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Communication

Glycoconjugates | *Very Important Paper* |

Structure and Reactivity of Glycosyl Isocyanides

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Abstract: 3D structural information was obtained from mono-, di- and trisaccharide formamide and isocyanide derivatives by analysis of their X-ray crystal structure and NMR spectroscopy. The isocyanide anomeric effect was observed. Data mining of the Cambridge Structural Database (CSD) was performed and statistically confirmed our findings. Application of the glycoside isocyanides in the synthesis of novel glycoconjugates as drug-like scaffolds by MCR chemistry underscores the usefulness of the novel building blocks.

Introduction

Carbohydrate chemistry, due to the structural diversity of sugars with unique shape and binding modes, can be applied to develop a broad range of complex therapeutic molecules and drugs.[1] Glycoconjugates is the general classification for carbohydrates covalently linked to other chemical species, termed aglycones.[2] They play a fundamental role in normal cell functions as well as in major disease pathologies including cancer, cardiovascular and inflammatory diseases.[3–6] Very often the aglycon part is of special interest with application in drug discovery; it can bind to a specific target, while the sugar moiety can enhance the transport properties through transporters and increase water solubility.[7,8]

Isocyanide-based multicomponent reactions (IMCRs), with their special driving force of diversity and complexity, can greatly contribute in building complex molecules combining moieties of special interest.[9,10] Thus, MCRs can be a really valuable tool towards that direction; they could enable a rapid and diverse incorporation of sugar isocyanides into drug-like scaffolds.[11–23]

Recent exciting applications of such glyco-MCR products include antiaging cosmetic preparations.[24] In continuation of our own studies on the glyco-IMCR,[25] besides D-glucose and L-arabinose, we investigate here our established strategy not only on important monosaccharides as D-galactose and D-ribose, but also on disaccharides as D-lactose and even trisaccharides such as α-D-maltotriose. Our approach has two defined objectives. First to obtain structural information of the synthesized sugar formamides and isocyanides by the X-ray structure analysis. This is of outmost importance since crystal structures of sugar formamides and isocyanides are scarce in literature.[26,27]

Apart of the crystal structural insights, our second objective is to effectively design novel glycoconjugates with bioactive molecules of general interest such as lactones or macrocycles (Figure 1).

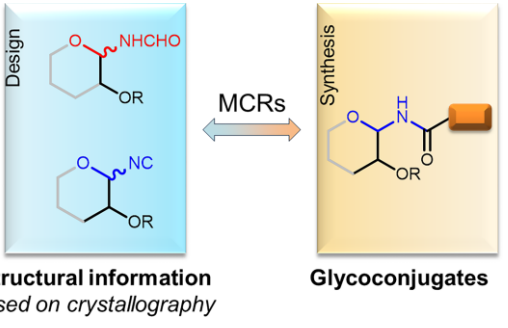

Figure 1. Graphical representation of the two main objectives of the current study; structural information on sugar formamide and isocyanide based on the X-ray crystal structure analysis and synthesis of glycoconjugates via multicomponent reaction chemistry.

Results and Discussion

Herein, we provide structural information and analysis of six different sugar formamides and twelve sugar isocyanides. In addition, we demonstrate our synthetic strategy to access different glycoconjugate scaffolds. Based on our recently disclosed Leuckart-Wallach (LW) approach[25,28,29] with some experimental improvements (reducing the refluxing temperature from 140 °C to 100 °C, increased dramatically the yield), we performed the regio- and stereospecifically the reductive amination on the 1-OH-unprotected sugars **1**, affording the corresponding glucosyl (**2**), galactosyl (**3**), arabinosyl (**4**), ribosyl (**5**), lactosyl (**6**) and maltotriosyl (**7**) formamides in good yields.

