On the Role of Neighboring Group Participation and Ortho Esters in β-Xylosylation: ^{13}C NMR Observation of a Bridging 2-Phenyl-1,3-dioxalenium Ion

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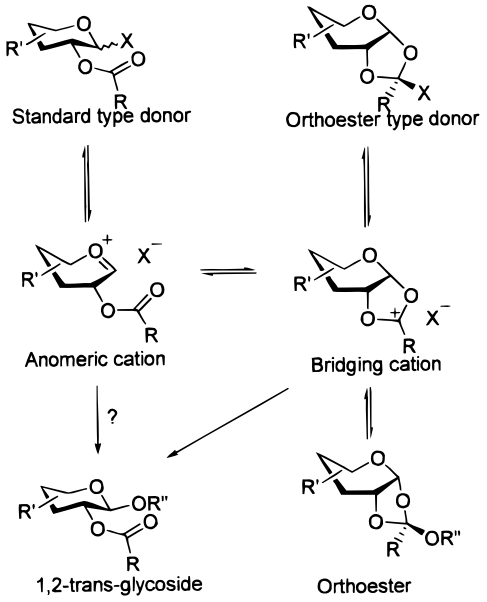
The role of ortho esters in the formation of 2,3,4-tri-*O*-benzoyl-β-xylopyranosides from various donor/promoter pairs has been investigated. It is concluded that for the activation of sulfoxides with Tf_2O, thioglycosides with PhSOTf, and bromides with AgOTf the anomeric configuration of the donor is of no consequence on the outcome of the reaction. In all methods studied, the presence or absence of a non-nucleophilic, hindered base is of crucial importance with ortho esters only being discernible in its presence. *S*-Phenyl 2,3,4-tri-*O*-benzoyl-1-deoxy-1-thia-β-D-xylopyranoside was synthesized enriched with ^{13}C at each of the three carbonyl carbons. Activation of this thioglycoside with PhSOTf in CD_2Cl_2 at −78 °C with or without the base permits, for the first time, the observation by ^{13}C NMR spectroscopy of a bridging dioxalenium ion as an intermediate in a neighboring group directed glycosylation. Quenching of this cation in the presence of the base leads to the ortho ester, whereas in the absence of the base the glycosides are the only products detected.

Introduction

The concept of neighboring group participation and the formation and isolation of ortho esters are intimately linked and central to the field of carbohydrate chemistry.[1] The synthesis of the 1,2-trans-type glycosidic bond, as typified by the β-glucopyranosides, relies heavily on the use of ester protecting groups for O-2 such that participation ensures the formation of the desired stereoisomer (Scheme 1). Ortho esters are frequent byproducts in this type of chemistry owing to the trapping of the intermediate bridging cation by the nucleophile as opposed to attack at the anomeric cation. On the other hand, the bridging cation may be entered from the ortho ester manifold under certain conditions, which give rise to the well-known ortho ester glycosylation method.[2−6] The essential question, therefore, in neighboring group-assisted trans-glycosylation is which conditions and esters favor attack at the anomeric position and minimize ortho ester formation. Direct trapping of the bridging cation, with ortho ester formation, brings about a change in hybridization and an increase in steric hindrance. For this reason, bulky pivalate esters have been a popular choice for minimizing ortho ester formation but they by no means eliminate it altogether,[7−12] and under some conditions the *tert*-butyl ortho ester may even predominate.[13] Very recently, Whitfield has published calculations that address the mechanism of neighboring group participation and that support the notion of a bridging cation as intermediate.[14] Furthermore, these calculations suggest, at least for the 2,6-di-*O*-acyl-3,4-*O*-isopropylidene-D-galactopyranosyl system studied, that the kinetic mode of attack by methanol is at the bridging cation.[14] Our interest in this area was stimulated by the observation[15] that activation of either thioglycoside **2**, or its sulfoxide (**3**), with benzenesulfenyl triflate, or triflic

Scheme 1



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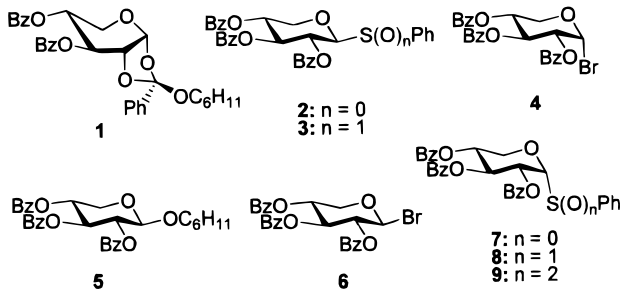
anhydride, respectively, at −78 °C in the presence of 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), followed by addition of cyclohexanol provided the ortho ester **1** in very high yield. This was in contrast to the use of the bromide **4** with activation by silver triflate, which provided the β-xyloside **5** smoothly. Here, we report the results of our investigation into the causes of this dichotomy as well as our direct observation, using ^{13}C-labeled analogues of **2**−**4**, of an intermediate bridging cation in CD_2Cl_2 solution.



