JOC Article

Influence of the 4,6-*O*-Benzylidene, 4,6-*O*-Phenylboronate, and 4,6-*O*-Polystyrylboronate Protecting Groups on the Stereochemical Outcome of Thioglycoside-Based Glycosylations Mediated by 1-Benzenesulfinyl Piperidine/Triflic Anhydride and *N*-Iodosuccinimide/Trimethylsilyl Triflate

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The effect of 4,6-*O*-benzylidene acetals, 4,6-*O*-phenylboronate esters, and 4,6-*O*-polystyrylboronate esters on the stereoselectivity of couplings to galacto-, gluco-, and mannopyranosyl thioglycosides, otherwise protected with benzyl ethers, has been investigated by the benzenesulfinyl piperidine/trifluoromethanesulfonic anhydride (BSP), diphenyl sulfoxide/trifluoromethanesulfonic anhydride (Ph_2SO), and *N*-iodosuccinimide/trimethylsilyl trifluoromethanesulfonate (NIS/TMSOTf) methods. The BSP and Ph_2SO methods give comparable results in all three systems whereas the NIS method affords significantly different stereoselectivities in both the gluco and manno, but not the galacto series. The benzylidene acetal and boronate esters influence the stereochemistry in a similar manner in the β-selective manno series and the α-selective galacto series but show significant differences with the glucose donors. The differences between the glucose, galactose, and mannose series reflect the established differences in reactivity and, especially for mannose, those in the anomeric effect and are best interpreted in terms of changes in the relative energetics between the α- and β-covalent triflate intermediates and the various contact ion pairs with which they are necessarily in equilibrium.

Introduction

We have previously remarked that the 4,6-*O*-benzylidene protecting group has a profound influence on the stereoselectivity of mannosylation reactions conducted by the sulfoxide/triflic anhydride method[1] or its functional equivalent the 1-benzenesulfinyl piperidine (BSP)/triflic anhydride/tri-*tert*-butylpyrimidine (TTBP) activated thioglycoside coupling protocol.[2] We have also shown that the 4,6-*O*-polystyrylboronate protecting group functions analogously, thereby enabling polymer-supported β-mannoside synthesis.[3] The stereodirecting influence of these protecting groups arises from their torsionally disarming effect on glycosyl cations[4] (oxacarbenium ions), which effectively shifts all equilibria toward the covalent α-glycosyl triflates,[5] thereby promoting S_N2-like displacements by the incoming acceptor alcohol. In the glucose series, the 4,6-*O*-benzylidene group has been demonstrated, on the other hand, to be α-directing.[2,6] In the mannose series, the resting state following activation has been demonstrated by NMR spectroscopy to be the α-mannosyl triflate,[5] and it is possible that the formation of the β-glycoside occurs by a direct S_N2 reaction or by its functional equivalent, an S_N1 substitution involving a contact ion pair as the minor component of an equilibrium with the α-triflate.[7] In the glucose series the α-triflate is also the only observable intermediate: it is possible that the α-selectivity arises because of the lower anomeric effect in glucose (versus mannose), which permits a small but sufficient population of the more reactive β-glucosyl triflate to influence the stereochemistry of the reaction either by a direct S_N2 reaction or a contact ion pair in which the triflate is closely associated with the β-face of the transient oxacarbenium ion.[6a,8] Recent computational work by Nukada and co-workers points to the involvement of ion pairs, but the definitive

(1) (a) Crich, D.; Sun, S. *J. Org. Chem.* **1997**, *62*, 1198−1199. (b) Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321−8348.

(2) (a) BSP: Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015−9020. (b) TTBP: Crich, D.; Smith, M.; Yao, Q.; Picione, J. *Synthesis* **2001**, 323−326. (c) BSP and TTBP are commercially available from www.lakeviewsynthesis.com.

(3) Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2002**, *124*, 8867−8869.

(4) Andrews, C. W.; Rodebaugh, R.; Fraser-Reid, B. *J. Org. Chem.* **1996**, *61*, 5280−5289.

