Are Glycosyl Triflates Intermediates in the Sulfoxide Glycosylation Method? A Chemical and ^{1}H, ^{13}C, and ^{19}F NMR Spectroscopic Investigation

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Abstract: The title question is addressed by low-temperature ^{1}H, ^{13}C, and ^{19}F NMR spectroscopies in CD$_2$Cl$_2$ as well as by the preparation of authentic samples from glycopyranosyl bromides and AgOTf. At −78 °C glycosyl triflates are cleanly generated with either nonparticipating or particpating protecting groups at O-2. The glycosyl triflates identified in this manner were allowed to react with methanol, resulting in the formation of methyl glycosides. Glycosyl triflates were generated at −78 °C in CD$_2$Cl$_2$ and allowed to warm gradually until decomposition was detected by ^{1}H and ^{19}F NMR spectroscopy. The decomposition temperature and products are functions of the protecting groups employed.

Introduction

The use of anomeric sulfoxides as glycosyl donors has rapidly gained a position of prominence in the field of oligosaccharide synthesis since its introduction by Kahne in 1989. This popularity stems from the very mild conditions and the ability to glycosylate even the most hindered alcohols in high yield.[1] The method has been successfully applied to an impressive variety of glycosyl acceptors including acetamide, phenols and hindered bile acids,[1] hydroxylamines,[2] hydroxylated amino acids,[3] tertiary alcohols,[4] and a broad selection of carbohydrates[1,5,6] by the Kahne group. Solid-phase oligosaccharide synthesis has also been achieved through the use of glycosyl sulfoxides by the Kahne and Still laboratories.[7,8] The formation of acyclic alkoxymethyl ethers by means of alkoxy methyl sulfoxides has also been demonstrated by the originators of the technique.[9] Other groups have applied the sulfoxide glycosylation strategy in the syntheses of complex natural products[10,11] as well as in oligosaccharide[12−17] and nucleoside syntheses.[18] The Stork variant on the intramolecular aglycone delivery approach to β-mannospyrannosides also makes use of the sulfoxide method.[19,20] Despite all of this interest no detailed discussion of the mechanism of this reaction has yet been published. Stimulated by an unanticipated reversal of anomeric stereoselectivity on the coupling of the sulfoxide **1** to the acceptor **2** in the presence of triflic anhydride (Tf$_2$O) and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) on simple reversal of the order of addition of the reactants to **1** (Scheme 1),[21] which we have since developed into an efficient protocol for the stereoselective synthesis of β-mannopyranosides,[22] we have investigated the mechanism of this reaction by low-temperature ^{1}H, ^{13}C, and ^{19}F NMR spectroscopies and report here on our findings.

Scheme 1

A: **1** + **2** + DTBMP, then Tf$_2$O, **3**:**4** = 6:58
B: **1** + DTBMP + Tf$_2$O, then **2**, **3**:**4** = 85:8
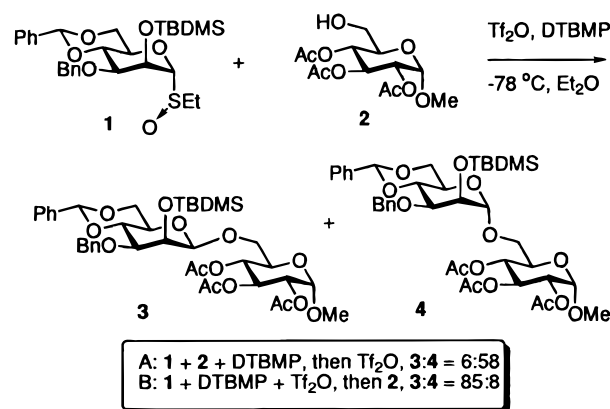
Results and Discussion

In the initial paper, Kahne and Kim reported the glucosylation of sterically hindered secondary alcohols, phenols, and acetamides with the donors **5** and **6**, of undefined stereochemistry,

[⊗] Abstract published in *Advance ACS Abstracts,* November 1, 1997.

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5   **6**

7

8

Scheme 2
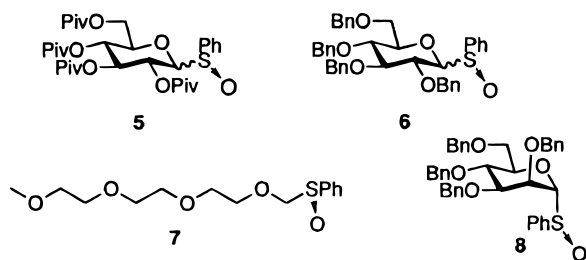
using Tf$_2$O as the activator in the presence of DTBMP as the base. These reactions were carried out in either toluene, dichloromethane, or propionitrile by addition of the sulfoxide to Tf$_2$O at −78 °C, followed by addition of the acceptor and the acid scavenger. Mixtures of α- and β-glucosides were obtained in excellent yield. For the pivalate-protected donor **5**, pure β-glucosides were obtained in all cases, which the authors attributed to neighboring group participation. With the perbenzyl derivative **6**, the β:α ratio increased with solvent polarity with the optimum selectivity seen in propionitrile. Reaction times and temperatures varied widely, ranging from a few minutes at −60 °C for hindered secondary alcohols to 12 h at room temperature for coupling to *N*-(trimethylsilyl)-acetamide, prompting the authors to comment on the remarkable stability and reactivity of the undefined, intermediate glycosyl donor. The pattern of β-glycoside formation with donors containing equatorial pivaloxy groups in the 2-position is a recurring theme in subsequent papers as is the obtention of mixtures when nonparticipating protecting groups are used. In most subsequent papers Kahne and co-workers adhere to the original protocol in terms of the sequence of combining the reagents, but occasionally, as in the use of glycosyl acceptors immobilized on a solid support,[7] Tf$_2$O is added to a preformed mixture of the sulfoxide and the acceptor. The recent full paper generalizing the method recommends activation of the sulfoxide with Tf$_2$O before addition of the glycosyl acceptor. Variations on the theme include activation with a catalytic amount of triflic acid[5] or with trimethylsilyl triflate.[12] When activation was achieved with catalytic TfOH, methyl propiolate was used as a sulfenic acid scavenger.[5] Alcohols have sometimes been converted to their tributylstannyl ether derivatives prior to use as glycosyl acceptors in the sulfoxide method,[23] presumably to increase their nucleophilicity.[24] Most frequently, phenyl sulfoxides are employed, sometimes with their reactivity modified by the incorporation of electron-donating or -withdrawing groups,[5] but as we have demonstrated through the use of ethyl sulfoxides,[25] the reaction is by no means limited to aryl sulfoxides. Interestingly, and even frustratingly,[26] Pummerer-type chemistry is not a competing reaction in the sulfoxide glycosylation protocol but has been noted to occur to some extent with the acyclic sulfoxide **7**.[9]