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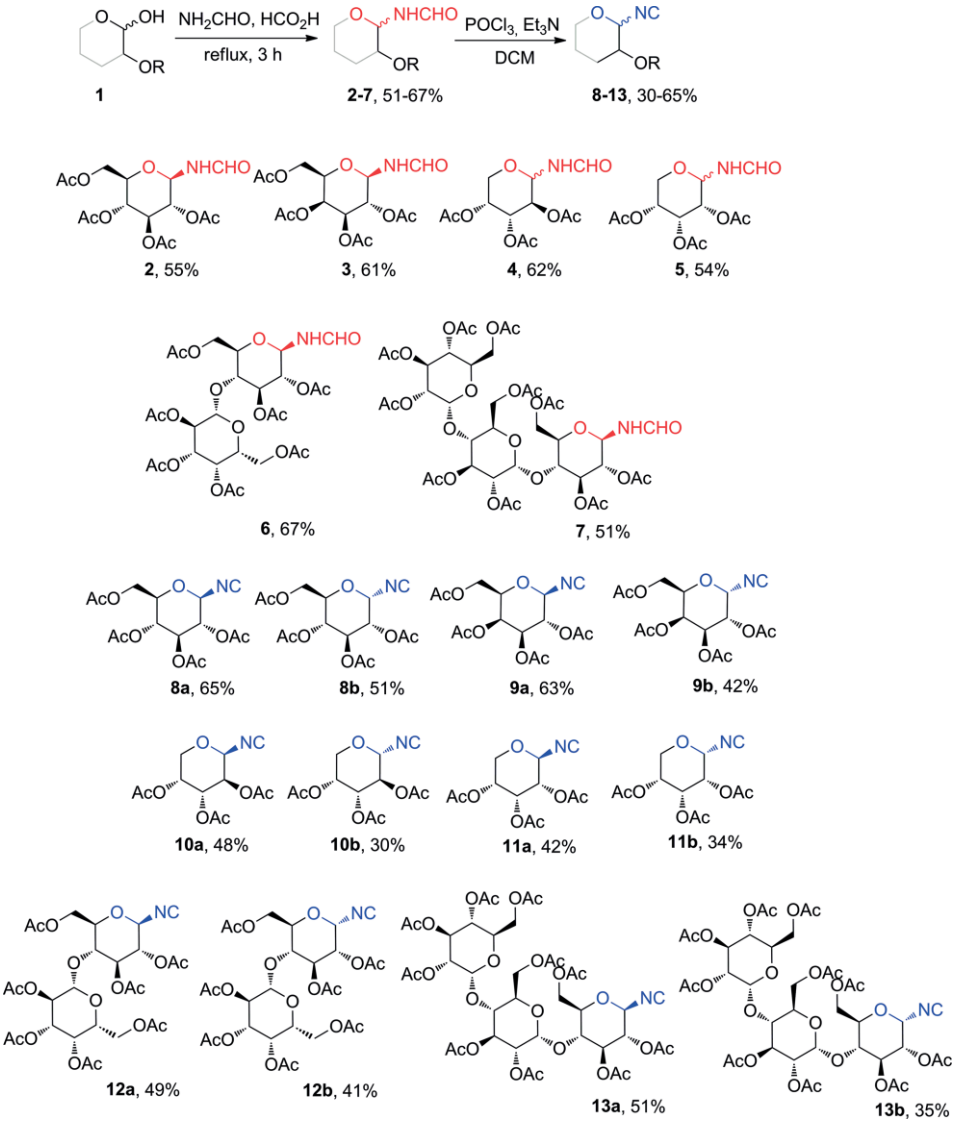
Since we were primarily interested in the structural information, we also resynthesized the glucosyl and arabinosyl formamides. As expected, the LW reaction afforded only the β-anomers (in case of glucose, galactose, lactose and maltotriose), except arabinose and ribose where we obtained a mixture of the α- and β-anomers due to probably a preferred intramolecular hydrogen bonding of the formamide with the neighboring acetyl group (Scheme 1).[25] As shown in NMR, all the synthesized formamides have *Z*-configuration. Then, we proceeded in the dehydration with $POCl_3/Et_3N$ which afforded the corresponding isocyanides **8**–**13**. In all cases, we got a mixture of an equimolar mixture of the α- and β-anomer which we were able to separate by chromatography (Scheme 1). All the synthesized formamides and isocyanides have the glycosylpyranose form. Although in most of the sugar formamides the β-anomer was the predominant one, epimerization occurred, most probably due to the basic conditions of the dehydration step (excess of Et_3N), yielding the anomeric mixture of isocyanides. Control of the anomeric center can be achieved by using triphosgene with 4-methylmorpholine as a base at –78 °C. For example, in case of β-glucosyl formamide (**2**), although substantial amount of the starting material was recovered (≈ 20 %), full retention of its stereochemistry was observed into the corresponding isocyanide (**8a**) (see Supporting Information, SI).

