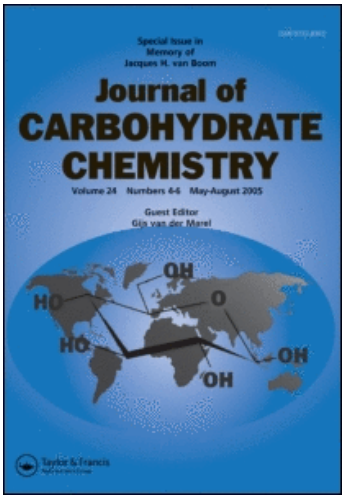

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CHEMISTRY OF GLYCOSYL TRIFLATES: SYNTHESIS OF β-MANNOPYRANOSIDES

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CHEMISTRY OF GLYCOSYL TRIFLATES: SYNTHESIS OF β-MANNOPYRANOSIDES*

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INTRODUCTION

Among the numerous and varied glycosyl donors known, the glycosyl sulfonates have been somewhat neglected in recent years, despite their considerable potential in stereoselective glycosylation having been demonstrated over 20 years ago by Schuerch and coworkers. This unfortunate circumstance perhaps arose because of the difficulties encountered by the early workers in the isolation of pure samples. Recent work from our laboratories in Chicago has revealed that glycosyl triflates may be very readily accessed from either glycosyl sulfoxides or thioglycosides and that these substances have excellent reactivity toward a broad spectrum of glycosyl acceptors even at −78°C. The main part of this chapter is therefore concerned with the development of the chemistry of the glycosyl triflates and, especially, with their applications in the synthesis of β-mannopyranosides. However, there are useful lessons to be learned from the precedents alluded to above, and it is with this in mind that we begin with an overview of the earlier work.

GLYCOSYL SULFONATES

The first reported preparation of a glycosyl sulfonate, in 1929, involved the heating of acetobromoglucose with silver toluenesulfonate in diethyl ether; Helferich and Gootz noted that the product was white and crystalline but decomposed in a matter of hours in chloroform solution at room temperature.[1] Many years after this inauspicious start, Schuerch and his coworkers turned their attention to an exploration of the

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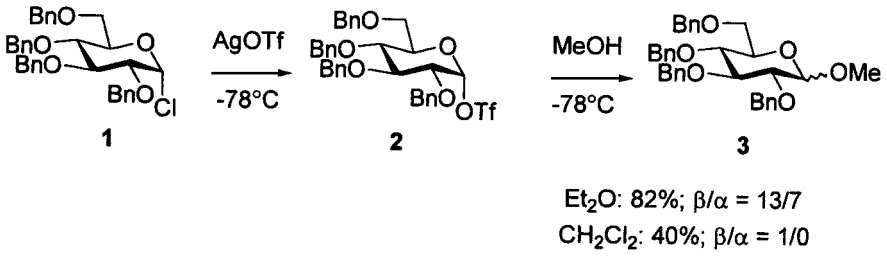
uses of glycosyl sulfonates as glycosyl donors. Thus, in a 1973 paper that presaged many of the later developments, Kronzer and Schuerch suggested that the treatment of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride (**1**) or bromide with silver triflate at −78°C in dichloromethane or diethyl ether provided the anomeric triflate **2** (Scheme 1).[2] They opined that, owing to the strongly electron-withdrawing nature of the triflate group, this substance probably had the α configuration. It was also noted that subsequent couplings with methanol, conducted at −78°C, were β-selective in dichloromethane but unselective in diethyl ether, and the difference was attributed to the superior shielding of the α face provided by the tighter ion pair in dichloromethane.[2] The rapidity of the reactions, both the initial formation of the triflate and its subsequent reaction with methanol at −78°C, were also noted at this time.[2]

Prompted by the extreme reactivity of the triflates and the desire to work with isolable, characterized intermediates, Schuerch and Eby subsequently turned their attention to the use of toluenesulfonates and mesylates.[3] Thus, 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl chloride, or bromide, was allowed to react with silver toluenesulfonate in acetonitrile at room temperature. The authors were able to use standard vacuum line techniques to remove the silver halide by filtration and obtain an ^{1}H NMR spectrum of the product in deuteriochloroform: the characteristics of the anomeric proton (δ 6.1, $^3J_{1,2}$ = 3.5 Hz) led to the attribution of the α stereochemistry. In the case of the analogous 2,3,4-tri-*O*-benzyl-6-*O*-(*N*-phenylcarbamoyl) series, signals attributed to the β-toluenesulfonate (δ 5.5, $^3J_{1,2}$ = 8.0 Hz) accounted for approximately 15% of the reaction mixture.[3] In agreement with the earlier report of Helferich and Gootz, complete decomposition was noted after several hours at room temperature. Coupling reactions of the so-formed 2,3,4,6-tetra-*O*-benzyl-1-*O*-tosyl-α-D-glucopyranose, conducted with methyl 2,3,4,-tri-*O*-benzyl-α-D-glucopyranoside in a range of solvents, gave moderate yields but little selectivity. Kinetic measurements, carried out polarimetrically, revealed no clear dependence of reaction rate on alcohol structure or concentration and suggested to the authors that the couplings were S_N1 in character and involved a series of interchanging tight ion pairs.[3] Eby and Schuerch also noted that the anomeric toluenesulfonates formed from silver toluenesulfonate and peracylated (acetyl, benzoyl) glucosyl halides were considerably more stable, and less reactive, and upon exposure to methanol led to mixtures of α- and β-glucosides as well as to orthoesters. These latter results prompted them to suggest that the esterified toluenesulfonates would probably be of little use in glycosylation.[3] Schuerch and his coworkers also investigated the galactopyranosyl toluenesulfonates and triflates. As in

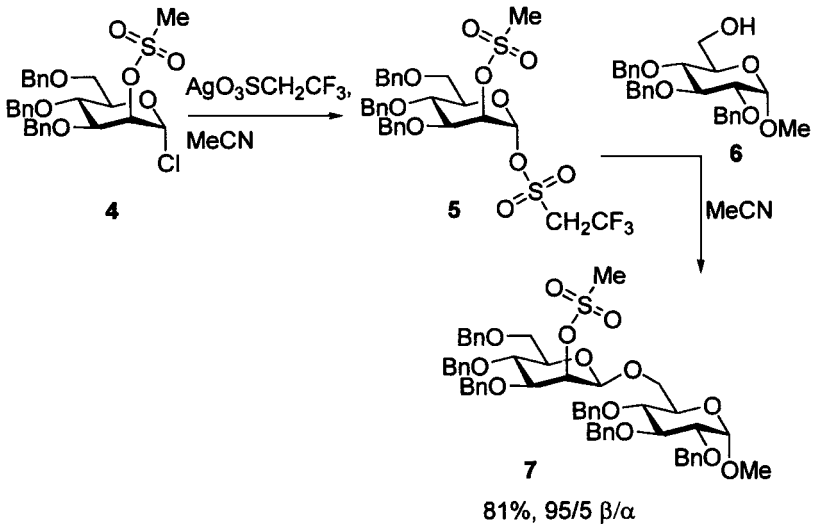


Scheme 1.

the glucose series, these were formed from the corresponding bromides by metathesis reactions with the appropriate silver sulfonates.[4,5] With a series of differentially 6-*O*-protected 2,3,4-tri-*O*-benzylgalactopyranosyl sulfonates, excellent yields and high α-selectivity were obtained upon coupling to a range of alcohols in various solvents. It was noted that the α-selectivity was minimized with the use of the triflate leaving group, albeit for reactions conducted at $-78°C$, in contrast to the other members of the series when room temperature was used. In the case of the reaction of the 4,6-di-*O*-(*N*-phenylcarbamoyl)-2,3-di-*O*-benzylgalactopyranosyl triflate with methanol, high β-selectivity was exceptionally obtained. These results were again all interpreted in terms of more or less tight ion pairs.[4,5]

Finally, Srivastava and Schuerch studied the formation of β-mannopyranosides and the related β-rhamnopyranosides, using a range of glycosyl sulfonates as donors.[6,7] In this most difficult series, the authors emphasized the increased anomeric effect resulting from the antiparallel dipoles of the C1O and C2O bonds and sought to maximize this contribution by installing a strongly electron-withdrawing, nonparticipating protecting group on O2. Thus, 3,4,6-tri-*O*-benzyl-2-*O*-mesyl-α-D-mannopyranosyl chloride (**4**) was prepared and reacted with a range of silver sulfonates to give the corresponding α-mannosyl sulfonates. Subsequent exposure to methanol or cyclohexanol, usually in acetonitrile, then gave the mannopyranosides in high yield and excellent β-selectivity. Only one carbohydrate-based alcohol (**6**) was used as glycosyl acceptor, but this too gave excellent β-selectivity especially with the 2,2,2-trifluoroethanesulfonate **5** as donor (Scheme 2).