The observation (Scheme 1) that the stereoselectivity in the coupling of **2** to **1** could be reversed, depending on whether Tf$_2$O was added to activate the sulfoxide **1** before or after the acceptor **2**, first sparked our curiosity in the mechanism of this extremely useful reaction. Our interest was heightened when it became apparent that the closely related glycosyl donor **8** gave poor β:α ratios on coupling to simple alcohols, and this irrespective of the mixing sequence. To our knowledge, prior to our work, there were no previous reports of the synthesis of
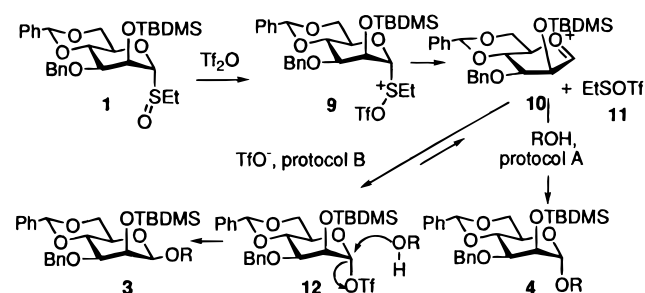
β-mannopyranosides, or other equatorial 1,2-*cis*-glycosides, using the sulfoxide method, although it was reported in a footnote to the original paper[1] that the stereochemistry at C2 of the donor influences the stereochemical outcome. Prior to our work[25] the use of 4,6-benzylidene acetals as protecting groups for the sulfoxide had also not been reported. The change in stereoselectivity on going from **1** to **8** as the donor suggests that this rigidifying system has a significant influence on the mechanism of the reaction. The questions foremost in our minds were therefore formulated as (i) what is the mechanism of β-mannoside formation with donor **1**; (ii) why does the stereoselectivity of coupling to **1** change according to the sequence of mixing the reagents; (iii) what is the nature of the intermediate glycosyl donor, derived from **6**, reactive enough to glycosylate hindered secondary alcohols at −60 °C, yet stable for many hours in toluene at room temperature;[1] (iv) are oxonium ions key intermediates in the glycosylation as has been suggested;[27] and (v) how does the 4,6-benzylidene protecting group influence the stereoselectivity of mannosylation.

A working hypothesis which rationalizes the observations of Scheme 1 is set out in Scheme 2. According to this rationale, Tf$_2$O serves to activate the donor **1** in the form of the sulfonium salt **9**. This collapses immediately to the oxacarbenium ion **10** and the sulfenyl triflate **11**. When the activation is carried out in the presence of the glycosyl acceptor, **10** is trapped directly, along the axial direction for the usual stereoelectronic reasons, to give the α-mannoside. When activation is conducted prior to addition of the glycosyl acceptor, **10** is trapped by triflate anion to give the α-mannosyl triflate **12**. On subsequent addition of the glycosyl acceptor **12** participates in an S$_N$2-like reaction with formation of the β-mannoside.

To probe this hypothesis, the simplified sulfoxide **13** was prepared by standard means and its ^{1}H NMR spectrum recorded in CD$_2$Cl$_2$ at −78 °C in the presence of DTBMP. A 10% excess of Tf$_2$O was then added, still at −78 °C, and a new ^{1}H NMR spectrum acquired. Inspection of this spectrum revealed that **13** was transformed quantitatively, within the <5 min required to carry out the manipulation and acquire the data, to a single new carbohydrate species characterized by its anomeric proton signal, a broad singlet at δ 6.20. The −78 °C ^{13}C NMR spectrum also indicated clean formation of a single new carbohydrate with an anomeric carbon signal resonating at δ 104.6. An ^{19}F NMR spectrum of the reaction mixture, still at −78 °C, revealed a number of signals at δ 4.26, −0.037, and −3.21. Those at δ −3.21 and 4.26 were assigned to di-*tert*-butylmethylpyridinium triflate and Tf$_2$O, respectively, with the aid of authentic samples. Methanol was then added to the reaction mixture, whereupon ^{1}H NMR spectroscopy indicated that the carbohydrate was consumed immediately in favor of the formation of the methyl α- and β-mannosides **14** and **15**, respectively, in the ratio 1:7. In the ^{19}F NMR spectrum the resonance at δ −0.037 disappeared in favor of that at δ −3.21,
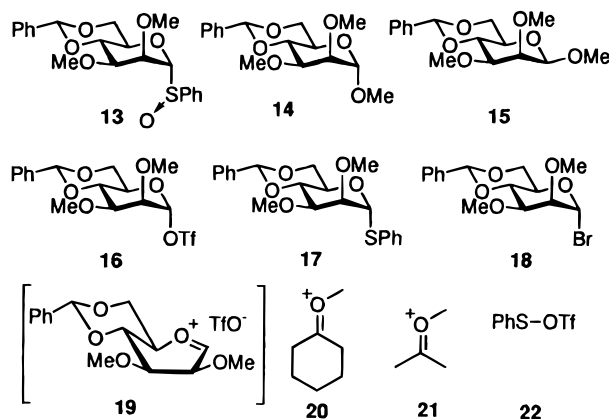
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13   **14**   **15**   **16**   **17**   **18**   **19**   **20**   **21**   **22**

assigned to the pyridinium triflate, suggesting that the former signal represents the true glycosyl donor and that this donor incorporates the triflate group as an intimate structural component, viz. the glycosyl triflate **16**. On a preparative scale **14** and **15** were isolated in 9 and 53% yields, respectively, along with 19% of the phenyl α-thiomannoside **17**. In a separate experiment, bromide **18** was treated with AgOTf and DTBMP in CD_2Cl_2 under the same conditions, resulting in the formation of a single species whose ^{1}H NMR spectrum was identical with that derived from treatment of the sulfoxide **13** with Tf_2O. In the ^{19}F NMR spectrum a single signal was observed at δ −0.056, which, given the high susceptibility of ^{19}F NMR chemical shifts to solvent and temperature,[28] we consider to be indistinguishable from that in the above experiment. Finally, methanol was added to this reaction, also resulting in the immediate formation of a 1:7 mixture of **14** and **15**. Thus, given the high correlation between the ^{1}H and ^{19}F NMR spectra derived from the two series of experiments, and identical outcomes on addition of methanol, we assign the glycosyl triflate **16** as the true glycosylating species in this 4,6-benylidene-protected system. The remote possibility that we are observing not **16** but rather a tight ion pair **19**, which would need to be stable in CD_2Cl_2 on the NMR time scale, may be excluded on chemical shift grounds. Thus, in superacid media, the sp[2] carbon in **20** and **21**, simple models for the ion pair **19**, are reported to resonate at δ 248.7[29] and 245.5,[30] respectively, whereas no ^{13}C NMR signal was observed with a chemical shift greater than δ 170 in the present experiments. The large disparity between the ^{13}C chemcal shifts for **20** and **21** and that of the anomeric carbon noted here (δ 104.6), even taking into account the different counterions and solvent, further suggests that any dynamic equilibrium between the anomeric triflate **16** and the ion pair **19** very much favors the covalently bound species.