(5) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217−11223.

(6) (a) Crich, D.; Cai, W. *J. Org. Chem.* **1999**, *64*, 4926−4930. (b) Bousquet, E.; Khitri, M.; Lay, L.; Nicotra, F.; Panza, L.; Russo, G. *Carbohydr. Res.* **1998**, *311*, 171−181. (c) Kim, K. S.; Kim, J. H.; Lee, Y. J.; Park, J. *J. Am. Chem. Soc.* **2001**, *123*, 8477−8481.

(7) (a) Crich, D. In *Glycochemistry: Principles, Synthesis, and Applications*; Wang, P. G., Bertozzi, C. R., Eds.; Dekker: New York, 2001, pp 53−75. (b) Crich, D. *J. Carbohydr. Chem.* **2002**, *21*, 663−686.

(8) All of these possible modes of reaction were invoked by Lemieux in his seminal paper on glycosylations, albeit with a different counterion: Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056−4062.

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experiments differentiating the two mechanisms have yet to be conducted.[9,10] Whatever the precise details of the reaction, direct S_N2 reaction or S_N1 on a transient contact ion pair, it is clear that the counterion has a critical role to play in glycosylation.[11]

We describe here a multifaceted study on the effect of the 4,6-*O*-benzylidene and 4,6-*O*-phenylboronate esters in the gluco- and galactopyranose series. Additionally, with a view to underlining the influence of the counterion, we offer a comparison between two different modes of activation, namely the 1-benzenesulfinyl piperidine/triflic anhydride system favored in this laboratory[2] and the popular *N*-iodosuccinimide system for the activation of thioglycsides.[12]

Results and Discussion

The present series of investigations was intended to address three principal questions. First, does the 4,6-*O*-benzylidene group enforce selectivity (α- or *β*-) in galactopyranosylation with otherwise armed thioglycoside donors? Second, do 4,6-*O*-phenyl- and polystyrylboronates behave analogously to 4,6-*O*-benzylidene acetals? Third, are the stereochemical results observed with the BSP/Tf_2O/thioglycoside and Tf_2O/glycosyl sulfoxide methods also seen in other systems, namely, the NIS/TMSOTf and the very recent diphenyl sulfoxide/Tf_2O[13] activating systems for thioglycosides?

With respect to the first question, it is very well-known that galactosides are more reactive than mannosides, which in turn are more reactive than glucosides, as exemplified in the relative rates of hydrolysis of methyl α-D-gluco-, α-D-manno-, and α-D-galactopyranosides of 1, 2.4, and 5.2, respectively.[14] This trend is mirrored in recent compilations of relative reactivity values for thioglycoside donors (Figure 1).[15]

This is usually attributed to the axial alcohol being subject to a less severe increase in torsional strain as the

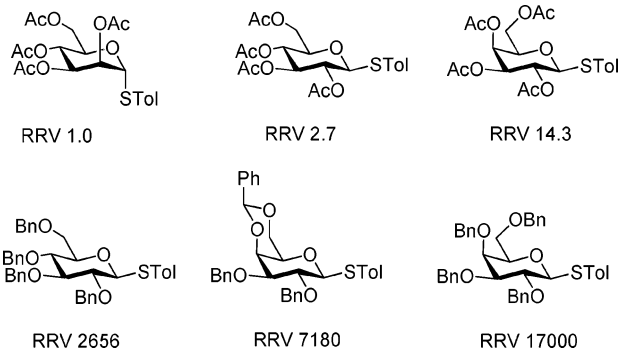

FIGURE 1. Pertinent relative reactivity values[15b] of glucose, galactose, and mannose donors for activation with NIS/TfOH at −40 °C to room temperature in dichloromethane. The apparent inconsistency in Figure 1 with the stated reactivity trend of galactose > mannose > glucose arises from the use of the α-thiomannoside as the comparison standard (RRV = 1.0) in the RRV series, which is otherwise comprised of *β*-thioglycosides. It is very well established that α-glycosides are less reactive than the corresponding *β*-anomers.

