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Versatile Synthesis of Diaminoxylosides via Iodosulfonamidation of Xylal Derivatives

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Dedicated to the memory of Professor Klaus Hafner (1927–2021).

D-Xylose is a special monosaccharide found in various organisms, which is characterized by conformational dynamics between different pyranose ring forms depending on the substitution pattern. With a perspective to study the conformational equilibria of xylosides and eventually use them as conformational switches, we sought an entry into a flexible synthesis of 2,4-diamino-xylosides. In particular, we synthesized 4-bromophenyl 2,4-diamino-3-*O*-(4-bromophenyl)-β-D-xyloside from L-arabinose utilizing a concomitant epimerization and differentiation at position 4 and iodosulfonamidation of a difunctional xylal at a later stage of the synthetic pathway. This strategy provides xylose derivatives with high stereochemical precision and a high degree of functionalization. The obtained xylose derivatives are of interest as conformational hinge molecules and as orthogonally protected triamino scaffold molecules.

Introduction

Carbohydrates are essential components of all living organisms playing fundamental roles in numerous biochemical processes in health and disease.[1] They constitute a class of biomolecules including oligo- and polysaccharides as well as various glycoconjugates, which is characterized by an unmatched molecular diversity and unprecedented molecular space.[2] This complexity is translated into biochemical function largely by interaction with specialized carbohydrate-recognizing proteins, the lectins.[3]

In order to better understand carbohydrate-dependent cell biology, much research has been dedicated to the elucidation of the structural factors governing carbohydrate recognition. These include stereochemical factors, regioselective substitution (phosphorylation, sulfation, acetylation, i.e.), important supramolecular effects (multivalence and heteromultivalence, glycoepitope presentation, i.e.),[4] and conformational dynamics.[5]

Here, we focus on the chemistry of a rare but special monosaccharide constituent of *N*-glycoproteins, namely D-xylose. Xylopyranosides are characterized by an equilibrium between ring conformations that depends on the substitution pattern and on the solvent in which it is studied.[6] This is of relevance both in the context of biology, chemistry and material science. Conformational effects in sugar rings are difficult to control and to study, though this would be highly desired in the field of glycobiology in order to advance our understanding of carbohydrate-protein interactions.[7] In carbohydrate chemistry on the other hand, the reactivity of glycosyl donors can be altered by conformational control.[8] In material science finally, D-xylose derivatives are of interest as molecular switches. Notably, Hashimoto and Yuasa have employed xylopyranosides as conformational hinge units in various context.[9] For example, 2,4-diamino-β-D-xylosides were switched between the $^4C_1$ and the $^1C_4$ chair conformation by complexation of the two amino groups with metal ions (Figure 1A).[9] Sakakibara and Ariga have employed a pyrene-functionalized methyl β-D-xyloside to flip the chair conformation of the sugar ring in a Langmuir monolayer by varying the surface pressure.[10] Here, ring flip was detected by excimer emission of staggered pyrene residues.

While the conformational control of monosaccharides appears highly interesting to achieve molecular machines and molecular sensors as well as to study carbohydrate foldamers,[11] few examples of monosaccharide switches have been published so far. Coutrot and Busseron showed that the conformation of a pyridinium mannoside can be switched in a supramolecular mannosyl [2]rotaxane.[12] Pedersen and coworkers controlled the chair conformation of a 2,4-di-pyridine-functionalized glucoside by metal-chelation in order to alter the stability of liposomes.[13] Otherwise, β-D-xylose derivatives have been employed as prime candidates for switching between monosaccharide conformers.[9] This is due to the fact that the energy barriers for puckering interconversions between β-D-xylose conformers are especially low (2.3 kcal/mol between $^1C_4$ and $^4C_1$).[14]

In order to further study and utilize the conformational dynamics of xylosides, we have commenced a project targeting β-D-xylose derivatives as molecular switches on the one hand and as functional molecular scaffolds on the other. In a first

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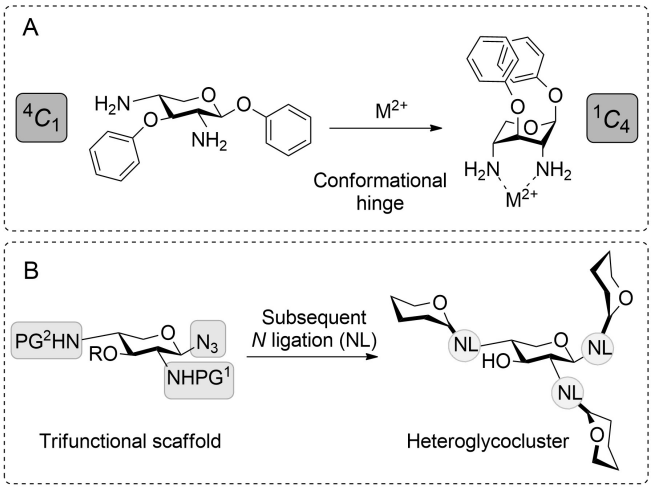

Figure 1. The synthesis of diamino-xylosides is the focus of this account because the conformational dynamics of 2,4-diamino-β-D-xylosides between the $^4C_1$ and the $^1C_4$ chair conformation requires further studies to control and utilize the conformational dynamics of monosaccharides. In particular, diamino-xylosides can be employed as molecular switches, for example by complexation of the two amino groups with metal ions (A). On the other hand, orthogonally protected 2,4-diamino-β-D-xylosyl azides are of interest as scaffold molecules for the synthesis of heteromultivalent glycoclusters (B). PG: protecting group.

part, we focused on the synthesis of orthogonally protected diamino xylose derivatives, in particular 3-*O*-aryl-substituted aryl β-D-xylosides (Figure 1A), and of orthogonally protected diamino-xylosyl azides as privileged scaffold molecules for the synthesis of heteromultivalent glycoclusters (Figure 1B).