Results and Discussion

In connection with the synthesis of a trisaccharide, we needed to form a β-xylopyranosyl linkage to a secondary alcohol. Following the literature precedent with a closely related target,[16] we achieved this successfully through use of the bromide **4** and activation with silver triflate in dichloromethane at −78 °C.[15,17] Our interest[18−20] in Kahne's sulfoxide method,[21,22] however, prompted us also to investigate its use in β-xylosylation. Accordingly, displacement of bromide from **4** with thiophenate provided the β-thioglycoside **2**, which was oxidized with Oxone to provide a separable mixture of diastereoisomeric sulfoxides **3**. Activation of either diastereomer of **3** in the presence of DTBMP in CH_2Cl_2 with triflic anhydride, followed by addition of cyclohexanol, as a model secondary acceptor, provided a crude reaction mixture, which, on inspection by ^1H and ^{13}C NMR spectroscopy, was found to be almost exclusively the ortho ester **1**.[15] Conversely, activation of bromide **4** in dichloromethane at −40 °C with silver triflate in the presence of the alcohol smoothly provided the β-xyloside **5**.[15] At the time, ortho esters had not been widely reported in the sulfoxide method, but their formation as byproducts had been noted by Kahne and co-workers[9−11] as well as by ourselves.[19] The very clean formation of **1** from **3** was therefore somewhat unexpected and unusual and prompted us to take a closer look at the underlying chemistry. It could be argued that the likelihood of observing ortho esters is maximized by working in the more conformationally labile pentopyranose series with benzoate esters, but that does not explain the dichotomy of the two donors **3** and **4** giving such markedly different product distributions.

In a given series, the rate of ortho ester formation has been found in some instances to be a function of anomeric stereochemistry. Thus, Lemieux reported that two anomeric, ester-protected glucopyranosyl bromides were converted to ortho esters at different rates with the β-anomer being the more reactive;[13] in the presence of added tetraalkylammonium bromide, ortho ester formation from the α-bromide is facilitated due to in situ formation of the more reactive β-bromide. Paulsen has similarly demonstrated that pentaacetyl-β-D-glucopyranose is readily converted to a crystalline bridging dioxolenium salt on treatment with $SbCl_5$, whereas the α-anomer leads to no such species.[23] However, Paulsen also noted that both anomers of acetochloroglucose proceeded rapidly to the same crystalline salt on exposure to $SbCl_5$,[23] which demonstrates that the dependence of such reactions on anomeric configuration is a function of the leaving group and method of activation. Nevertheless, the possibility that the dichotomy might be a function of the differing anomeric configurations of **3** and **4** had to be entertained. To test this hypothesis, we required the β-xylopyranosyl bromide **6**, the α-xylopyranosyl thioglycoside **7**, and its sulfoxide **8**. Bromide **6** was prepared uneventfully, according to the literature, by reaction of β-xylopyranose tetrabenzoate with $TiBr_4$.[24] Exposure of **6** to thiophenol and triethylamine then cleanly afforded the α-thioglycoside **7**. Oxidation of **7** with either Oxone or *m*-CPBA provided a single diastereomer of the required sulfoxide **8**, which we assign the S_R configuration on the basis of literature precedent.[25] A byproduct having a very similar R_f to **7** in these oxidations was isolated and shown to be the corresponding sulfone **9**, which adopts a twist-boat conformation in order to minimize 1,3-diaxial interactions. Reaction of thioglycoside **7** with PhSOTf in CH_2Cl_2 at −78 °C in the presence of DTBMP followed by treatment with cyclohexanol led to a crude reaction mixture consisting of a 90/10 mixture of the ortho ester **1** and the β-xyloside **5**. A similar result was obtained with sulfoxide **8** on activation with Tf_2O in the presence of DTBMP, followed by addition of cyclohexanol. On the other hand, the β-bromide **6** afforded the β-xyloside **5** on treatment with AgOTf and cyclohexanol in CH_2Cl_2. Clearly, in these particular reactions the anomeric configuration of the donor has little or no effect on outcome of the reaction, with both bromides leading to the β-xyloside and both sulfoxides and both thioglycosides providing mainly the ortho ester. Exactly analogous results were obtained when methanol was used as glycosyl acceptor.