The hypothetical mechanism (Scheme 2) predicts the formation of a sulfenyl triflate in an equal amount to that of the glycosyl triflate. To assist in identification of this species in the ^{19}F NMR spectrum, an authentic sample was prepared by reaction of benzenesulfenyl chloride with silver triflate[31] in CD_2Cl_2 at −78 °C in the probe of the NMR spectrometer. The ^{19}F NMR spectrum consisted of a single resonance at δ −3.17, which we therefore assign to **22**. Somewhat to our surprise, this signal did not correspond to any of those observed on treatment of **13** with Tf_2O.[32] This unanticipated absense led

us to surmise that the powerfully electrophilic **22** itself reacts with, and activates, the sulfoxide **13** as it is formed and in effective competition with Tf_2O. To probe this hypothesis **22**, formed in situ at −78 °C was added in CD_2Cl_2 to **13**, whereupon the glycosyl triflate (**16**) was immediately formed. This nicely explains the absence of **22** from the reaction mixture on treatment of **13** with Tf_2O, the incomplete consumption of Tf_2O in the same experiment despite full conversion of the sulfoxide, and the ability, noted by Kahne,[5] for sulfoxide glycosylations to be carried out in high yield with only 0.5 mol equiv of Tf_2O.

We next turned our attention to the more conformationally labile glycosyl donors **23** and **24**. Treatment of sulfoxide **23**

23   **24**   **25**   **26**   **27**   **28**
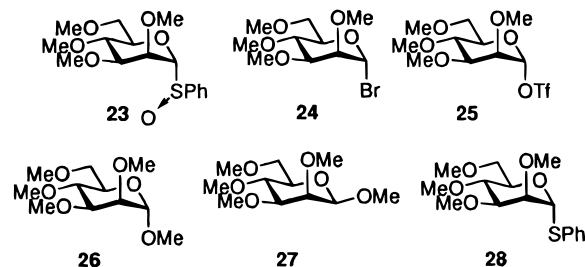
and DTBMP in CD_2Cl_2 with Tf_2O at −78 °C resulted in complete conversion to single new carbohydrate characterized by its anomeric resonance at δ 6.17 in the ^{1}H NMR spectrum and a signal at δ −0.033 in the ^{19}F NMR spectrum. Attempted characterization of this new species by ^{13}C NMR spectroscopy at −78 °C failed owing to decomposition over the several hours required to acquire a spectrum with a sufficient signal-to-noise ratio. As in the 4,6-benzylidene-protected series, benzenesulfenyl triflate (**22**) was not identified in the reaction mixture. Reaction of **24** with AgOTf in CD_2Cl_2 at −78 °C resulted in the identical signals, so confirming the formation of the glycosyl triflate **25** as a key intermediate in these reactions. Workup of either NMR experiment with methanol at −78 °C resulted in the formation of approximately 1:1 mixtures of the methyl mannosides **26** and **27**. On a slightly larger scale, treatment of **23** with Tf_2O and DTBMP at low temperatures, followed by treatment with methanol, led to the isolation of **26** and **27** in 26 and 40% yields, respectively, and of the thioglycoside **28** in 12% yield.

The assignment of anomeric stereochemistry for both **16** and **25** is based on two factors. First, the chemical shift of the anomeric proton in both **16** and **25**, at δ 6.20 and 6.17, respectively, is most consistent with the α-glycoside. Schuerch has previously prepared the α- and β-glucosyl toluenesulfonates **29** and **30** and finds the anomeric protons to resonate at δ 6.1

29   **30**   **31**   **32**   **33**   **34**

and 5.5,[33] respectively. A similar correlation is also found with

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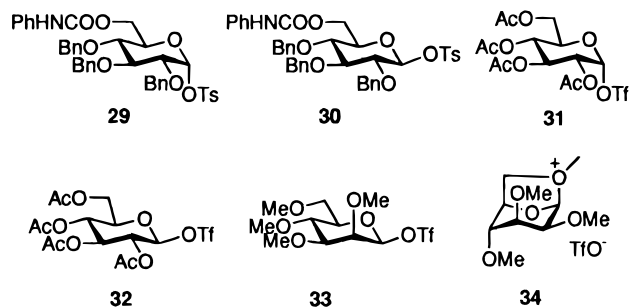
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(32) In a control experiment, under similar concentration and temperature, PhSOTf and DTBMPH[+]TfO[−] were fully resolved by ^{19}F NMR spectroscopy, indicating that PhSOTf is truly absent from the reaction mixture and not simply obscured by the signal due to the pyridinium triflate.

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the chemical shifts of the anomeric protons in the triflates **31** and **32** (vide infra, δ 6.21 and 5.60, respectively). In both **16** and **25** the anomeric signal is a broad singlet, compatible with either the α- or β-stereochemistry with a small unresolved $^3J_{1,2}$ scalar coupling. Second, a gated decoupled ^{13}C NMR spectrum of **16**, recorded at −78 °C, revealed a $^1J_{CH}$ coupling of 184.5 Hz for the anomeric carbon which is fully consistent with an α-mannoside carrying a somewhat electronegative substituent at C1.[34] NOE correlations between the anomeric proton and H3 and/or H5, whose detection would definitely establish the β-configuration, were not attempted due to the unresolved nature of the majority of the ring protons and methoxy residues.

The differing stereoselectivity on coupling of **13** and **23** with alcohols, as indeed that of their more preparatively useful counterparts **1** and **8**, respectively, is all the more intriguing in view of the fact that both give a single triflate intermediate. The formation of β-mannosides from the α-triflates **16** and **25** is entirely in accord with the S_N2-like mechanism advanced in Scheme 2, but that of α-mannosides from **25** demands an alternative route. It is conceivable that the α-triflate (**25**) is in equilibrium with a trace of its less stable but more reactive β-anomer (**33**), much as in Lemieux's bromide ion catalyzed formation of α-glucosides from α-acetobromoglucose,[35] but this does not offer a satisfactory explanation for the difference between the two series of compounds. Neither does such an equilibrium provide an explanation for the inversion of stereoselectivity observed with the change in mixing order for **1** (Scheme 1).