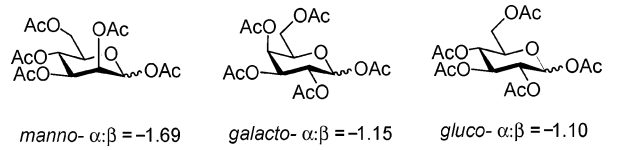

FIGURE 2. Equilibrium anomeric effects in peracetylated pyranoses[17] in 1:1 HOAc/Ac_2O (kcal, mol^{-1}).

$^4C_1$ donor flattens to the sofa conformation of the oxacarbenium ion.[14a,15c] It has also been suggested that the enhanced reactivity of galactose is due to a minimization of unfavorable interactions between the axial 4-C−O bond and a ring oxygen lone pair in the course of the same distortion.[16] Conversely, the anomeric effect in activated derivatives of galactose is comparable to that in glucose and significantly lower than that in mannose (Figure 2).[17] Thus, on grounds of simple reactivity, galactosyl donors might be expected to be more α-selective than glucose and mannose, as they have a higher tendency toward oxacarbenium formation. Similarly, due to the reduced anomeric effect vis-à-vis mannose, both glucosyl and galactosyl donors should be more α-selective than comparable mannosyl donors if the glycosylation mechanism involves S_N2-like displacement on a more reactive intermediate *β*-triflate at equilibrium with the predominant α-form.

Turning to the question of cyclic boronate esters,[18] we were intrigued by the possibility that the slightly longer B−O bond lengths, compared to the C−O bond lengths in benzylidene acetals, and the sp^2 hybridization of the boron and oxygen atoms, as opposed to the sp^3 acetal carbon and oxygens in benzylidene acetals, may make the boronate esters sufficiently different from the benzylidene acetals as to confer a different reactivity pattern. Added to the obvious conformational difference of the

(9) Nukada, T.; Bérces, A.; Whitfield, D. M. *Carbohydr. Res.* **2002**, *337*, 765−774.

(10) Jencks and co-workers have estimated the pseudo-first-order rate constant for trapping of glycosyl cations in water to be 10^{12} s^{-1}, consistent with a lifetime too short to allow complete diffusional equilibration with dilute solutes or even with solvent molecules, which further points to the need to include counterions, whether covalently bound or in contact ion pairs, when considering glycosylation mechanisms: Amyes, T. L.; Jencks, W. L. *J. Am. Chem. Soc.* **1989**, *111*, 7888−7900. Also see: (a) Richard, J. P.; Amyes, T. L.; Toteva, M. M. *Acc. Chem. Res.* **2001**, *123*, 981−988. (b) Zhu, J.; Bennet, A. J. *J. Am. Chem. Soc.* **1998**, *120*, 3887−3893.

(11) Against this background, it is remarkable that papers continue to be published that purport to describe glycosylation reactions in nonpolar solvents in terms of naked oxacarbenium ions, that is, in absentia the counterion: Abdel-Rahman, A. A.-H.; Jonke, S.; El Ashry, E. S. H.; Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 2972−2974.

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(14) Green, L. G.; Ley, S. V. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinaÿ, P., Eds.; Wiley-VCH: Weinheim, 2000; Vol. 1, pp 427−448.

(15) (a) Douglas, N. L.; Ley, S. V.; Lucking, U.; Warriner, S. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 51−65. (b) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734−753. (c) Namchuk, M. N.; McCarter, J. D.; Becalski, A.; Andrews, T.; Withers, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 1270−1277.

(16) Miljkovic, M.; Yeagley, D.; Deslongchamps, P.; Dory, Y. L. *J. Org. Chem.* **1997**, *62*, 7597−7604.

(17) Lemieux, R. U. In *Molecular Rearrangements, Part 2*; De Mayo, P., Ed.; Wiley: New York, 1964; pp 709−769.