Attention was next focused on the influence of the base (DTBMP), which was present in all reactions of the sulfoxides **3** and **8** and of the thioglycosides **2** and **7**, but not of the bromides **4** and **6**. Coupling of the β-bromide **6** with methanol in CH_2Cl_2 at −40 °C in the presence of DTBMP, with activation by AgOTf, provided a 36/64 mixture of the ortho ester[26] **10** and the β-xyloside **11**,[15] as judged by NMR spectroscopy of the crude reaction mixture. On the other hand, activation of the thioglycosides or sulfoxides with PhSOTf or Tf_2O, respectively, in the absence of base followed by reaction with methanol led to relatively complex reaction mixtures containing the

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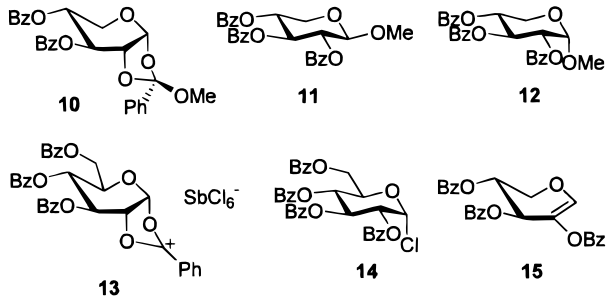
β- and α-xylosides **11** and **12**.[27] It is therefore evident that the decisive factor in the chemoselectivity of all of the above reactions is the hindered base. It buffers the reaction conditions and permits the isolation of ortho esters; otherwise, the β-xylosides are obtained. The same conclusion was reached previously by the Garegg and Bundle groups, both working in the glucopyranose series.[28,29] More recently, Kahne and co-workers, conscious of the requirement for the hindered base in their sulfoxide method but needing to avoid the formation of ortho ester byproducts, introduced the combination of DTBMP and BF_3.[12] In this system, DTBMP serves to buffer any Bronsted acidity and to activate phenolic nucleophiles but is too hindered to complex the Lewis acid, which, therefore, provides the necessary acidity to promote the rearrangement of any ortho esters to the glycosides.[12]

It has been suggested several times that ortho esters are the kinetic products in silver- and mercury-promoted glycosylation reactions, using ester-protected glycosyl halides as donors and that, in the absence of base, these then rearrange in situ to the 1,2-trans-glycosides.[28−30] In the case of mercuric cyanide promoted reactions of 2-*O*-acetyl-3,4,6-tri-*O*-methyl-α-D-glucopyranosyl bromide with cyclohexanol, it has been conclusively demonstrated that the kinetic product is the ortho ester and that, in the absence of buffer, it subsequently rearranges to the β-glucoside.[31] The obvious, and oft-suggested, corollary to this mechanistic hypothesis is that a bridging dioxolenium ion is an intermediate on the pathway.[28−31] The recent calculations of Whitfield support this notion.[14] Paulsen has demonstrated that such bridging cations may be precipitated from solution as their $SbCl_6^-$ salts on treatment of the appropriate glycosyl chloride with $SbCl_5$, as, for example, in the isolation of **13** from a CCl_4 solution of **14** in 85% yield.[23] This type of experiment, however, cannot reflect on the relative proportions of the various species in solution as any equilibrium is necessarily driven by the precipitation of the insoluble salt. Thus, we were prompted to probe the nature of any intermediates in the above chemistry by means of low-temperature ^1H and ^{13}C NMR spectroscopy.

A series of low-temperature NMR experiments were conducted in which the α-sulfoxide (**8**) was dissolved in CD_2Cl_2 in the presence of DTBMP and cooled to −78 °C before treatment with precooled Tf_2O. The NMR tube was then immediately inserted in the precooled probe (−78 °C) of the spectrometer, and the ^1H and ^{13}C spectra were recorded. The ^1H NMR spectrum obtained in this manner was far more complex than had been anticipated and indicated, aside from the complete consumption of the substrate, the formation of several new xylose-based species. The complexity of the ^1H NMR spectrum with its multiple and broad signals suggests the possibility of a dynamic equilibrium involving several species. A comparable result was obtained with the anomeric β-sulfoxide (**3**). Similar NMR experiments conducted with the thioglycosides **2** and **7**, on activation by preformed PhSOTf, and with bromide **4** and AgOTf gave comparable spectra but with differing relative intensities of the various multiplets, suggesting that the position of any equilibrium is significantly affected by the reaction conditions. When sulfoxide **8** was activated at −78 °C with Tf_2O, in the presence of DTBMP, and the probe allowed to warm gradually in 10 °C steps, monitoring by ^1H NMR indicated the appearance of a further set of signals that grew in beginning gradually around −38 °C. Between −18 and −8 °C, complete decomposition of the original species occurred in favor of the new set of signals which then completely dominated the spectra, indicating that all of the species formed at low temperature were eventually channeled into the one product. This substance was subsequently isolated and shown to be the elimination product **15**. In a preparative-scale experiment, **15** was isolated in 64% yield following activation of β-thioglycoside **2** at −78 °C with the PhSOTf/DTBMP combination and warming to room temperature.