After quite some efforts, we were able to obtain good quality crystals of the β-glucosyl (**2**), β-galactosyl (**3**) and α-arabinosyl (**4**) formamides and determine their 3D structure, verifying our previous NMR analysis[25] and offering very useful information for the design of analogous derivatives. Both the stereochemistry on the anomeric center and the (*Z*)-configuration of the formamide (the hydrogen of the anomeric carbon is oriented on the same direction with the carbonyl group of the formamide) is proven beyond doubt (Figure 2, A). As expected, the formamido group occupies an equatorial position in all the synthesized derivatives. In addition, we determined several X-ray crystal structures of the isocyanides such as α- and β-glucosyl (**8a,b**), β-galactosyl (**9a**), β-arabinosyl (**10a**) and the disaccharide β-lactosyl isocyanide (**12a**) (Figure 2, B). For once more, we



Scheme 1. Rapid access to sugar formamides **2**–**7** and isocyanides **8**–**13** by a Leuckart-Wallach reductive amination and a subsequent dehydration.

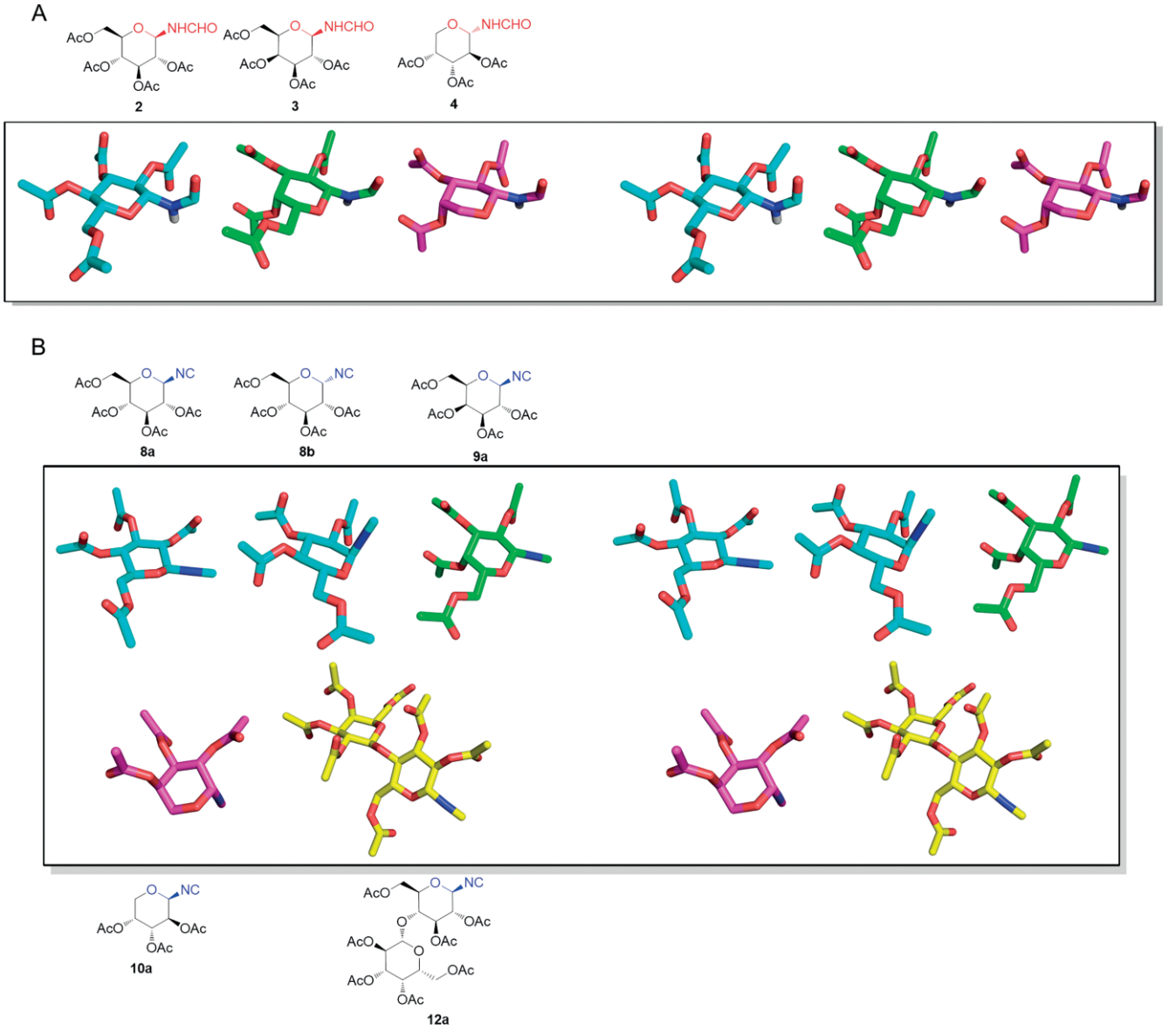


Figure 2. Stereoscopic view of the molecular geometries in the crystal structures of corresponding formamides and isocyanides; (A) β-glucosyl formamide **2** (CCDC 1869941), β-galactosyl formamide **3** (CCDC 1869945) and α-arabinosyl formamide **4** (CCDC 1870508); (B) β-glucosyl isocyanide **8a** (CCDC 18670509), α-glucosyl isocyanide **8b** (CCDC 1870510), β-galactosyl isocyanide **9a** (CCDC 1869944), β-arabinosyl isocyanide **10a** (CCDC 1869943) and β-lactosyl isocyanide **12a** (CCDC 1869946).

