DOI: 10.1002/chem.201003251

Direct Experimental Evidence for the High Chemical Reactivity of α- and β-Xylopyranosides Adopting a $^{2,5}B$ Conformation in Glycosyl Transfer

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Dedicated to Professor Pierre Sinaÿ

Abstract: The effect of a $^{2,5}B$ boat conformation on xyloside reactivity has been investigated by studying the hydrolysis and glycosylation of a series of synthetic xyloside analogues based on a 2-oxabicyclo[2.2.2]octane framework, which forces the xylose analogue to adopt a $^{2,5}B$ conformation. The locked β-xylosides were found to hydrolyze 100–1200 times faster than methyl β-D-xylopyranoside, whereas the locked α-xylosides hydrolyzed up to 2×10^4 times faster than methyl α-D-xylopyranoside. A significant rate enhancement was also observed for the glycosylation reaction. The high reactivity of these conformers can be related to the imposition of a $^{2,5}B$ conformation, which approximates a transition state (TS) boat conformation. In this way, the energy penalty required to go from the chair to the TS conformation is already paid. These results parallel and support the observation that the GH-11 xylanase family force their substrate to adopt a $^{2,5}B$ conformation to achieve highly efficient enzymatic glycosidic bond hydrolysis.

Keywords: conformation analysis · enzyme catalysis · glycosides · glycosylation · hydrolysis · structure–activity relationships

Introduction

Glycosyl transfer is a biologically important process.[1] An in-depth understanding of its mechanism is of central importance for synthetic manipulations of sugars[2] and for elucidating the biochemical requirements by which glycosidases act on nature's oligosaccharides.[3] Dramatic progress has been achieved in recent years on understanding chemical and enzymatic glycosyl transfer reactions. X-ray crystallographic analysis of glycosidases in the presence of 2-deoxy-2-fluorosugars[4] enabled the trapping of both covalent glycosyl–enzyme intermediates and Michaelis complexes, allowing dissection of the mechanism at the atomic level of an increasing number of glycosidases. The chemical hydrolysis of glycosides has also been much studied and is known to proceed by a specific acid-catalyzed process in which the rate-determining step is the formation of a cyclic oxacarbenium-like ion intermediate.[5] Although an understanding of the mechanism has reached a high level of sophistication,[6] some of its more subtle aspects, including transition-state

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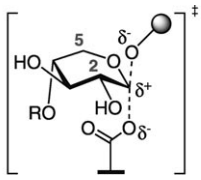
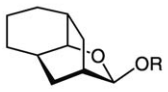
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201003251.

(TS) conformation, are still under investigation, because the transient nature of the cyclic oxacarbenium ion has so far prevented its direct observation.[7] Several techniques have been exploited to gain further insight into this conformational aspect, including kinetic isotope effect measurements[8] and computational chemistry.[9] Kinetic studies of the hydrolysis of glycosides and analogues is also a powerful method to probe the pseudorotational itinerary of glycosides during glycosyl transfer.

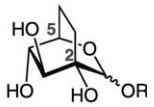
The hydrolysis of glycosides proceeds via transition states that display substantial oxacarbenium-ion like structures with a double-bond character of the O5–C1 bond and an sp^2 hybridization of the anomeric carbon. This demands that at, or extremely close to, this transition state, C5, O5, C1, and C2 lie in an approximately coplanar conformation, an arrangement accommodated only by $^4H_3$, $^3H_4$, $B_{2,5}$, and $^{2,5}B$ conformations.[10] Whereas half-chair conformers have been extensively invoked in glycosyl transfer, boat conformers have aroused some controversy[11] despite an increasing body of independent experimental data in glycosyl transfer. Indeed, a $^{2,5}B$ conformation has been observed by X-ray crystallography for the xylosyl unit of a covalently linked α-2-fluoro-xylobioside-enzyme intermediate located in the "−1" subsite of the GH-11 β-xylanase family active site, and has been proposed for the corresponding transition state **A**.[12] This hypothesis has been further supported by MM-PBSA free energy analysis[13] of Xyl11–substrate complexes and by recent molecular dynamic simulations using hybrid QM/MM methodology applied to noncovalent complexes of phenyl β-xyloside with BCX xylanase and a Tyr69Phe mutant.[14] Such a conformation is attained more easily for xylosides than for glucosides owing to the lack of a bulky hydroxymethyl substituent, which is forced into a pseudo-axial orientation in the latter case. This could explain the high specificity of the GH-11 xylanase family for xylosyl units, in contrast to the more promiscuous behavior of the GH-10 xylanase family, which utilizes a $^4C_1$ conformation for the intermediate.[15] The $^{2,5}B$ conformation has also been suggested by Hosie and Sinnott for the enzymatic hydrolysis of glucosides.[16]



$^{2,5}B$ oxocarbenium-like TS for family 11 xylanase **A**



tetrahydropyranyl acetal **B**

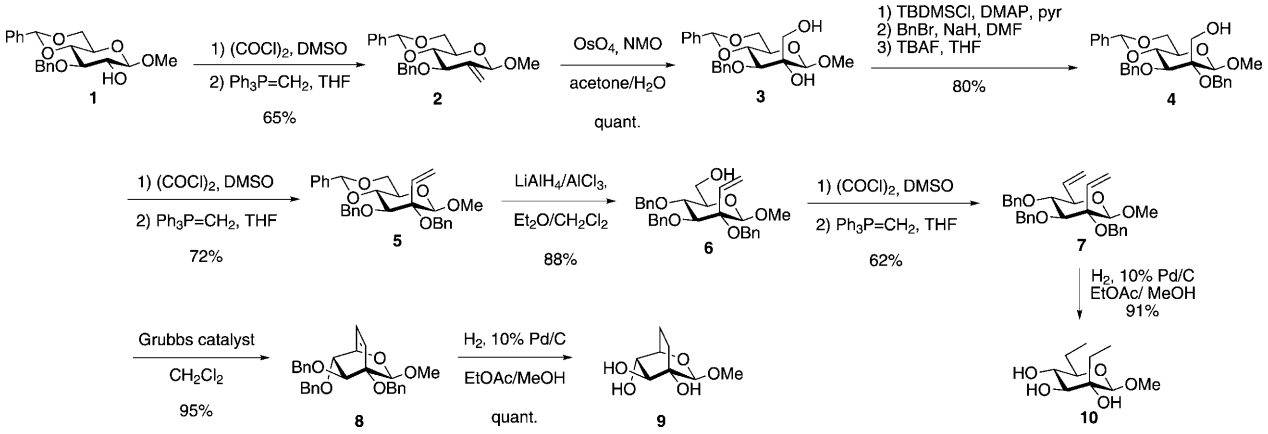


locked xyloside **C**

As part of an ongoing program on the implication of boat conformations in glycosyl transfer,[17] and regarding the importance of the $^{2,5}B$ conformation in enzymatic xyloside hydrolysis, we were interested in evaluating the anomeric reactivity of xylopyranosides when moving from the classic $^4C_1$ conformation to the invoked $^{2,5}B$ conformation, which may stereoelectronically assist the formation and breakdown of the glycosidic bond. The influence of a boat conformation on the reactivity of simple tetrahydropyranyl acetals was previously investigated by Kirby, Deslongchamps and coworkers,[18] who studied acetals of type **B** in which the THP ring was fixed in the symmetrical boat conformation by a three-carbon bridge. An increase of reactivity towards spontaneous hydrolysis was observed for these compounds, and some part of this higher reactivity was attributed to the higher ground-state energy of the boat conformation. For our purpose, we used a similar strategy to design and study xylopyranoside analogues locked in the requisite $^{2,5}B$ boat conformation. The atomic framework mimicking xylopyranose has to be sufficiently rigid to restrict conformational preferences but not too constraining to avoid undesired alternative pathways for the reaction. To retain all the hydroxyl groups of the parent glycoside, unlike previously reported glucoside analogues,[19] and force the pyranose ring into a boat conformation, a 2-oxabicyclo[2.2.2]octane skeleton was selected to generate xyloside analogues of type **C**. Tethering of the xylopyranose C-2 and C-5 carbon atoms with a two-carbon bridge, starting from a 2*R*,5*S*-bis-vinyl xylopyranoside derivative and exploiting the powerful ring-closing metathesis (RCM) methodology,[20] was chosen. The synthesis of dixyloside mimics containing the bicyclic xyloside was also achieved.

Results and Discussion

Glycoside synthesis: The synthesis of the methyl β-xyloside analogue was first investigated; this required a glucopyranose precursor in which hydroxyl groups at the 2- and 6-positions could be sequentially modified (Scheme 1). The orthogonally protected sugar **1**[21] was selected as a suitable starting material. Because installation of the "vinylic arm" at C-2 by addition of vinyl magnesium bromide onto a methyl β-2-uloside would predominantly give the wrong manno-like stereoisomer,[22] sugar **1** was oxidized and olefinated at the 2-position to afford the exomethylenic derivative **2**[23] (65% yield over two steps). Further dihydroxylation proceeded exclusively from the α-face to quantitatively afford diol **3**. Oxidation of the neopentylic position was found to be problematic and required preliminary protection of the tertiary alcohol as its benzyl ether through a silylation/benzylation/desilylation sequence (80% yield over three steps). The resulting alcohol **4** was oxidized and olefinated to yield the unsaturated derivative **5** (72% yield). Installation of the second vinylic appendage at C-5 was achieved through regioselective opening of the benzylidene group to yield alcohol **6** (88% yield), which was transformed into the key diene **7** (62%).[24] Bicycle ring closure was then examined. Whereas RCM of **7** failed with first generation Grubbs' catalyst, cyclization took place smoothly with the second-generation catalyst to give the highly strained unsaturated bicycle **8** in excellent 95% yield. Final hydrogena-



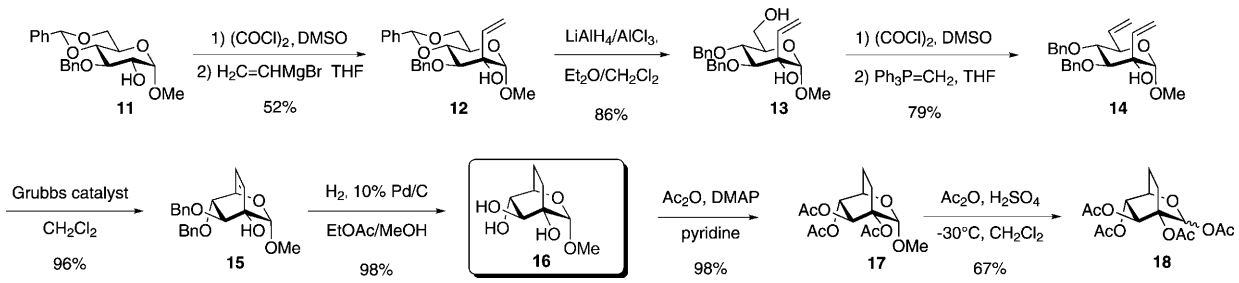
Scheme 1. Synthesis of locked β-xyloside **9** and diethyl β-xyloside **10**.

tion quantitatively furnished the target methyl β-xyloside analogue **9**. In parallel, diene **7** was hydrogenolyzed to yield the diethyl derivative **10**, a β-xyloside analogue adopting a conformation close to a $^4C_1$ chair ($J(3,4)=J(4,5a)=8.3$ Hz), which was subsequently used as a control compound in the hydrolysis experiments (Scheme 1).