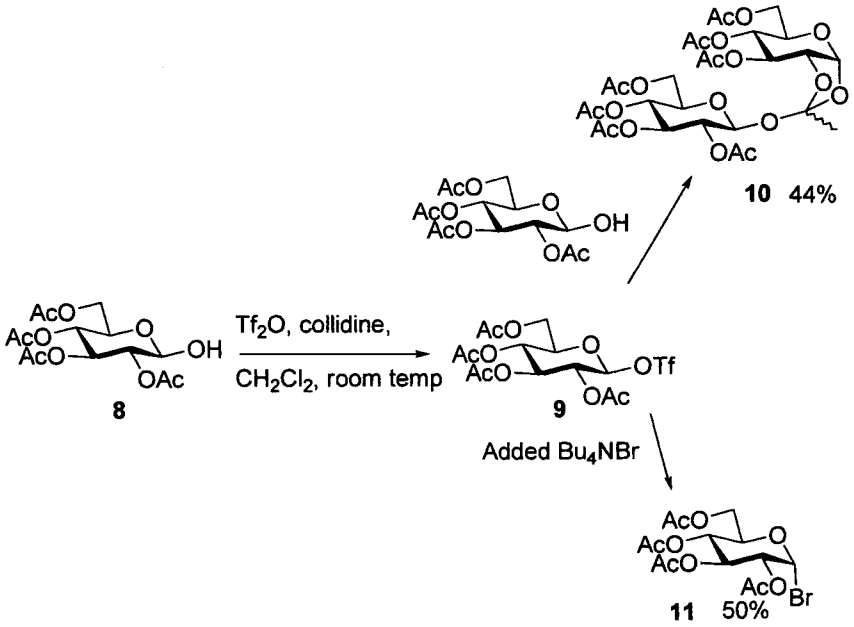
In considering the mechanism of their mannosylation reaction, Srivastava and Schuerch suggested that the electron-withdrawing sulfonate ester at the 2-position served to render the reactive ion pair in the S_N1 mechanism tighter on the α face than was the case in the glucose and galactose series. In this manner the α face was considered to be highly shielded toward approach of the nucleophile, with the dis-



Scheme 2.

placement taking on the high stereoselectivity normally associated with S_N2 processes.[6,7] Similar β-selectivities were obtained from a 3,4-di-*O*-benzyl-2-*O*-mesyl–L-α-rhamnopyranosyl tosylate.[6,7] Although the authors obtained excellent β-selectivity and yields in their mannosylations and rhamnosylations, they repeatedly alluded to the high moisture sensitivity of the anomeric sulfonates, as in the earlier glucose and galactose series, and the need to work on vacuum lines. Presumably this, and the need to remove the somewhat unconventional 2-*O*-mesylate protecting group subsequent to coupling, prevented them from developing the full potential of the method and applying it in the synthesis of oligosaccharides.

More or less contemporaneously with the work of Schuerch, Leroux and Perlin studied the sulfonylation of pyranoses. Thus, 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose was treated in cold dichloromethane with triflic anhydride in the presence of 2,4,6-collidine, leading to a purported anomeric triflate. However, the authors noted that subsequent addition of methanol or ethanol did not lead to the formation of the glycoside in acceptable yields.[8,9] Subsequently, it was discovered that conducting the triflation in the presence of tetrabutylammonium bromide resulted in the formation of the α-glucopyranosyl bromide and that addition of an alcohol then led cleanly to the glycoside. In these reactions Perlin and Leroux typically carried out the triflation/bromide displacement at $-70°C$, noting that bromide formation was complete after 15–30 min; the reaction mixture was warmed to room temperature before addition of the alcohol. However, it was also noted that bromide formation could be conducted at room temperature without apparent detriment. These workers also investigated the use of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose (**8**), with its potentially participating protecting groups, as substrate. In the presence of collidine but the absence of bromide



Scheme 3.

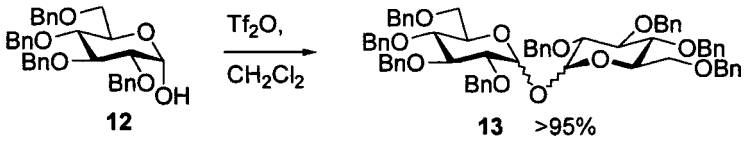
ion, an orthoester (**10**) was isolated in 44% yield. When bromide ion was included in the reaction mixture, acetobromoglucose (**11**) was isolated in 50% yield and there was no indication of orthoester formation. It was suggested that both reactions proceeded by way of the β-triflate (**9**), which was trapped either by further pyranose or by bromide ion according to the conditions employed (Scheme 3).[8,9]

The reaction of methanesulfonic anhydride with 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose in dichloromethane in the presence of collidine, followed by addition of methanol, resulted in the formation of a 3:2 α/β mixture of the methyl glycosides, isolated in 87% yield. Since glycosylation was achieved without the need for addition of the quaternary ammonium bromide, unlike the case of triflic anhydride, it was concluded that the glucosyl mesylate was considerably more stable and allowed for the displacement reaction to take place. Moreover, the anomeric ratio suggested that the α and β anomers of this mesylate were in equilibrium, with displacement of the β anomer occurring more rapidly. When 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranose was treated with methanesulfonic anhydride, a crystalline product was obtained in 74% yield and assigned as the α-glucosyl mesylate. Indeed the characteristics of this substance were comparable to those of the compound obtained by Schuerch upon treatment of acetobromoglucose with silver methanesulfonate.[8,9]

When methanesulfonyl chloride was allowed to react with 2,3,4,6-tetra-*O*-benzyl-glucopyranose and collidine in dichloromethane, the α-glucopyranosyl chloride was isolated regardless of whether the quaternary ammonium bromide was included. Addition of methanol to the reaction mixture resulted in the formation of an anomeric mixture of methyl glycosides. Similar results were obtained with toluenesulfonyl chloride, although it was noted that the initial sulfonylation was somewhat slower.[8,9] The use of tosyl chloride in the dehydrative coupling of alcohols with pyranoses was later revisited by Szeja and his coworkers, with the difference that aqueous phase transfer conditions were used, and glycosyl toluenesulfonates were implied as intermediates.[10,11] Koto and coworkers investigated the coupling of tetra-*O*-benzyl-α-D-glucopyranose and a range of acceptor alcohols with the aid of a mixture of 4-nitrobenzenesulfonyl chloride and silver triflate.[12–15] In the presence of triethylamine, the α-glycoside predominated, whereas the inclusion of *N,N*-dimethylacetamide resulted in the isolation of the β anomer. It was suggested that the anomeric hydroxyl group was sulfonylated with the sulfonyl chloride to a glucopyranosyl 4-nitrobenzenesulfonate and subsequently converted to the active glycosyl donor, the glucopyranosyl triflate, by the action of silver triflate. However, given the relative acidities of triflic and 4-nitromethanesulfonic acid and the related work of Szeja, carried out in the absence of silver triflate, the formation of a covalent glycosyl triflate in this work appears to be somewhat unlikely. The inversion of stereoselectivity on inclusion of the *N,N*-dimethylacetamide was explained by invoking the formation of an α-*N,N*-dimethylacetimidate ester.[12,13]

Pavia et al. revisited the reactions of tetra-*O*-benzylglucopyranose (**12**) with trifluoromethanesulfonic anhydride, but in the absence of base. They discovered that the corresponding trehalose derivatives (**13**) were formed in good yield, predominantly as the α,α form (Scheme 4).[16] Comparable results were obtained in the galacto-, manno-, and arabinopyranose series as with fructofuranose.[16] When trifluoromethanesulfonic anhydride was added to a mixture of a perbenzyl-protected glycopyranose and an acceptor alcohol, such as various serine, threonine and hydroxproline derivatives, coupling was achieved in good yield.[17]

58



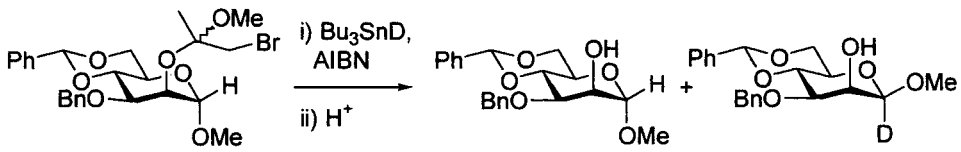
Scheme 4.