Acquisition of the ^{13}C NMR spectra in the above low-temperature NMR experiments was largely futile as the signal-to-noise ratio was so poor as to obliterate any resonances due to the ring carbons. The only observable signals in these ^{13}C NMR traces were those of the base and the benzoate rings. The poor signal-to-noise ratios again suggested dynamic equilibria, with considerable broadening on the ^{13}C NMR time scale. To address this problem, the triply ^{13}C-labeled thioxyloside **16** was synthesized by Zemplen deprotection of **2** followed by esterification with benzoyl chloride mono-^{13}C-labeled in the carbonyl carbon. Activation of **16** with PhSOTf/DTBMP in CD_2Cl_2 at −78 °C in the probe of the NMR spectrometer provided an ^1H NMR spectrum analogous to that obtained in the unlabeled series. On the other hand, the ^{13}C NMR spectrum (Figure 1a) now revealed a cluster of signals between δ 163 and 166 and several smaller signals between δ 127 and 135. The only upfield signals corresponded to those of the *tert*-butyl and methyl groups of the pyridine base and its salts. In addition to the above groups of signals, all attributable to the base, its salts, and the benzoate groups, an intense new signal at δ 180.3 was observed. We assign this resonance to the cationic carbon in the bridging cation **17**, the chemical shift being fully consonant with the value of δ 182.9 found for C-2 in the authentic related dioxolenium ion **18** and with those of other related α,α-dialkoxybenzyl cations.[32] The spectrum also contains a smaller but significant resonance at δ 120.9 that may represent the ortho ester carbon in covalent bridging triflate **19** or, more likely, the hemiortho ester **20** arising from the introduction of

(27) We suspect that the α/β mixture of xylosides obtained in this experiment is a function of scrambling of anomeric stereochemistry under the strongly acidic conditions rather than of any lack of selectivity in the initial glycoside-forming reaction.

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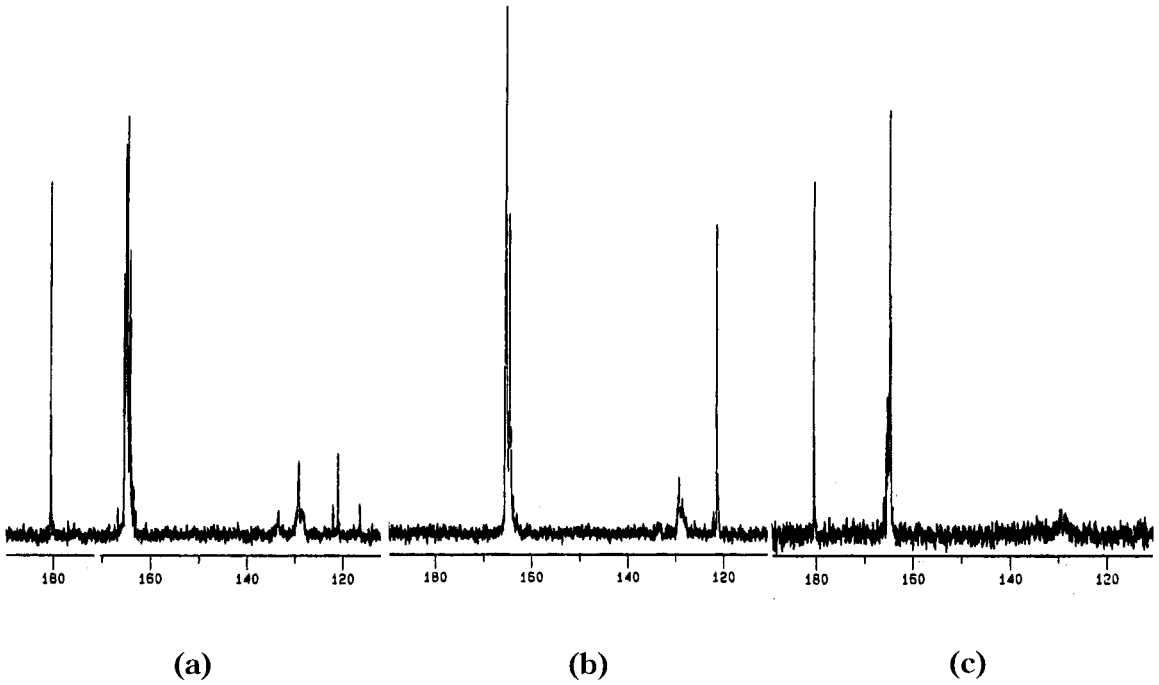