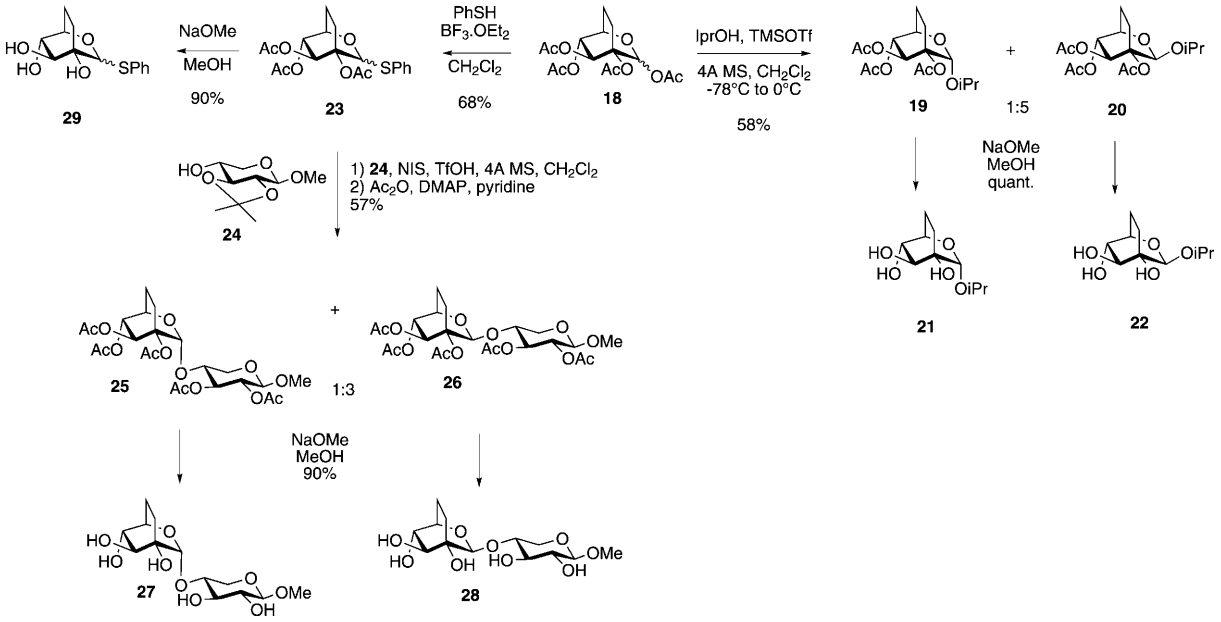
For the locked methyl α-xyloside, the available methyl α-glucoside **11**[25] was oxidized to the 2-uloside and alkylated with vinyl magnesium bromide to generate the expected *gluco*-like branched derivative **12** (52% yield) along with its *manno*-like C-2 epimer (18% yield). An identical sequence to the one used for xyloside **9** was then applied to yield the locked methyl α-xyloside **16**. To expand the number of locked xylosides displaying various aglycons, the synthesis of a conformationally locked xylosyl donor was required. α-Xyloside **16** was peracetylated to yield triacetate **17**, which furnished the locked xylosyl donor **18** in 67% yield upon acetolysis at low temperature (Scheme 2). Glycosylation of isopropanol with **18** in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in anhydrous CH_2Cl_2 yielded a separable mixture of isopropyl α- and β-xylosides **19** and **20** (58% yield) in a 1:5 ratio, respectively (Scheme 3). The partial anomeric β-selectivity observed might account for a perturbed anchimeric assistance of the acetate group at the 2-position due to the unique conformation of xylosyl donor **18**. Deacetylation under Zemplen conditions furnished the locked α- and β-isopropyl xylosides **21** and **22**, respectively (Scheme 3). The synthesis of pseudodixylosides incorporating the bicyclic xylopyranoside unit was necessary for the structure to resemble the xylanase substrate. Xylosyl donor **18** was therefore transformed into a more reactive thioxylosyl donor **23** (thiophenol, $BF_3{\cdot}OEt_2$), which was obtained as mixture of anomers. Coupling of **23** with methyl β-xyloside **24**[26] yielded an inseparable mixture of disaccharides in which the isopropylidene present in **24** had been removed.[27] Peracetylation of the crude mixture furnished the separable peracetylated α-disaccharide **25** and β-disaccharide **26** (57% yield over two steps, unoptimized, 1:3 ratio). The crystal structure of the latter was solved. Final deprotection afforded the α-linked disaccharide **27** and the methyl β-xylobioside analogue **28**, respectively. In parallel, the bicyclic thioxyloside **23** was deacetylated to yield the unprotected xylosyl donor **29** as a mixture of anomers (Scheme 3).

Conformational analysis: The conformation of the xyloside analogues was first examined in the solid state. X-ray structures of compounds **9**, **16**, and **22** were solved and are shown in Figure 1.

As expected, the locked methyl α-xyloside **16** adopts a $^{2,5}B$ conformation whereas the β-isopropyl xyloside **22** adopts a $^2S_0$ conformation close to that of the $^{2,5}B$ boat. Interestingly, two independent molecules were observed in the crystal lattice for the locked methyl β-xyloside **9**, which can adopt either a $^{2,5}B$ or a $^2S_0$ conformation, indicating some



Scheme 2. Synthesis of locked α-xyloside **16** and xyloside donor **18**.



Scheme 3. Synthesis of xyloside analogues **21**, **22**, **27**, and **28**.

flexibility is allowed by the 2-oxabicyclo[2.2.2]octane skeleton. The ring conformation for each xyloside in the solid state was also determined by calculations[28] and proved to match or resemble a $^{2,5}B$ conformation (Table 1).

Structural features including bond lengths and Φ torsion angles around the anomeric center were obtained from the X-ray structures. The methyl α-derivative **16** displays a longer C1−O5 distance (1.435 Å) than methyl α-xyloside[29] (1.413 Å) and a shortening of the C1−O1 distance (1.390 vs. 1.400 Å). The methyl and isopropyl β-glycosides **9** and **22**, respectively, show a lengthening of the C1−O1 bond (1.408 and 1.412 Å) compared with the unlocked methyl β-xyloside[30] (1.381 Å) and a similar C1−O5 distance (ca. 1.42 Å). The Φ torsion angle of the locked xylosides were measured and found to be close to the values observed for a normal exoanomeric orientation (−69° for methyl β-xyloside and +70° for methyl α-xyloside). The conformation of xylosides **9**, **16**, **21**, and **22** in solution was also investigated by NMR spectroscopy and molecular modeling. The spatial arrangement of the pyranose ring in the four xyloside analogues after energy minimization are fairly similar, even starting from different geometries, and indeed adopt a boat-like conformation (see the Supporting Information for details). Good agreement between the experimental and computed data was observed and additional experimental couplings were detected that confirmed the existence of boat-like $^{2,5}B$ conformers.[31]

Table 1. X-ray structural data for xylosides **9**, **16**, and **22**.

	9	**9**	**16**	**22**
conformation: observed	$^{2,5}B$	$^{2}S_{0}$	$^{2,5}B$	$^{2}S_{0}$
conformation: calculated	$^{2,5}B$	$^{2}S_{0}$	$^{2,5}B$	$^{2}S_{0}$
bond lengths [Å]				
O5−C1	1.418	1.426	1.435	1.424
C1−O1	1.408	1.405	1.390	1.412
torsion angle Φ [°] (O5-C1-O1-Csubs)	−81.1	−66.8	+72.7	−59.2

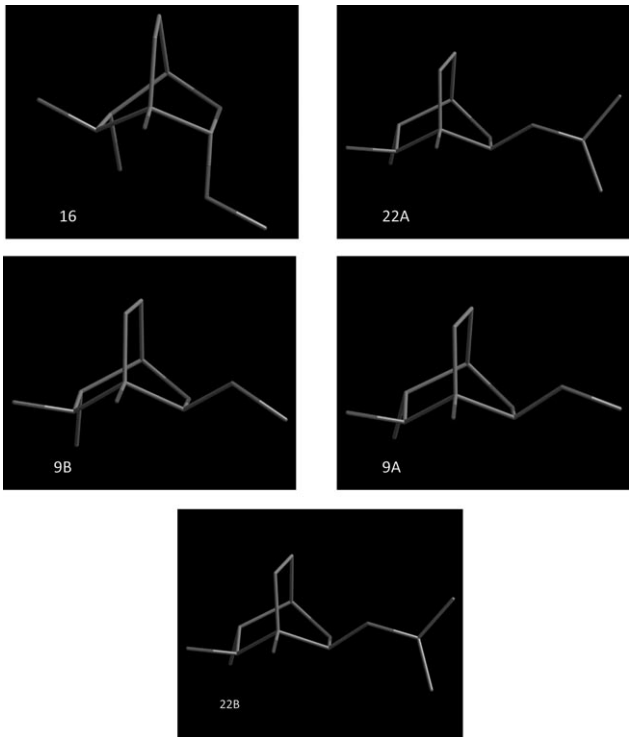


Figure 1. Crystal structures of xyloside analogues **9**, **16**, and **22**.

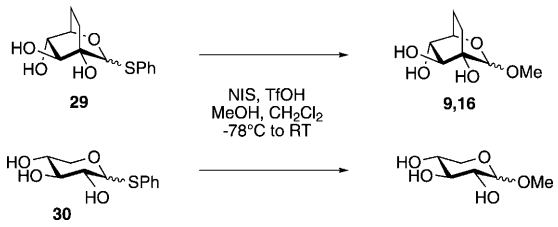
Hydrolysis of xylosides: The hydrolysis of methyl xylopyranosides has been studied by Indurugalla and Bennet and is believed to proceed through an exocyclic bond cleavage

pathway.[32] Acid-catalyzed hydrolysis of the synthetic locked xylosides was investigated and monitored either by polarimetry or by NMR analysis (depending on the amount of glycoside available) and was shown to follow pseudo-first-order kinetics.

Hydrolysis of α-xylosides: The results of kinetics studies on the hydrolysis of α-xylosides in 2 M HCl at 35 °C is reported in Table 2. As a reference, the rate of hydrolysis of methyl α-xylopyranoside was first determined ($k=0.43\times10^{-6}\,s^{-1}$). The hydrolysis of locked α-xylosides was then examined. For methyl α-xyloside **16**, a rate constant of $3100\times10^{-6}\,s^{-1}$ was obtained. Similarly, hydrolysis of locked isopropyl α-xyloside **21** was measured, giving a rate constant of $10100\times10^{-6}\,s^{-1}$ (Table 2, entry 3). The hydrolysis rate of α-xylobioside **27** could not be measured precisely, because the lack of material only allowed a single experiment. However, it was possible to ascertain that the hydrolysis rate was much faster than $3000\times10^{-6}\,s^{-1}$ (Table 2, entry 4). Overall, all the locked α-xylosides are extremely reactive toward aqueous acid, reacting much faster than methyl α-xylopyranoside, being hydrolyzed at least 5000 times faster.

Hydrolysis of β-xylosides: Acid hydrolysis of the locked β-xyloside analogues was also investigated at 35 °C in 2 M HCl (Table 3). The rate of hydrolysis for methyl β-xylopyranoside was measured by polarimetry, giving a rate constant of $3.49\times10^{-6}\,s^{-1}$ at 35 °C and $20.1\times10^{-6}\,s^{-1}$ at 50 °C (Table 3, entry 1), which is close to the value reported in the literature ($12.6\times10^{-6}\,s^{-1}$).[33] It can be argued that the pyranosidic ring substitution pattern of the bicyclic xylosides can be solely responsible for the high hydrolysis rate observed. To this end, hydrolysis of the diethyl methyl β-xylopyranoside **10** was measured and this compound, which displays two extra axial and equatorial ethyl groups at C-2 and C-5 respectively, was found to hydrolyze ten times faster at 50 °C than methyl β-xylopyranoside (200×10^{-6} vs. $20.1\times10^{-6}\,s^{-1}$; Table 3, entry 2). For the locked β-xylosides, a significant increase in the rate of hydrolysis was again observed. The bicyclic methyl β-xyloside **9** hydrolyzed 88 times faster ($k=310\times10^{-6}\,s^{-1}$ at 35 °C; Table 3, entry 3), the isopropyl derivative **22** hydrolyzed 1210 times faster ($k=4212\times10^{-6}\,s^{-1}$; Table 3, entry 4), and the pseudo disaccharide **28** approximately 800 times ($k=2700\times10^{-6}\,s^{-1}$; Table 3, entry 5). By comparison, locked xyloside **9** proved to hydrolyze 165 times faster at 50 °C ($k=3330\times10^{-6}\,s^{-1}$) than diethyl xyloside **10**. The higher reactivity of compound **10** compared with methyl β-xylopyranoside is undoubtedly due to a minor extent to the electron donation from the two extra ethyl groups, which stabilize the oxacarbenium ion intermediate and thus increase the glycosyl transfer rate. However, the main contribution probably comes from the fact that the 2-C-ethyl substituent is sterically crowdedin the axial position, and stabilizes the $^1C_4$ conformation. The $^1C_4$ conformer is about 100-fold more reactive, and an increase of just 10% in the presence of this conformer will be enough to cause the observed rate increase.[34]

Glycosylation: The other main glycosyl transfer reaction, glycosylation, was also examined using the locked and unlocked thioxylosides **29** and **30** as glycosyl donors, *N*-iodosuccinimide/trifluoromethanesulfonic acid as the promotor system, and methanol as the acceptor (Scheme 4).