Pavia and coworkers carried out a careful study of the mechanism of these reactions using ^{19}F-NMR spectroscopy. They concluded that they were observing simple acid-catalyzed dehydrative couplings in which water was removed from the equilibrium in the form of a salt with triflic acid (TfO^- H_3O^+), which is insoluble in dichloromethane. The authors specifically excluded the intermediacy of a covalently bound glucosyl triflate on the grounds that the reaction did not occur below 15°C, whereas Perlin's reactions succeeded at -70°C.[18]

MANNOSYL TRIFLATES FROM MANNOSYL SULFOXIDES AND THIOGLYCOSIDES: THE β-MANNOSYLATION REACTION

Several years ago in Chicago, we were engaged in developing a solution to the well-known β-mannoside problem[19] involving the inversion of the much more readily accessible α-mannosides by a sequence of hydrogen atom abstraction, radical inversion, and diastereoselective quenching (Scheme 5).[20,21]

With the fundamental chemistry, which was developed using commercially available α-methyl mannopyranoside as substrate in hand, it became necessary to prepare a genuine α-disaccharide for inversion. We selected Kahne's excellent sulfoxide method[22–24] for numerous reasons, which included the reported excellent yields for coupling to extremely hindered alcohols at low temperatures, the absence of any metal salt as promoter, and the implication that the coupling proceeded through quenching of the oxacarbenium ion, hence should provide the α-mannoside. Other than a brief footnote in their original communication noting that the anomeric stereoselectivity was a function of the stereochemistry at C2 of the sulfoxide donor,[22] Kahne and his coworkers had not described the application of their method to the mannose series. Jarmila Brunckova thus prepared *S*-ethyl 4,6-benzylidene-α-D-thiomannopyranoside by standard means and converted it to the 3-*O*-benzyl-2-*O*-*tert*-butyldimethylsilyl derivative (**14**) by the aegis of dibutyltin oxide and benzyl bromide,

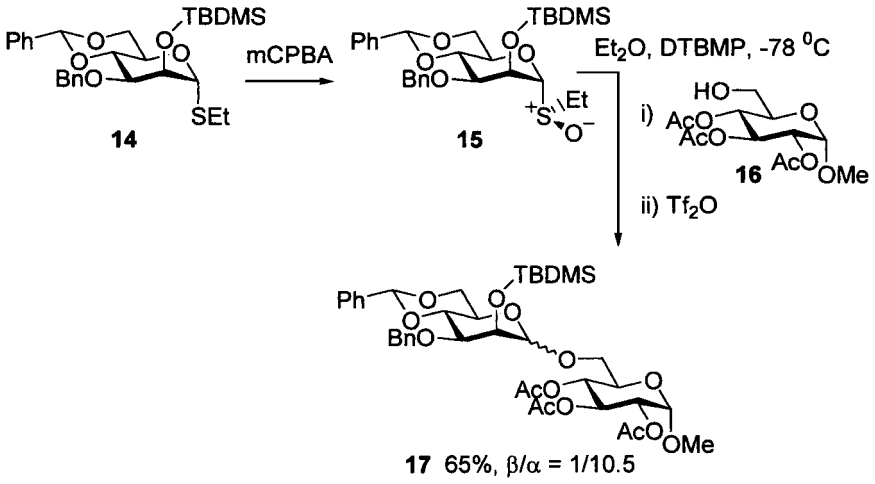


Scheme 5.

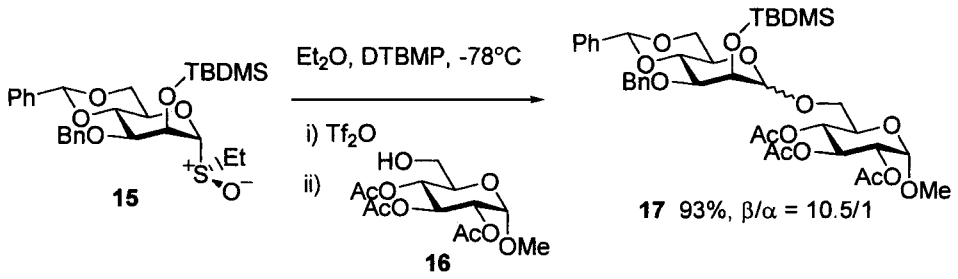
then TBDMS triflate. Oxidation with mCPBA then gave the sulfoxide (**15**) required for coupling.[21] Brunckova noted the highly selective sulfoxidation process, which gave essentially a single diastereomer, in contrast to the unselective oxidations β-thioglycosides observed previously,[23] but was unable to assign configuration at the time. In fact it was several years before Jan Mataka and Sanxing Sun were able to prepare crystalline derivatives suitable for X-ray analysis and so assign the configuration as S_R.[25] Brunckova then mixed the sulfoxide with methyl 2,3,4-tri-*O*-acetyl-α-D-glucopyranoside (**16**) and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP), a hindered base, in diethyl ether at $-78^{\circ}C$ and activated the sulfoxide by dropwise addition of triflic anhydride. In line with our expectations, a good yield of a 10:1 mixture of glycosides (**17**) favoring the α anomer was obtained (Scheme 6).[21] The TBDMS protecting group was removed and was replaced by the radical precursor, and the radical inversion procedure was conducted with moderate success, comparable to that seen with the α-methyl mannoside.[21]

Sanxing Sun, a new student, sought to prepare more of the α-disaccharide (**17**) and subsequently to improve the radical inversion process. He repeated Brunckova's preparation with the minor, but fortuitous, difference that the sulfoxide was activated with triflic anhydride before addition of the acceptor alcohol. To our amazement, an excellent yield was obtained of an anomeric mixture favoring the β-mannoside by a factor of roughly 10 (Scheme 7).[26,27]

Consideration of this unanticipated reversal of diastereoselectivity led us to propose a mechanism in which, under all conditions, the sulfoxide **15** (Scheme 8) undergoes rapid sulfonylation leading to a sulfonium ion **18**. We then postulated that this sulfonium ion collapses to the oxacarbenium ion **19** which, when generated in the presence of the donor à la Brunckova, is trapped axially to give the anticipated α-mannoside (**17**α). On the other hand, we suggested that, under the Sun conditions, the oxacarbenium ion is trapped by triflate anion to give an α-mannosyl triflate **20**. Then,



Scheme 6.