(18) Reviewed in (a) Duggan, P. J.; Tyndall, E. M. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1325−1339. (b) Ferrier, R. J. *Adv. Carbohydr. Chem. Biochem.* **1978**, *35*, 31−80.

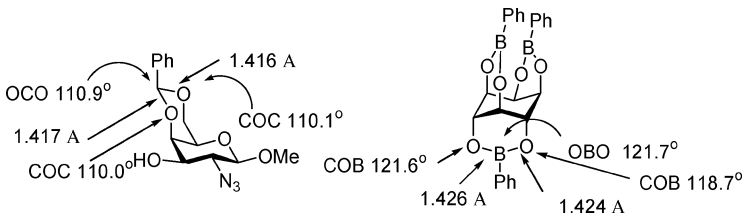
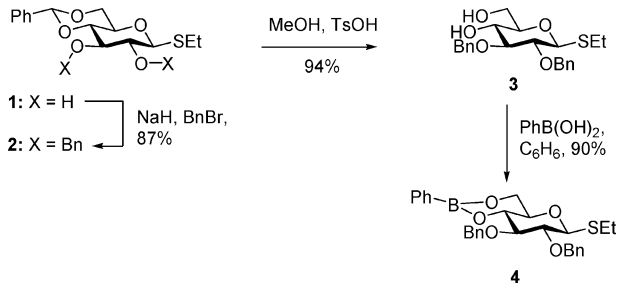
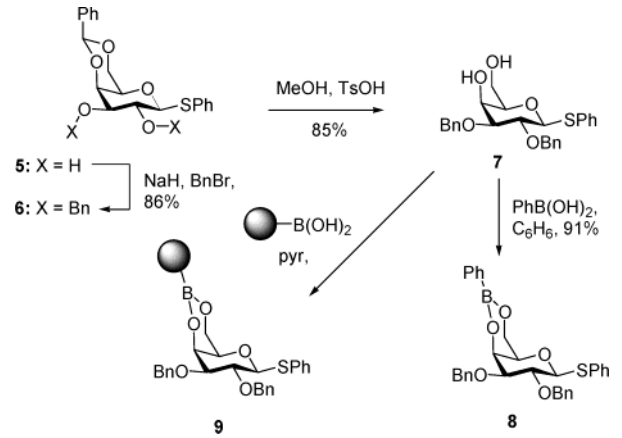


FIGURE 3. Pertinent structural features from X-ray crystal structures.[19]

SCHEME 1. Assembly of Glucosyl Donors

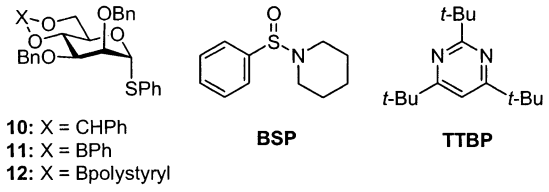


SCHEME 2. Assembly of Galactosyl Donors



boronate esters, there is also the more electropositive nature of boron (2.0), as compared to carbon (2.5), which admits the possibility that the 4,6-*O*-boronates might also function in part as a more classical electron-withdrawing, disarming protecting group (Figure 3).[19]

With these considerations in mind, a series of donors was rapidly assembled as set out in Schemes 1 and 2. For comparison purposes, several couplings were also conducted with the known mannosyl donors **10**−**12**.[1−3]