Scheme 4. Glycosylation with glycosyl donors **29** and **30**.

Table 2. Hydrolysis of methyl α-xylosides and locked xylosides.

	Compound	Anomeric substituent	k [s^{-1}] (35 °C)	Relative hydrolysis rate (2 M HCl, 35 °C)
1	methyl α-xylopyranoside	Me	0.43×10^{-6}	1
2	**16**	Me	3100×10^{-6}	7209
3	**21**	*i*Pr	10100×10^{-6}	23413
4	**27**	methyl β-xylopyranoside	$\gg3000\times10^{-6}$	$\gg6976$

Table 3. Hydrolysis of methyl β-xylosides and locked xylosides.

	Compound	Anomeric substituent	k [s^{-1}] (35 °C)	Relative hydrolysis rate (2 M HCl, 35 °C)
1	methyl β- xylopyranoside	Me	3.49×10^{-6}	1
			20.1×10^{-6}[a]	
2	**10**	Me	200×10^{-6}[a]	10[a]
3	**9**	Me	310×10^{-6}	88
			3330×10^{-6}[a]	165[a]
4	**22**	*i*Pr	4212×10^{-6}	1210
5	**28**	methyl β-xylopyranoside	2700×10^{-6}	770

[a] Measured at 50 °C.

Assuming that the rate-determining step is the formation of the cyclic oxacarbenium ion, formation of iodine was monitored by changes in UV absorption as an expression of the relative reaction rate.[35] The two glycosylation reactions were carried out at room temperature under pseudo-first-order conditions, using an excess of both the acceptor and promotor. Since it was noticed that, under the reaction conditions, NIS itself releases iodine, a minor background rate was subtracted for each donor concentration. The results demonstrated a significant enhancement in

reactivity of the locked thioxyloside **29** ($k = 1900 \times 10^{-4}\ s^{-1}$) that was 226-fold faster than the conformationally flexible thioxyloside **30**[36] ($k = 8.4 \times 10^{-4}\ s^{-1}$) at performing glycosylation. In this case, release of steric strain can be excluded as an explanation for the observed effect. This result can, in part, be explained by the armed–disarmed–superarmed[37] or conformational arming[38] principle because the ring hydroxyl groups at C-3 and C-4 become pseudoaxial in the bicyclic xyloside **29**. Nevertheless, it has been shown that moving from a fully equatorial to a fully axial glycosyl donor bearing benzyl and TIPS protecting groups, respectively, which display similar electronic effects, causes a 20-fold glycosylation rate enhancement.[35]

Discussion

Reactivity of the constrained xylosides: The clear conclusion from the results summarized in Tables 2 and 3 is that the locked xylosides are hydrolyzed at much faster rates than the corresponding unconstrained xylosides. High to very high rate enhancements are observed for the hydrolysis or glycosylation reactions with the locked xylosides. The mechanism by which the bicyclic xylosides are hydrolyzed may follow a classical "exocyclic" pathway, because rate enhancements in the same range of magnitude are observed for the hydrolysis and the glycosylation; the latter being known to proceed through an exocyclic cleavage mechanism. Additionally, bicyclic xylosides **22** and **26**, the structures of which have been solved by X-ray crystallography, have been obtained by glycosylation with locked xylosyl donors **18** and **23**, supporting an exocyclic pathway.

The very high reactivity of the locked xylosides can be directly related to their unusual boat conformation. Ground state destabilization and the imposition of conformations on the substrate that approximate those of the oxacarbenium ion have been investigated by other groups,[39] and it was found that reactivity increased, because much of the energy penalty required to go from the chair to the TS conformation had been already paid. This is also the case here and a dramatic effect is observed. The locked xylosides are spatially maintained in a conformation domain that is either close to or identical to the expected $^{2,5}B$ conformation for the oxacarbenium TS, which perfectly fulfills the stereochemical requirements demanded of an oxacarbenium ion. Glycosyl transfer can therefore take place with only minimal nuclear motion through a subtle electrophilic migration of the anomeric carbon. It can be argued that such a pathway presents an endocyclic lone pair contribution more akin to *syn* elimination geometry and, indeed, Deslongchamps and Kirby provided solid evidence for such *syn* geometries.[40] If we examine the stereoelectronic effects that can take place in the locked α- and β-xylosides, a significant antiperiplanar n_O–σ^*_{C-OR} interaction can be excluded, but synperiplanar lone pairs can interact with the σ^*_{C-OR} of both anomers and, apparently, stabilize the developing oxacarbenium ion character in the transition state very efficiently during acid-catalyzed cleavage. Additionally, the unusual structure of the xyloside analogues can generate specific steric effects that can also ease the glycosidic bond hydrolysis to a lesser extent. Ground state energy differences between different conformers are generally not directly correlated with the transition state energies, but the conformational constraint imposed by the [2,2,2] bicyclic system might play a role and favor some release of ring strain during glycosyl transfer while keeping the bicycle integrity. Other minor factors, such as solvation effects,[41] can also play a role in explaining the important structural discrepancies between the locked and unlocked xylosides studied in this work.

Conclusions

Four monosaccharides **9**, **16**, **21**, and **22** locked in a $^{2,5}B$ conformation have been synthesized as xyloside mimics. Incorporation of the locked xylosyl unit in two disaccharides **27** and **28** has been also achieved. All these sugar mimics were found to hydrolyze very fast in acid and 10^2–10^4 times faster than the corresponding unlocked xylosides; the α-glycosides being much more reactive than the β-glycosides. A 200-times rate enhancement was also observed for the glycosylation reaction using locked xylosyl donors. These data demonstrate that xylosides can have their anomeric reactivity boosted during chemical glycosyl transfer when adopting a $^{2,5}B$ or close $^2S_0$ conformation. This is possible because the $^{2,5}B$ conformation can theoretically be adopted by the TS during xyloside hydrolysis, because the sterically encumbering C5 hydroxymethyl group (which can generate unfavorable C2–C5 flagpole positioning in the boat conformation) is absent. Therefore, the very high reactivity observed can be directly related to the fact that much of the energy penalty required to go from the chair to the TS conformation has been already paid in this case. This trick is already being used by several glycosidases that distort the pyranose ring of their substrate towards unusual conformations to achieve a highly efficient catalytic cycle. This work parallels and supports substrate distortion towards a $^{2,5}B$ conformation observed for the GH-11 xylanase family.[12] These results also suggest that transient $^{2,5}B$ conformations of xylosides can indeed be acceptable candidates for direct acid hydrolysis, as suggested by Berti and Tanaka on the basis of kinetic isotope effect studies.[42]

Experimental Section

Kinetic studies: Rates of hydrolysis of the xylosides were determined either by polarimetry or NMR analysis depending on the amount of glycoside available.

Polarimetric method: A solution of glycoside (ca. 5 mg mL^{-1} in 2 M aq. HCl) was added to a cuvette that was pre-heated to the desired temperature. The polarimeter was reset, whereupon the cuvette was positioned in the apparatus. The optical rotation was measured as a function of time (sodium lamp). Measurement was continued until the rotational value had stabilized. The rate of the reaction K was determined at each tem-

perature as the slope of the linear regression $\ln[(\alpha(t)-\alpha(\infty))/(\alpha(0)-\alpha(\infty))]$ versus time ($\alpha(t)$ is the rotation measured at time t, $\alpha(\infty)$ is the rotation measured at the end of reaction and $\alpha(0)$ is the rotation measured at the beginning of reaction). From these temperature experiments the hydrolysis rate was determined at 35 °C.

NMR method: An NMR spectrum of a solution of glycoside (ca. 2 mg mL^{-1} in DCl (2 M in D_2O)) was taken every 5 min at 35 °C until the signal of the starting material disappeared. DMSO was used as a standard for the shift and integration calibration. The rate of the reaction K at 35 °C was determined as the slope of the linear regression ln(signal integration) versus time.

Crystallography: CCDC-679052 (**9**), 703314 (**16**), 703315 (**22**), and 682061 (**26**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General: Optical rotations were measured at (20±2) °C with a Perkin–Elmer Model 241 digital polarimeter, using a 10 cm, 1 mL cell. Mass spectra (CI (ammonia)) were obtained with a JMS-700 spectrometer. ^{1}H NMR spectra were recorded at 400 MHz with a Brüker DRX 400 for solutions in $CDCl_3$ or D_2O at RT. Assignments were confirmed by COSY experiments. ^{13}C NMR spectra were recorded at 100.6 MHz with a Brüker DRX 400 spectrometer. Assignments were confirmed by J-mod and HMQC techniques. Reactions were monitored by thin-layer chromatography (TLC) using Silica Gel 60 F_{254} precoated plates (layer thickness 0.2 mm; E. Merck, Darmstadt, Germany) and detected by charring with either a 10% ethanolic solution of H_2SO_4 or with a solution of 0.2% w/v cerium sulfate and 5% ammonium molybdate in 2 M H_2SO_4. Flash column chromatography was performed using silica gel 60 (230–400 mesh, E. Merck).

Compound 2: Anhydrous DMSO (3.43 mL, 48.4 mmol) was added dropwise to a solution of oxalyl chloride (3.17 mL, 36.3 mmol) in anhydrous CH_2Cl_2 (80 mL) at −78 °C under argon. After 15 min, a solution of alcohol **1** (4.50 g, 12.1 mmol) in anhydrous CH_2Cl_2 (40 mL) was added dropwise and the solution was stirred at −78 °C for 1 h. Triethylamine (10.1 mL, 72.6 mmol) was then added and the reaction mixture was allowed to reach RT and stirred for 90 min. Water (60 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×80 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude ketone was coevaporated with toluene and used directly without further purification. *n*-Butyl lithium (2.5 M in *n*-hexanes, 19.4 mL, 48.4 mmol) was added dropwise to a solution of Ph_3PCH_2Br (17.3 g, 48.4 mmol) in anhydrous THF (80 mL) at 0 °C under argon. The reaction mixture was stirred for 30 min at 0 °C until a bright-orange color persisted. A solution of the crude ketone in anhydrous THF (70 mL) was then quickly added and the reaction mixture was stirred for 2 h at RT. The reaction mixture was diluted with water (50 mL) and CH_2Cl_2 (100 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (cyclohexane/EtOAc, 20:1 then cyclohexane/EtOAc, 4:1) afforded alkene **2** (2.90 g, 65% over two steps) as a white solid. M.p. 183–184 °C (cyclohexane/EtOAc); $[\alpha]_D = -89.4$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.56–7.29 (m, 10H; ArH), 5.62 (s, 1H; H-7), 5.57 (app t, 2H; H-8, H-8′), 4.92 (d, J = 12.1 Hz, 1H; CHPh), 4.86 (d, J = 12.1 Hz, 1H; CHPh), 4.81 (s, 1H; H-1), 4.39 (dd, J = 4.9, 10.5 Hz, 1H; H-6a), 4.18 (br d, J = 9.3 Hz, 1H; H-3), 3.85 (t, J = 10.5 Hz, 1H; H-6′), 3.74 (t, J = 9.3 Hz, 1H; H-4), 3.63 (s, 3H; OCH_3), 3.56 ppm (ddd, J = 4.9, 9.3, 10.5 Hz, 1H; H-5); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 141.8 (C-2), 138.7, 137.9 (*ipso* ArC), 129.4–126.5 (10× ArC), 111.4 (C-8), 101.6 (C-1, C-7), 84.0 (C-4), 78.5 (C-3), 73.8 (CH_2Ph), 69.9 (C-6), 66.9 (C-5), 57.9 ppm (OCH_3); HRMS (CIMS): m/z calcd for $C_{22}H_{28}O_5N$: 386.1967 $[M+NH_4]^+$; found: 386.1970.