Plausible alternative mechanisms for α-glycoside formation with **25** involve participation of the 6-*O*-Me group generating a highly reactive α-donor **34** or simply invoke the oxacarbenium ion **35**. In the 4,6-benzylidene series a bridged species akin to
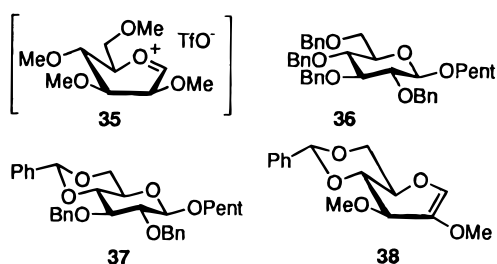

34 is impossible but not the corresponding oxacarbenium ion **19**. Without being able in any way to rule out participation by the 6-*O*-Me group as in **34** in the conformationally labile system, we were intrigued by the possibility that the difference in selectivity between the two series was a factor of the relative stabilities of **35** and **19**, with the latter being significantly higher in energy and so not making a significant contribution to the reaction manifold. Support for this hypothesis may be gleaned from the work of Fraser-Reid and co-workers wherein it was demonstrated computationally that the slower hydrolysis of the pentenyl glucoside **37** with respect to **36** was due to the torsional strain engendered in the trans-fused 4,6-benzylidene group on going to the sofa conformation of the intermediate oxacarbenium ion.[36] Direct experimental support for any difference in stability of two such fleeting species as **35** and **19** is extremely difficult to come by. Certainly, any direct measure by ^1H or ^{13}C NMR spectroscopy in CD_2Cl_2 is not possible and any eventual observation in superacid media of questionable relevance to the

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Scheme 3
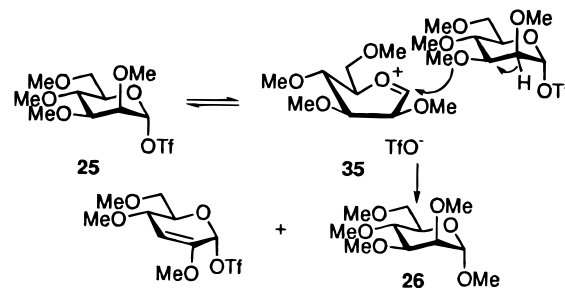
problem in hand. However, we reasoned that a difference in stability of **35** and **19** would be reflected in the more experimentally accessible decomposition temperatures of the precursor triflates **16** and **25** in the absence of effective nucleophiles. Toward this end **16** and **25** were each prepared in CD_2Cl_2, in the now standard manner by reaction of **13** and **23** with Tf_2O and DTBMP at −78 °C, and allowed to warm gradually with monitoring by ^1H and ^{19}F NMR spectroscopies every 10 °C until the onset of decomposition, whereupon the products were investigated by ^1H NMR spectroscopy. In the case of the 4,6-benzylidene-protected triflate **16** decomposition began at −10 °C and provided, uniquely, the glycal **38** which could be isolated in 95% yield. This species clearly arises from rapid deprotonation of the oxacarbenium ion **19**. In contrast, decomposition of triflate **25** was evident at −30 °C and resulted in the formation of a complex mixture of products from which the α-methyl mannoside **26** and the thioglycoside **28** were isolated in 61 and 5% yields, respectively. A number of minor products were insufficently resolved, both by ^1H NMR spectroscopy and on subsequent silica gel chromatography, and were consequently not identified. We rationalize the formation of **26**, and of the multiple, minor decomposition products, by nucleophilic attack of one mannose residue upon the oxacarbenium ion **35** of a second. One example of the many variations possible is given in Scheme 3.

It is clear that the activation barrier for expulsion of the triflate anion is higher in the 4,6-benzylidene series. Moreover, once formed **19** decomposes rapidly by proton loss whereas **35** undergoes intermolecular nucleophilic attack by such poor nucleophiles as ether oxygens. At a constant temperature of −78 °C the equilibrium constant for formation of **19** from **16** will be much lower than that of **35** from **25** which satisfactorily explains the difference in stereoselectivity of the two systems. A further indication of the difference in stabilities of triflates **16** and **25** may be gleaned from the ^{13}C NMR investigations. At −78 °C in CD_2Cl_2 **16** showed no decomposition over the 5−6 h required for aquisition, as judged from a ^1H NMR spectrum recorded immediately after the ^{13}C, whereas **25** was substantially decomposed in the same time frame so putting the ^{13}C data beyond reach.

Next, we turned our attention to the glucosyl donor **39** with its potentially participating, stereodirecting 2-*O*-acetate group. Reaction of this sulfoxide with Tf_2O and DTBMP in CD_2Cl_2 at −78 °C resulted in the formation of two new signals in the ^{19}F NMR spectrum aside from unreacted Tf_2O (δ 4.10). One of these (δ −3.36) is assigned to $DTBMPH^+TfO^-$ and the second (δ 0.26) to an intermediate, triflate-bearing glycosyl donor. It is noteworthy that benzenesulfenyl triflate (**22**) was again not observed. The ^1H NMR spectrum revealed consumption of the substrate in favor of two new anomeric signals at δ 6.21, a doublet with $J = 3.5$ Hz, and 5.60, a double doublet with $J = 7.6$ and 2.3 Hz, in the ratio 1.4:1. Addition of methanol resulted in the formation of the β-glycoside **40** and the ortho ester **41**. When the reaction was conducted on a slightly larger scale **40**

39   **40**   **41**

42   **43**   **44**

45   **46**   **47**

48   **49**   **50**
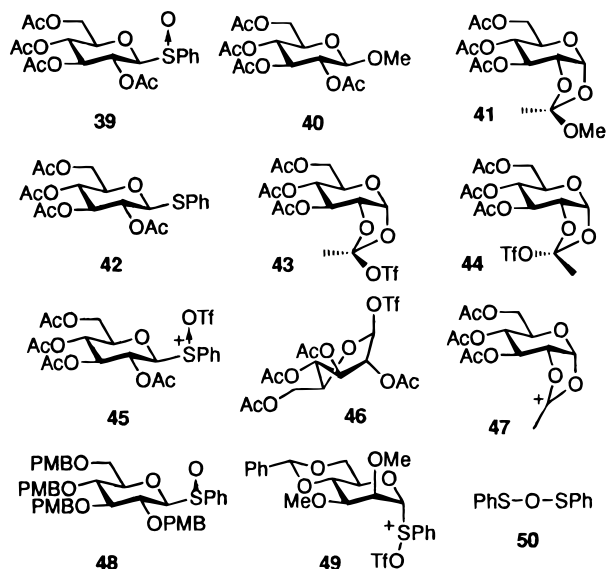
and **41** were isolated in 39% yield each, together with 19% of the β-thioglycoside **42**. It is clear from the ^{1}H NMR spectrum that two carbohydrate-derived intermediates are formed in this reaction, yet in the ^{19}F NMR spectrum, only one signal is observed, aside from Tf$_2$O and DTBMPH$^+$TfO$^-$, hinting that the two species are very similar types of triflates. These might be two anomeric triflates **31** and **32**, or two diastereomeric ortho esters **43** and **44**. To distinguish between the two possibilities a ^{13}C NMR spectrum was recorded at -78 °C. Eight resonances corresponding to carbonyl carbons were detected at δ 171.8, 171.9, 172.3, 172.4, 172.5, 172.9, 173.0, and 173.1, but only a single anomeric carbon at δ 102.9 could be identified. No evidence was found for ortho ester carbons. Thus, both the ^{1}H NMR spectrum and the number of carbonyl carbons in the ^{13}C NMR spectrum indicated a mixture of two carbohydrates, whereas our inability to identify two anomeric carbons or triflate ester signals suggested that these must be very similar. The gated decoupled ^{13}C NMR revealed a $^1J_{CH}$ coupling constant of 184.5 Hz, consistent with an α-anomer.[34] However, the more downfield of the two lines in the doublet assigned to C1 had a $w_{1/2}$ of $\sim$ 10 Hz, suggesting that the doublet was in fact two very similar, superimposed doublets with closely related coupling constants and chemical shifts. In subsequent variable-temperature experiments, involving gradual warming of the initial 1.4:1 mixture of **31**:**32**, the anomeric ratio was seen to be a function of temperature, increasing to 3.8:1 in favor of **31** before the onset of decomposition around 0 °C. The increased ratio was mirrored by a corresponding simplification of the ^{13}C NMR spectrum at the higher temperatures. Both substances decomposed at around 0 °C with the minor one doing so more rapidly, as judged by ^{1}H NMR spectroscopy. No attempt was made to characterize the products of these decompositions. Very revealingly, if a -10 °C solution was recooled to -78 °C, the original product ratio was essentially restored, indicating that the two substances are in dynamic equilibrium. This last observation is sufficient in itself to exclude the possibility that either one of the two substances is the initial sulfonium salt (**45**). The complete data set is best interpreted in terms of two triflates (**31**) and (**32**). The α-anomer (**31**) predominates and adopts the standard ^{4}C$_1$ conformation as indicated by the $^3J_{H1H2}$ coupling constant in the ^{1}H NMR spectrum. The minor, less stable β-anomer (**32**) must exist substantially in the ^{1}S$_5$ twist boat conformation **46** which gives rise to the reduced $^3J_{H1H2}$ coupling constant, smaller than that typically found in β-glucopyranosides in the ^{4}C$_1$ conformation, and which permits the