Beginning in the glucose series (Table 1) the rhamnosyl acceptor **13** was challenged with the donors **2** and **4** differing in only the 4,6-*O*-protecting group by each of three different coupling methods, from which two trends emerge. First, the BSP and diphenyl sulfoxide methods give comparable selectivities, favoring the α-anomer with both **2** and **4** but to a greater extent with the benzylidene protected system **2**. The α-selectivity in couplings to **2** by these methods is consistent with our expectations from the earlier studies.[2,6] With NIS/TMSOTf the selectivity is considerably lower with **2** but higher with **4**. Self-evidently, the NIS/TMSOTf reaction proceeds through a different mechanism to the BSP and diphenyl sulfoxide reactions, and this mechanism is affected in a different manner by the switch from 4,6-*O*-benzylidene to 4,6-*O*-phenylboronate. When the coupling of **4** to the less hindered alcohol 3*β*-cholestanol (**16**) was studied, no selectivity was observed by the BSP method, whereas the standard NIS/TMSOTf conditions resulted only in the formation of the α-anomer, thereby accentuating the differences between the BSP and NIS methods. Interestingly, when **4** was preactivated with NIS/TMSOTf prior to the addition of the acceptor, bringing the conditions closer to those used in the BSP method, a dramatic change in selectivity was observed with the two anomers formed in a 1:1 mixture.[20] With 1-adamantanol as nucleophile, coupling to **4** by the BSP method afforded a 2.8:1 α:*β* mixture of anomers. This is to be contrasted with the previous coupling of 1-adamantanol to the α-phenylthio analogue of the benzylidene-protected donor **2** with activation by benzenesulfenyl triflate, an antecedent of the more convenient BSP method, when only the α-anomer was formed.[6a] The standard NIS/TMSOTf protocol for the coupling of **4** and adamantanol again provided the clean α-anomer. Overall, in the glucose series it is clear that results observed with 4,6-*O*-benzylidene protected donors cannot be directly transposed to the corresponding 4,6-*O*-phenylboronate donors owing to a general erosion of the α-selectivity. Similarly, in the glucose series the use of the NIS/TMSOTf method results in considerably different stereoselectivities to those obtained by the BSP and diphenyl sulfoxide methods.

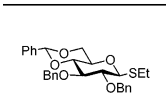
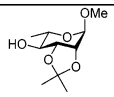
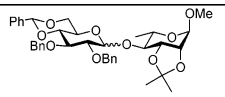
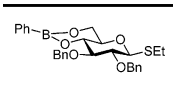
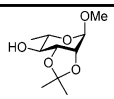
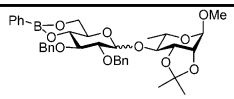
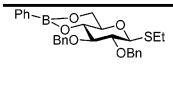
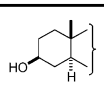
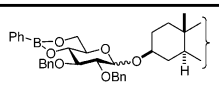
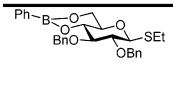
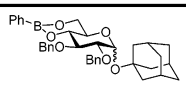
In the galactose series (Table 2), coupling of the 4,6-*O*-benzylidene-protected donor **6** by the BSP/Tf_2O method with the rhamnosyl acceptor **13** gave an 81% yield of the galactoside **20** as a 4.8:1 mixture favoring the α-anomer. Coupling of the comparable 4,6-*O*-phenylboronate-protected donor **8** with **13** under the same conditions gave a comparable yield and selectivity. Application of the NIS/TMSOTf method to the coupling of **8** and **13** resulted in a 75% isolated yield of the α-galactoside with none of the *β*-anomer observed.

With the less reactive glucosyl 4-OH acceptor **25**, 4,6-*O*-benzylidene-protected **6** gave moderate yields of the α-galactoside **26** as the only isolated product by both the

(19) (a) Salazar-Pereda, V.; Martinez-Martinez, L.; Flores-Para, A.; Rosales-Hoz, M. J.; Ariza-Castolo, A.; Contreras, R. *Heteroatom Chem.* **1994**, *5*, 139−143. (b) Gururaja, T. L.; Venugopalan, P.; Levine, M. J. *J. Chem. Crystallogr.* **1998**, *28*, 747−759.

(20) This change in selectivity with NIS/TMSOTf with order of mixing recalls that observed[1] for the mannosyl sulfoxides and warrants further investigation.