Previously, 2,4-diamino xylosides were synthesized from the respective methyl 2,4-diazido-functionalized β-D-xyloside (D in Figure 2), where the two azido functional groups were introduced via a tandem ring opening of a Černý epoxide (C) with sodium azide.[15] As a disadvantage of this step, regioisomeric diazides are obtained as side products. Furthermore, in order to exchange the methyl aglycone in D and achieve various other xylosides, further steps are required, involving acetolysis of the methyl xyloside and conversion into a suitable xylosyl donor. However along this synthetic path, the desired xylosides are obtained as anomeric mixtures owing to the lack of anomeric control of the 2-azido group.[9d,e]

In order to overcome the weaknesses of the established route towards 2,4-diamino-β-D-xylopyranosides and moreover, to enable the introduction of two orthogonally protected amino groups at positions 2 and 4, we envisaged a synthetic route starting from L-arabinose, the C-4-epimer of D-xylose. The axial orientation of the 4-OH group in L-arabinose allows to distinguish this position from all others and achieve D-*xylo*-configured intermediates like E (Figure 2) bearing a protected amino function at C-4 after epimerization (S_N2 reaction). The glycosylbromide E can be converted into the orthogonally functionalized glycal F with only two remaining stereocenters. However, F gives rise to the strictly stereoselective synthesis of the desired β-D-xylosides G employing Danishefsky's iodosulfonamidation[16] as the key step of this synthetic pathway (Figure 2). Iodosulfonamidation of F allows to establish the second, orthogonally protected amino function at position 2 of the xyloside as well as the β-stereospecific installation of various aglycone moieties at the anomeric center, including an azide function, which can be employed as a third, masked amino function.

In this account we demonstrate the power of the outlined synthetic route from L-arabinose to D-xylosides with the synthesis of various 2,4-diamino-β-D-xylopyranoside derivatives, which can eventually be utilized to study (i) the conformational dynamics of xylosides, (ii) to make new carbohydrate-based

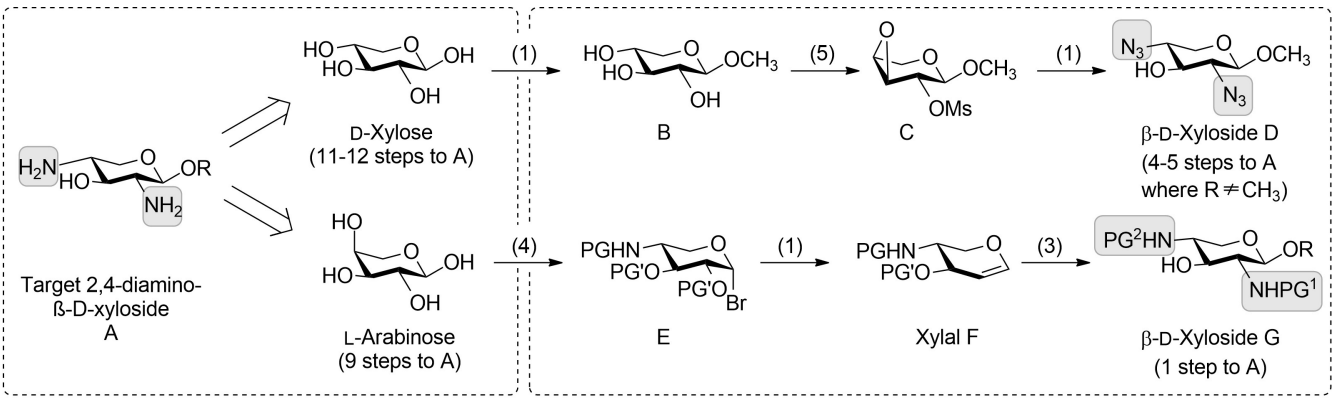

Figure 2. We seeked a synthetic route towards 2,4-diamino-β-D-xylopyranosides A with variable aglycone R that includes the option of orthogonal protection of the amino groups (PG^1 and PG^2 in G). A literature-known route is based on the conversion of methyl β-D-xyloside B, which is derived from D-xylose in one step. The Černý epoxide C is reached in 5 steps from B and then a tandem ring opening of C with NaN_3 delivers the 2,4-diazido-dideoxy-β-D-xylopyranoside D, in which the azido groups mask the desired amino functions.[9a] However, in order to exchange the methyl aglycone in D, another 4 to 5 steps are required, depending on which xylosyl donor is chosen.[9a,b] Our new approach to 2,4-diamino-β-D-xylopyranosides starts from L-arabinose to facilitate the discrimination of the 4-position, furnishing the xylosylbromide E in 4 steps including epimerization at C-4. From E, the orthogonally protected xylal F is obtained in one step and then iodosulfonamidation as the key step of this pathway allows to convert F into various xylosides G with the important advantage of full regio- and stereoselectivity. In addition, the amino groups at C-2 and C-4 can be orthogonally protected (PG^1 and PG^2). Note that the number of steps between the depicted intermediates is given in brackets above the reaction arrows. Ms: mesyl, PG: protecting group.

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molecular switches and (iii) to serve as orthogonally protected multifunctional scaffold molecules.