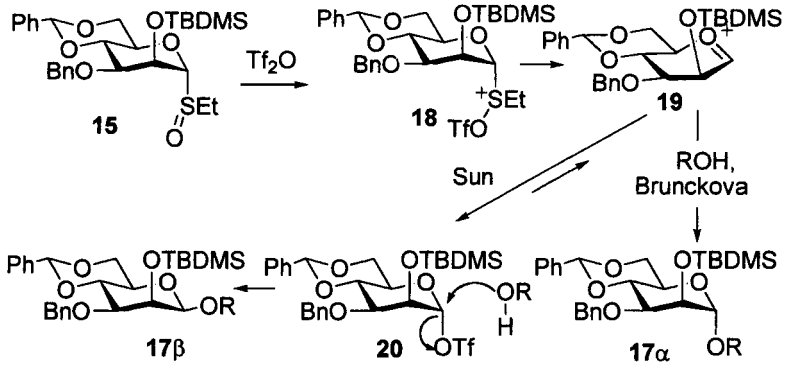


Scheme 7.

on subsequent addition of the acceptor, an S_N2-like process occurs with formation of the β-mannoside (**17**β).[27,28]

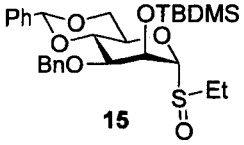
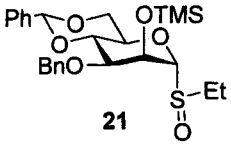
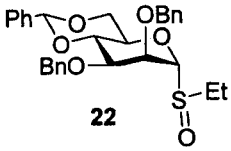
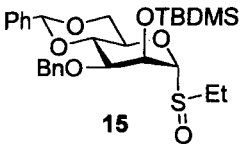
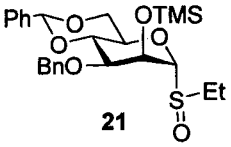
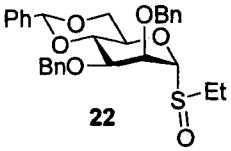
This mechanistic hypothesis also provided a reason for the poor β-selectivity observed with secondary alcohol acceptors, even under the Sun conditions, namely, the well-known retardation of S_N2 reactions by steric hindrance, leading to the interference of a dissociative mechanism via a Curtin–Hammett type of kinetic scheme. We predicted therefore that reducing the size of the O2 protecting group on mannose would accelerate the S_N2 process for any given alcohol and so lead to increased β-selectivity. We also predicted that a change in solvent from diethyl ether to dichloromethane would further shift any ion pair/covalent triflate equilibrium toward the covalent triflate and so similarly lead to enhanced β-selectivity.[27,28] Both hypotheses were readily tested and confirmed. Thus, the series of sulfoxides **15**, **21** and **22**, with decreasing bulk of the O2 protecting group, were prepared and coupled to the rhamnosyl acceptor **23**. As seen from Table 1, selectivity increases both as the size of the protecting group decreases and as the solvent is changed from diethyl ether to dichloromethane. Ultimately, with the 2-*O*-benzyl donor in dichloromethane as solvent, the α anomer of the product was not detectable.[28]

These conditions were then applied to the β-mannosylation of a range of primary and secondary carbohydrate acceptors with considerable success (Table 2).[27,28]

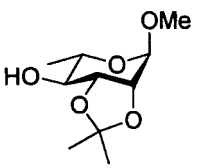


Scheme 8.

Table 1. Reaction of Glycosyl Donors with **23** in Ether and CH_2Cl_2

Donor	Solvent	Protocol[a]	Product and yield (%)[b] β-Mannoside	Product and yield (%)[b] α-Mannoside	$\beta:\alpha$
 **15**	Et_2O	A	**24**β, 49	**24**α, 30	1.6:1
 **21**	Et_2O	A	**25**β, 76	**25**α, 15	5.1:1
 **22**	Et_2O	A	**26**β, 74	**26**α, 11	6.7:1
 **15**	CH_2Cl_2	B	**24**β, 82	**24**α, 11	7.5:1
 **21**	CH_2Cl_2	B	**25**β, 92	**25**α, 7	13.1:1
 **22**	CH_2Cl_2	B	**26**β, 90	**26**α, 0	>25:1

[a]A, Protocol A: addition of ROH to premixed donor, Tf_2O, and DTBMP in ether/benzene; Protocol B, addition of ROH to premixed donor, Tf_2O, and DTBMP in CH_2Cl_2.
[b]All except **26**β and **26**α isolated after treatment of the reaction mixture with TBAF.


23

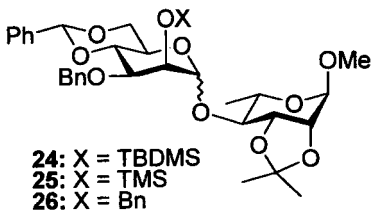
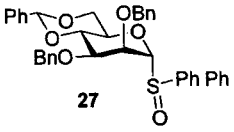
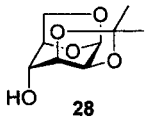
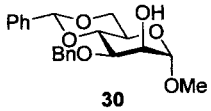
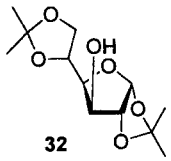
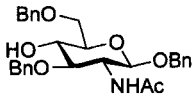
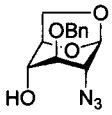
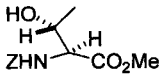
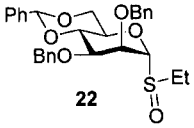
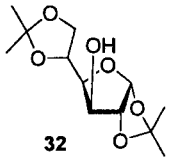
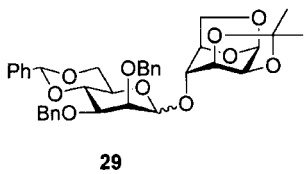

24: X = TBDMS
25: X = TMS
26: X = Bn

Table 2. Coupling of Secondary Acceptors to **22** and **27** in CH_2Cl_2

Donor	Acceptor	Product and yield (%)		
		β-Mannoside	α-Mannoside	$\beta:\alpha$
 **27**	 **28**	**29**β, 93	**29**α, 5	18.6:1
27	 **30**	**31**β, 90	**31**α, 6	15.0:1
27	 **32**	**33**β, 94	**33**α, 5	18.8:1
27	 **34**	**35**β, 31	**35**α, 8	3.8:1[a]
27	 **36**	**37**β, 72	**37**α, 13	5.5:1
27	 **38**	**39**β, 94	**39**α, 3	31.3:1
 **22**	 **32**	**33**β, 91	**33**α, 7	13.0:1

[a]The reaction mixture was allowed to come to room temperature and stirred there for 24 h before workup.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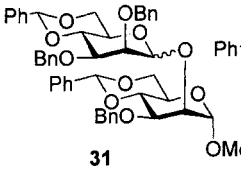
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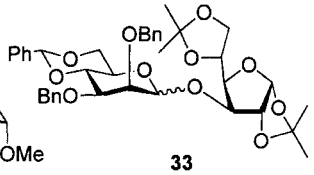
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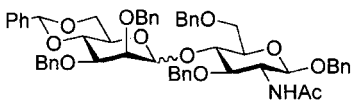
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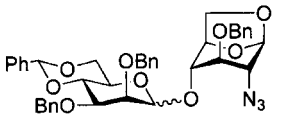
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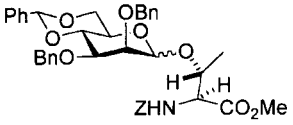
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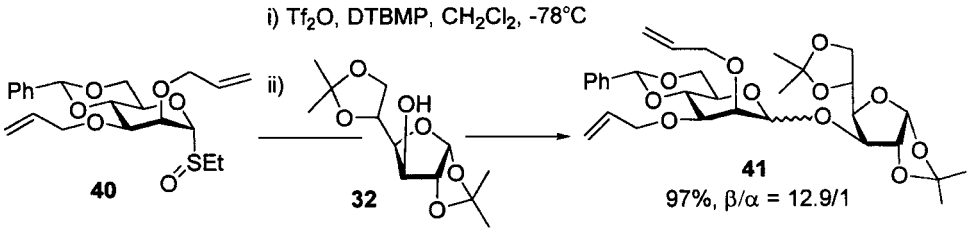
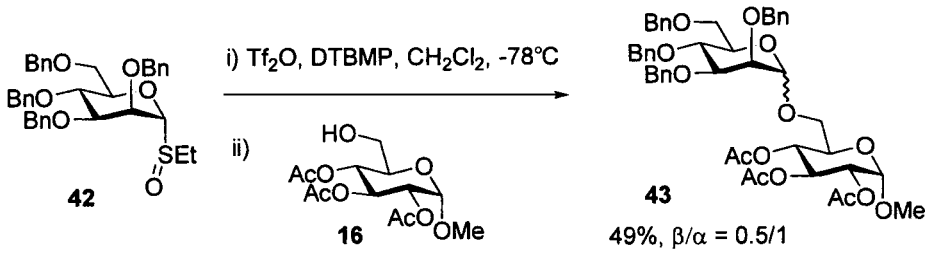