Figure 1. (a) Partial ^{13}C NMR spectrum obtained in CD_2Cl_2 on activation of **16** with PhSOTf and DTBMP at −78 °C. (b) Partial ^{13}C NMR spectrum obtained in CD_2Cl_2 on activation of **16** with PhSOTf and DTBMP at −78 °C followed by addition of methanol. (c) Partial ^{13}C NMR spectrum obtained in CD_2Cl_2 on activation of **16** with PhSOTf at −78 °C.

adventitious water. Indeed, inspection of the carbonyl region suggests that at least two different sugars are present in agreement with the multiplicity of peaks seen in the ^1H NMR experiments. Addition of cold methanol to this −78 °C solution results in the immediate disappearance of the signal at δ 180.3 in favor of a strong signal at δ 121.1 (Figure 1b), which we assign to the ortho ester carbon of **21**.

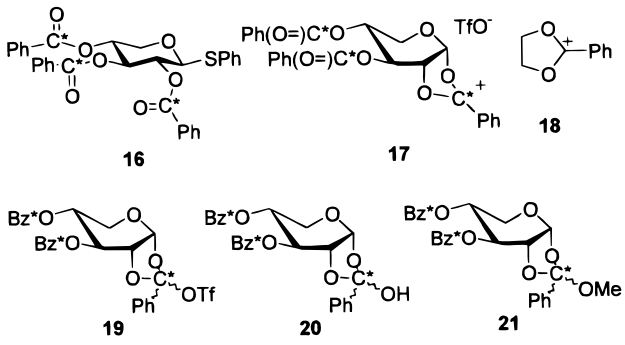

Figure 1c is a ^{13}C NMR spectrum taken immediately after activation of **16** with PhSOTf in CD_2Cl_2 at −78 °C in the absence of DTBMP; self-evidently the bridging cation **17** is again formed in high yield. However, on addition of methanol at −78 °C, the ortho ester is not seen, indicating that in the absence of base the cation either goes directly to the glycosides or the ortho ester rearranges extremely rapidly under the acidic reaction conditions. These experiments, with observation of the bridging cation **16**, provide for the first time a direct, experimental insight into neighboring group participation, in glycosylation reactions. Both in the presence and absence of base the 2-*O*-benzoate group captures any activated anomeric species leading to a dynamic equilibrium of which a major component is a bridging cation. Importantly, the base plays no significant role in this first step but is decisive in the subsequent reaction with an alcohol. In the presence of base, the acid-sensitive ortho ester is the major product, whereas in its absence the glycosides are formed directly. Unfortunately, owing to the rapidity of the reactions, even at −78 °C, we are unable to say whether the glycosides are formed directly from the bridging cation **17** or result from a very rapid acid-catalyzed rearrangement of an initial ortho ester. These conclusions are in good agreement with the recent computations of Whitfield[14] and the earlier inferences of several groups derived from isolation experiments.[28−31]

The position of any equilibrium involving a bridging cation (Scheme 1), whatever the point of entry, will depend on the reaction milieu and, hence, on the method of activation, on the nature of the substituents around the pyranose ring, and especially on the group R directly bonded to the dioxolenium ion. Evidently, in working with the conformationally labile xylopyranose series, which is readily able to accommodate the fused ring system, and with the benzoate esters, leading to benzylic stabilization, we chose conditions most likely to favor the bridging cation. That does not mean that in general the use of a benzoate ester is most likely to lead to isolation of an ortho ester, as benzoate-derived ortho esters are the ones most likely to heterolyze to the bridging cation and rearrange to the glycoside if the conditions are sufficiently ionizing. Indeed, Garegg and co-workers previously noted that metal-promoted glycosidations with benzoate-protected glycosyl bromides gave higher yields of glycoside than the corresponding acetates.[29] More recently, Danishefsky and co-workers have reported that ortho ester formation was less of a problem when benzoates were employed than acetates in methyl triflate promoted couplings with thioglycoside donors.[33]

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Experimental Section

General Methods. Solvents were dried and distilled by standard methods. All reactions were conducted under an atmosphere of dry nitrogen or argon. ^{1}H and ^{13}C NMR experiments were conducted at 300 and 75 MHz, respectively, with a Bruker AC 300 spectrometer equipped with a QNP probe and a VT attachment. Chemical shifts are in ppm downfield from tetramethylsilane. Microanalyses were conducted by Midwest Microlabs, Indianapolis, IN. Compounds **2**,[15] **3**,[15] **4**,[34] and **6**[24] were prepared according to the literature methods.