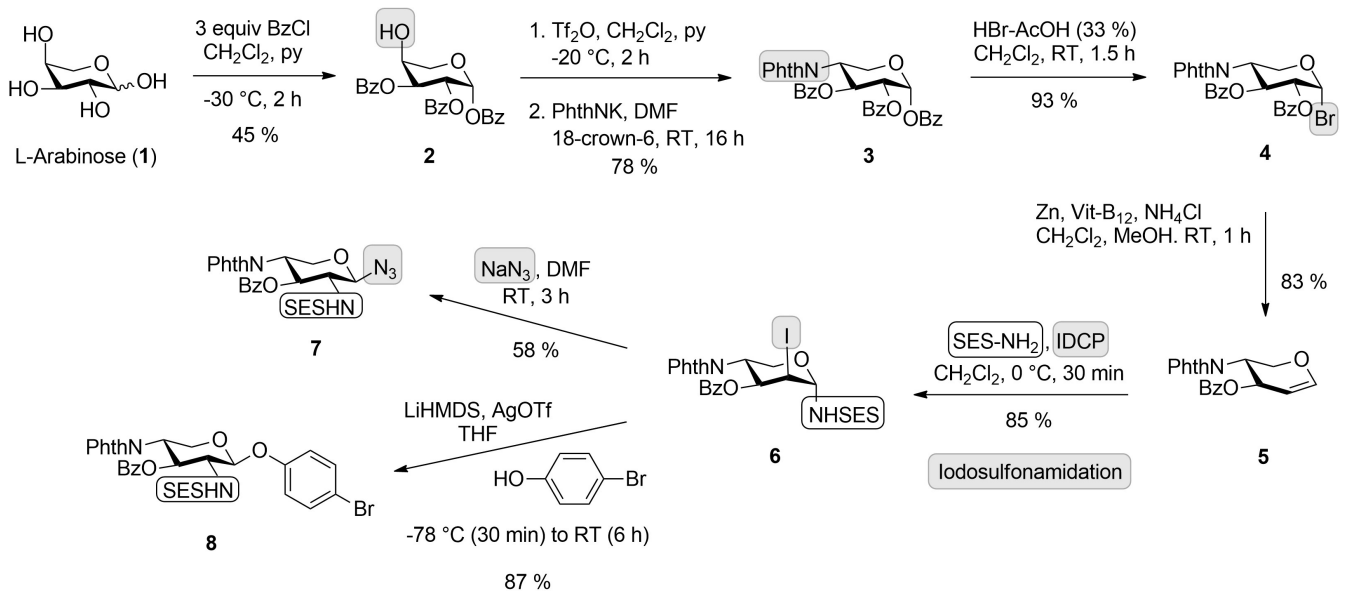
Results

Starting with L-arabinose (**1**), the axial 4-hydroxy group being the least reactive one allows regioselective benzoylation[17] to achieve the known 1,2,3-tri-*O*-benzoylated arabinose derivative **2**[18] (Scheme 1). Next, activation of the free hydroxy group with triflic anhydride under standard conditions, followed by nucleophilic substitution of the intermediate 4-triflate with potassium phthalimide yielded the epimerized *xylo*-configured pentose **3**. The reaction benefits from the addition of potassium-complexing crown ether, improving the yield from approx. 60% to almost 80% over two steps. Hydrogen bromide in acetic acid converts the xylose derivative **3** into the respective glycosyl bromide **4** which serves as the starting material for the synthesis of the xylal **5** representing the key intermediate of this synthetic route towards the orthogonally amino-functionalized xylose derivatives **7** and **8**.

Glycals are classical intermediates in carbohydrate chemistry and numerous procedures for their synthesis have been described.[19] Here, a combination of zinc powder and vitamin B_{12} delivers the di-functionalized xylal **5** in high yield under optimized reaction conditions. In this reaction, cobalt(I), which results from the vitamin B_{12} cobalt(III) after reduction with zinc, inserts into the anomeric C–Br bond in an oxidative addition step, followed by reductive elimination to the corresponding glycal.[20]

In order to establish a protected amino group at the 2-position, we first employed xylal **5** in Lemieux's classical azidonitration reaction applying sodium azide and ceric ammonium nitrate (CAN).[21] Azidonitration has frequently been used for the aminohydroxylation of glycals via the respective 2-azido-2-deoxy-glycosyl nitrates. While the main advantage of this reaction is its high regioselectivity, delivering the azido group strictly at C-2, its stereoselectivity strongly depends on the configuration and the protecting group pattern of the employed glycal.[22] In fact, azidonitration of the xylal **5** unfortunately delivered a mixture of 2-azido-2-deoxy-glycosyl nitrates of the *xylo* and the *lyxo* series. Therefore, we turned to Danishefsky's iodosulfonamidation[23] where iodonium di-*sym*-collidine perchlorate (IDCP) and a suited sulfonamide are employed to convert glycals into *trans*-diaxial iodosulfonamides. We used 2-(trimethylsilyl)ethanesulfonamide (SES-NH_2) as the trimethylsilylethyl group is fluoride-labile and can be removed under conditions orthogonal to the cleavage of the phthalimide protecting group at C-4.[23] IDCP attacks the glycal from the β-face forming a strained three-membered iodonium ring which is opened by the nucleophilic sulfonamide affording the *trans*-diaxial *lyxo*-configured iodosulfonamide **6** as the only stereoisomer in 85% yield (Scheme 1). However, it is crucial to stop the reaction after 30 min at 0 °C to avoid anomerization of the *trans*-diaxial product into the inactive 1,2-*cis* isomer, an unwanted epimerization which is facilitated by electron-withdrawing groups.[24]

By simple stirring with sodium azide in DMF, the iodosulfonamide **6** rearranges to the 2-(trimethylsilyl)ethanesulfonamido-functionalized β-D-xylosyl azide **7**. This stereoselective reaction is believed to proceed via a *N*-sulfonyl aziridine intermediate, which is opened by the azide nucleophile from the β-face.[25] It delivers 2-amino-glycosyl azides with inverted configuration at C-1 and C-2. Hence, this synthetic sequence allows to prepare protected (respectively masked) triamino sugars from xylal **5** with perfect regio- and stereoselectivity.



Scheme 1. The key reaction en route to the orthogonally amino-functionalized xylose derivatives **7** and **8** is the iodosulfonamidation of the bifunctional xylal **5**, which is derived from L-arabinose after inversion at C-4 and reductive 1,2-elimination. IDCP: iodonium di-*sym*-collidine perchlorate, SES-NH_2: 2-(trimethylsilyl)ethanesulfonamide ($TMSCH_2CH_2SO_2NH_2$).

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Likewise, the iodosulfonamide **6** can be converted into glycosides, however, this reaction requires the addition of a silver salt promoter (AgOTf) and a base (LiHMDS) in order to deprotonate the attacking alcohol (here a phenol derivative) and the NHSES group. This option widens the scope of the reaction allowing the synthesis of a vast diversity of 2-amino-glycosides. Because we wish to eventually study diaminoxylosides as conformational switches, we planned to install aromatic moieties at position 1 and 3 of the sugar ring, to allow stabilization of the $^1C_4$ chair conformation by π-π interactions. Hence, the glycosylsulfonamide **6** was treated with 4-bromophenol, LiHMDS and AgOTf to obtain the trifunctional 4-bromophenyl β-D-xyloside **8** in high yield and again with complete regio- and stereoselectivity.