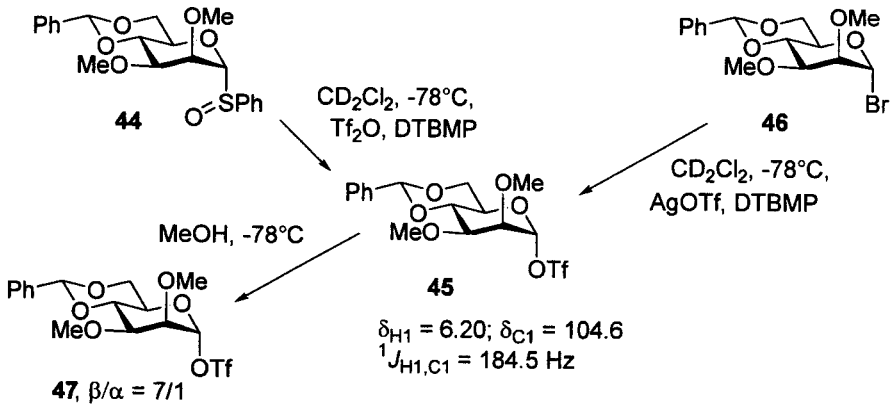
Scheme 9.

Attention was next focused on the use of alternative, nonparticipating protecting groups for the mannosyl donor, and the allyl group was found to be satisfactory at both O2 and O3 (Scheme 9).[27] Indeed, Zongmin Dai and Greg Barba subsequently used a 2-*O*-allyl protected donor to form the *β*-mannoside linkage in the *Hyriopsis schlegelii* trisaccharide and the caloporside disaccharide, respectively.[29–31] Further work, however, revealed the 4,6-benzylidene group to be indispensable for high *β*-selectivity, inasmuch as a 2,3,4,6-tetra-*O*-benzyl protected mannosyl donor gave very poor selectivity (Scheme 10).[27,28]

With a series of successful couplings in hand, we returned to the question of mechanism and the hypothesis of glycosyl triflates as the key reaction intermediates. A donor **44**, lacking any diastereotopic benzyl hydrogens, was prepared and its ^{1}H-NMR spectrum recorded in CD_2Cl_2 in the presence of DTBMP at $-78°C$. Cold ($-78°C$) Tf_2O was then added, and a rapidly recorded spectrum showed the sulfoxide to have been completely consumed and converted to a new carbohydrate species.[32] This new substance was characterized in the ^{1}H-NMR spectrum by its anomeric proton, a broad singlet, which resonated at δ 6.20. In the ^{13}C-NMR spectrum the anomeric carbon had a chemical shift δ of 104.6 and a $^{1}J_{CH}$ coupling of 184.5 Hz. These data indicated that a strongly electron-withdrawing group was covalently linked through oxygen to the α position of the mannopyranose ring, providing strong support for the α-mannosyl triflate (**45**) hypothesis. Confirmatory evidence was obtained when treatment of the mannsoyl bromide **46** with AgOTf and DTBMP in CD_2Cl_2 gave indistinguishable spectra.[32] This experiment also provided strong support for Schuerch's earlier hypothesis that glycosyl triflates were formed at low temperature upon treatment of glycosyl halides with AgOTf (see above). Addition of methanol at $-78°C$ to these NMR tube experiments resulted in the very rapid formation of



Scheme 10.

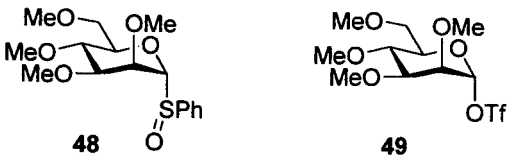


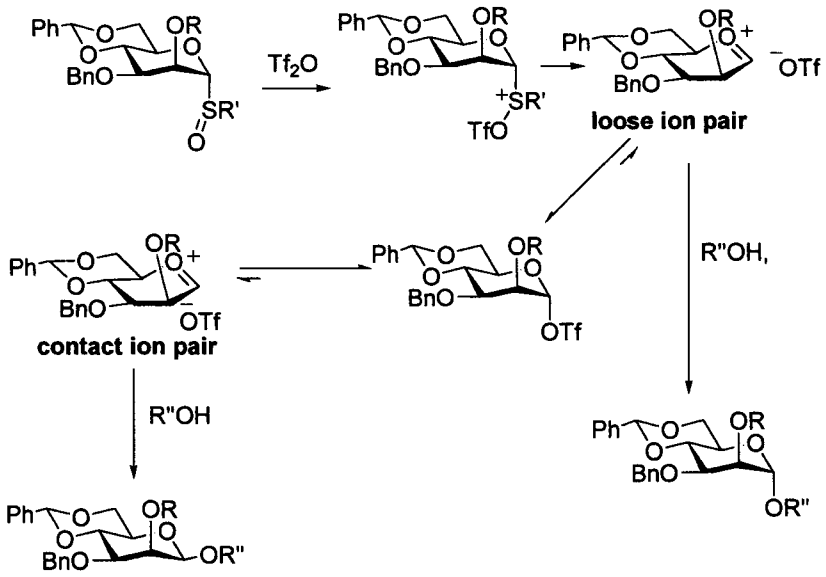
Scheme 11.

mannosides (**47**) with high β-selectivity, in full agreement with the general mechanism proposed (Scheme 11).[32]

A tetra-*O*-methylmannosyl sulfoxide **48** was prepared as a surrogate for the unselective tetrabenzyl donor **42**. Again, low-temperature ^{1}H and ^{13}C NMR experiments indicated clean formation of a covalently oxygen-linked intermediate and, again, the same spectra were obtained going out from the bromide and AgOTf.[32]

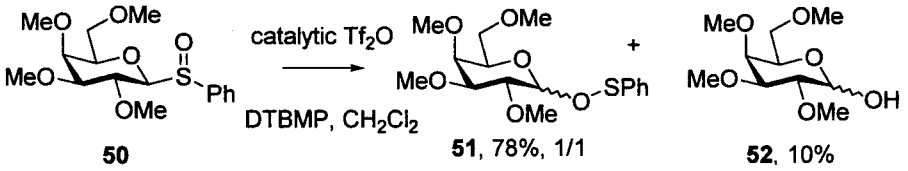
A first clue to reasons underlying the differing selectivity of the tetramethyl (or benzyl) and 4,6-benzylidene series was obtained in the course of attempts to record a CH-gated, coupled ^{13}C-NMR spectrum of **49**. Substantial decomposition occurred over the acquisiton time, unlike the case of the 4,6-benzylidene donor (**44**), which prevented us from obtaining the $^{1}J_{CH}$ coupling constant. This difference in stability was confirmed by a series of variable temperature experiments, which revealed the 4,6-benzylidene protected triflate (**45**) to decompose around $-10°C$, whereas its tetramethyl congener (**49**) did so some 20 degrees lower ($-30°C$). These latter observations provide strong support for the notion that the α/β-selectivity in these couplings is a function of the equilibrium between the covalently bound triflate and the ion pair. The less stable the triflate, as reflected in the lower decomposition temperature, the greater the population of the ion pair and the greater the likelihood that α-mannosylation will occur through a Curtin–Hammett type of kinetic scheme. The increased stability of the 4,6-benzylidene protected triflates may be rationalized in terms of Fraser-Reid's concept of a torsionally disarming protecting group.[33] In effect, the sofa conformation of the oxacarbenium ion imposes a twist and torsional strain on the acetal ring, which increases the energy of the oxacarbenium ion with respect to that of the covalently bound triflate. This effect is not present in the per-ether protected systems.