Compound 3: Exoalkene **2** (2.40 g, 6.51 mmol) was dissolved in a 20:1 acetone/water mixture (105 mL) and NMO (1.75 g, 13.03 mmol) followed by OsO_4 (2.5% in *t*BuOH, 1.60 mL, 0.13 mmol) were added. The reaction mixture was stirred for 2 d at RT until TLC indicated complete consumption of the starting material. The reaction was quenched by addition of aqueous saturated solution of $Na_2S_2O_3$. The reaction mixture was stirred for 30 min, extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated under vacuo. Purification by column chromatography (cyclohexane/EtOAc, 2:1) afforded diol **3** (2.63 g, quantitative yield) as a colorless oil; $[\alpha]_D = -140.5$ ($c=2.0$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.52–7.29 (m, 10H; ArH), 5.59 (s, 1H; H-7), 4.92 (d, J = 11.6 Hz, 1H; CHPh), 4.87 (d, J = 11.6 Hz, 1H; CHPh), 4.44 (s, 1H; H-1), 4.40 (dd, J = 4.8, 10.4 Hz, 1H; H-6), 4.07 (dd, J = 4.7, 11.8 Hz, 1H; H-8), 4.00 (dd, J = 8.9, 11.8 Hz, 1H; H-8′), 3.84–3.79 (m, 2H; H-3, H-6b), 3.65 (t, J = 9.8 Hz, 1H; H-4), 3.64 (app s, 1H; OH), 3.59 (s, 3H; OCH_3), 3.48 (ddd, J = 4.8, 9.8, 10.0 Hz, 1H; H-5), 2.70 ppm (dd, J = 4.7, 8.9 Hz, 1H; OH); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 138.6, 137.6 (*ipso* ArC), 129.4–126.4 (10× ArC), 107.9 (C-1), 101.8 (C-7), 82.5 (C-3), 80.2 (C-4), 76.0 (CH_2Ph), 75.5 (C-2), 69.1 (C-6), 67.6 (C-5), 61.1 (C-8), 58.6 ppm (OCH_3); HRMS (CIMS): m/z calcd for $C_{22}H_{27}O_7$: 403.1757 $[M+H]^+$; found: 403.1760.

Compound 4: *tert*-Butyldimethylsilyl chloride (2.89 g, 19.29 mmol) and DMAP (0.39 g, 3.21 mmol) were added to a solution of diol **3** (2.60 g, 6.43 mmol) in anhydrous pyridine (7 mL) at RT under argon. The reaction mixture was stirred at RT overnight and then at 60 °C for 3 h to complete the reaction. The reaction mixture was co-evaporated with toluene under reduced pressure and then diluted with CH_2Cl_2 (100 mL) and water (40 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. The crude silylated product was directly engaged in the next step. Sodium hydride (1.00 g, 25.72 mmol, 60% w/w) was added to a solution of the crude silylated product in anhydrous DMF (20 mL) at 0 °C. After 30 min stirring, BnBr (4.60 mL, 38.57 mmol) was added at 0 °C and the reaction mixture was stirred overnight at RT. Methanol (10 mL) was added and the mixture was concentrated under reduced pressure. The residue was then diluted with Et_2O (100 mL) and water (40 mL). The aqueous layer was extracted with Et_2O (3×80 mL) and the organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude, fully protected product was engaged in the next step without further purification. TBAF (1 M in THF, 19.29 mL, 19.29 mmol) was added to a solution of the fully protected product in THF (15 mL). After 6 h, the reaction mixture was diluted with water (30 mL) and CH_2Cl_2 (80 mL) and the aqueous layer was extracted with CH_2Cl_2 (3× 60 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (cyclohexane/EtOAc, 5:1) afforded alcohol **4** (2.53 g, 80% over three steps) as a white solid; m.p. 112 °C (cyclohexane/EtOAc); $[\alpha]_D = -22.8$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.58–7.34 (m, 15H; ArH), 5.68 (s, 1H; H-7), 5.07 (d, J = 11.1 Hz, 1H; CHPh), 5.00 (d, J = 10.9 Hz, 1H; CHPh), 4.97 (d, J = 10.9 Hz, 1H; CHPh), 4.87 (d, J = 11.1 Hz, 1H; CHPh), 4.54 (s, 1H; H-1), 4.48–4.43 (m, 2H; H-6, H-8), 4.31 (dd, J = 3.5, 13.1 Hz, 1H; H-8′), 4.04–3.98 (m, 2H; H-3, H-4), 3.89 (t, J = 10.2 Hz, 1H; H-6′), 3.74 (dd, J = 3.5, 8.4 Hz, 1H; CH_2OH), 3.59 (s, 3H; OCH_3), 3.58–3.52 ppm (m, 1H; H-5); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 139.8, 138.2, 137.7 (*ipso* ArC), 129.5–126.5 (15× ArC), 107.5 (C-1), 101.8 (C-7), 85.2 (C-3 or C-4), 81.0 (C-4 or C-3), 80.0 (C-2), 76.5 (CH_2Ph), 69.2 (C-6), 67.6 (C-5), 67.3 (CH_2Ph), 59.4 (C-8), 58.1 ppm (OCH_3); HRMS (CIMS): m/z calcd for $C_{29}H_{36}O_7N$: 510.2492 $[M+NH_4]^+$; found: 510.2486.

Compound 5: Anhydrous DMSO (1.52 mL, 21.44 mmol) was added dropwise to a solution of oxalyl chloride (1.56 mL, 17.87 mmol) in anhydrous CH_2Cl_2 (20 mL) at −78 °C under argon. After 15 min, a solution of alcohol **4** (0.88 g, 1.79 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise and the reaction mixture was stirred for 1 h. Triethylamine (3.74 mL, 26.80 mmol) was then added and the reaction mixture was stirred for 90 min and allowed to reach RT. Water was added to the reaction mixture (10 mL) and the aqueous layer was extracted with CH_2Cl_2 (3×40 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude aldehyde was coevaporated with toluene and used without further purification. *n*-Butyllithium (2.5 M in *n*-hexanes, 2.86 mL, 7.15 mmol) was added dropwise to a solution of Ph_3PCH_2Br (2.55 g, 7.15 mmol) in anhydrous THF (20 mL) at 0 °C under argon. The reaction mixture was stirred for 30 min at 0 °C until a bright-orange color persisted, and a solution of the crude aldehyde in anhydrous THF (10 mL) was quickly added. The reaction mixture was stirred for 90 min at RT, quenched with water (10 mL) and diluted with CH_2Cl_2 (40 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. Purification by flash column chromatography (cyclohexane/EtOAc, 20:1) afforded vinyl derivative **5** (0.63 g, 72% over two steps) as

a colorless oil; $[\alpha]_D = -86.3$ ($c = 2.0$ in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 7.52–7.28$ (m, 15H; ArH), 6.04 (dd, $J = 12.0$, 11.4 Hz, 1H; H-8), 5.79 (dd, $J = 2.0$, 12.0 Hz, 1H; H-9), 5.67 (dd, $J = 2.0$, 11.4 Hz, 1H; H-9′), 5.59 (s, 1H; H-7), 4.94 (d, $J = 11.7$ Hz, 1H; CHPh), 4.89 (d, $J = 11.7$ Hz, 1H; CHPh), 4.82 (d, $J = 12.3$ Hz, 1H; CHPh), 4.73 (d, $J = 12.3$ Hz, 1H; CHPh), 4.53 (s, 1H; H-1), 4.41 (dd, $J = 4.8$, 10.3 Hz, 1H; H-6), 3.86 (d, $J = 9.5$ Hz, 1H; H-3), 3.84 (t, $J = 10.3$ Hz, 1H; H-6′), 3.73 (t, $J = 9.5$ Hz, 1H; H-4), 3.54 (s, 3H; OCH_3), 3.57–3.51 ppm (m, 1H; H-5); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 140.3$, 139.1, 137.8 (*ipso* ArC), 130.9 (C-8), 129.3–126.5 (15×ArC), 122.5 (C-9), 107.6 (C-1), 101.6 (C-7), 83.6 (C-3), 83.4 (C-2), 80.5 (C-4), 75.9 (CH_2Ph), 69.2 (C-6), 68.0 (C-5), 67.4 (CH_2Ph), 57.7 ppm (OCH_3); HRMS (CIMS): *m/z* calcd for $C_{30}H_{33}O_6$: 489.2277 $[M+H]^+$; found: 489.2259.

Compound 6: Lithium aluminum hydride (0.23 g, 6.15 mmol) was carefully added in portions to a solution of alkene **5** (0.60 g, 1.23 mmol) dissolved in a 1:1 CH_2Cl_2/Et_2O mixture (20 mL) at 0 °C under argon. After 10 min, the reaction mixture was warmed to 40 °C, and a solution of $AlCl_3$ (0.49 g, 3.69 mmol) in Et_2O (10 mL) was added dropwise under argon. The reaction was stirred for 90 min by which time TLC indicated no trace of starting material remained. The reaction mixture was cooled to 0 °C and quenched by slow addition of EtOAc followed by water. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (cyclohexane/EtOAc, 4:1 then cyclohexane/EtOAc, 2:1) afforded the primary alcohol **6** (0.53 g, 88%) as a white solid. M.p. 121 °C (cyclohexane/EtOAc); $[\alpha]_D = -19.6$ ($c = 1.0$ in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 7.55–7.44$ (m, 15H; ArH), 6.21 (dd, $J = 11.4$, 18.0 Hz, 1H; H-7), 5.96 (dd, $J = 2.1$, 18.0 Hz, 1H; H-8), 5.82 (dd, $J = 2.1$, 11.4 Hz, 1H; H-8′), 5.24 (d, $J = 11.0$ Hz, 1H; CHPh), 5.05 (d, $J = 10.9$ Hz, 1H; CHPh), 5.00 (d, $J = 11.0$ Hz, 1H; CHPh), 4.98 (d, $J = 12.3$ Hz, 1H; CHPh), 4.92 (d, $J = 12.3$ Hz, 1H; CHPh), 4.76 (d, $J = 10.9$ Hz, 1H; CHPh), 4.61 (s, 1H; H-1), 4.07 (dd, $J = 2.3$, 11.9 Hz, 1H; H-6), 3.98 (d, $J = 9.5$ Hz, 1H; H-3), 3.91 (dd, $J = 4.4$, 11.9 Hz, 1H; H-6′), 3.74 (t, $J = 9.5$ Hz, 1H; H-4), 3.63 (s, 3H; OCH_3), 3.62–3.59 ppm (m, 1H; H-5); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 140.6$, 139.4, 138.8 (*ipso* ArC), 131.1 (C-7), 129.0–127.7 (15×ArC), 122.3 (C-8), 107.0 (C-1), 87.7 (C-3), 83.4 (C-2), 77.0 (C-4), 76.6 (CH_2Ph), 76.5 (C-5), 75.7 (CH_2Ph), 67.6 (CH_2Ph), 62.5 (C-6), 57.6 ppm (OCH_3); HRMS (CIMS): *m/z* calcd for $C_{30}H_{38}O_6N$: 508.2699 $[M+NH_4]^+$; found: 508.2709.