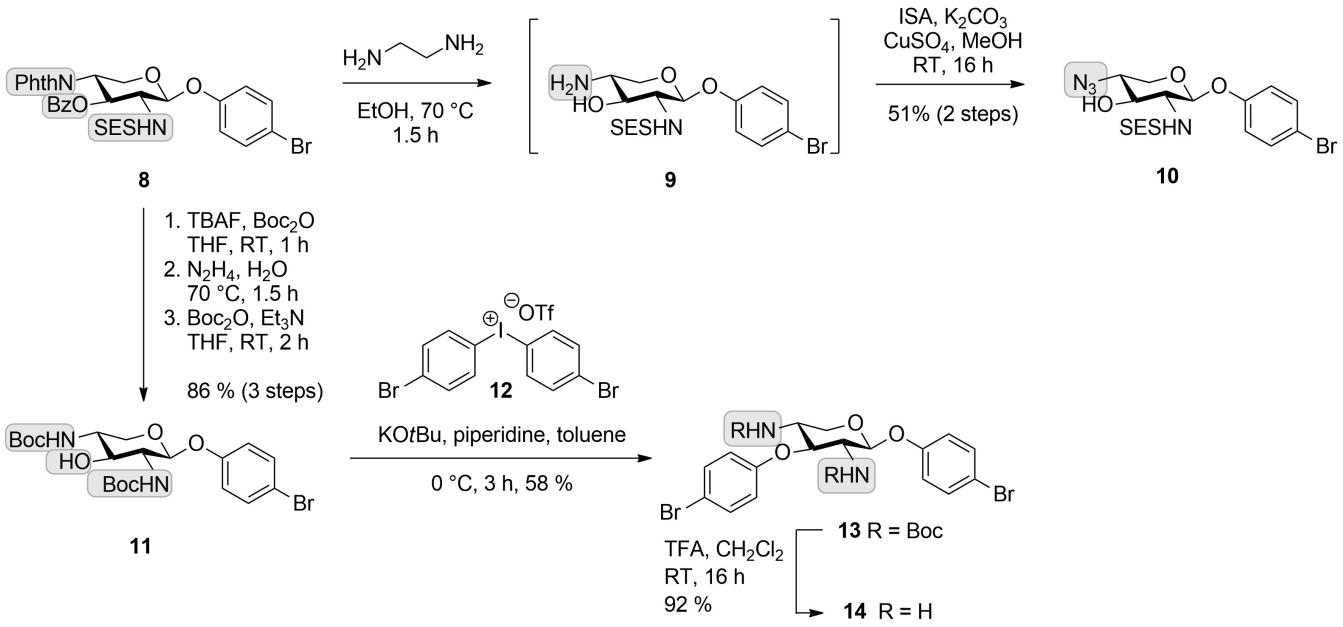
The masked amino groups of **7** and **8** can be addressed independently from each after orthogonal activation. In this account, the xyloside **8** was carried on, in order to functionalize the 3-position with a 4-bromophenyl moiety, which would interact with the 4-bromophenyl aglycone in the $^1C_4$ chair conformation. To this end, it was planned to remove the 3-*O*-benzoyl protecting group under basic conditions and subsequently establish the desired ether. However, the benzoyl protecting group could not be removed while leaving the phthalimide intact. For example, Zemplèn conditions (NaOMe in MeOH) cleave the phthalimide delivering the respective *ortho*-methoxycarbonyl amide. Thus, we employed ethylenediamine at 70 °C to concomitantly remove the 3-*O*-benzoyl and 4-phthalimido group yielding the amine **9**, which was treated in situ with the azide transfer reagent imidazole-1-sulfonyl azide (ISA) to give the corresponding azide **10** in fair yield (51% over two steps, Scheme 2). Xyloside **10** represents another orthogonally masked diamino sugar, which can be utilized, i. a., for the synthesis of heteromultivalent glycoclusters (cf. Figure 1B and **7** and **8**).

In order to achieve an etherification at position 3 of the xyloside **8**, it is necessary to first remove the SES protecting group as it represents the more nucleophilic group in comparison to alcohols which are employed in an etherification reaction. Removal of the SES group with TBAF was possible under mild conditions with addition of Boc_2O to obtain the respective amine as Boc derivative as reported earlier.[26] Hydrazinolysis of the phthalimide at position 4 and again in situ Boc protection delivered the uniformly protected diamine **11** in a one-pot reaction and 86% overall yield.

For the introduction of the desired 4-bromophenyl ether, Olofsson's *O*-arylation method using diaryliodonium triflates was employed.[27] When the xyloside **11** was treated with the iodonium triflate **12**[28] in the presence of KO*t*Bu, the desired xyloside **13** was obtained. In order to prevent the formation of regioisomers arising from an unwanted aryne intermediate,[29] piperidine (0.3 equiv) was added as an aryne scavenger. In the last step, the Boc-protected 2- and 4-amino groups were liberated by treatment with TFA to furnish the desired diamino xyloside **14** with quantitative conversion.

Discussion and Conclusion

N-Functionalized carbohydrates are of utmost importance as constituents of cell surface glycoconjugates and glycosylated drugs such as steroidal glycosides.[30] D-Xylose is a special monosaccharide constituent of glycoconjugates, as it can constitute a conformational equilibrium between various pyranose ring forms depending on the substitution pattern at the



Scheme 2. Deprotection of the xyloside **8** and access to the target 1,3-arylated 2,4-diamino-β-D-xyloside **14**. ISA: imidazole-1-sulfonyl azide; TBAF: tetra-*n*-butylammonium fluoride.

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sugar ring.[6,14,31] Due to this special feature, xylose has been utilized as conformational switch.[9]

In order to further study and utilize the conformational dynamics of xylosides, we sought a flexible synthetic strategy for the preparation of 2,4-diamino-β-D-xylosides and of orthogonally protected or masked, respectively, di- and triamino xylose derivatives to eventually achieve switchable xylose-based heteroglycoclusters.

It turned out that starting from L-arabinose, 4-amino-functionalized D-xylose derivatives such as **3** can be readily accessed, giving rise to difunctional xylals such as **5** (Scheme 1). Then, iodosulfonamidation and the following rearrangement of the resulting 2-deoxy-2-iodo-glycosyl sulfonamides (**6**) provide access to a wide range of orthogonally protected 2,4-diamino xylosides with high precision. This is a robust and flexible synthetic route, reducing the number of steps of synthetic pathways used before and circumventing their downsides.[9] The beauty of this synthetic pathway lies in its convincing stereo- and regiochemistry, its tolerance to a wide range of protecting groups, and its flexibility regarding the stereoselective introduction of various anomeric moieties. Iodosulfonamidation is the method of choice for the synthesis of 2-amino-xylosyl azides and 2-amino-xylosides, including thioglycosides. Combined with our approach to difunctional xylals, it also allows the versatile synthesis of privileged scaffold molecules like **7**, possessing two orthogonally protected amino functional groups at C-2 and C-4 and a masked amino function (N_3) at the anomeric center.

So far, ^{1}H NMR spectroscopy suggests that the $^4C_1$ conformation is predominating in all synthesized xylose derivatives with the exception of the bis-Boc-protected 2,4-diamino-xylosides **11** and **13**, where signal line broadening indicates an equilibrium of various ring conformations, which cannot be resolved by NMR spectroscopy. The exciting conformational dynamics of especially **13** will be further studied. Moreover, we will utilize both installed bromophenyl moieties at positions 1 and 3 of the pyranose ring to achieve the respective biphenyl cluster glycosides and investigate them as conformational switches. Di- and trifunctional xylose derivatives such as **7**, **8**, and **10** will be employed in the synthesis of heterovalent glycoclusters.