$^4J_{H1H3}$ W-type coupling of 2.3 Hz observed for the anomeric proton. At the same time the ^{1}S$_5$ conformation puts the β-triflate group in a pseudoaxial position, so explaining the close similarities in the ^{13}C and ^{19}F NMR spectra of the two triflates. This conformation is a consequence of the strongly electronegative nature of the triflate group and of the anomeric effect. Although such conformations are somewhat unusual in the glucopyranose series, Hall has previously discussed the tetraacetate of β-glucopyranosyl fluoride in terms of the closely related ^{1,4}B conformation to explain the magnitude of the $^3J_{H1H2}$ coupling constant. As here, the preference of the strongly electronegative anomeric substituent for the (pseudo)axial position was invoked to explain this conformation.[37] Although the triflates **31** and **32** are plainly identified as intermediates in the chemistry of **39** and Tf$_2$O, the isolation of two β-glucosides (**40**) and (**42**) and the ortho ester **41** suggests that the actual glucosylation reaction occurs at least in part through formation of a transient acetoxonium ion **47** and that a similar mechanism is operative for the perpivalated derivative (**5**) originally employed by Kahne.[1]

Is it possible to detect other intermediates prior to the formation of glycosyl triflates in this chemistry? In a recent paper employing the sulfoxide **48** Boeckman and Liu noted the formation of a very reactive intermediate on activation with Tf$_2$O at -90 °C, too unstable for use even at -78 °C, but which rapidly glycosylated alcohols with high β-selectivity at -90 °C.[10] Naturally, this comment aroused our curiosity and we, therefore, repeated the reactions of **13**, **23**, and **39** with Tf$_2$O in CD$_2$Cl$_2$ at -90 °C in the hope of identifying **49** and its congenors before collapse to the glycosyl triflates. In this we were disappointed as the triflate was the only identifiable carbohydrate product. It therefore seems likely that the unstable intermediate identified by Boeckman was simply the α-triflate whose PMB protecting groups rendered it unstable at higher temperatures.

Finally, it is appropriate to ask, what is the ultimate fate of the sulfenate moiety in these glycosylation reactions? As we have seen, benzenesulfenyl triflate (**22**) is a powerful electrophile and reacts with the sulfoxide more rapidly than Tf$_2$O, presumably resulting in the formation of the unknown sulfenic anhydride **50**. The chemistry of such unstable species is complex, and we have made no attempt to characterize it. We only point out here that in all of these reactions diphenyl disulfide is one of the several byproducts observed which must ultimately derive from **22** and/or **50**. Likewise, we note the isolation of the thioglycosides **17**, **28**, and **42** as byproducts in some of our reactions. The implication is that thiophenol is also produced in the decomposition of **22** and/or **50**, which must involve a series of disproportionation reactions.[38]

Conclusion

The answer to the title question is, at least for the three examples studied, a resounding yes. Glycosyl triflates are intermediates in the sulfoxide glycosylation method when the sulfoxide is activated with Tf$_2$O prior to addition of the glycosyl acceptor. As suggested in Scheme 2, method A, the possible exception involves activation of the sulfoxide in the presence of the acceptor, which is more nucleophilic than triflate anion. The stability of the anomeric triflates formed is a function of the protecting groups and, doubtless, the solvent. Kahne's intermediate glycosyl donor, reactive to hindered alcohols at low temperature yet stable in toluene for prolonged periods at room temperature, was most likely the glycosyl triflate. The

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sulfoxide method is a very convenient means of generating glycosyl triflates in situ in essentially quantitative yield. It is not the purpose of this paper to delineate the precise mechanism of glycoside formation subsequent to formation of the triflate. Indeed, this will be substrate-dependent and very much a function of a the protecting groups and solvent. In some instances glycoylation will occur via the intermediacy of transient ion pairs in an S_N1-like manner. In others, when the protecting groups are disarming either by virtue of their electronegativity or for torsional reasons, the glycosylation reaction will follow an S_N2-like pathway. In yet others, neighboring group participation through transient dioxolenium ions, e.g. **47**, can be expected to play a role. Such details, which will need to be worked out for each individual case through kinetic studies, are beyond the scope of this study. However, it is very likely that in the 4,6-benzylidene-protected series α-mannosyl triflates are displaced S_N2-like in dichloromethane at low temperatures to give β-glycosides. The reactivity of glycosyl triflates and the high stereoselectivity achieved with them and other anomeric sulfonate esters in glycosylation reactions had been previously noted by Schuerch[33,39−41] but little exploited because of the difficulty involved in their generation at the time. In light of these results it would seem entirely reasonable that glycosyl triflates are immediates in a whole range of glycosylation reactions employing AgOTf or TMSOTf as activating species, at least when activation is carried out prior to addition of the glycosyl acceptor. Indeed, Schuerch suggested in 1973 that glycosyl triflates were intermediates in the AgOTf-mediated coupling of pyranosyl bromides with alcohols.[39] In full agreement with the conditions noted here, Schuerch reported that couplings could be conducted very efficiently at −78 °C in dichloromethane in a matter of minutes.[39] In subsequent work, Hanessian also reported the coupling of glycosyl bromides with alcohols mediated by AgOTf but conducted his reactions for periods of several hours at 0 °C.[42] Apparently, such temperatures and reaction times were unnecessary as more recent work from the same laboratory is described as proceeding rapidly and efficiently at −78 °C, in agreement with Schuerch and ourselves.[43] Perlin and co-workers studied the coupling of pyranoses and alcohols mediated by triflic anhydride and considered that the aldose reacts with the anhydride to give a glycosyl triflate.[44,45] However, under the unspecified reaction conditions employed, the products of the reaction of the pyranose with triflic anhydride were found to be unstable and to be unsuitable for glycosylation reactions. When the reaction was conducted in the presence of Bu₄NBr, the unstable intermediate was converted to the pyranosyl bromide in high yield, which could then be employed in glycosylation in the usual manner.[44,45] A later ¹⁹F NMR investigation of the reaction of pyranoses with triflic anhydride or triflic acid at −40 °C in dichloromethane, however, found no evidence for the formation of glycosyl triflates as intermediates in this reaction and came to the conclusion that the coupling reactions were simply dehydrative reactions mediated by the strong acid $H_3O^+TfO^-$ generated in situ.[46,47]