TABLE 1. Coupling Reactions with Glucosyl Donors

Donor	Acceptor	Conditions	Product (% Yield)	α:β Ratio
				
2	**13**	BSP, Tf_2O, TTBP, -60 °C	**14** (95)	3.2:1
2	**13**	Ph_2SO, Tf_2O, TTBP, -60 °C	**14** (76)	4:1
2	**13**	NIS, TMSOTf, rt	**14** (82)	1:1
				
4	**13**	BSP, Tf_2O, TTBP, -60 °C	**15** (76)	2:1
4	**13**	Ph_2SO, Tf_2O, TTBP, -60 °C	**15** (72)	2.7:1
4	**13**	NIS, TMSOTf, rt	**15** (85)	4.5:1
				
4	**16**	BSP, Tf_2O, TTBP, -60 °C	**17** (81)	1:1
4	**16**	NIS, TMSOTf, rt	**17** (91)	α only
4	**16**	NIS, TMSOTf, rt, preactivated	**17** (91)	1:1
				
4	**18**	BSP, Tf_2O, TTBP, -60 °C	**19** (89)	2.8:1
4	**18**	NIS, TMSOTf, rt	**19** (82)	α only

BSP/Tf_2O method and the more recent diphenyl sulfoxide/Tf_2O method introduced by van Boom and co-workers. The coupling of **25** to the 4,6-*O*-polystyrylboronate-protected glycosyl donor **9** was also investigated, resulting after cleavage from the resin in the isolation of the α-galactoside **27** as the only coupled product in excellent yield by both the BSP and NIS methods. The polystyrylboronate-supported donor **9** was also coupled to the galactosyl 2-OH acceptor **28** by both the BSP and NIS methods, resulting in both cases in the isolation of the α-coupled product in high yield and selectivity.[21]

We next turned to the use of 1-adamantanol as glycosyl acceptor: with the 4,6-*O*-benzylidene-protected donor **6**, the reaction was high yielding and moderately *β*-selective, whether promoted by BSP/Tf_2O or NIS/TMSOTf. On the other hand, the coupling of adamantanol to the 4,6-*O*-phenylboronate **8** and to the corresponding polystyrylboronate **9** was α-selective with ratios varying between 2:1 and 4.8:1, dependent on the coupling method employed. This reversal in anomeric selectivity observed with 1-adamantanol on going from the benzylidene acetal to either of the two boronate esters is the only instance of such a change that we observed and deserves comment. In general, in our studies, we have found 1-adamantanol to be an excellent acceptor alcohol: in the case of the 4,6-*O*-benzylidene-protected mannosyl donors, it consistently provides the *β*-glycoside with excellent selectivity, whether the reaction is carried out with activation by benzenesulfenyl triflate[1b] or BSP/Tf_2O.[2] Likewise, it gives excellent *β*-selectivity with a 4,6-*O*-polystyrylboronate-protected mannosyl donor[3] and with a 2-*O*-sulfonyl-protected rhamnosyl donor.[22,23] Indeed, 1-adamantanol is typically such a good nucleophile in these reactions that, ultimately, it is a poor model with which to probe the stereoselectivity of a particular system. The most reasonable explanation for the results observed here is that most couplings observed in Table 2 proceed via the aegis of a loose ion pair, that is, with nucleophilic attack on a glycosyl oxacarbenium ion in an α-selective manner. The formation of the adamantanyl *β*-galactoside **23** is best explained by an S_N2-like attack of the more nucleophilic adamantanol on an intermediate α-galactosyl triflate or the contact ion pair with which it is in equilibrium. On going from the 4,6-*O*-benzylidene-protected system to the more open 4,6-*O*-boronate esters, a shift to the right in the covalent-triflate/contact ion pair equilibrium/solvent

(21) The formation of the α-galactoside in the coupling of **9** and **28** was contrary to our initial expectations, as it had been reported that with NIS/TMSOTf the *β*-galactoside was obtained: Belogi, G.; Zhu, T.; Boons, G.-J. *Tetrahedron Lett.* **2000**, *41*, 6965−6968. However, it was subsequently established that this was a drawing error and that the original data supported the structure reported here: Belogi, G. Ph.D. Thesis; The University of Birmingham, 2000. We thank Prof. Geert-Jan Boons for his help in clarifying this matter.