Experimental Section

General Methods: Moisture-sensitive reactions were carried out in flame-dried glassware and under a positive pressure of nitrogen. Analytical thin layer chromatography (TLC) was performed on silica gel plates (GF 254, Merck). Visualization was achieved by UV light and/or with 10% sulfuric acid in ethanol, vanillin (3.0 g vanillin and 0.5 mL H_2SO_4 in 100 mL EtOH) or ninhydrin, followed by heat treatment at approx. 200 °C. The products were purified by flash chromatography on silica gel columns (Merck, 230–400 mesh, particle size 0.040–0.063 mm) or by automated flash chromatography using a puriFlash 450 device from the Interchim® company. Optical rotations were measured with a PerkinElmer 241 polarimeter with a sodium d-line (589 nm) and a cuvette of 10 cm path length, in the solvents indicated. Proton (^{1}H) nuclear magnetic resonance spectra and carbon (^{13}C) nuclear magnetic resonance spectra were recorded on a Bruker DRX-500 and AV-600 spectrometer. Chemical shifts are referenced to internal standard tetramethylsilane (TMS) or to the residual proton of the NMR solvent. Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad signal), coupling constant in Hertz (Hz) and integration. Full assignment of the signals was achieved by using 2D NMR techniques (^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC, ^{1}H–^{1}H COSY-DQF). Infrared (IR) spectra were measured with a PerkinElmer FT-IR Paragon 1000 (ATR) spectrometer and were reported in cm^{-1}. ESI mass spectra were recorded on a LCQ Classic from Thermo Finnigan.

The preparation and analytical data of compounds **2**–**4** and **10** are described in the Supporting Information together with the NMR spectra of all synthesized compounds.

3-O-Benzoyl-4-deoxy-4-phthalimido-D–xylal 5: Vitamin B_{12} (97.3 mg, 71.8 μmol) was dissolved in dry MeOH (25 mL) and zinc powder (5.63 g, 86.2 mmol) and ammonium chloride (2.89 g, 86.2 mmol) were added. The suspension was stirred vigorously for 45 min. Then, the xylosyl bromide **4** (3.95 g, 7.18 mmol) was dissolved in dry CH_2Cl_2 (10 mL) and the solution added to the reaction mixture. Stirring at RT was continued for 1 h. The mixture was diluted with CH_2Cl_2 and filtered over a pad of celite. The solvent was removed under reduced pressure and the crude product was taken up in CH_2Cl_2 and H_2O. It was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, it was filtered, and the filtrate concentrated to dryness under reduced pressure. Purification by flash column chromatography (cyclohexane/ethyl acetate, 3:1) led to **5** (2.08 g, 5.96 mmol, 83%) as a colorless solid. R_f 0.40 (cyclohexane/ethyl acetate, 9:1); $[\alpha]^{20}_D = -207.82$ (*c* 0.05, CH_2Cl_2); IR (ATR): ν_{max}/cm^{-1} = 3061, 2249, 1778, 1708, 1645, 1379, 1268, 1069, 910, 711; ^{1}H NMR (500 MHz, $CDCl_3$, 300 K): δ = 7.95–7.92 (m, 2H, 2 Bz–CH_{ortho}), 7.85–7.81 (m, 2H, 2 NPhth–CH_{ortho}), 7.74–7.68 (m, 2H, 2 NPhth–CH_{meta}), 7.54–7.49 (m, 1H, 2 Bz–CH_{para}), 7.42–7.36 (m, 2H, 2 Bz–CH_{meta}), 6.56 (dd, $^4J_{1,3}$ = 6.1 Hz, $^3J_{1,2}$ = 1.4 Hz, 1H, H-1), 6.32–6.27 (m, 1H, H-3), 4.99 (dd, $^3J_{2,3}$ = 6.1 Hz, $^3J_{1,2}$ = 1.4 Hz, 1H, H-2), 4.91 (ddd, $^3J_{4,5a}$ = 12.0 Hz, $^3J_{4,3}$ = 8.7 Hz, $^3J_{4,5b}$ = 4.1 Hz, 1H, H-4), 4.81 (dd, $^3J_{5a,4}$ = 12.0 Hz, $^2J_{5a,5b}$ = 10.6 Hz, 1H, H-5a), 4.11 (dd, $^2J_{5a,5b}$ = 10.6 Hz, $^3J_{5b,4}$ = 4.1 Hz, 1H, H-5b) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 300 K): δ = 167.78 (2 C(O)-Phth), 166.23 (C(O)Ph), 146.79 (C-1), 134.25 (2 Phth–CH_{meta}), 133.11 (Bz–CH_{para}), 131.56 (Bz-C_{quart}), 129.70 (2 Bz–CH_{ortho}), 128.36 (2 Bz–CH_{meta}), 123.56 (2 Phth–CH_{ortho}), 100.47 (C-2), 67.66 (C-3), 65.04 (C-5), 49.02 (C-4) ppm; ESI-HRMS: *m/z* = 372.0840 $[M+Na]^+$ (calcd *m/z* = 372.0842 for $[M+Na]^+$).

3-*O*-Benzoyl-2,4-dideoxy-2-iodo-4-phthalimido-α-D–lyxopyranosyl-2-(trimethylsilyl)ethanesulfonamide 6: The xylal **5** (50.0 mg, 143 μmol) and 2-(trimethylsilyl)ethanesulfonamide (104 mg, 572 μmol) were dissolved in dry CH_2Cl_2 (1.00 mL) and 4 Å molecular sieve (freshly activated) was added. It was stirred for 30 min at RT. The mixture was cooled to 0 °C and iodonium di-*sym*-collidine perchlorate (IDCP) (268 mg, 572 μmol) was added. It was stirred for 30 min at 0 °C. Then the reaction mixture was diluted with ethyl acetate and filtered over a pad of celite. The organic phase was washed with sodium thiosulfate, copper sulfate and brine, dried over $MgSO_4$. It was filtered and the filtrate concentrated to dryness under reduced pressure. Purification by column chromatography (toluene/ethyl acetate, 9:1) gave **6** (79.8 mg, 122 μmol, 85%) as a colorless solid. R_f 0.40 (cyclohexane/ethyl acetate, 2:1); $[\alpha]^{20}_D = -18.64$ (*c* 0.05, CH_2Cl_2); IR (ATR): ν_{max}/cm^{-1} = 3304, 2953, 2253, 1774, 1714, 1383, 1263, 1022, 840, 709, 529; ^{1}H NMR (500 MHz, $CDCl_3$, 300 K): δ = 7.97–7.91 (m, 2H, 2 Bz–CH_{ortho}), 7.85−7.80 (m, 2H, 2 NPhth–CH_{ortho}), 7.74−7.69 (m, 2H, 2 NPhth–CH_{meta}), 7.57−7.51 (m, 1H, Bz–CH_{para}), 7.42–7.37 (m, 2H, Bz–CH_{meta}), 6.07 (d, $^3J_{NH,1}$ = 8.3 Hz, 1H, NH), 5.65 (dd, $^3J_{NH,1}$ = 8.5 Hz, $^3J_{1,2}$ = 2.9 Hz, 1H, H-1), 5.35 (dd, $^3J_{3,4}$ = 9.0 Hz, $^3J_{2,3}$ = 4.1 Hz, 1H, H-3), 5.03−4.94 (m, 2H, H-2, H-4), 4.26