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Experimental Section

General Procedures. NMR experiments were conducted at 300, 75, and 282 MHz for ¹H, ¹³C, and ¹⁹F, respectively, using a Bruker AC300 instrument equipped with a switchable QNP (¹H, ¹³C, ¹⁹F, and ³¹P) probe enabling back-to-back data acquistion for the different nuclei without the need to remove the sample or tune the probe. Chemical shifts are downfield from tetramethylsilane for ¹H and ¹³C NMR and from trifluoroacetic acid for ¹⁹F NMR spectra. All solvents were dried and distilled by standard techniques. Microanalyses were conducted by Midwest Microlabs, Indianapolis, IN.

Phenyl 4,6-*O*-Benzylidene-2,3-di-*O*-methyl-1-deoxy-1-thio-α-D-mannopyranoside (17). To a stirred mixture of the thioglycoside phenyl 4,6-*O*-benzylidene-1-deoxy-1-thio-α-D-mannospyranoside[48] (0.58 g, 1.6 mmol) and NaH (60%, 0.32 g, 8.0 mmol) in THF (10 mL) was added MeI (0.60 mL, 9.7 mmol). Stirring was continued at room temperature for 4 h before the reaction mixture was concentrated, and the residue taken up with dichloromethane and washed with water, saturated aqueous NH₄Cl, and brine. Concentration and column chromatography on silica gel (eluent: hexane/ethyl acetate = 10:1) afforded **17** (0.62 g, 100%): $[\alpha]_D^{20} = +166.7$ ($c = 3.7$, CHCl₃); ¹H NMR (CDCl₃), δ 3.53 (s, 3H), 3.60 (s, 3H), 3.74 (dd, $J = 3.1, 9.9$ Hz, 1H), 3.88 (t, $J = 9.9$ Hz, 1H), 3.93 (dd, $J = 1.4, 3.1$ Hz, 1H), 4.17 (t, $J = 9.9$ Hz, 1H), 4.23 (dd, $J = 4.8, 9.9$ Hz, 1H), 4.29−4.38 (m, 1H), 5.61 (s, 1H), 5.64 (d, $J = 1.4$ Hz, 1H), 7.25−7.38 (m, 6H), 7.47−7.52 (m, 4H); ¹³C NMR (CDCl₃), δ 58.9, 59.1, 64.9, 68.4, 77.7, 79.1, 80.3, 85.8, 101.6, 126.1, 127.6, 128.2, 128.9, 129.1, 131.3, 133.8, 137.4. Anal. Calcd for C₂₁H₂₄O₅S: C, 64.93; H, 6.23. Found: C, 64.60; H, 6.15.

Phenyl 4,6-*O*-Benzylidene-2,3-di-*O*-methyl-1-deoxy-1-thio-α-D-mannopyranoside S-Oxide (13). To a stirred solution of **17** (0.93 g, 2.4 mmol) in dichloromethane (60 mL) at −78 °C was added MCPBA (60%, 0.69 g, 2.4 mmol) followed by warming to −30 °C in 30 min. The reaction was then quenched with saturated aqueous NaHCO₃ and washed with brine. Concentration and column chromatography on silica gel (eluent: hexane/ethyl acetate = 4:1) afforded **13** as a single, unassigned isomer (0.83 g, 86%): $[\alpha]_D^{20} = +0.27$ ($c = 2.6$, CHCl₃); ¹H NMR (CDCl₃), δ 3.43 (s, 3H), 3.63 (s, 3H), 3.72 (t, $J = 10.1$ Hz, 1H), 4.00−4.09 (m, 2H), 4.15−4.22 (m, 2H), 4.27 (dd, $J = 1.3, 3.4$ Hz, 1H), 4.53 (d, $J = 1.3$ Hz, 1H), 5.59 (s, 1H), 7.34−7.38 (m, 3H), 7.47−7.51 (m, 2H), 7.56−7.60 (m, 3H), 7.65−7.69 (m, 2H); ¹³C NMR (CDCl₃), δ 59.1, 59.2, 68.0, 69.8, 74.9, 77.6, 78.0, 96.4, 101.7, 124.4, 126.0, 128.2, 129.0, 129.4, 131.8, 137.0, 141.5.

4,6-*O*-Benzylidene-2,3-di-*O*-methyl-α-D-mannopyranosyl Bromide (18). To a stirred solution of the thioglycoside **17** (0.35 g, 0.90 mmol) in dichloromethane (12 mL) was added bromine (93 μL, 1.8 mmol) and the stirring continued for 20 min. Concentration and column chromatography on silica gel (eluent: hexane/ethyl acetate = 10:1) afforded **18** as an unstable oil (0.23 g, 71%): $[\alpha]_D^{20} = +169.9$ ($c = 1.6$, CHCl₃); ¹H NMR (CDCl₃), δ 3.55 (s, 3H), 3.59 (s, 3H), 3.81−3.90 (m, 2H), 4.00−4.17 (m, 3H), 4.28 (dd, $J = 4.6, 10.1$ Hz, 1H), 5.59 (s, 1H), 6.50 (d, $J = 1.4$ Hz, 1H), 7.35−7.40 (m, 3H), 7.47−7.51 (m, 2H); ¹³C NMR (CDCl₃), δ 59.3, 59.6, 67.7, 67.8, 75.9, 78.4, 82.3, 86.5, 101.6, 126.0, 128.2, 129.0, 137.1.