verified the previous NMR analysis concerning the anomeric stereochemistry of the sugars. We have also obtained crystal structures of the corresponding per-*O*-acetylated α-D-ribose (CCDC 1870512) and α-D-deoxyribose (CCDC 1870511) in which most of the acetyl groups are oriented axially (see SI, section 4).

It is noteworthy, that in the cases of **8a** and **10a** the isocyano group is axially oriented (Figure 2, B). In addition, most of the acetyl groups (with frequent exception of the 5-substituted ones in **9a**, **4** and **10a**) adopt an equatorial conformation which corresponds to our observations based on the CSD data analysis (see SI, section 5).

Data mining of the Cambridge Structural Database (CSD, ConQuest™)[30] with a torsion angle inspection, confirmed the aforementioned findings; analyzing 92 structures of different sugar amides (Figure 3, A), the -NHCOR substituent has predominately an equatorial orientation (≥ ±150, TOR1, Figure 3, B) and almost exclusively the *(Z)*-configuration (TOR2, Figure 3, C), which is in line the previously published results.[26]

The conformational analysis in the crystalline state revealed also the anomeric effect of the nitrogen atom of the isocyanide group which verifies the NMR studies and results of Ichikawa et al.[27] They described that in certain xylopyranosyl isocyanides, the isocyano group adopts an axial orientation displaying the anomeric effect. The inspection of bond lengths and angles confirms the anomeric effect. Due to the electron withdrawing character of the isocyano group, the lone pair of oxygen is delocalized through the anomeric effect (Figure 4, Antiperiplanar Lone Pair Hypothesis). This leads to a O1–C2 double-bond character, which should tend to render the atoms involved some-