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(dd, $^2J_{5a,5b}$ = 11.7 Hz, $^3J_{5a,4}$ = 10.1 Hz, 1H, H-5a), 3.93 (dd, $^2J_{5a,5b}$ = 11.8 Hz, $^3J_{5b,4}$ = 5.6 Hz, 1H, H-5b), 3.15–3.05 (m, 2H, CH_2), 1.22–1.06 (m, 2H, CH_2), 0.05 (s, 9H, TMS) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 300 K): δ = 167.93 (2 C(O)Phth), 164.92 (C(O)Ph), 134.62 (2 Phth–CH_{meta}), 133.81 (Bz–CH_{para}), 131.27 (Bz-C_{quart}), 130.11 (2 Bz–CH_{ortho}), 128.51 (2 Bz–CH_{meta}), 123.65 (2 Phth–CH_{ortho}), 84.27 (C-1), 67.02 (C-3), 59.76 (C-5), 51.38 (CH_2), 48.44 (C-4), 29.41 (C-2), 10.27 (CH_2), −1.99 (3 C, $Si(CH_3)_3$) ppm; ESI-HRMS: *m/z* = 679.0396 $[M+Na]^+$ (calcd *m/z* = 679.0402 for $[M+Na]^+$).

3-*O*-benzoyl-2,4-dideoxy-4-phthalimido-2-[2-(trimethylsilyl) ethanesulfonamido]-β-D–xylopyranosyl azide 7: To a solution of iodosulfonamide **6** (40.0 mg, 115 μmol) in dry DMF (400 μL) was added sodium azide (15.0 mg, 230 μmol) at 0 °C. The mixture was allowed to warm to RT and stirring was continued for 3 h. The reaction mixture was diluted with CH_2Cl_2 and subsequently washed with sodium bicarbonate solution and brine. It was dried over $MgSO_4$, filtered and the filtrate concentrated to dryness under reduced pressure. Column chromatography (cyclohexane/ethyl acetate, 4:1) of the resulting residue provided **7** as (28.4 mg, 66.7 μmol, 58 %) a colorless solid. R_f 0.34 (cyclohexane/ethyl acetate, 3:1); $[\alpha]^{20}_D$ = −98.64 (*c* 0.04, CH_2Cl_2); IR (ATR): ν_{max}/cm^{-1} = 3286, 2954, 2116, 1712, 1383, 1261, 710; ^{1}H NMR (500 MHz, $CDCl_3$, 300 K): δ = 7.93-7.88 (m, 2H, 2 Bz–CH_{ortho}), 7.83–7.79 (m, 2H, 2 NPhth–CH_{ortho}), 7.73–7.68 (m, 2H, 2 NPhth–CH_{meta}), 7.51–7.45 (m, 1H, Bz–CH_{para}), 7.36–7.31 (m, 2H, Bz–CH_{meta}), 6.15 (t, $^3J_{3,4}$ = 10.3 Hz, $^3J_{2,3}$ = 10.3 Hz, 1H, H-3), 5.52 (d, $^3J_{NH,2}$ = 9.2 Hz, 1H, NH), 5.02 (d, $^3J_{1,2}$ = 9.1 Hz, 1H, H-1), 4.74 (td, $^3J_{4,5a}$ = 10.8 Hz, $^3J_{4,3}$ = 10.8 Hz, $^3J_{4,5b}$ = 5.2 Hz, 1H, H-4), 4.60 (t, $^2J_{5a,5b}$ = 11.5 Hz, $^3J_{5a,4}$ = 11.5 Hz, 1H, H-5a), 4.09 (dd, $^2J_{5a,5b}$ = 11.5 Hz, $^3J_{5b,4}$ = 5.3 Hz, 1H, H-5b), 3.85–3.74 (m, 1H, H-2), 2.98–2.83 (m, 2H, CH_2), 0.95–0.88 (m, 2H, CH_2), −0.18 (s, 9H, TMS) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 300 K): δ = 167.80 (2 C, C(O)Phth), 166.89 (C(O)Ph), 134.56 (2 Phth–CH_{meta}), 133.79 (Bz–CH_{para}), 131.17 (Bz-C_{quart}), 130.11 (2 Bz–CH_{ortho}), 128.59 (2 Bz–CH_{meta}), 123.74 (2 Phth–CH_{ortho}), 90.07 (C-1), 70.68 (C-3), 63.64 (C-5), 58.46 (C-2), 51.10 (CH_2), 50.51 (C-4), 10.27 (CH_2), −2.28 (3 $Si(CH_3)_3$) ppm; ESI-HRMS: *m/z* = 594.1450 $[M+Na]^+$ (calcd *m/z* = 594.1449 for $[M+Na]^+$).