Phenyl 2,3,4,6-Tetra-*O*-methyl-1-deoxy-1-thio-α-D-mannopyranoside (28). **28** was prepared from the α-phenylthio mannospyranoside[49] similarly as for **17** in 98% yield: $[\alpha]_D^{20} = +136.9$ ($c = 1.5$, CHCl₃); ¹H NMR (CDCl₃), δ 3.38 (s, 3H), 3.46 (s, 3H), 3.48−3.69 (m, 10H), 3.84 (dd, $J = 1.6, 3.1$ Hz, 1H), 4.06−4.13 (m, 1H), 5.66 (d, $J = 1.6$ Hz, 1H); ¹³C NMR (CDCl₃), δ 57.7, 58.0, 59.1, 60.6, 71.2, 72.1, 76.2, 78.7, 81.5, 84.6, 127.2, 128.9, 131.0, 134.6. Anal. Calcd for C₁₆H₂₄O₅S: C, 58.51; H, 7.37. Found: C, 58.21; H, 7.51.

(47) A very recent modification of this reaction has been described in which the pyranose is activated with triflic anhydride in the presence of diphenyl sulfoxide at −78 °C, prior to the addition of the acceptor alcohol. Here, the order of mixing the reagents and the reactivity patterns described suggest that a glycosyl triflate may be formed as an intermediate. Garcia, B. A.; Poole, J. L.; Gin, D. Y. *J. Am. Chem. Soc.* **1997**, *119*, 7597−7598.

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Phenyl 2,3,4,6-Tetra-*O*-methyl-1-deoxy-1-thio-α-D-mannopyranoside *S*-Oxide (23). Prepared similarly to **13**, as a single, unassigned isomer, in 94% yield: $[\alpha]_D^{20} = -46.5$ ($c = 1.9$, CHCl$_3$), ^{1}H NMR (CDCl$_3$), δ 3.35 (2 × s, 6H), 3.47−3.62 (m, 9H), 3.82 (dd, $J = 3.3$, 9.3 Hz, 1H), 3.89−3.95 (m, 1H), 4.19 (dd, $J = 1.7$, 3.3 Hz, 1H), 4.54 (d, $J = 1.7$ Hz, 1H), 7.51−7.55 (m, 3H), 7.65−7.68 (m, 2H); ^{13}C NMR (CDCl$_3$), δ 57.9, 58.2, 59.2, 60.7, 71.4, 73.5, 75.3, 77.3, 80.9, 94.9, 124.4, 129.1, 131.4, 141.8. Anal. Calcd for C$_{16}$H$_{24}$O$_6$S: C, 55.80; H, 7.02. Found: C, 55.73; H, 7.05.

2,3,4,6-Tetra-*O*-methyl-α-D-mannopyranosyl Bromide (24). An unstable oil prepared similarly to **18** in 74% yield: $[\alpha]_D^{20} = +196.8$ ($c = 2.5$, CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ 3.35 (s, 3H), 3.46 (s, 3H), 3.49 (s, 3H), 3.50 (s, 3H), 3.51−3.65 (m, 3H), 3.71−3.79 (m, 2H), 3.89 (dd, $J = 3.3$, 9.6 Hz, 1H), 6.53 (bs, 1H); ^{13}C NMR (CDCl$_3$) δ 57.9, 59.0, 59.1, 60.7, 70.4, 75.4, 75.5, 79.6, 80.7, 87.1.

Reaction of 13 with Tf$_2$O and DTBMP at −78 °C: Isolation of 14, 15, and 17. To a solution of the sulfoxide **13** (11.1 mg, 0.027 mmol) and DTBMP (11.3 mg, 0.055 mmol) in CD$_2$Cl$_2$ (1 mL) in a 5 mm NMR tube at −78 °C was added Tf$_2$O (5.1 μL, 0.030 mmol). The glycosyl triflate **16** [anomeric δ_H: 6.20; anomeric δ_C: 104.6 ($^1J_{CH}$ 184.5 Hz); δ_F: −0.037] was instantly formed. Other signals in the ^{19}F NMR spectrum were located at δ 4.26 (Tf$_2$O) and −3.21 (DTBMPH$^+$TfO$^-$). Then, after the addition of MeOH (4.4 ul, 0.11 mmol), ^{1}H and ^{19}F NMR spectroscopies indicated that the triflate **16** was consumed immediately to give the mannosides **14** and **15** (1:7). In a larger scale reaction (61.0 mg of **13**), the isolated products were as follows: **15**, 53%; **14**, 9%; **17**, 19%. **15:** $[\alpha]_D^{20} = -53.1$ ($c = 2.3$, CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ 3.30−3.38 (m, 1H), 3.43 (dd, $J = 3.1$, 9.9 Hz, 1H), 3.55 (s, 3H), 3.56 (s, 3H), 3.66 (s, 3H), 3.76 (dd, $J = 0.7$, 3.1 Hz, 1H), 3.91 (t, $J = 10.3$ Hz, 1H), 4.04 (t, $J = 9.9$ Hz, 1H), 4.33 (dd, $J = 4.9$, 10.3 Hz, 1H), 4.42 (d, $J = 0.7$ Hz, 1H), 5.57 (s, 1H), 7.31−7.37 (m, 3H), 7.45−7.49 (m, 2H); ^{13}C NMR (CDCl$_3$) δ 57.4, 58.8, 62.0, 67.2, 68.5, 78.6, 78.7, 80.1, 101.5, 103.0, 126.0, 128.1, 128.8, 137.3. Anal. Calcd for C$_{16}$H$_{22}$O$_6$: C, 61.92; H, 7.15. Found: C, 61.71; H, 7.20. **14**[50] is readily identified by its anomeric signal at δ 4.79 (d, $J = 1.6$ Hz). **17** was identical with the above sample.

Thermal Decomposition of Triflate 16. 1,5-Anhydro-4,6-*O*-benzylidene-2,3-di-*O*-methyl-D-*arabino*-hex-1-enitol (38). **16** was generated from **13** at −78 °C as in the above experiment and allowed to warm at 10 °C per 10 min with monitoring by ^{1}H and ^{19}F NMR spectroscopies. Decomposition began at −10 °C. ^{1}H NMR spectroscopy demonstrated that **38** was the exclusive product. Silica gel chromatography enabled isolation of **38** in 95% yield: $[\alpha]_D^{20} = +1.8$ ($c = 2.7$, CHCl$_3$); ^{1}H NMR (CDCl$_3$) δ 3.55 (s, 3H), 3.62 (s, 3H), 3.70−3.86 (m, 2H), 3.99 (dd, $J = 7.3$, 10.0 Hz, 1H), 4.24 (dd, $J = 0.9$, 7.3 Hz, 1H), 4.36 (dd, $J = 4.4$, 10.0 Hz, 1H), 5.59 (s, 1H), 6.18 (d, $J = 0.9$ Hz, 1H), 7.25−7.42 (m, 3H), 7.48−7.53 (m, 2H); ^{13}C NMR (CDCl$_3$) δ 56.1, 59.2, 68.3, 68.8, 76.5, 79.7, 101.0, 126.0, 126.4, 128.2, 129.0, 137.0, 140.6. Anal. Calcd for C$_{15}$H$_{18}$O$_5$: C, 64.74; H, 6.52. Found: C, 64.59; H, 6.59.