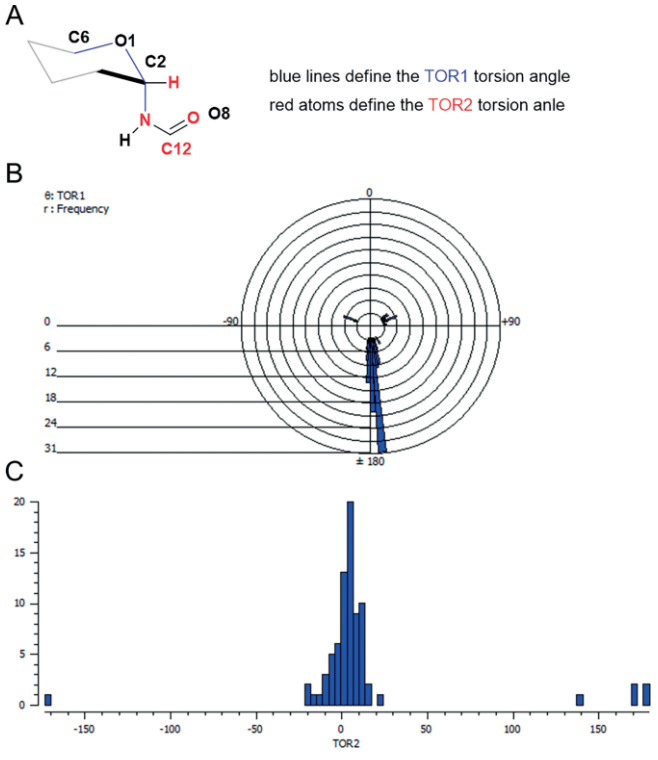


Figure 3. (A) Geometrical features of sugar formamides (92 hits); torsion angle C6–O1–C2–N (namely TOR1, marked as blue lines) and torsion angle H–N–C12–O8 (namely TOR2, marked as red atoms); (B) polar histogram of the TOR1 distribution showing the dominant fraction of molecules in the equatorial conformation [±150°–(±190°)];[31] (C) histogram presenting the TOR2 distribution, confirming predominant *(Z)*-configuration.

what trigonal in character. Indeed, comparing the crystal structures **8b** and **10a** with **8a**, **9a** and **12a**, the O1–C2 bond in axial orientation is shorter than in equatorial [1.406(6) Å and 1.402(3) Å compared with 1.414(4) Å and 1.417(2) Å, respectively] whereas the C2–N bond is longer [1.443(8) Å and 1.455(4) Å compared with 1.423(4) Å and 1.431(4) Å, respectively]. Moreover, the angles of C6–O1–C2 [113.1(4)° and 113.5(2)° compared with 110.2(2)°, 110.9(1)° and 109.8(3)°, respectively] and O1–C2–N [110.5(5)° and 110.2(2)° compared with 107.4(3)°, 105.8(1)° and 107.0(3)°, respectively] are wider than the corresponding equatorial ones demonstrating a more "trigonal" conformation (SI, Table S2).

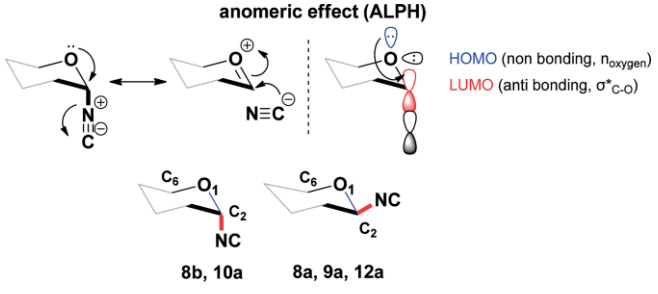


Figure 4. Structural geometrical parameters selected for the anomeric effect confirmation (antiperiplanar lone pair hypothesis, ALPH) for molecules with the isocyano group in axial position; O1–C2 bond is shorter than the typical O–C and C2–N bond is longer than the typical C–N bond. Also, C6–O1–C2 and the O1–C2–N angles are wider than a typical tetrahedral angle.

A thorough analysis in the ConQuest™ confirmed the existence of the anomeric effect of the nitrogen of the isocyanide group that is observed when the latter occupies an axial orientation. We statistically inspected the angles of C6–O1–C2 (namely ANG1) and O1–C2–N (namely ANG2) vs. the torsion angle C6–O1–C2–X (namely TOR1) of 1954 structures of substituted sugars with similar substitution pattern and compared with our isocyanides (X = O or N) considering both in axial and equatorial orientation (Figure 5, A). The mean values of the two above mentioned angles for the axial position (ANG1 = 113.5°, ANG2 = 111°) are higher than the corresponding equatorial ones (ANG1 = 112, ANG2 = 108°) and are very similar with these measured for our structures (Figure 5, B,C, Table S2).