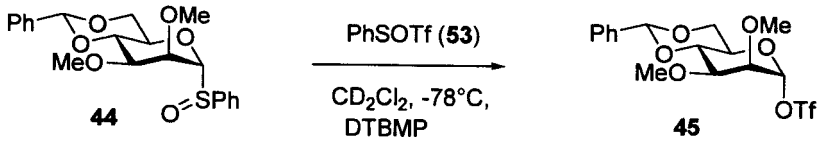


Scheme 12.

The basic mechanistic hypothesis (Scheme 8) suggests that the β-mannosides are formed in an S_N2-like manner from the α-triflate. The NMR experiments provide overwhelming support for the formation of these triflates and, in the 4,6-benzylidene series, for their stereochemistry. However, there remains the possibility, which we cannot rule out, that the covalently bound triflates simply serve as a reservoir for the storage of extremely reactive contact ion pairs. In this hypothesis, which echoes that of Schuerch (see above), the α-triflate dissociates to a contact ion pair in which the anion is intimately associated with the α face of the oxacarbenium ion and so sterically prevents approach from that face. In this hypothesis, reduced selectivity, as seen with the per-ether protected donors, arises from intervention of solvent and of solvent-separated ion pairs. This hypothesis therefore requires a change in the equilibrium between contact ion pairs and solvent-separated ion pairs in going from the 4,6-benzylidene series to the per-ether protected series. Again we fall back on the extra strain imposed on the oxacarbenium ion by the 4,6-benzylidene group, which will have the effect of shifting the CIP/covalent triflate equilibrium toward the covalently bound species, hence of reducing the likelihood of intervention of a solvent-separated ion pair. This variation of the original mechanism is presented in Scheme 12.



Scheme 13.



Scheme 14.

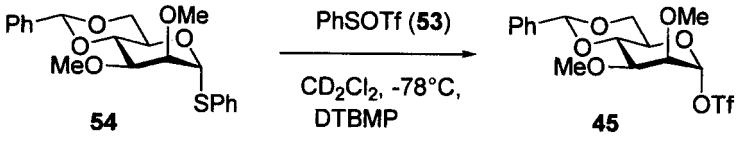
Although we have provided compelling evidence for the formation of mannosyl triflates in our system, it is not implied that related triflates are formed in all sulfoxide glycosylation reactions. Indeed, Kahne and his coworkers subsequently investigated the mechanism of their reaction and found that in many cases the original sulfoxide is rearranged to isolable sulfenate esters, which also serve as glycosyl donors as shown, for example, in Scheme 13.[34] The precise reasons for the different reactivity patterns are not clear and are the subject of ongoing research in our laboratory.

In the course of our investigations into the mechanism of the reaction, we became aware of the extreme electrophilicity of the by-product benzenesulfenyl triflate (**53**). As demonstrated by control experiments, this species is itself able to convert glycosyl sulfoxides into glycosyl triflates on a time scale comparable to that of the Tf_2O activation (Scheme 14).[32]

Sanxing Sun was so struck by the electrophilicity of PhSOTf that he tested its ability to convert thioglycosides into triflates at $-78°C$. His curiosity was immediately rewarded when low-temperature NMR experiments indeed showed this reagent to cleanly convert a mannosyl thioglycoside (**54**) into triflate (**45**) within the space of minutes at $-78°C$ (Scheme 15).[27,35]

Sun then went on and provided a series of examples of his new reaction, involving coupling to primary, secondary, and tertiary alcohols as set out in Table 3.[27,35] The obvious advantage of this new method is that it eliminates the need to oxidize thioglycosides to sulfoxides. The disadvantage is that the reagent has to be freshly prepared in situ from AgOTf and benzenesulfenyl chloride which, itself, has only limited shelf life.

In 1997 Gin and coworkers published an intriguing new method for the dehydrative coupling of pyranoses with alcohols in which the pyranose (**61**) is activated with a mixture of diphenyl sulfoxide and triflic anhydride before addition of the acceptor alcohol, leading to the formation of the coupled product (**63**) in excellent yield.[36] It was suggested that this chemistry, a development of that of Perlin and Pavia (see above), proceeds via the sulfonylation of the sulfoxide and attack of the pyranose on the so-formed sulfonium salt (**62**). In a NMR experiment, the mannosyl sulfonium salt (**65**) has been shown to be stable at low temperature in the absence of nucleophiles (Scheme 16). Indeed, it could even be generated by addition of diphenyl sulfoxide to



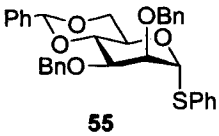
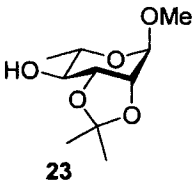
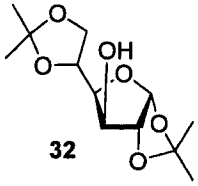
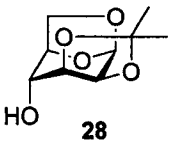
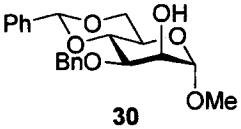
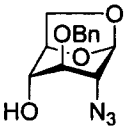
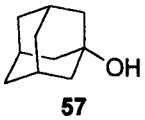
Scheme 15.

the corresponding glycosyl triflate (**49**), which was generated from the fluoride (**64**) with trimethylsilyl triflate. Glycosyl triflates therefore appear not to be intermediates in this chemistry.[37]

β-THIOMANNOSIDES

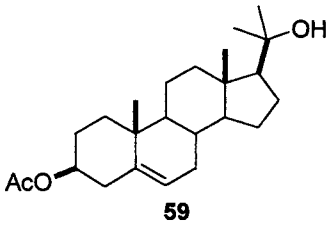
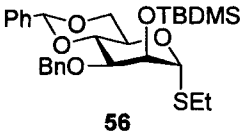
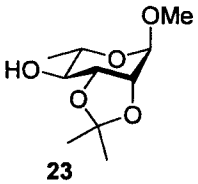
Thiols are generally regarded as better nucleophiles than alcohols in substitution reactions. Accordingly, Hongmei Li investigated the use of thiols as nucleophiles in our

Table 3. β-Mannoside Formation from Thioglycosides with PhSOTf in CH_2Cl_2

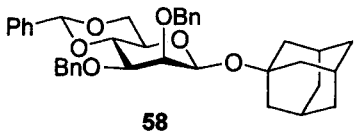
Glycosyl donor	Glycosyl acceptor	Product and yield (%)	β:α
 **55**	 **23**	**26**, 95	>25:1
55	 **32**	**33**, 95	<25:1
55	 **28**	**29**, 95	23:1
55	 **30**	**31**, 97	18:1
55	 **36**	**37**, 85	5.1:1
55	 **57**	**58**, 94	>25:1

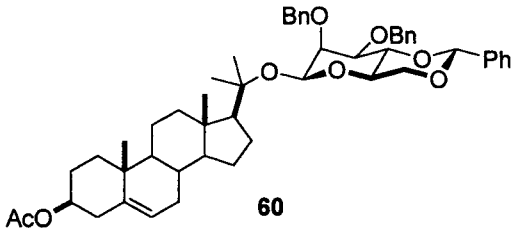
(*continued*)

Table 3. Continued

Glycosyl donor	Glycosyl acceptor	Product and yield (%)	$\beta:\alpha$
55	 **59**	**60**, 90	>25:1
 **56**	 **23**	**26**,[a] 80	10:1

[a]After treatment with TBAF.