Compound 7: Anhydrous DMSO (1.28 mL, 18.00 mmol) was added dropwise to a solution of oxalyl chloride (1.22 mL, 14.00 mmol) in anhydrous CH_2Cl_2 (20 mL) at −78 °C under argon. After 15 min, a solution of primary alcohol **6** (0.98 g, 2.00 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise and the reaction was stirred for 1 h. Triethylamine (3.30 mL, 24.00 mmol) was then added and the reaction mixture was stirred for 90 min and allowed to reach RT. Water (20 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×60 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude aldehyde was coevaporated with toluene and used without further purification. *n*-Butyllithium (2.5 M in *n*-hexanes, 3.20 mL, 8.00 mmol) was added dropwise to a solution of Ph_3PCH_2Br (2.86 g, 8.00 mmol) in anhydrous THF (15 mL) at 0 °C under argon. The reaction mixture was stirred for 30 min at 0 °C until a bright-orange color persisted, and a solution of the crude aldehyde in anhydrous THF (15 mL) was then quickly added. The reaction mixture was stirred for 2 h at RT, quenched with water (20 mL) and diluted with CH_2Cl_2 (80 mL). The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (cyclohexane/EtOAc, 30:1) afforded the bis vinyl derivative **6** (0.60 g, 62% over two steps) as a white solid. M.p. 113 °C (cyclohexane/EtOAc); $[\alpha]_D = -128.1$ ($c = 1.0$ in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 7.41–7.31$ (m, 15H; ArH), 6.10–6.00 (m, 2H; H-6, H-8), 5.82 (dd, $J = 1.9$, 17.9 Hz, 1H; H-9), 5.67 (dd, $J = 1.9$, 11.4 Hz, 1H; H-9′), 5.54 (d, $J = 17.3$ Hz, 1H; H-7), 5.35 (d, $J = 10.6$ Hz, 1H; H-7′), 5.07 (d, $J = 11.0$ Hz, 1H; CHPh), 4.86–4.77 (m, 4H; 2×CH_2Ph), 4.59 (d, $J = 10.5$ Hz, 1H; CHPh), 4.49 (s, 1H; H-1), 3.91 (dd, $J = 5.9$, 9.5 Hz, 1H; H-5), 3.81 (d, $J = 9.5$ Hz, 1H; H-3), 3.54 (s, 3H; OCH_3), 3.33 ppm (t, $J = 9.5$ Hz, 1H; H-4); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 140.5$, 139.3, 138.7 (*ipso* ArC), 135.4 (C-6), 131.1 (C-8), 128.8–127.5 (15×ArC), 122.0 (C-9), 118.1 (C-7), 106.6 (C-1), 87.4 (C-3), 83.3 (C-2), 81.4 (C-4), 76.7 (C-5), 76.5 (CH_2Ph), 75.6 (CH_2Ph), 67.4 (CH_2Ph), 57.4 ppm (OCH_3); HRMS (CIMS): *m/z* calcd for $C_{31}H_{38}O_5N$: 504.2750 $[M+NH_4]^+$; found: 504.2746.

Compound 8: Compound **7** (350 mg, 0.72 mmol) was dissolved in anhydrous CH_2Cl_2 (90 mL) and the solution was degassed three times followed by addition of 2nd generation Grubbs catalyst (61 mg, 0.07 mmol) under argon. The reaction mixture was heated to reflux overnight, cooled at RT, and an excess of $[Pb(OAc)_4]$ was added. The reaction mixture was stirred for 2 h, filtered through a Celite plug, eluted with CH_2Cl_2, and concentrated under reduced pressure. Purification by flash column chromatography (cyclohexane/EtOAc, 4:1) afforded the bicyclic alkene **8** (315 mg, 95%) as a white solid. M.p. 93 °C (cyclohexane/EtOAc); $[\alpha]_D = -62.2$ ($c = 1.0$ in $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz): $\delta = 7.45–7.29$ (m, 15H; ArH), 6.58 (app dd, $J = 1.2$, 8.8 Hz, 1H; H-7), 6.44 (dd, $J = 5.6$, 8.8 Hz, 1H; H-6), 4.91 (d, $J = 1.2$ Hz, 1H; H-1), 4.88 (s, 2H; CH_2Ph), 4.73 (d, $J = 11.8$ Hz, 1H; CHPh), 4.71 (d, $J = 12.0$ Hz, 1H; CHPh), 4.65–4.62 (m, 2H; CHPh, H-5), 4.54 (d, $J = 12.0$ Hz, 1H; CHPh), 3.69 (br s, 1H; H-3), 3.51 (t, $J = 1.6$ Hz, 1H; H-4), 3.45 ppm (s, 3H; OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 139.6$, 138.4, 138.1 (*ipso* ArC), 133.4 (C-7), 128.9–128.1 (12×ArC), 127.95 (C-6), 127.8–127.6 (3×ArC), 101.3 (C-1), 84.5 (C-4), 81.5 (C-2), 79.5 (C-3), 73.1 (CH_2Ph), 71.4 (CH_2Ph), 68.7 (C-5), 68.0 (CH_2Ph), 56.2 ppm (OCH_3); HRMS (CIMS): *m/z* calcd for $C_{29}H_{34}O_5N$: 476.2437 $[M+NH_4]^+$; found: 476.2442.

Compound 9: Palladium on carbon (10% w/w, 78 mg, 120 mg mmol^{-1} of starting material) was added to a solution of bicyclic alkene **8** (300 mg, 0.66 mmol) dissolved in a 2:1 EtOAc/MeOH mixture (12 mL). The solution was degassed three times, and air was replaced by H_2. After stirring for 1.5 h at RT, the reaction mixture was filtered through a Rotilabo Nylon 0.45 μm filter and the solvent was evaporated to afford the xyloside analogue **9** (125 mg, quantitative yield) as a white crystalline solid. M.p. 131 °C (EtOAc); $[\alpha]_D = -80.7$ ($c = 1.0$ in MeOH); ^1H NMR (D_2O, 400 MHz): $\delta = 4.47$ (d, $J = 1.3$ Hz, 1H; H-1), 3.75–3.72 (m, 1H; H-5), 3.66 (dd, $J = 2.5$, 1.1 Hz, 1H; H-4), 3.47 (t, $J = 2.5$ Hz, 1H; H-3), 3.41 (s, 3H; OCH_3), 1.95–1.87 (m, 1H; H-6), 1.77–1.69 (m, 1H; H-7), 1.66- 1.58 (m, 1H; H-6′), 1.57–1.50 ppm (m, 1H; H-7′); ^{13}C NMR (D_2O, 100 MHz): $\delta = 103.3$ (C-1), 77.9 (C-3), 77.6 (C-4), 72.9 (C-5), 71.8 (C-2), 56.7 (OCH_3), 22.2 (C-6), 16.7 (C-7); HRMS (CIMS): *m/z* calcd for $C_8H_{18}O_5N$: 208.1185 $[M+NH_4]^+$; found: 208.1189.

Compound 10: Palladium on carbon (6.2 mg, 120 mg mmol^{-1} of starting material) was added to a solution of derivative **7** (25 mg, 50 μmol) dissolved in a 2:1 EtOAc/MeOH mixture (3 mL). The solution was degassed three times, and air was replaced by H_2. After stirring for 23 h at RT, the reaction mixture was filtered through a Rotilabo Nylon 0.45 μm filter eluted with methanol and concentrated under reduced pressure. Purification by flash column chromatography (toluene/acetone, 1:1) afforded the corresponding diethyl derivative **10** (10 mg, 91%) as a colorless oil; $[\alpha]_D = -20.5$ ($c = 0.2$ in MeOH); ^1H NMR (D_2O, 400 MHz): $\delta = 4.26$ (s, 1H; H-1), 3.48 (s, 3H; OCH_3), 3.40 (d, $J = 8.3$ Hz, 1H; H-3), 3.31–3.22 (m, 2H; H-4, H-5), 1.87 (dq, $J = 7.4$, 14.8 Hz, 1H; H-6a), 1.63 (q, $J = 7.5$ Hz, 2H; H-8a, H-8b), 1.44 (dq, $J = 7.4$, 14.8 Hz, 1H; H-6b), 0.97 (t, $J = 7.4$ Hz, 3H, CH_3), 0.95 ppm (t, $J = 7.5$ Hz, 3H; CH_3); ^{13}C NMR (D_2O, 100 MHz): $\delta = 107.0$ (C-1), 79.8 (C-3), 78.3 (C-4 or C-5), 75.6 (C-2), 72.2 (C-4 or C-5), 57.9 (OCH_3), 24.3 (C-6), 20.7 (C-8), 9.3, 8.3 ppm (2×CH_3); HRMS (ESI): *m/z* calcd for $C_{10}H_{20}O_5Na$: 243.1208 $[M+Na]^+$; found: 243.1210.

Compound 12: Anhydrous DMSO (4.6 mL, 64.69 mmol) was added dropwise to a solution of oxalyl chloride (4.2 mL, 48.20 mmol) in anhydrous CH_2Cl_2 (60 mL) at −78 °C under argon. After 15 min, a solution of primary alcohol **6** (6.07 g, 9.76 mmol) in anhydrous CH_2Cl_2 (40 mL) was added dropwise and the reaction was stirred for 1 h. Anhydrous triethylamine (11.5 mL) was then added and the reaction mixture was stirred for 90 min and allowed to reach RT. Water (150 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude aldehyde was coevaporated with toluene and used without further purification. Vinyl magnesium bromide (1 M in THF, 10.5 mL) was added to a solution of the crude ketone in anhydrous THF (15 mL) cooled at 0 °C and the reaction mixture was stirred at RT

for 2 h. Saturated ammonium chloride (20 mL) and water (10 mL) were added and the aqueous layer was extracted with EtOAc (3×50 mL). The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (cyclohexane/EtOAc, 8:1) afforded the vinyl derivative **12** (3.40 g, 52% over two steps) as an oil. $[\alpha]_D = +38$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR($CDCl_3$, 400 MHz): $\delta = 7.52$–7.30 (m, 10H; ArH), 6.19 (dd, $J = 11.1$, 17.5 Hz, 1H; H-7), 5.66 (dd, $J = 1.6$, 17.5 Hz, 1H; H-8), 5.61 (s, 1H; CHPh), 5.45 (dd, $J = 1.6$, 11.1 Hz, 1H; H-8′), 4.94 (d, $J = 12.1$ Hz, 1H; CHPh), 4.89 (d, $J = 12.1$ Hz, 1H; CHPh), 4.57 (s, 1H; H-1), 4.35 (dd, $J = 4.3$, 9.8 Hz, 1H; H-6), 3.97–3.79 (m, 4H; H-3, H-4, H-5, H-6′), 3.49 ppm (s, 3H; OMe); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta =$ 138.7, 137.4 (*ipso* ArC), 135.8 (C-7), 128.9–127.4 (ArC), 117.4 (C-8), 103.5 (C-1), 101.3 (CHPh), 80.9 (C-4), 80.5 (C-3), 76.7 (C-2), 74.8 (CH_2Ph), 69.0 (C-6), 63.4 (C-5), 55.4 ppm (OMe); MS (CI, NH_3): m/z (%): 416 (100) $[M+NH_4]^+$; HRMS (FAB+): m/z calcd for $C_{23}H_{26}O_6Na$: 421.1627 $[M+Na]^+$; found: 421.1629. Further elution afforded the C-2 epimer (1.14 g, 18% over two steps) as an oil. $[\alpha]_D = -53$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.57$–7.32 (m, 10H: ArH), 5.79 (dd, $J = 10.7$, 17.2 Hz, 1H; H-7), 5.66 (s, 1H; CHPh), 5.55 (dd, $J = 0.9$, 17.2 Hz, 1H; H-8), 5.40 (dd, $J = 0.9$, 10.7 Hz, 1H; H-8′), 4.91 (d, $J =$ 11.4 Hz, 1H; CHPh), 4.74 (d, $J = 11.4$ Hz, 1H; CHPh), 4.41 (dd, $J = 4.9$, 10.4 Hz, 1H; H-6), 4.35 (s, 1H; H-1), 4.19 (t, $J = 9.4$ Hz, 1H; H-4), 3.95 (t, $J = 10.4$ Hz, 1H; H-6′), 3.62 (d, $J = 9.4$ Hz, 1H; H-3), 3.55 (s, 3H; OMe), 3.53–3.45 ppm (m, 1H; H-5); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta =$ 138.2 (C-7), 138.3, 138.0 (*ipso* ArC), 129.4–126.5 (ArC), 117.5 (C-8), 104.0 (C-1), 101.8 (CHPh), 80.1 (C-4), 79.9 (C-3), 77.7 (C-2), 75.5 (CH_2Ph), 69.0 (C-6), 67.0 (C-5), 58.2 ppm (OMe); MS (CI, NH_3): m/z (%): 416 (100) $[M+NH_4]^+$; HRMS (FAB+): m/z calcd for $C_{23}H_{26}O_6Na$: 421.1627 $[M+Na]^+$; found: 421.1626.

