; Carpenter, N. E. The Allylic Trihaloacetimidate Rearrangement. *Org. React.* **2005**, *66*, 1−107. (b) Fernandes, R. A.; Kattanguru, P.; Gholap, S. P.; Chaudhari, D. A Recent Advances in the Overman Rearrangement: Synthesis of Natural Products and Valuable Compounds. *Org. Biomol. Chem.* **2017**, *15*, 2672−2710. See also: (c) *Domino and Intramolecular Rearrangement Reactions as*

Advanced Synthetic Methods in Glycoscience;, Witczak, Z. J., Bielski, R., Eds.; John Wiley & Sons: Hoboken, NJ, 2016.

(18) Ichikawa, Y.; Yamaoka, T.; Nakano, K.; Kotsuki, H. Synthesis of (−)-Agelastatin A by [3.3] Sigmatropic Rearrangement of Allyl Cyanate. *Org. Lett.* **2007**, *9*, 2989−2992.

(19) For representative examples, see: (a) Stecko, S. Total Synthesis of Lacosamide. *J. Org. Chem.* **2014**, *79*, 6342−6346. (b) Szcześniak, P.; Październiok-Holewa, A.; Klimczak, U.; Stecko, S. Synthesis of β-and γ-Hydroxy α-Amino Acids via Enzymatic Kinetic Resolution and Cyanate-to-Isocyanate Rearrangement. *J. Org. Chem.* **2014**, *79*, 11700−11713. (c) Narczyk, A.; Stecko, S. The synthesis of unnatural α-alkyl- and α-aryl-substituted serine derivatives. *Org. Biomol. Chem.* **2020**, *18*, 1204−1213. (d) Henrion, S.; Carboni, B.; Cossío, F. P.; Roisnel, T.; Villalgordo, J. M.; Carreaux, F. Stereospecific Synthesis of α-Amino Allylsilane Derivatives through a [3,3]-Allyl Cyanate Rearrangement. Mild Formation of Functionalized Disiloxanes. *J. Org. Chem.* **2016**, *81*, 4633−4644. (e) Henrion, S.; Macé, A.; Vallejos, M. M.; Roisnel, T.; Carboni, B.; Villalgordo, J. M.; Carreaux, F. Asymmetric synthesis of *trans*-4,5-disubstituted γ-butyrolactones involving a key allylboration step. First access to (−)-nicotlactone B and (−)-galbacin. *Org. Biomol. Chem.* **2018**, *16*, 1672−1678.

(20) (a) Ichikawa, Y.; Kobayashi, C.; Isobe, M. Synthesis of Nitrogen-containing Unsaturated Carbohydrates through an Allyl Cyanate-to-isocyanate Rearrangement. *Synlett* **1994**, *1994*, 919−921. (b) Ichikawa, Y.; Osada, M.; Ohtani, I. I.; Isobe, M. A New Synthetic Method for the Preparation of Amino Sugars through an Allyl Cyanate to-Isocyanate Rearrangement. *J. Chem. Soc., Perkin Trans. 1* **1997**, *1*, 1449−1455.

(21) Donohoe, T. J.; Logan, J. G.; Laffan, D. D. P. Trichloro-Oxazolines as Activated Donors for Aminosugar Coupling. *Org. Lett.* **2003**, *5*, 4995−4998.

(22) Yang, J.; Mercer, G. J.; Nguyen, H. M. Palladium-Catalyzed Glycal Imidate Rearrangement: Formation of α- and β-N-Glycosyl Trichloroacetamides. *Org. Lett.* **2007**, *9*, 4231−4234.

(23) Ji, L.; Xiang, S.-H.; Leng, W.-L.; Mai Hoang, K. L.; Liu, X. W. Palladium-Catalyzed Glycosylation: Novel Synthetic Approach to Diverse N-Heterocyclic Glycosides. *Org. Lett.* **2015**, *17*, 1357−1360.

(24) Ichikawa, Y.; Matsukawa, Y.; Isobe, M. Synthesis of Urea-Tethered Neoglycoconjugates and Pseudooligosaccharides in Water. *J. Am. Chem. Soc.* **2006**, *128*, 3934−3938.

(25) Hoberg, J. O. Formation of Seven-Membered Oxacycles through Ring Expansion of Cyclopropanated Carbohydrates. *Carbohydr. Res.* **1997**, *300*, 365−367.

(26) Banert, K.; Melzer, A. The First Direct Observation of an Allylic [3,3] Sigmatropic Cyanate−Isocyanate Rearrangement. *Tetrahedron Lett.* **2001**, *42*, 6133−6135.

(27) For DFT computational studies, see: Koch, R.; Finnerty, J. J.; Murali, S.; Wentrup, C. [3, 3]-Sigmatropic Shifts and Retro-ene Rearrangements in Cyanates, Isocyanates, Thiocyanates, and Isothiocyanates of the Form RX-YCN and RX-NCY. *J. Org. Chem.* **2012**, *77*, 1749−1759.

(28) Perrin, C. L.; Kuperman, J. Anomeric Effects Versus Steric Hindrance to Ionic Solvation in Protonated Glucosylanilines and Cyclohexylanilines. *J. Am. Chem. Soc.* **2003**, *125*, 8846−8851.

(29) (a) Wang, Y.; Carder, H. M.; Wendlandt, A. E. Synthesis of Rare Sugar Isomers through Site-Selective Epimerization. *Nature* **2020**, *578*, 403−408. (b) Sui, L.; Dong, Y.; Watanabe, Y.; Yamaguchi, F.; Hatano, N.; Izumori, K.; Tokuda, M. The Inhibitory Effect and Possible Mechanisms of d-Allose on Cancer Cell Proliferation. *Int. J. Oncol.* **2005**, *27*, 907−912.

(30) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation. *Chem. Rev.* **1994**, *94*, 2483−2547. (b) Dransfield, P. J.; Gore, P. M.; Prokeš, I.; Shipman, M.; Slawin, A. M. Z. Preparation and Reactivity of Iminoglycals: Stereocontrolled, Divergent Approach to Imino Sugars. *Org. Biomol. Chem.* **2003**, *1*, 2723−2733.

(31) Donohoe, T. J.; Callens, C. K. A.; Lacy, A. R.; Winter, C. Tethered Aminohydroxylation Reaction and Its Application to Total Synthesis. *Eur. J. Org. Chem.* **2012**, *2012*, 655−663.

(32) Joseph, R.; Dyer, F. B.; Garner, P. Rapid Formation of N-Glycopeptides via Cu(II)-Promoted Glycosylative Ligation. *Org. Lett.* **2013**, *15*, 732−735.