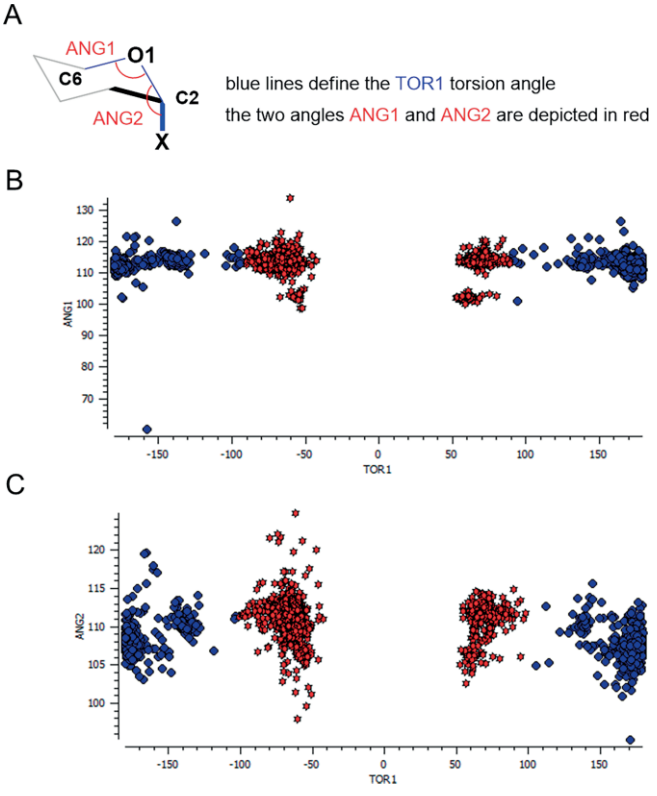
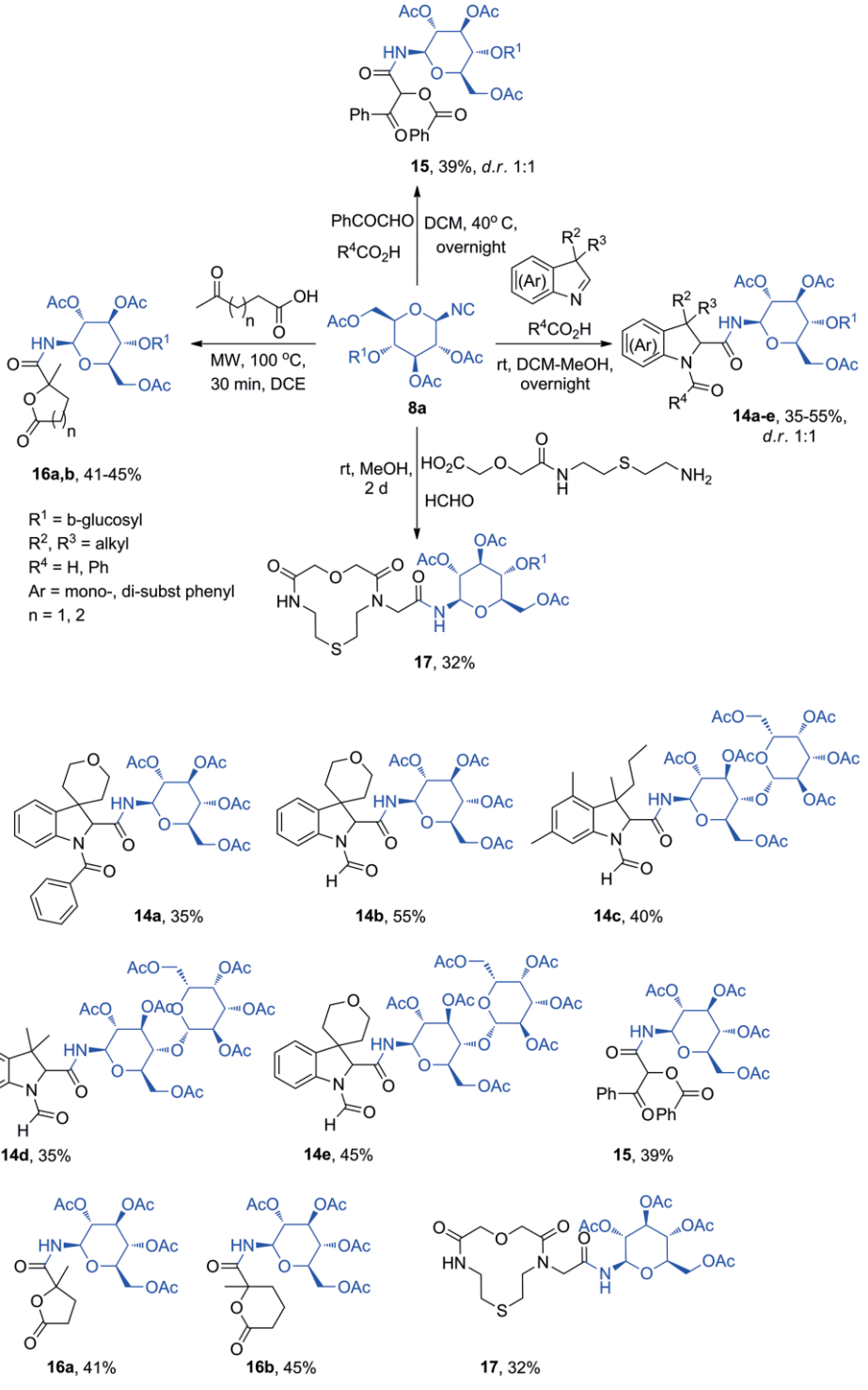