Compound 13: Lithium aluminum hydride (1.09 g, 29.15 mmol) was carefully added in portions to a solution of alkene **12** (2.3 g, 5.78 mmol) dissolved in a 1:1 CH_2Cl_2/Et_2O mixture (60 mL) at 0°C under argon. After 10 min, the reaction mixture was warmed to 40°C, and a solution of $AlCl_3$ (3.26 g, 24.55 mmol) in Et_2O (30 mL) was added dropwise under argon. The reaction was stirred for 90 min, by which time TLC revealed no trace of starting material remained. The reaction mixture was cooled to 0°C and quenched by slow addition of EtOAc followed by water. A solution of 1 M HCl (10 mL) was added and the organic layer was washed with $NaHCO_3$ (100 mL) and water (100 mL), separated, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (cyclohexane/EtOAc, 3:1) afforded the diol **13** (1.96 g, 86%) as an oil. $[\alpha]_D = +69$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.40$–7.30 (m, 10H; ArH), 6.11 (dd, $J = 11.0$, 17.2 Hz, 1H; H-7), 5.66 (dd, $J = 1.9$, 17.2 Hz, 1H; H-8), 5.43 (dd, $J = 1.9$, 11.0 Hz, 1H; H-8′), 5.02 (d, $J = 11.4$ Hz, 1H; CHPh), 4.91 (d, $J = 11.0$ Hz, 1H; CHPh), 4.82 (d, $J = 11.4$ Hz, 1H; CH_2Ph), 4.63 (d, $J = 11.0$ Hz, 1H; CHPh), 4.49 (s, 1H; H-1), 3.93 (d, $J = 9.0$ Hz, 1H; H-3), 3.89–3.65 (m, 4H; H-4, H-5, H-6, H-6′), 3.45 ppm (s, 3H; OMe); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta =$ 138.7, 138.1 ($2\times C_{ipso}$), 135.6 (C-7), 128.4–127.9 (ArC), 117.2 (C-8), 102.9 (C-1), 84.9 (C-3), 76.1 (C-4), 75.3 (CH_2Ph), 75.1 (CH_2Ph), 71.4 (C-5), 65.6 (C-2), 62.0 (C-6), 55.3 ppm (OMe); MS (CI, NH_3): m/z (%): 418 (100) $[M+NH_4]^+$; HRMS (CI, NH_3): m/z calcd for $C_{23}H_{32}O_6N$: 418.2230 $[M+NH_4]^+$; found: 418.2232.

Compound 14: Anhydrous DMSO (0.267 mL) was added dropwise to a solution of oxalyl chloride (0.242 mL) in anhydrous CH_2Cl_2 (4 mL) at −78°C under argon. After 15 min, a solution of primary alcohol **13** (415 mg, 2.00 mmol) in anhydrous CH_2Cl_2 (3 mL) was added dropwise and the reaction was stirred for 1 h. Triethylamine (0.66 mL) was then added and the reaction mixture was stirred for 90 min and allowed to reach RT. Water (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×5 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude aldehyde was coevaporated with toluene and used without further purification. *n*-Butyllithium (2.5 M in *n*-hexanes, 1.5 mL) was added dropwise to a solution of Ph_3PCH_2Br (1.34 g) in anhydrous THF (10 mL) at 0°C under argon. The reaction mixture was stirred for 30 min at 0°C until the bright-orange color persisted, and a solution of the crude aldehyde in anhydrous THF (5 mL) was then quickly added. The reaction mixture was heated to reflux for 2 h, cooled to RT, quenched with water (20 mL), and diluted with CH_2Cl_2 (80 mL). The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated. Purification by flash chromatography (cyclohexane/EtOAc, 7:1) afforded the divinyl derivative **14** (0.294 g, 79% over two steps) as an oil. $[\alpha]_D = +56$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 7.39$–7.29 (m, 10H; ArH), 6.14 (dd, $J = 11.0$, 17.4 Hz, 1H; H-8), 6.01 (ddd, $J = 6.4$, 10.4, 17.1 Hz, 1H; H-6), 5.67 (dd, $J = 1.7$, 17.4 Hz, 1H; H-9), 5.51 (tt, $J = 1.1$, 17.1 Hz, 1H; H-7), 5.43 (dd, $J = 1.7$, 11.0 Hz, 1H; H-9′), 5.34 (dt, $J = 1.1$, 10.5 Hz, 1H; H-7′), 4.99 (d, $J = 11.4$ Hz, 1H; CHPh), 4.82 (d, $J = 11.4$ Hz, 1H; CHPh), 4.80 (d, $J =$ 10.6 Hz, 1H; CHPh), 4.60 (d, $J = 10.6$ Hz, 1H; CHPh), 4.50 (s, 1H; H-1), 4.18 (dd, $J = 6.4$, 9.5 Hz, 1H; H-5), 3.91 (d, $J = 9.5$ Hz, 1H; H-3), 3.46 (s, 3H; OMe), 3.39 (t, $J = 9.5$ Hz, 1H; H-4), 2.62 ppm (s, 1H; OH); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 138.5$, 137.8 ($2\times C_{ipso}$), 135.7 (C-6), 135.1 (C-8), 128.3–127.5 (ArC), 118.1 (C-7), 117.1 (C-9), 102.7 (C-1), 84.7 (C-3), 80.9 (C-4), 75.4 (CH_2Ph), 75.1 (CH_2Ph), 71.9 (C-5), 55.3 ppm (OMe); MS (CI, NH_3): m/z (%): 414 (100) $[M+NH_4]^+$; HRMS (CI, NH_3): m/z calcd for $C_{24}H_{32}O_5N$: 414.2280 $[M+NH_4]^+$; found: 414.2278.

Compound 15: Compound **14** (655 mg, 1.35 mmol) was dissolved in anhydrous CH_2Cl_2 (200 mL) and the solution was degassed three times followed by addition of 2nd generation Grubbs catalyst (141 mg, 10% mol) under argon. The reaction mixture was heated to reflux for 18 h, cooled at RT, and an excess of $[Pb(OAc)_4]$ (110 mg, 1.5 equiv. of catalyst) was added. The reaction mixture was stirred for 3 h, filtered through a Celite plug eluted with CH_2Cl_2 and concentrated under reduced pressure. Purification by flash column chromatography (cyclohexane/EtOAc, 4:1) afforded the bicyclic alkene **15** (583 mg, 96%) as an oil. $[\alpha]_D = +11$ ($c = 1.0$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) $\delta = 7.41$–7.30 (m, 10H; ArH), 6.34 (dd, $J = 5.0$, 8.4 Hz, 1H; H-6), 6.31 (dt, $J = 1.5$, 8.4 Hz, 1H; H-7), 4.72 (d, $J = 12.3$ Hz, 1H; CHPh), 4.68 (d, $J = 11.6$ Hz, 1H; CHPh), 4.67–4.65 (m, 1H; H-5), 4.59 (d, $J = 11.6$ Hz, 1H; CHPh), 4.57 (d, $J = 12.3$ Hz, 1H; CHPh), 4.52 (s, 1H; H-1), 3.97 (s, 1H; H-3), 3.56 (s, 3H; OMe), 3.44 (t, $J = 1.5$ Hz, 1H; H-4), 2.73 ppm (s, 1H; OH); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 138.0$, 137.9 ($2\times C_{ipso}$), 136.7 (C-7), 128.8 (C-6), 128.4–127.7 (ArC), 102.1 (C-1), 82.3 (C-3), 77.3 (C-4), 76.2 (C-2), 72.5 (CH_2Ph), 70.6 (CH_2Ph), 69.7 (C-5), 56.8 ppm (OMe); MS (CI, NH_3): m/z (%): 386 (100) $[M+NH_4]^+$; HRMS (CI, NH_3): m/z calcd for $C_{22}H_{28}O_5N$: 386.1967 $[M+NH_4]^+$; found: 386.1963.

Compound 16: Palladium on carbon (10% w/w, 58 mg) was added to a solution of bicyclic alkene **15** (582 mg, 1.28 mmol) dissolved in a 1:1 EtOAc/MeOH mixture (25 mL). The solution was degassed three times, and air was replaced by H_2. After stirring for 2 h at RT, the reaction mixture was filtered through a Rotilabo Nylon 0.45 μm filter and the solvent was evaporated. Purification by flash column chromatography (AcOEt/MeOH, 10:1) afforded the xyloside analogue **16** (294 mg, 98%) as a white crystalline solid; mp 113–114°C (EtOAc/MeOH); $[\alpha]_D = +129$ ($c =$ 1.2 in MeOH); ^{1}H NMR (D_2O, 400 MHz): $\delta = 4.63$ (s, 1H; H-1), 3.92–3.90 (m, 1H; H-5), 3.89–3.87 (m, 1H; H-3), 3.61 (t, $J = 1.8$ Hz, 1H; H-4), 3.42 (s, 3H; OMe), 2.04–1.90 (m, 2H; H-6, H-7), 1.66 (dddd, $J = 1.2$, 3.7, 11.6, 14.8 Hz, 1H; H-6′), 1.36 ppm (dddd, $J = 1.9$, 6.0, 13.1, 14.8 Hz, 1H; H-7′); ^{13}C NMR (D_2O, 100 MHz): $\delta = 104.3$ (C-1), 76.3 (C-3), 73.9 (C-4), 73.0 (C-5), 71.5 (C-2), 56.7 (OMe), 23.3 (C-6), 21.3 ppm (C-7); MS (CI, NH_3): m/z (%): 208 (70) $[M+NH_4]^+$; HRMS (CI, NH_3): m/z calcd for $C_8H_{18}O_5N$: 208.1185 $[M+NH_4]^+$; found: 208.1187.

Compound 17: Acetic anhydride (3 mL) and a catalytic amount of DMAP (14 mg) were added to a solution of triol **16** (213 mg, 1.12 mmol) in dry pyridine (5 mL) under argon. The reaction mixture was stirred for 12 h, the solvent was evaporated, and the residue was dissolved in EtOAc (5 mL) and washed with water (4 mL), 1 M HCl (4 mL), and brine (4 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated, and the residue was purified by flash column chromatography (cyclohexane/AcOEt, 1:1) to afford triacetate **17** as a white solid (349 mg, 98%). $[\alpha]_D = +40$ ($c = 1.0$ in $CHCl_3$); m.p. 109–110°C (cyclohexane/AcOEt, 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 5.64$ (s, 1H; H-1), 5.51–5.50 (m, 1H; H-5), 4.69 (t, $J = 1.9$ Hz, 1H; H-4), 4.02–3.99 (m, 1H; H-3), 3.44 (s, 3H; OMe), 2.51 (dddd, $J = 1.9$, 4.5, 12.3, 13.4 Hz, 1H; H-6), 2.22–1.95 (m, 2H; H-6′, H-7′), 2.14 (s, 3H; OAc), 2.13 (s, 3H; OAc), 2.02 ppm (s, 3H; OAc); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 170.3$, 169.8, 169.4 (3×C=O), 98.4 (C-1), 78.7 (C-2), 76.6 (C-4), 72.0 (C-5), 68.7 (C-3),

55.2 (OMe), 23.9 (C-7), 21.8, 20.9, 20.9 (3×OAc), 18.4 ppm (C-6); MS (CI, NH_3): *m/z* (%): 334 (100) $[M+NH_4]^+$, 317 (20) $[M+H]^+$; HRMS (CI, NH_3): *m/z* calcd for $C_{14}H_{24}O_8N$: 334.1502 $[M+NH_4]^+$; found: 334.1493.