***S*-Phenyl 2,3,4-Tri-*O*-benzoyl-1-deoxy-thia-α-D-xylopyranoside (7).** A solution of bromide **6** (917 mg, 1.7 mmol) and PhSH (1.93 g, 17 mmol) in CH_2Cl_2/Et_3N (28 mL/15 mL) was stirred for 1 night at room temperature, after which time the reaction mixture was diluted with 3 M NaOH and extracted with Et_2O. The combined extracts were washed with NH_4Cl and then brine, dried ($MgSO_4$), and evaporated. The residue was purified via flash chromatography (eluent: 0/100 to 10/90 AcOEt/hexane), providing 820 mg (87%) of the α-thioglycoside. $[\alpha]^{20}_D = +68.8°$ ($c = 0.9$, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 4.20 (dd, $J = 11.5$, 5.4 Hz, 1H); 4.42 (dd, $J = 11.5$, 9.6 Hz, 1H); 5.43 (m, 1H); 5.55 (dd, $J = 9.4$, 5.2 Hz, 1H); 6.03 (d, $J = 5.0$ Hz, 1H); 6.07 (t, $J = 9.1$ Hz, 1H); 7.21−7.60 (m, 14H); 7.91−8.10 (m, 6H). ^{13}C NMR δ: 60.5, 69.6, 69.9, 71.4, 86.0, 127.7, 128.4, 128.4, 128.5, 129.1, 129.7, 129.8, 130.0, 131.9, 133.3, 133.4, 133.5. Anal. Calcd for $C_{32}H_{26}O_7S$: C, 69.30, H, 4.73. Found: C, 69.14, H, 4.74.

***S*-Phenyl 2,3,4-Tri-*O*-benzoyl-1-deoxy-1-thio-α-D-xylopyranoside *S*-Oxide (8).** Oxidation of the α-thioglycoside (**7**) with MCPBA at −78 °C in CH_2Cl_2 gave the title sulfoxide 72% yield as a single anomer. $[\alpha]^{20}_D = +9.3°$ ($c = 3.3$, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ: 3.96 (1H, dd, $J = 13.2$, 2.3 Hz, H-5), 4.33 (1H, br d, $J = 13.2$ Hz, H-5), 4.67 (1H, d, $J = 2.2$ Hz, H-1), 5.16 (1H, br d, $J = 2.5$ Hz, H-4), 5.68 (1H, t, $J = 2.8$ Hz, H-2), 5.97 (1H, t, $J = 2.9$ Hz, H-3), 7.10 (2H, t, $J = 7.0$ Hz), 7.35−7.70 (10H, m), 7.85 (4H, m), 8.05 (2H, d, $J = 7.5$ Hz), 8.25 (2H, d, $J = 7.5$ Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ: 66.3, 66.7, 67.0, 67.5, 93.3, 125.4, 128.4, 128.7, 128.8, 129.3, 129.4, 130.0, 130.1, 130.6, 131.8, 133.6, 133.8, 134.0, 141.8, 164.3, 165.3. Anal. Calcd for $C_{32}H_{26}O_8S\cdot{}^1/_2H_2O$: C, 66.30; H, 4.70. Found: C, 66.41; H, 4.70.

Coupling of α-Thioxyloside 7 with Cyclohexanol in the Presence of DTBMP. AgOTf (51 mg, 0.2 mmol) was suspended in dichloromethane (3 mL) under N_2 at −78 °C and treated with PhSCl (19 μL, 0.17 mmol). After the mixture was stirred vigorously for 5 min, a solution of **7** (37 mg, 0.067 mmol) and DTBMP (41 mg, 0.2 mmol) in dichloromethane (1.5 mL) was added followed, after 5 min, by cyclohexanol (15 μL, 0.14 mmol). The reaction mixture was allowed to warm with stirring to −30 °C before it was diluted with saturated aqueous $NaHCO_3$ and then allowed to come to room temperature. Extraction with Et_2O, washing with brine, drying ($MgSO_4$), and concentration gave a crude reaction mixture that, on inspection by ^{1}NMR spectroscopy and with the aid of authentic samples,[15] was shown to be a 90:10 mixture of ortho ester **1** and β-xyloside **5**.