Generation of Mannosyl Triflate 16 from Bromide 18. To AgOTf (42.3 mg, 0.165 mmol) in a 5 mm NMR tube at −78 °C was added a cold solution of the glycosyl bromide **18** (9.8 mg, 0.027 mmol) and DTBMP (11.3 mg, 0.055 mmol) in CD$_2$Cl$_2$ (1.0 mL) with vigorous shaking. ^{1}H and ^{19}F NMR spectroscopies indicated the essentially quantitative formation of the glycosyl triflate **16** [^{1}H NMR δ 6.20 (br. s, anomeric H); ^{19}F NMR δ −0.056] with only experimentally insignificant chemical shift differences from the sample generated from sulfoxide **13**. On addition of MeOH (4.4 μL, 0.11 mmol), the glycosides **14** and **15** (1:7) were immediately formed.

Reaction of 13 with PhSOTf and DTBMP at −78 °C. To AgOTf (34.9 mg, 0.14 mmol) in a 5 mm NMR tube at −78 °C was added a cold solution of PhSCl (7.9 mg, 0.054 mmol) in CD$_2$Cl$_2$ (0.5 mL), and the tube was shaken vigorously at this temperature for 5 min. ^{19}F NMR spectroscopy indicated the formation of PhSOTf[31] (^{19}F NMR, δ −3.17). Then a cold solution of the sulfoxide **13** (11.0 mg, 0.027 mmol) and DTBMP (11.2 mg, 0.054 mmol) in CD$_2$Cl$_2$ (0.5 mL) was added at the same temperature. ^{1}H and ^{19}F NMR spectroscopies indicated the immediate formation of the glycosyl triflate **16** [^{19}F NMR δ −0.122; ^{1}H NMR δ 6.20 (anomeric H)]. On addition of MeOH (4.4 ul, 0.11 mmol), the mannosides **14** and **15** were formed (1:9).

Reaction of 23 with Tf$_2$O and DTBMP at −78 °C: Isolation of 26, 27, and 28. To a solution of the sulfoxide **23** (9.3 mg, 0.027 mmol) and DTBMP (11.3 mg, 0.054 mmol) in CD$_2$Cl$_2$ (1.4 mL) in a 5 mm NMR tube at −78 °C was added Tf$_2$O (5.7 μL, 0.035 mmol). The glycosyl triflate **25** [^{1}H NMR δ 6.17 (anomeric H); ^{19}F NMR δ −0.033] was instantly formed. Other signals were observed at δ 4.29 (Tf$_2$O) and −3.07 (DTBMPH$^+$TfO$^-$) in the ^{19}F NMR spectrum. After the addition of MeOH (4.4 μL, 0.11 mmol), the triflate **25** was consumed immediately, giving the glycosides **26** and **27** (~1:1). On a larger scale (60.0 mg of **23**), the isolated products were as follows: **27**, 40%; **26**, 26%; **28**, 12%. **26**[51] and **27**[51] are identified by their anomeric protons at δ 4.80 (d, $J = 1.8$ Hz) and 4.30 (br. s), respectively. **28** was identical with the above authentic sample.

Thermal Decomposition of Triflate 25. **25** was generated from **23** at −78 °C as in the above experiment and allowed to warm at 10 °C/10 min with monitoring by ^{1}H and ^{19}F NMR spectroscopies. Decomposition began at −30 °C and led to a complex mixture from which **26** and **28**, identical with authentic samples, were isolated in 61 and 5% yields, respectively.

Generation of Mannosyl Triflate 25 from Bromide 24. To AgOTf (51.4 mg, 0.20 mmol) in a 5 mm NMR tube at −78 °C was added a cold solution of the glycosyl bromide **24** (12.0 mg, 0.040 mmol) and DTBMP (32.9 mg, 0.16 mmol) in CD$_2$Cl$_2$ (1.5 mL) and the tube shaken vigorously. ^{1}H and ^{19}F NMR spectra indicated the clean formation of the glycosyl triflate **25** [^{1}H NMR δ 6.17 (anomeric H); ^{19}F NMR δ −0.150]. On addition of MeOH (6.5 μL, 0.16 mmol) glycosides **26** and **27** were immediately formed (1:1).

Reaction of 39 with Tf$_2$O and DTBMP at −78 °C: Isolation of 40, 41, and 42. To a solution of the sulfoxide **39** (a mixture of diastereomers at S)[52] (9.5 mg, 0.021 mmol) and DTBMP (8.5 mg, 0.042 mmol) in CD$_2$Cl$_2$ (1.1 mL) in a 5 mm NMR tube at −78 °C was added Tf$_2$O (5.3 μL, 0.031 mmol). ^{1}H and ^{19}F NMR spectroscopies indicated the instant formation of the glycosyl triflates **31** and **32** [1.4:1; ^{1}H NMR δ 6.21 (d, $J = 3.5$ Hz, anomeric H, α-isomer) and 5.60 (dd, $J = 7.6$ and 2.3 Hz, anomeric H, β-isomer); ^{19}F NMR δ 0.25; ^{13}C NMR δ 171.8, 171.9, 172.3, 172.4, 172.5, 172.9, 173.0, 173.1 (8 × carbonyl C), and 102.9 ($^1J_{CH}$ 184.5 Hz, anomeric C)]. On addition of MeOH (3.4 μL, 0.083 mmol), both triflates were consumed immediately to give the glycoside **40** and the ortho ester **41** (~1:1). **40**[53] is identified by δ 4.43 (d, $J = 7.8$ Hz) and **41**[54] by 5.73 (d, $J = 5.0$ Hz) in the ^{1}H NMR spectrum. In a larger scale reaction (70.0 mg of **39**), the isolated products were **40** (39%), **41** (39%), and **42**[54] (19%).

Thermal Decomposition of Triflates 31 and 32. A mixture of **31** and **32** was generated from **39** at −78 °C as in the above experiment and allowed to warm at 10 °C/10 min with monitoring by ^{1}H and ^{19}F NMR spectroscopies. The initial ratio of **31:32** of ~1.4:1 increased to ~3.8:1 before decomposition began around 0 °C, with the β-anomer doing so more rapidly at that temperature. No attempt was made to isolate or characterize products from this decomposition. At −10 °C it was possible to attribute the following resonances in the ^{13}C NMR spectrum to the major isomer: δ 60.7, 66.8, 68.4, 68.5, 71.8, 103.4, 169.5 (2C), 169.9, 170.5.

Supporting Information Available: ^{1}H and ^{19}F NMR spectra for the reactions of **13**, **23**, and **39** with Tf$_2$O (6 pages). See any current masthead page for ordering and Internet access instructions.

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