Compound 18: Acetic anhydride (1.3 mL) was added to a solution of triacetate **17** (348 mg, 1.10 mmol) in anhydrous CH_2Cl_2 (7 mL) at −30 °C. Sulfuric acid (43 μL, 0.78 mmol) was then added dropwise and the reaction mixture was allowed to reach 0 °C over a period of 90 min. The reaction mixture was neutralized by slow addition of saturated aqueous $NaHCO_3$. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated. Purification by flash column chromatography (cyclohexane/EtOAc, 4:1) afforded tetracetate **18** (253 mg, 67%) as a white solid and as a 2:5 α/β anomeric mixture. Spectroscopic data for α anomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.81 (s, 1H; H-1α), 5.54 (s, 1H; H-3α), 4.74 (t, *J* = 1.8 Hz, 1H; H-4α), 4.12–4.11 (m, 1H; H-5α), 2.61–2.59 (m, 1H; H-7α), 2.39–2.09 (m, 2H; H-6α, H-7′α), 2.17, 2.16, 2.15, 2.00 (4×s, 12H; 4×OAc α), 1.91–1.77 ppm (m, 1H; H-6′α); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.0, 169.7, 169.4, 169.4 (4×CO α), 91.3 (C-1α), 76.0 (C-4α), 71.9 (C-5α), 69.6 (C-3α), 23.3 (C-6α), 21.7, 21.1, 21.1, 20.9 (4×OAc α), 18.2 ppm (C-7α). Spectroscopic data for β anomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 6.83 (d, *J* = 1.3 Hz, 1H; H-1β), 5.88 (t, *J* = 2.5 Hz, 1H; H-3β), 4.86 (dd, *J* = 1.1, 2.5 Hz, 1H; H-4β), 4.01–4.00 (m, 1H; H-5β), 2.39–2.09 (m, 2H; H-6β, H-7β), 2.05–2.03 (m, 1H; H-7′β), 2.14, 2.12, 1.98 (3×s, 12H; 4×OAc β, 1.91–1.77 ppm (m, 1H; H-6′β); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.4, 169.6, 169.3, 169.2 (4×CO β), 90.8 (C-1β), 77.2 (C-4β), 72.8 (C-5β), 70.1 (C-3β), 22.2 (C-6β), 21.5, 21.1, 20.9, 20.7 (4×OAc β), 17.6 ppm (C-7β); HRMS (CIMS): *m/z*: calcd for $C_{15}H_{24}O_9N$: 362.1446 $[M+NH_4]^+$; found: 362.1451.

Compound 19: A suspension of compound **18** (253 mg, 0.73 mmol), 4 Å molecular sieves (550 mg) and dry isopropanol (82 μL) in dry CH_2Cl_2 (4 mL) was stirred under argon at RT for 2 h. The reaction mixture was cooled to −78 °C, TMSOTf (200 μL) was added dropwise and the solution was allowed to reach 0 °C. After 2.5 h (TLC showed some decomposition) the reaction was quenched by addition of triethylamine. The suspension was filtered through a Celite plug eluted with CH_2Cl_2. The filtrate was washed with sat. $NaHCO_3$ (5 mL) and water (5 mL), dried ($MgSO_4$), filtered, and concentrated. Purification by flash column chromatography (toluene/AcOEt, 10:1) afforded a mixture of compounds **19** and **20** (148 mg, 58%) in a 1:5 ratio as an oil. Spectroscopic data for α-anomer **19**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.85 (s, 1H; H-1), 5.54–5.52 (m, 1H; H-3), 4.69 (t, *J* = 1.8 Hz, 1H; H-4), 4.02–3.94 (m, 2H; H-5, H-8), 2.56–2.55 (m, 1H; H-7), 2.32–1.97 (m, 2H; H-6, H-6′), 2.16, 2.15, 2.13, 2.02, 2.01 (6×s, 18H; 6×OAc), 1.84–1.74 (m, 1H; H-7′), 1.27 (d, *J* = 6.3 Hz, 3H; CH_3 isopropyl), 1.12 ppm (d, *J* = 6.3 Hz, 3H; CH_3 isopropyl); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.5, 169.6, 169.6 (3×CO), 95.5 (C-1), 78.0 (C-4), 72.4 (C-3), 69.9 (C-8), 68.4 (C-5), 24.0 (C-6), 23.5 (CH_3 isopropyl), 21.8 (CH_3 isopropyl), 21.6, 21.6, 21.1, 21.0, 21.0, 20.8 (6×OAc), 18.5 ppm (C-7); MS (CI, NH_3): *m/z* (%): 362 (100) $[M+NH_4]^+$, 345 (70) $[M+H]^+$; HRMS (CI, NH_3): *m/z* calcd for $C_{16}H_{28}O_8N$: 362.1815 $[M+NH_4]^+$; found: 362.1819.

Spectroscopic data for β-anomer 20: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.83 (d, *J* = 1.2 Hz, 1H; H-1), 5.82 (d, *J* = 2.7 Hz, 1H; H-3), 2.45 (dd, *J* = 1.4, 2.7 Hz, 1H; H-4), 4.02–3.94 (m, 1H; H-8), 3.93–3.90 (m, 1H; H-5), 2.32–1.97 (m, 3H; H-6, H-7, H-7′), 2.16, 2.15, 2.13, 2.02, 2.01 (5×s, 18H; 6×OAc), 1.84–1.74 (m, 1H; H-6′), 1.26 (d, *J* = 6.3 Hz, 3H; CH_3 isopropyl), 1.13 ppm (d, *J* = 6.3 Hz, 3H; CH_3 isopropyl); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.5, 169.6, 169.6 (3×CO), 95.0 (C-1), 78.0 (C-4), 73.3 (C-3), 70.4 (C-8), 69.1 (C-5), 23.6 (CH_3 isopropyl), 22.5 (C-6), 21.9 (CH_3 isopropyl), 21.6, 21.6, 21.1, 21.0, 21.0, 20.8 (6×OAc), 17.5 ppm (C-7).

Compound 21: A mixture of compounds **19** and **20** (85 mg, 0.25 mmol) was dissolved in MeOH (5 mL), the solution was cooled to 0 °C, and a catalytic amount of NaOMe was added. The reaction mixture was stirred at RT for 1 h then neutralized by addition of Amberlite IR-120 H^+ resin. The solution was filtered, concentrated, and purified by flash column chromatography (AcOEt) to afford compound **21** (11 mg, 0.05 mmol) quantitatively as an oil. Further elution afforded compound **22** (44 mg, 0.2 mmol) as a solid. Spectroscopic data for triol **21**: $[\alpha]_D$ = −21 (*c* = 0.4 in MeOH); ^{1}H NMR (D_2O, 400 MHz): δ = 4.90 (s, 1H; H-1), 4.00–3.89 (m, 3H; CH isopropyl, H-4, H-5), 3.62 (t, *J* = 1.8 Hz, 1H; H-3), 2.02–1.86 (m, 2H; H-6, H-7), 1.68 (dddd, *J* = 1.6, 3.5, 11.1, 17.2 Hz, 1H; H-7′), 1.53–1.33 (m, 1H; H-7′), 1.20 (d, *J* = 6.1 Hz; CH_3 isopropyl), 1.16 ppm (d, *J* = 6.1 Hz; CH_3 isopropyl); ^{13}C NMR (D_2O, 100 MHz): δ = 100.9 (C-1), 76.5 (C-3), 73.9 (C-4), 73.0 (C-5), 72.3 (C-8), 71.4 (C-2), 23.3 (C-6), 22.7 (C-9), 21.5 (C-7), 21.1 ppm (C-9′); MS (CI, NH_3): *m/z* (%): 236 (100) $[M+NH_4]^+$; HRMS (CI, NH_3): *m/z* calcd for $C_{10}H_{22}O_5N$: 236.1498 $[M+NH_4]^+$; found: 236.1499.

Compound 22: $[\alpha]_D$ = −88 (*c* = 1.0 in MeOH); ^{1}H NMR (D_2O, 400 MHz) δ = 4.72 (d, *J* = 1.2 Hz, 1H; H-1), 3.95 (hept, *J* = 6.3 Hz, 1H; CH isopropyl), 3.77 (m, 1H; H-5), 3.71 (dd, *J* = 1.2, 2.8 Hz, 1H; H-4), 3.53 (t, *J* = 2.8 Hz, 1H; H-3), 2.05–1.96 (m, 1H; H-6), 1.76 (ddd, *J* = 1.3, 6.4, 7.8 Hz, 1H; H-7), 1.70–1.62 (m, 2H; H-6′, H-7′), 1.22 (d, *J* = 6.3 Hz, 3H; CH_3 isopropyl), 1.16 ppm (d, *J* = 6.3 Hz, 3H; CH_3 isopropyl); ^{13}C NMR (D_2O, 100 MHz): δ = 100.2 (C-1), 78.0 (C-3), 77.6 (C-4), 72.6 (C-8), 72.6 (C-5), 71.6 (C-2), 22.7 (C-9′), 22.1 (C-6), 21.4 (C-9), 16.5 ppm (C-7); MS (CI, NH_3): *m/z* (%): 236 (100) $[M+NH_4]^+$, 219 (20) $[M+H]^+$; HRMS (CI, NH_3): *m/z* calcd for $C_{10}H_{19}O_5$: 219.1232 $[M+H]^+$; found: 219.1230.

Compound 23: Thiophenol (24 μL, 0.227 mmol) and $BF_3{\cdot}OEt_2$ (58 μL, 0.453 mmol) were added to a solution of tetracetate **18** (52 mg, 0.151 mmol) in anhydrous CH_2Cl_2 (1 mL) at 0 °C under argon. After stirring for 20 min at 0 °C, the reaction mixture was diluted with CH_2Cl_2 (2 mL) and neutralized with sat. $NaHCO_3$ (2 mL). The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash column chromatography (cyclohexane/EtOAc, 2:1) afforded the thiophenyl derivative **23** (41 mg, 68%) as a colorless oil and as a 1:5 α/β anomeric mixture. Spectroscopic data for α anomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.56–7.30 (m, 5H; ArH), 6.36 (s, 1H; H-1), 5.58 (t, *J* = 2.2 Hz, 1H; H-3), 4.83 (t, *J* = 2.2 Hz, 1H; H-4), 4.05–4.04 (m, 1H; H-5), 2.75–2.68 (m, 1H; H-6), 2.30–2.27 (m, 1H; H-7), 2.24–2.13 (m, 1H; H-7′), 2.21, 2.19, 2.08 (3×s, 9H; OAc), 2.21–1.97 ppm (m, 1H; H-6′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.5, 169.0, 166.9 (3×C=O), 133.2 (*ipso* ArC), 132.6–127.6 (ArC), 87.7 (C-1), 77.3 (C-2), 77.1 (C-4), 73.0 (C-3), 69.7 (C-5), 23.6 (C-6), 21.8, 21.1, 20.9 (3×OAc), 20.1 ppm (C-7). Spectroscopic data for β anomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 7.56–7.30 (m, 5H; ArH), 6.51 (d, *J* = 2.2 Hz, 1H; H-1), 5.90 (t, *J* = 2.0 Hz, 1H; H-3), 4.86 (t, *J* = 2.0 Hz, 1H; H-4), 4.03–4.01 (m, 1H; H-5), 2.48–2.39 (m, 1H; H-6), 2.24–2.13 (m, 1H; H-7), 2.15, 2.14, 2.00 (3×s, 9H; OAc), 2.10–2.06 (m, 1H; H-7′), 1.89 ppm (ddt, *J* = 1.8, 3.9, 12.0 Hz, 1H; H-6′); ^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.3, 169.5, 169.3 (3×C=O), 133.2 (*ipso* ArC), 132.5–127.6 (ArC), 87.1 (C-1), 77.6 (C-2), 77.5 (C-4), 77.7 (C-3), 69.5 (C-5), 22.7 (C-6), 21.6, 21.0, 20.8 (3×OAc), 19.8 ppm (C-7); HRMS (CIMS): *m/z* calcd for $C_{19}H_{26}O_7SN$: 412.1424 $[M+NH_4]^+$; found: 412.1419.