Coupling of β-Xylosyl Bromide 6 with Cyclohexanol in the Absence of DTBMP. Cyclohexanol (17 μL, 0.16 mmol) was dissolved in dichloromethane (2 mL) and stirred with 4A molecular sieves (20 mg) for 10 min and then cooled to −40 °C followed sequentially by addition of the β-bromide **6** (42 mg, 0.08 mmol) in dichloromethane (2 mL) and then AgOTf (41 mg, 0.16 mmol) in toluene (1 mL). After being stirred for 0.5 h, the reaction mixture was allowed to come to 0 °C before it was washed with aqueous Na_2SO_3 and then brine, dried ($MgSO_4$), and concentrated to give a crude reaction mixture consisting mainly of the β-xyloside **5**. Chromatography on silica gel (eluent: AcOEt/hexane 9/1) enabled the isolation of **5** (30 mg, 69%) identical to an authentic sample.[15]

Coupling of β-Xylosyl Bromide 6 with Methanol in the Presence of DTBMP. Methanol (7 μL, 0.17 mmol) and DTBMP (52 mg, 0.26 mmol) were dissolved in dichloromethane (2 mL) in the presence of 4A molecular sieves (20 mg) and cooled with stirring under N_2 to −40 °C. Bromide **6** (45 mg, 0.085 mmol) in dichloromethane (1 mL) was then added, followed by AgOTf (44 mg, 0.17 mmol) in toluene (1 mL), and stirring was continued for 20 min before the reaction mixture was allowed to warm to 0 °C and worked up by addition of saturated aqueous $NaHCO_3$. Ether extraction, washing with brine, drying, and evaporation ($MgSO_4$) provided a crude reaction mixture that was shown to consist of a 36/64 mixture of the known ortho ester[26] **10** and the β-xyloside **11**, which was identical with an authentic sample.[15] Attempted isolation of this ortho ester by silica gel chromatography resulted in extensive decomposition, mainly to **11**, such that a pure sample could not be obtained.

Coupling of β-Sulfoxide 3 with Methanol in the Absence of DTBMP. The β-sulfoxide **3** (40 mg, 0.07 mmol) was dissolved in dichloromethane (1 mL) and cooled with stirring under N_2 to −78 °C. Tf_2O (14 μL, 0.084 mmol) was then added followed, after stirring for 5 min, by methanol (6.9 μL, 0.17 mmol). The reaction mixture was then allowed to come to room temperature with stirring before it was diluted with saturated aqueous $NaHCO_3$ and extracted with ether. The extracts were dried (Mg_2SO_4) and concentrated to give a crude reaction mixture that consisted of a 41/59 mixture of the β- and α-xylosides **11**[15] and **12**,[15] respectively.

***S*-Phenyl 1-Deoxy-1-thia-β-D-xylopyranoside.** β-Thioglycoside **2** (278 mg, 0.5 mmol) was dissolved in a NaOMe solution prepared by adding Na (1 mg, 0.05 mmol) to dry MeOH (10 mL). After being stirred for 24 h, the reaction was quenched with HCl (1 M in Et_2O) and concentrated to dryness. The residue was crystallized from Et_2O providing 100 mg (83%) of the title compound,[35] which was used without further purification. ^{1}H NMR (methanol-d_4) δ: 3.22 (m, 2H); 3.36 (t, $J = 9.2$ Hz, 1H); 3.48 (m, 1H); 3.95 (dd, $J = 11.2$, 5.0 Hz, 1H); 4.58 (d, $J = 9.2$ Hz, 1H); 7.30 (m, 3H); 7.51 (m, 2H). ^{13}C NMR δ: 70.4, 71.0, 73.8, 79.2, 90.2, 128.7, 130.0, 133.2, 135.0.

***S*-Phenyl 2,3,4-Tri-*O*-benzoyl-1-deoxy-1-thia-β-D-xylopyranoside-$^{13}C_3$ (16).** To a cooled (0 °C) solution of *S*-phenyl 1-deoxy-1-thia-β-D-xylopyranoside (140 mg, 0.36 mmol) and DMAP (43 mg, 0.43 mmol) in pyridine (2 mL) was added a solution of ^{13}C-benzoyl chloride[36] (monolabeled in the carbonyl C) in CH_2Cl_2 (1 mL). After being stirred overnight at room temperature, the reaction was diluted with water and extracted three times with Et_2O. The organic layer was washed with saturated aqueous $CuSO_4$ and brine, dried ($MgSO_4$), and evaporated. The residue was purified via flash chromatography (eluent: 0/100 to 20/80 AcOEt/hexane) providing 60 mg (37%) of **16**. ^{1}H NMR ($CDCl_3$) δ: 3.82 (dd, $J = 12.3$, 6.5 Hz, 1H); 4.51 (dd, $J = 12.3$, 4.0 Hz, 1H); 5.30 (m, 1H); 5.30 (d superimposed, $J = 6.1$ Hz, 1H); 5.49 (td, $J = 5.0$ Hz and $^3J_{C-H} = 3.8$ Hz, 1H); 5.80 (td, $J = 6.6$ Hz and $^3J_{C-H} = 3.7$ Hz, 1H); 7.30−7.45 (m, 9H); 7.46−7.60 (m, 5H); 7.96−8.10 (m, 6H). ^{13}C NMR ($CDCl_3$) δ: 165.3, 165.4, 165.7.