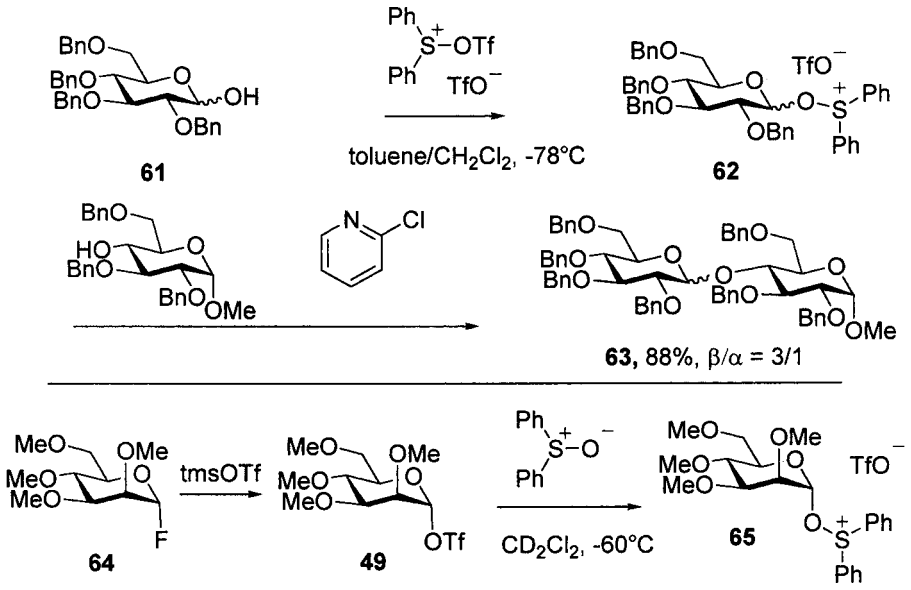

58


60

β-mannosylation protocol, with the expectation that even higher β-selectivity would be observed. This proved to be the case with a range of primary, secondary, and tertiary thiols (Table 4) with no α-thiomannoside being detected in any case. The yields, although good, were nevertheless somewhat less than we had typically observed with alcohols.[38] We attribute this phenomenon to the partial capture of the soft nucleophiles by one or other of the several sulfur-based electrophilic by-products present in the reaction mixture.

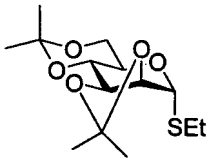
α-SELECTIVE MANNOSYLATION REACTIONS

In our continuing search for alternatives to the 4,6-benzylidene protecting group, and for 2,3-protecting groups that will confer enhanced selectivity even in the 4,6-benzylidene series, we have encountered several systems, which, contrary to our initial expectations, were highly α-selective. Zongmin Dai, recalling the very early work of Perlin in which the 2,3-*O*-carbonate was found to be highly β-selective when used in the mannosyl bromide/insoluble silver salt method,[39] prepared the 2,3-*O*-



Scheme 16.

carbonate (**77**) of *S*-phenyl 4,6-benzylidene-α-D-mannothiopyranoside and investigated its reaction with 1,2;3,4-diacetone-D-galactose (**78**) by the benzenesulfenyl triflate method (Scheme 17). She found to her surprise that the only product isolated was the α-mannoside **79**.[40] Earlier Sanxing Sun had looked at the use of the 2,3;4,6-diacetonide **80** as glycosyl donor in conjunction with methyl 2,3,4-tri-*O*-acetyl-α-D-glucpyranoside as acceptor and had obtained a 1:1 ratio fo the α- and *β*-mannosides.[27] Again, this result was surprising in view of the fact that Garegg had earlier successfully employed the 2,3;4,6-dicyclohexylidene protecting system in the synthesis of *β*-mannosides by the mannosyl bromide/insoluble silver salt method.[41]



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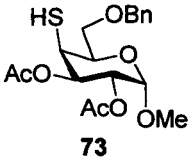
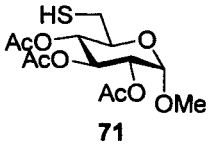
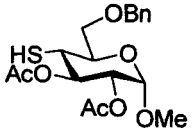
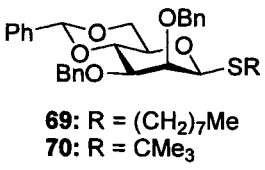
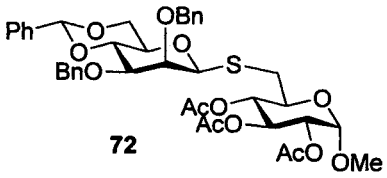
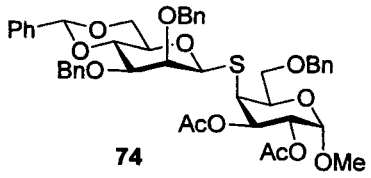
We interpret both these results in terms of the general mechanism and the effect of the protecting groups on the covalent triflate/ion pair equilibrium. Thus, the five-membered cyclic 2,3-O protecting groups lead to considerable flattening of the pyranose ring and so raise the ground state energy of the triflate. The barrier to formation of the flattened oxacarbenium is therefore reduced and the equilibrium shifted more in its favor. This effect is more pronounced in the carbonate than the acetonide, owing to the sp^2 nature of the atoms in the bridge, and so leads to higher α-selectivity in that case.

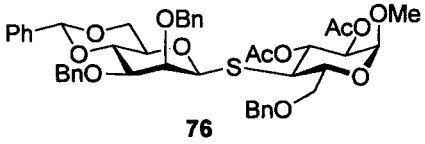
Table 4. Synthesis of β-Thiomannosides from Sulfoxide **27**

Acceptor	Product	Yield (%)	Acceptor	Product	Yield (%)
$Me(CH_2)_7SH$ **67**	**69**	74	 **73**	**74**	71
Me_3CSH **68**	**70**	77			
 **71**	**72**	54	 **75**	**76**	63

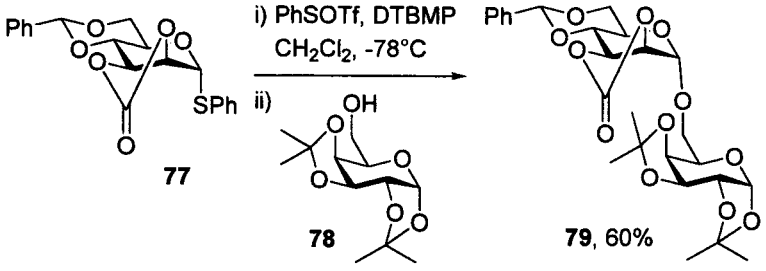






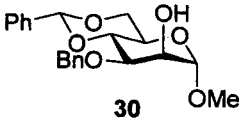
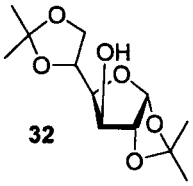
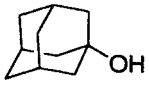
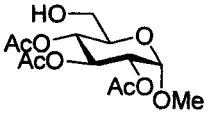
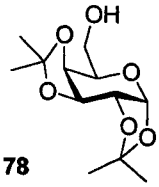


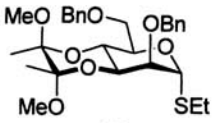
Zongmin Dai also investigated the use of a 2-*O*-TBDMS-3-*O*-benzoyl protected 4,6-*O*-benzylidene donor (**81**) but, again, excellent α-selectivity was observed.[40] This result must arise from neighboring group participation by the 3-*O*-benzoate. Models demonstrate that the twist-boat conformation (**82**) imposed by such participa-

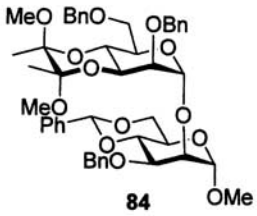


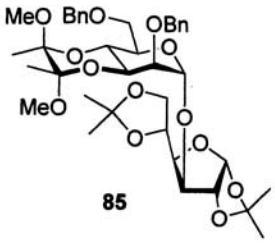
Scheme 17.