4-Bromophenyl 3-*O*-benzoyl-2,4-dideoxy-4-phthalimido-2-[2-(trimethylsilyl)ethanesulfonamido]-β-D–xylopyranoside 8: The iodosulfonamide **6** (43.0 mg, 65.5 μmol) and 4-bromophenol (17.0 mg, 98.2 μmol) were dissolved in dry THF (720 μL). Then at −78 °C lithium hexamethyldisilazane (1 M in THF, 144 μL, 144 μmol) was added dropwise. It was stirred for 10 min before a solution of silver triflate (25.2 mg, 98.2 μmol) in dry THF (150 μL) was added. The flask was covered with aluminium foil and it was allowed to warm to RT. The reaction mixture was stirred for 5.5 h. Then an excess of ammonium chloride was added and stirring was continued for further 10 min before the mixture was filtered over a pad of celite and the filtrate concentrated to dryness under reduced pressure. Purification by column chromatography (cyclohexane/ethyl acetate, 2:1) gave **8** (40.0 mg, 57.0 μmol, 87 %) as a colorless solid. R_f 0.34 (cyclohexane/ethyl acetate, 2:1); $[\alpha]^{20}_D$ = −12.3 (*c* 0.1, CH_2Cl_2); IR (ATR): ν_{max}/cm^{-1} = 3314, 1779, 1715, 1487, 1384, 1331, 1235, 1068, 839, 712, 653; ^{1}H NMR (500 MHz, $CDCl_3$, 300 K): δ = 7.94–7.89 (m, 2H, 2 Bz–CH_{ortho}), 7.75–7.70 (m, 2H, 2 NPhth–CH_{ortho}), 7.69–7.65 (m, 2H, 2 NPhth–CH_{meta}), 7.54–7.46 (m, 1H, Bz–CH_{para}), 7.43–7.39 (m, 2H, OPhe–CH), 7.38–7.32 (m, 2H, Bz–CH_{meta}), 7.02–6.98 (m, 2H, OPhe–CH), 6.11 (t, $^3J_{3,4}$ = 10.4 Hz, $^3J_{2,3}$ = 10.4 Hz, 1H, H-3), 5.26 (d, $^3J_{1,2}$ = 8.1 Hz, 1H, H-1), 5.00 (d, $^3J_{NH,2}$ = 8.6 Hz, 1H, NH), 4.80 (td, $^3J_{4,5a}$ = 10.6 Hz, $^3J_{4,3}$ = 10.6 Hz, $^3J_{4,5b}$ = 5.3 Hz, 1H, H-4), 4.51 (t, $^2J_{5a,5b}$ = 11.7 Hz, $^3J_{5a,4}$ = 11.4 Hz, 1H, H-5a), 4.11–4.02 (m, 2H, H-2, H-5b), 2.98–2.85 (m, 2H, CH_2), 0.99–0.89 (m, 2H, CH_2), −0.19 (s, 9H, TMS) ppm; ^{13}C NMR (125 MHz, $CDCl_3$, 300 K): δ = 167.76 (2 C(O) Phth), 166.91 (C(O)Ph), 155.68 (OPhe-C_{quart}), 134.47 (2 Phth–CH_{meta}), 133.77 (Bz–CH_{para}), 132.65 (2 OPhe–CH_{ortho}), 131.19 (Bz-C_{quart}), 130.05 (2 Bz–CH_{ortho}), 128.61 (2 Bz–CH_{meta}), 123.75 (2 Phth–CH_{ortho}), 118.98 (2 OPhe–CH_{meta}), 115.89 (Phe-CBr_{quart}), 100.83 (C-1), 70.46 (C-3), 61.80 (C-5), 58.66 (C-2), 51.19 (CH_2), 50.05 (C-4), 10.28 (CH_2), −2.06 (3 C, $Si(CH_3)_3$) ppm; ESI-HRMS: *m/z* = 723.0807 $[M+Na]^+$ (calcd *m/z* = 723.0803 for $[M+Na]^+$).

4-Bromophenyl 2,4-dideoxy-2,4-*N*-Boc-β-D–xylopyranoside 11: The xyloside **8** (268 mg, 382 μmol) was dissolved in dry THF (13.5 mL) and di-*tert*-butyl carbonate (2.45 mL, 11.5 mmol) was added. It was stirred at RT for 5 min before tetra-*n*-butylammonium fluoride (1 M in THF, 3.82 mL, 3.82 mmol) was added. The mixture was stirred at RT for 1 h. Then it was diluted with ethyl acetate and washed with H_2O, dried over $MgSO_4$, it was filtered, and the filtrate concentrated to dryness under reduced pressure. The crude product was dissolved in EtOH (1.00 mL) and hydrazine monohydrate (50.0 μL) was added. The mixture was heated to 70 °C and stirred for 1.5 h. Then the volatiles were removed under reduced pressure and the residue was co-evaporated with toluene (3 x). The crude product was dissolved in THF/H_2O (10 mL, 9:1) and trimethylamine (500 μL) and di-*tert*-butyl carbonate (100 μL, 469 μmol) were added. The mixture was stirred for 2 h at RT, diluted with ethyl acetate and washed with H_2O. The organic phase was dried over $MgSO_4$, it was filtered, and the filtrate concentrated to dryness under reduced pressure. Purification by column chromatography (cyclohexane/ethyl acetate, 2:1) gave **11** (116 mg, 230 μmol, 86 %) as a colorless solid. R_f 0.40 (cyclohexane/ethyl acetate, 1:1); $[\alpha]^{20}_D$ = −6.00 (*c* 0.1, acetone); IR (ATR): ν_{max}/cm^{-1} = 3307, 2980, 1682, 1538, 1487, 1237, 1169, 1035, 983, 658; ^{1}H NMR (500 MHz, acetone-d_6, 300 K): δ = 7.47–7.42 (m, 2H, OPhe–CH), 7.00–6.95 (m, 2H, OPhe–CH), 6.20 (S, 1H, NHBoc), 6.03 (S, 1H, NHBoc), 5.07 (d, $^3J_{1,2}$ = 8.0 Hz, 1H, H-1), 4.45 (d, $^3J_{3,OH}$ = 4.8 Hz, 1H, OH), 4.02 (dd, $^2J_{5a,5b}$ = 11.4 Hz, $^3J_{5a,4}$ = 5.1 Hz, 1H, H-5a), 3.81–3.71 (m, 1H, H-3), 3.67–3.57 (m, 2H, H-2, H-4), 3.39 (t, $^2J_{5a,5b}$ = 11.0, Hz, $^3J_{5a,4}$ = 11.0 Hz, 1H, H-5b), 1.41 (s, 9H, $C(CH_3)_3$), 1.40 (s, 9H, $C(CH_3)_3$) ppm; ^{13}C NMR (125 MHz, acetone-d_6, 300 K): δ = 158.06 (OPhe-C_{quart}), 156.75 (NH–C(O)), 156.71 (NH–C(O)), 133.12 (2 OPhe–CH_{ortho}), 119.65 (2 OPhe–CH_{meta}), 114.87 (Phe-CBr_{quart}), 101.40 (C-1), 79.10 ($\underline{C}(CH_3)_3$), 78.96 ($\underline{C}(CH_3)_3$), 72.47 (C-3), 64.83 (C-5), 58.91 (C-2), 54.41 (C-4), 28.61 (3 C, $C(\underline{C}H_3)_3$), 28.57 (3 C, $C(\underline{C}H_3)_3$) ppm; ESI-HRMS: *m/z* = 525.1213 $[M+Na]^+$ (calcd *m/z* = 525.1207 for $[M+Na]^+$).