Compounds 25 and 26: A solution of thioglycosyl donor **23** (25 mg, 63.4 μmol) and xylosyl acceptor **24** (40 mg, 196 μmol) in anhydrous CH_2Cl_2 (1.5 mL) was cooled to - 50 °C under argon and activated 4 Å molecular sieves (60 mg) and NIS (45 mg, 126.8 mmol) were added to the solution. The reaction mixture was degassed three times, and air was replaced with argon followed by addition of TfOH (1 μL, 6.34 μmol). The reaction mixture was stirred at RT for 5 min when TLC indicated complete consumption of the thioglycosyl donor **23**. The reaction mixture was filtered through Celite, and eluted with CH_2Cl_2. The filtrate was washed with sat. $NaHCO_3$ (5 mL) and sat. $Na_2S_2O_3$ (5 mL). The organic layer was separated, dried ($MgSO_4$), and the solvent was removed under reduced pressure. NMR analysis of the crude mixture indicated the absence of isopropylidene group on the synthesized disaccharides. Unfortunately, the crude mixture of α and β anomers (1:4) proved to be inseparable by flash chromatography. The resulting disaccharides were then peracetylated. The crude mixture of disaccharides (19 mg) was dissolved in anhydrous pyridine (1 mL), and acetic anhydride (0.5 mL) was added. The reaction mixture was stirred overnight at RT, then the reaction mixture was coevaporated with toluene and concentrated under reduced pressure. Purification by flash column chromatography (cyclohexane/acetone, 4:1) afforded the β-disaccharide **26** (15 mg, 45%) as a white crystalline solid. M.p. 142 °C (EtOAc); $[\alpha]_D$ = −80 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.87 (s, 1H; H-1′), 5.71 (d, *J* = 2.1 Hz, 1H; H-3′), 5.18 (t, *J* = 9.2 Hz; H-3),

4.90 (dd, $J=7.7$, 9.2 Hz, 1H; H-2), 4.81 (dd, $J=1.5$, 2.1 Hz, 1H, H-4′), 4.35 (d, $J=7.7$ Hz, 1H; H-1), 3.99 (dd, $J=5.5$, 11.6 Hz, 1H; H-5a), 3.93–3.86 (m, 2H; H-4, H-5′), 3.50 (s, 3H; OMe), 3.27 (dd, $J=9.9$, 11.6 Hz, 1H; H-5b), 2.15 (s, 3H; OAc), 2.13 (s, 3H; OAc), 2.09 (s, 3H; OAc), 2.06–2.03 (m, 1H; H-6′a), 1.99 (s, 3H; OAc), 2.00–1.95 (m, 2H; H-7′a, H-7′b), 1.79–1.72 ppm (m, 1H; H-6′b); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=$ 170.3, 170.2, 169.7, 169.6, 169.5 (5×C=O), 102.1 (C-1), 96.5 (C-1′), 78.1 (C-2′), 77.7 (C-4′), 74.5 (C-4), 73.0 (C-3), 72.8 (C-3′), 71.2 (C-2), 69.1 (C-5′), 63.3 (C-5), 56.8 (OMe), 22.2 (C-6′), 21.5, 21.0, 20.9, 20.8, 20.7 (5× OAc), 17.0 (C-7′); HRMS (CIMS): m/z calcd for $C_{23}H_{36}O_{14}N$: 550.2136 $[M+NH_4]^+$; found: 550.2133.

Further elution afforded α disaccharide **25** (4 mg, 12%) as a colorless oil: $[\alpha]_D=-56$ ($c=0.3$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta=5.87$ (s, 1H; H-1′), 5.83 (dd, $J=2.0$, 2.7 Hz, 1H; H-3′), 5.21 (t, $J=9.0$ Hz, 1H; H-3), 4.89–4.83 (m, 2H; H-4′, H-4), 4.38 (d, $J=6.9$ Hz, 1H; H-1), 4.08 (dd, $J=5.3$, 11.7 Hz, 1H; H-5a), 3.95–3.94 (m, 1H; H-5′), 3.80 (dd, $J=6.9$, 9.0 Hz, 1H; H-2), 3.52 (s, 3H; OMe), 3.34 (dd, $J=9.1$, 11.7 Hz, 1H; H-5b), 2.34–2.33 (m, 2H; H-6′a, H-7′b), 2.13 (s, 3H; OAc), 2.10 (s, 6H; 2× OAc), 2.04 (s, 3H; OAc), 2.10–1.95 (m, 1H; H-7′b), 1.99 (s, 3H; OAc), 1.78–1.74 ppm (m, 1H; H-6′b); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta=171.0$, 170.9, 170.5, 170.2, 169.9 (5×CO), 103.5 (C-1), 96.5 (C-1′), 78.6 (C-2′), 78.4 (C-4′), 74.3 (C-2), 73.9 (C-3), 73.2 (C-3′), 70.2 (C-5′), 70.1 (C-4), 62.7 (C-5), 56.9 (OMe), 22.3 (C-6′), 21.9, 21.5, 21.4, 21.2, 21.2 (5×OAc), 17.9 ppm (C-7′); HRMS (CIMS): m/z calcd for $C_{23}H_{36}O_{14}N$: 550.2136 $[M+NH_4]^+$; found: 550.2131.

Compound 27: A few drops of 0.1 M NaOMe were added dropwise to a solution of disaccharide **25** (4 mg, 7.5 μmol) in MeOH (1 mL) until pH 9–10 and the mixture was stirred for 3 h at RT. The reaction mixture was neutralized with Amberlite IR 120 (H^+) resin for 30 min, filtered, and concentrated under reduced pressure to afford the α-disaccharide **27** (2.4 mg, quantitative yield) as a colorless oil. $[\alpha]_D=-68$ ($c=0.1$ in MeOH); ^{1}H NMR (D_2O, 400 MHz): $\delta=4.87$ (s, 1H; H-1′), 4.42 (d, $J=$ 7.4 Hz, 1H; H-1), 3.93 (dd, $J=3.6$, 10.8 Hz, 1H; H-5a), 3.79 (m, 1H; H-5′), 3.70 (d, $J=2.4$ Hz, 1H; H-4′), 3.64–3.57 (m, 2H; H-3, H-4), 3.54–3.51 (m, 4H; H-3′, OCH_3), 3.42 (t, $J=7.4$ Hz, 1H; H-2), 3.30 (dd, $J=6.0$, 10.8 Hz, 1H; H-5b), 2.09–1.91 (m, 1H; H-6′a), 1.79–1.63 ppm (m, 3H; H-6′b, H-7′a, H-7′b); ^{13}C NMR (D_2O, 100 MHz): $\delta=103.0$ (C-1), 102.6 (C-1′), 78.8 (C-2), 77.3 (C-3′), 77.2 (C-4′), 75.2 (C-3 or C-4), 72.7 (C-5′), 72.2 (C-2′), 69.1 (C-3 or C-4), 64.6 (C-5), 57.0 (OMe), 21.6 (C-6′), 16.4 ppm (C-7′); HRMS (ESI): m/z calcd for $C_{13}H_{26}O_9N$: 340.1608 $[M+NH_4]^+$; found: 340.1604.

Compound 28: A few drops of 0.1 M NaOMe were added dropwise to a solution of disaccharide **26** (13 mg, 24.4 μmol) in MeOH (3 mL) until pH 9–10 and the mixture was stirred for 40 min at RT. The reaction mixture was neutralized with Amberlite IR 120 (H^+) resin for 30 min, filtered, and concentrated under reduced pressure. Purification by flash column chromatography (CH_2Cl_2/MeOH, 9:2) afforded the β-disaccharide **28** (7.8 mg, quantitative yield) as a colorless oil. $[\alpha]_D=-87$ ($c=0.5$ in MeOH); ^{1}H NMR (D_2O, 400 MHz): $\delta=4.75$ (s, 1H; H-1′), 4.35 (d, $J=$ 7.8 Hz, 1H; H-1), 4.11 (dd, $J=5.3$, 11.8 Hz, 1H; H-5a), 3.87–3.86 (m, 1H; H-5), 3.76 (dd, $J=0.8$, 2.1 Hz, 1H; H-4), 3.75 (ddd, $J=5.3$, 9.1, 10.3 Hz, 1H; H-4), 3.59 (t, $J=9.1$ Hz, 1H; H-3), 3.56 (d, $J=2.1$ Hz, 1H; H-3′), 3.55 (s, 3H; OMe), 3.37 (dd, $J=10.3$, 11.8 Hz, 1H; H-5b), 3.31 (dd, $J=7.8$, 9.1 Hz, 1H; H-2), 2.14–2.05 (m, 1H; H-6′a), 1.83–1.76 (m, 1H; H-7′a), 1.75–1.67 ppm (m, 2H; H-6′b, H-7′b); ^{13}C NMR (D_2O, 100 MHz): $\delta=104.2$ (C-1), 100.8 (C-1′), 77.8 (C-3′), 77.6 (C-4′), 75.5 (C-4), 74.4 (C-3), 73.2 (C-2), 73.2 (C-5′), 71.9 (C-2′), 63.3 (C-5), 57.5 (OMe), 22.2 (C-6′), 16.6 ppm (C-7′); HRMS (CIMS): m/z calcd for $C_{13}H_{26}O_9N$: 340.1608 $[M+NH_4]^+$; found: 340.1600.

Compound 29: A few drops of 0.1 M NaOMe were added to a solution of thioglycoside **23** (9 mg, 22.8 μmol) in MeOH until pH 9–10 and the mixture was stirred for 90 min at RT. The reaction mixture was neutralized with Amberlite IR 120 (H^+) resin for 30 min, filtered, and concentrated under reduced pressure to afford the thioxyloside analogue **29** (6 mg, 90% yield) as a colorless oil and as a 1:5 mixture of α/β anomers. Spectroscopic data for the α anomer: ^{1}H NMR (D_2O, 400 MHz): $\delta=7.54$–7.34 (m, 5H; ArH), 5.38 (s, 1H; H-1), 3.91 (s, 1H; H-3), 3.87 (d, $J=2.3$ Hz, 1H; H-5), 3.73 (s, 1H; H-4), 2.22–1.91 (m, 2H; H-6, H-7), 1.81–1.71 (m, 1H; H-6′), 1.51–1.44 ppm (m, 1H; H-7′); ^{13}C NMR (D_2O, 100 MHz): $\delta=$ 133.4 (*ipso* ArC), 131.9, 129.4, 127.9 (ArC), 93.2 (C-1), 76.7 (C-4), 75.1 (C-3), 73.3 (C-5), 71.2 (C-2), 23.3 (C-6), 22.9 ppm (C-7). Spectroscopic data for the β anomer: ^{1}H NMR (D_2O, 400 MHz): $\delta=7.54$–7.34 (m, 5H; ArC), 5.25 (br s, 1H; H-1), 3.83 (br s, 1H; H-5), 3.75 (s, 1H; H-4), 3.60 (s, 1H; H-3), 2.22–1.91 (m, 2H; H-6, H-7), 1.81–1.71 ppm (m, 2H; H-6′, H-7′); ^{13}C NMR (D_2O, 100 MHz): $\delta=133.3$ (*ipso* ArC), 131.6, 129.4, 127.8 (ArC), 92.0 (C-1), 79.1 (C-3), 77.2 (C-4), 73.3 (C-5), 71.2 (C-2), 22.1 (C-6), 18.4 ppm (C-7); HRMS (ESI): m/z calcd for $C_{13}H_{16}O_4SNa$: 291.06670 $[M+Na]^+$; found: 291.06663.

Acknowledgements

F. Marcelo, L. Amorim, and L. Nieto thank respectively YFundação para a Ciência e Tecnologia (FCT, Portugal), the European Community (HPRN-CT-2002-00173), and the Ministry of Education and Science of Spain (CTQ-2009-08576) for financial support.

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Received: November 11, 2010
Published online: May 12, 2011