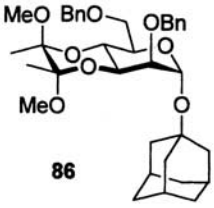
Table 5. α-Mannoside Formation from Thioglycoside **83** with PhSOTf in CH_2Cl_2

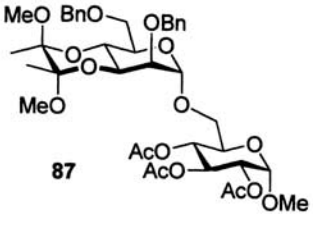
Glycosyl acceptor	Product and yield (%)	$\alpha:\beta$
 **30**	**84**, 52	>95:5
 **32**	**85**, 57	>95:5
 **57**	**86**, 88	>95:5
 **16**	**87**, 62	>95:5
 **78**	**88**, 60	>95:5

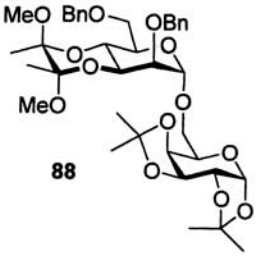

83


84

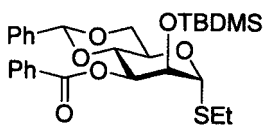

85


86

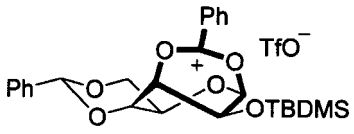

87


88

tion on the pyranose ring is not unduly straining even though the system is 4,6-benzylidene protected.



81



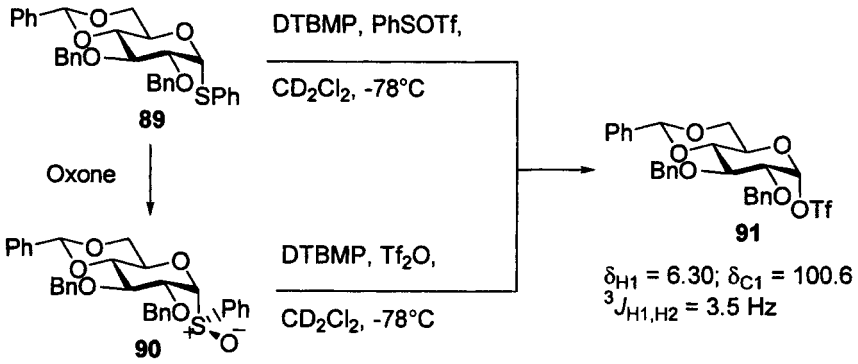
82

Weiling Cai prepared and investigated the Ley type[42,43] 3,4-bisacetal protected donor **83** in the expectation that the second ring would serve a similar rigidifying function as the 4,6-benzylidene group. This was not to be the case, and again excellent α-selectivity was observed in coupling to a number of acceptors (Table 5).[40]

With hindsight this result could have been predicted, inasmuch as Fraser-Reid's earlier experimental and computational work on the formation of oxacarbenium ions from pentenyl glycosides showed this to be more facile with a six-membered ring bridging the 3- and 4-positions than in the absence of such a ring, and certainly much more facile than in the case of 4,6-benzylidene protected systems.[33] Thus, this system also fits the general mechanistic scheme, with the α-selectivity being again due to a shift in the covalent trfilate/ion pair equilibrium. Furthermore, the reversal of selectivity seen across the series 4,6-benzylidene/tetrabenzyl/3,4-bisacetal is in full agreement with the increasing stability of the oxacarbenium ions, as predicted computationally by Fraser-Reid in the glucose series.[33]

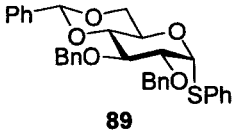
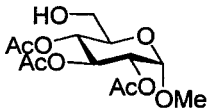
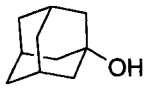
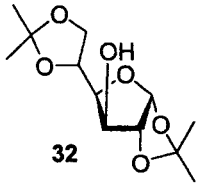
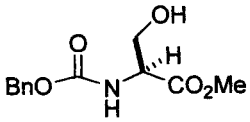
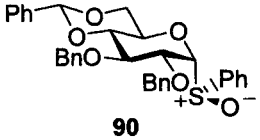
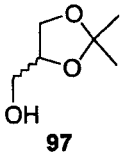
4,6-BENZYLIDENE PROTECTED GLUCOSYL TRIFLATES

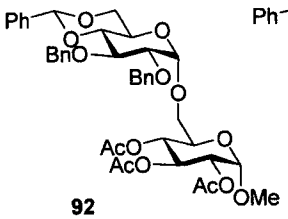
Weiling Cai prepared a 4,6-*O*-benzylidene-2,3-di-*O*-benzyl-α-D-glucopyranosyl thioglycoside **89** and oxidized it to the sulfoxide **90** in the expectation that activation under the standard conditions for β-mannosylation would lead to the formation of β-glucosides. Low-temperature studies in CD_2Cl_2 showed that both the sul-



Scheme 18.

Table 6. α-Glucoside Formation

Glucosyl donor	Glycosyl acceptor	Product and yield (%)	α:β
 **89**	 **16**	**92**, 98	>95:5
89	 **57**	**93**, 87	>95:5
89	 **32**	**94**, 70	>95:5
89	 **95**	**96**, 85	>95:5
 **90**	 **97**	**98**, 89	>95:5
90	MeOH	**99**, 72	>1:7.5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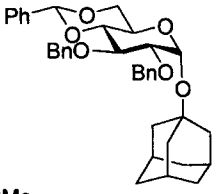
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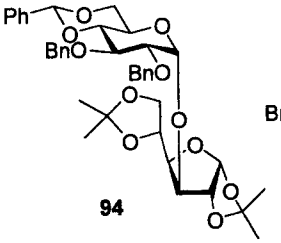
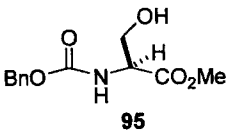

94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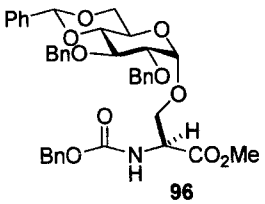
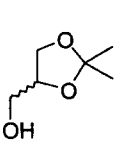
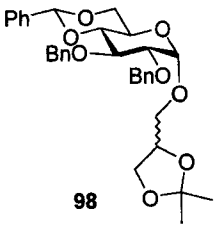
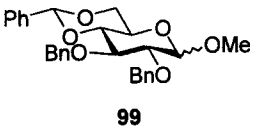

96


97


98


99

foxide and the thioglycoside, upon activation with Tf_2O or PhSOTf, respectively, provided the α-glucosyl triflate **91** ($\delta_{H1} = 6.3$; $\delta_{C1} = 100.6$; $^3J_{H1,H2} = 3.5$ Hz) in high yield (Scheme 18). However, all couplings except that to methanol were highly α-selective (Table 6).[44]

It is unlikely that this reversal of selectivity can be explained by reduced stability of the glucosyl triflate: variable temperature NMR studies showed that decomposition of the triflate did not set in until above 0°C (i.e., above the decomposition temperature of the corresponding mannosyl triflate). We believe that this result is a function of the differing extent of the anomeric effect in the two series. In effect it is known that the anomeric effect is considerably stronger in mannopyranose than glucopyranose derivatives.[45,46] Thus we suggest that the α- and β-triflates are in dynamic equilibrium and that the reduced anomeric effect in the glucose series permits a population of the more reactive β-triflate sufficient for it to serve as a donor in an S_N2-like fashion, with Curtin–Hammett kinetics, leading preferentially to the α-glucosides observed. A similar rationale was advanced decades ago by Lemieux for the formation of α-glucosides from α-acetobromoglucose in the presence of added bromide ion.[45,47]

SUMMARY

Glycosyl triflates may be prepared rapidly and cleanly at −78°C in CH_2Cl_2 solution from anomeric sulfoxides or thioglycosides upon activation with triflic anhydride or benzenesulfenyl triflate, respectively. These triflates are extremely reactive glycosyl donors and, when applied in conjunction with the 4,6-benzylidene protecting group, provide a very facile entry into the β-mannopyranosides.

ACKNOWLEDGMENTS

I thank the numerous talented students and postdoctorals whose hard work and diligence has contributed, and continues to contribute, to the development of glycosyl triflate chemistry in my laboratory. The National Institutes of Health (GM 57335) are gratefully acknowledged for their support of this work.

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