4-Bromophenyl 2,4-dideoxy-2,4-*N*-Boc-3-O-(4-bromophenyl)-β-D–xylopyranoside 13: Potassium *tert*-butoxide (5.36 mg, 47.8 μmol) was suspended in dry toluene (160 μL) and xyloside **11** (20.0 mg, 39.8 μmol) was added. The mixture was stirred for 15 min at RT. It was cooled down to 0 °C and piperidine (1.18 μL, 11.9 μmol) was added followed by bis(4-bromophenyl)iodonium triflate[26] (**12**, 28.2 mg, 47.8 μmol). The mixture was allowed to warm to RT and stirring was continued for 3 h. Then satd. ammonium chloride solution was added, and it was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, it was filtered, and the filtrate concentrated to dryness under reduced pressure. Purification by column chromatography (cyclohexane/ethyl acetate, 9:1→4:1) gave **13** (15.3 mg, 23.2 μmol, 58 %) as a colorless solid. R_f 0.42 (cyclohexane/ethyl acetate, 3:1); $[\alpha]^{20}_D$ = −28.54 (*c* 0.1, acetone); IR (ATR): ν_{max}/cm^{-1} = 3325, 2977, 1681, 1538, 1487, 1303, 1228, 1172, 1031, 818; ^{1}H NMR (500 MHz, acetone-d_6, 300 K): δ = 7.47 (d, ^3J = 8.9 Hz, 2H, OPhe–CH), 7.38 (d, ^3J = 8.9 Hz, 2H, OPhe–CH), 7.07–6.98 (m, 4H, OPhe–CH), 6.48 (d, $^3J_{NH,2}$ = 9.0 Hz, 1H, NH), 6.32 (d, $^3J_{NH,4}$ = 8.0 Hz, 1H, NH), 5.35 (d, $^3J_{1,2}$ = 7.7 Hz, 1H, H-1), 4.88 (t, $^3J_{3,4}$ = 9.1 Hz, $^3J_{2,3}$ = 9.1 Hz, 1H, H-3), 3.99 (dd, $^2J_{5a,5b}$ = 11.2 Hz, $^3J_{5a,4}$ = 4.7 Hz, 1H, H-5a), 3.88 (m, 1H, H-4), 3.91–3.84 (m, 1H, H-2), 3.80–3.65 (m, 2H, H-2, H-5b), 1.32 (s, 9H, $C(CH_3)_3$), 1.30 (s, 9H, $C(CH_3)_3$) ppm; ^{13}C NMR (125 MHz, acetone-d_6, 300 K): δ = 160.13 (C3-O-$\underline{C}_{quart}$), 157.84 (C1-O-$\underline{C}_{quart}$), 156.20 (C2-NH–$\underline{C}$(O)), 156.12 (C4-NH–$\underline{C}$(O)), 133.21 (2 OPhe–CH_{ortho}), 132.80 (2 OPhe–CH_{ortho}), 119.83 (2 OPhe–CH_{meta}), 119.81 (2 OPhe–CH_{meta}), 115.17 (Phe-CBr_{quart}), 113.73 (Phe-CBr_{quart}), 100.41 (C-1), 79.25 (2 $\underline{C}(CH_3)_3$), 79.20 (C-3),

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64.58 (C-5), 57.71 (C-2), 53.08 (C-4), 28.50 (6 C($\underline{C}H_3)_3$) ppm; ESI-HRMS: $m/z = 679.0629$ $[M+Na]^+$ (calcd $m/z = 679.0625$ for $[M+Na]^+$).

4-Bromophenyl 2,4-diamino-2,4-dideoxy-3-*O*-(4-bromophenyl)-β-D–xylopyranoside 14: The xyloside **13** (39.0 mg, 382 μmol) was dissolved in CH_2Cl_2 (1.5 mL) and trifluoroacetic acid (250 μL) was added. It was stirred at RT for 16 h. Then the mixture was diluted with CH_2Cl_2 and neutralized by adding Amberlyst® A21. The mixture was filtered, and the volatiles were removed under reduced pressure. The crude product was purified by column chromatography (CH_2Cl_2/MeOH/NH_3, 96:3:1) to yield **14** (25.0 mg, 54.6 μmol, 92%) as a colorless solid. R_f 0.40 (CH_2Cl_2/MeOH/Et_2NH, 96:3:1); $[\alpha]^{20}_D = -10.57$ (*c* 0.08, CH_2Cl_2); IR (ATR): $\nu_{max}/cm^{-1} = 3304$, 2922, 1578, 1484, 1226, 1068, 1004, 820, 659; ^1H NMR (600 MHz, acetone-d_6, 300 K): $\delta = 7.46–7.42$ (m, 2H, OPhe–CH), 7.36–7.31 (m, 2H, OPhe–CH), 7.03–6.97 (m, 2H, OPhe–CH), 6.95–6.89 (m, 2H, OPhe–CH), 5.28 (d, $^3J_{1,2} = 7.6$ Hz, 1H, H-1), 4.58 (t, $^3J_{3,4} = 9.2$ Hz, $^3J_{2,3} = 9.2$ Hz, 1H, H-3), 4.00–3.94 (m, 1H, H-4), 3.91 (dd, $^3J_{2,3} = 9.3$ Hz, $^3J_{1,2} = 7.6$ Hz, 1H, H-2), 3.81–3.76 (m, 2H, H-5a, H-5b) ppm; (600 MHz, $CDCl_3$, 298 K, TMS): $\delta = 7.43–7.37$ (m, 4H, OPhe–CH), 7.06–7.02 (m, 2H, OPhe–CH), 7.05–6.88 (m, 2H, OPhe–CH), 4.84 (d, $^3J_{1,2} = 7.6$ Hz, 1H, H-1), 4.07–4.01 (m, 1H, H-3, H-5a), 3.36–3.24 (m, 3H, H-2, H-4, H-5b) ppm; ^{13}C NMR (125 MHz, acetone-d_6, 300 K): $\delta = 160.43$ (C3-O-$\underline{C}_{quart}$), 157.82 (C1-O-$\underline{C}_{quart}$), 133.08 (2 OPhe–CH_{ortho}), 132.56 (2 OPhe–CH_{ortho}), 119.67 (2 OPhe–CH_{meta}), 119.64 (2 OPhe–CH_{meta}), 114.82 (Phe-CBr_{quart}), 113.37 (Phe-CBr_{quart}), 102.27 (C-1), 84.74 (C-3), 66.67 (C-2), 66.16 (C-5), 61.83 (C-4) ppm; (125 MHz, $CDCl_3$, 300 K): $\delta = 159.19$ (C3-O-$\underline{C}_{quart}$), 156.23 (C1-O-$\underline{C}_{quart}$), 132.82 (2 OPhe–CH_{ortho}), 132.60 (2 OPhe–CH_{ortho}), 118.86 (2 OPhe–CH_{meta}), 118.33 (2 OPhe–CH_{meta}), 115.52 (OPhe-CBr_{quart}), 114.32 (OPhe-CBr_{quart}), 102.84 (C-1), 85.81 (C-3), 67.35 (C-5), 56.79 (C-2), 52.46 (C-4) ppm; ESI-HRMS: $m/z = 456.9761$ $[M+Na]^+$ (calcd $m/z = 456.9757$ for $[M+Na]^+$).

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Carbohydrates · Conformational switches · Diamino xylosides · Molecular scaffolds · Protecting groups

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