1,5-Anhydro-2,3,4-tri-*O*-benzoyl-D-*threo*-pent-1-enitol (15). To a stirred solution of AgOTf (69 mg, 0.27 mmol) in CH_2Cl_2 (2 mL) at −78 °C was added PhSCl (32 mg, 0.22 mmol). After the mixture was stirred for 5 min at −78 °C, a solution of **2** (49 mg, 0.088 mmol) and DTBMP (55 mg, 0.27 mmol) in CH_2Cl_2 (1 mL) was added, and the reaction mixture was allowed to warm to room temperature before quenching with $NaHCO_3$ and extracting with Et_2O. The combined extracts were dried ($MgSO_4$) and evaporated. The residue was purified via flash chromatography (eluent: 0/100 to 10/90 AcOEt/hexane) providing 25 mg (64%) of the title compound.[26] ^{1}H NMR ($CDCl_3$) δ: 4.21 (bd, $J = 11.4$ Hz, 1H); 4.51 (dt, $J = 12.4$, 2.2 Hz, 1H); 5.42 (m, 1H); 5.91 (m, 1H); 7.05 (s, 1H); 7.35−7.61 (m, 9H); 8.02−8.20 (m, 6H). ^{13}C NMR δ: 64.0, 65.5, 68.1,

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(36) Benzoic acid 99% enriched with ^{13}C in the carbonyl carbon was obtained from Cambridge Isotope Laboratories, Woburn, MA 01801.

127.7, 128.6, 128.7, 129.4, 129.5, 129.6, 130.0, 130.3, 133.5, 133.6, 133.7, 142.1. Anal. Calcd for $C_{26}H_{20}O_7$: C, 70.27; H, 4.54. Found: C, 70.04; H, 4.71.

Variable Temperature NMR Experiment with α-Sulfoxide 3 in CD_2Cl_2. Sulfoxide **3** (10.3 mg, 0.018 mmol) and DTBMP (7.4 mg, 0.036 mmol) were dissolved in CD_2Cl_2 (0.5 mL) and cooled to −78 °C in the probe of the NMR spectrometer. A ^{1}H NMR spectrum was recorded, and then the tube was removed and stored in a dry ice/acetone bath while Tf_2O (3.95 μL, 0.023 mmol, precooled in the same bath) was added. The tube was vigorously shaken and quickly reinserted in the cold probe, and a further ^{1}H NMR spectrum was taken. The spectrum showed multiple, poorly resolved signals, and no attempt at assignment was made. Nevertheless, it was clear that the sulfoxide had been consumed. The ^{13}C NMR spectrum, recorded immediately afterward, had a very poor signal-to-noise ratio, with the only discernible peaks being those of the base and its salts. The probe was gradually warmed and a ^{1}H NMR spectrum recorded every 10 °C. At the lower temperatures, the main changes were gradual sharpening of the signals and a slow change in their relative intensities. Signals for the pentenitol **15** (see above isolation) grew in slowly beginning between −48 and −38 °C with complete decomposition to **15** occurring between −18 and −8 °C. This behavior was typical of that observed in similar VT-NMR experiments with the thioglycosides and the bromides except for the relative intensities of the signals, which varied with the different donor/promoter pairs.

Activation of the ^{13}C-Labeled Thioglycoside 16 in the Presence of DTBMP: Observation of Cation 17 and of Ortho Ester 21. AgOTf (23 mg, 0.09 mmol) and PhSCl (6.7 μL, 0.06 mmol) were stirred in CD_2Cl_2 (0.5 mL) under Ar at −78 °C and then transferred quickly to a −78 °C solution of the labeled thioglycoside **16** (16 mg, 0.028 mmol) and DTBMP (11.9 mg, 0.06 mmol) in CD_2Cl_2 (0.5 mL) under Ar. The tube was shaken and inserted into the probe of the spectrometer precooled to −78 °C, and the ^{13}C NMR spectrum illustrated in Figure 1a was recorded. The tube was removed from the probe and cold (−78 °C) methanol (2 μL) added. The tube was then immediately replaced in the cold (−78 °C) probe, and the ^{13}C NMR spectrum presented in Figure 1b was recorded.

Activation of the ^{13}C-Labeled Thioglycoside 16 in the Absence of DTBMP: Observation of Cation 17. A NMR tube experiment was conducted exactly as described above except for the omission of the base. The spectrum recorded immediately after mixing of **16** with the preformed PhSOTf is given in Figure 1c. A further ^{13}C NMR spectrum was recorded after the addition of methanol; no ortho ester signals were detected, and all of the intensity was in the region of the carbonyl carbons.

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