Figure 5. (A) 1-Substituted sugar derivative with X = O, N; (B,C) scatterplot of TOR1 vs. ANG1 and ANG2, respectively; blue dots represent the substituents of the 2-position in equatorial conformation (torsion angle: ±150°–(±190°);[31] whereas red spots represent the corresponding ones in axial conformation [torsion angle: ±30°–(±90°)].[31]

In order to demonstrate the potential of incorporating sugar moieties in bioactive molecules, such as macrocycles or sp^3 hybridized derivatives, we performed Ugi and Passerini three component reactions (U-3CR, P-3CR) (Scheme 2). We successfully combined sugars with spiro indole-based compounds,[32] lactones,[33] and artificial macrocycles.[34] Thus, we performed an U-3CR on the indole-based imines yielding compounds **14a**–**e**. Then, utilizing phenyl glyoxal in a Passerini reaction, we were able to synthesize compound **15** which could be transformed to a variety of derivatives.[35–37] In addition, we performed a Passerini reaction with keto-carboxylic acids affording the corresponding γ- and δ-lactone derivatives **16a**,**b**. In the cases of compounds **14** and **15**, we obtained the epimeric mixture



Scheme 2. An easy access to chimeric derivatives **14**–**17** containing sugar moieties with organic molecules such as macrocycle, lactones and spiro indoles.

(*dr* ≈1:1) whereas, regarding **16a**,**b**, it seems that one epimer is the predominant one. Artificial macrocycles showed promising results with certain protein–protein interactions and control of physicochemical properties. Herein, based on our recent synthetic strategy, we synthesized the macrocycle **17** bearing a sulfur atom combined with β-glucose via an Ugi-macrocyclization reaction (Scheme 2).

Conclusions

In conclusion, we were able to synthesize various unprecedented mono-, di- and trisaccharide formamides and isocyanides. The anomeric effect of isocyano glycosides was described by their X-ray structures and CSD data mining. Based on the obtained results, we provided a structural analysis with clarifica-

tions on the stereochemistry and useful insights into the anomeric effect of the isocyano group. Additionally, we incorporated the aforementioned sugars into drug-like molecules, providing novel glyconjugates. Knowing the three-dimensional structure of a molecule is of outmost importance in the design of molecules of specific shape and size. This design is nowadays applied to the drug design and drug discovery campaigns. A future work, which is undergoing, includes the screen of these compounds in various protein–protein interactions, taking advantage the obtained structural information.

Experimental Section

Supporting information contains general procedures, characterization data of all the compounds, crystal structure determination and data mining of the CSD.

CCDC 1870512 (for **β-D-ribose**), and 1870511 (for **β-D-deoxyribose**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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Keywords: Amides · Isocyanides · Oligosaccharides · Multicomponent reactions · Anomeric effect

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