(22) Crich, D.; Picione, J. *Org. Lett.* **2003**, *5*, 781−784.

(23) For the synthesis of an adamantanyl *β*-D-rhamnoside, see: Crich, D.; Yao, Q. *Org. Lett.* **2003**, *5*, 2189−2191.

TABLE 2. Coupling Reactions with Galactosyl Donors

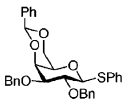
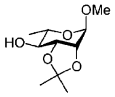
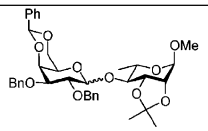
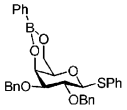
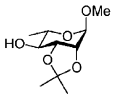
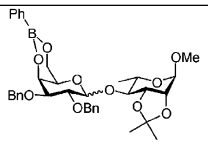
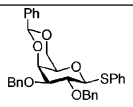
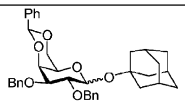
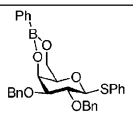
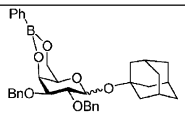
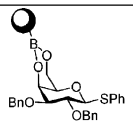
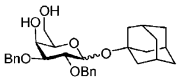
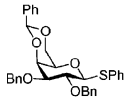
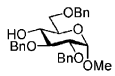
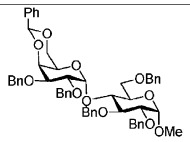
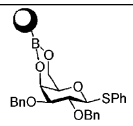
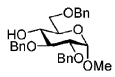
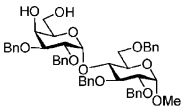
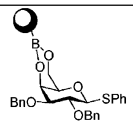
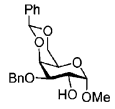
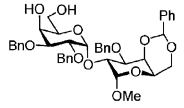
Donor	Acceptor	Conditions	Product (% Yield)	α:β Ratio
				
6	**13**	BSP, Tf_2O, TTBP, -60 °C	**20** (81)	4.8:1
				
8	**13**	BSP, Tf_2O, TTBP, -60 °C	**21** (83)	4:1
8	**13**	NIS, TMSOTf, rt	**21** (75)	α only
				
6	**18**	BSP, Tf_2O, TTBP, -60 °C	**22** (90)	0.23:1
6	**18**	NIS, TMSOTf, rt	**22** (85)	0.25:1
				
8	**18**	BSP, Tf_2O, TTBP, -60 °C	**23** (88)	3.75:1
8	**18**	NIS, TMSOTf, rt	**23** (83)	2.9:1
				
9	**18**	BSP, Tf_2O, TTBP, -60 °	**24** (76)	4.8:1
9	**18**	NIS, TMSOTf, rt	**24** (70)	2:1
				
6	**25**	BSP, Tf_2O, TTBP, -60 °C	**26** (64)	α only
6	**25**	Ph_2SO, Tf_2O, TTBP, -60 °C	**26** (53)	α only
				
9	**25**	BSP, Tf_2O, TTBP, -60 °C	**27** (92)	α only
9	**25**	NIS, TMSOTf, rt	**27** (83)	α only
				
9	**28**	BSP, Tf_2O, TTBP, -60 °C	**29** (90)	α only
9	**28**	NIS, TMSOTf, rt	**29** (80)	α only

TABLE 2 (Continued)

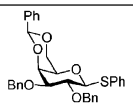
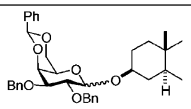
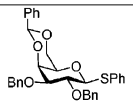
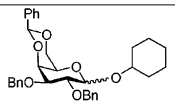
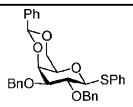
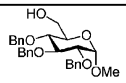
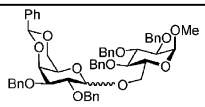
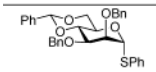
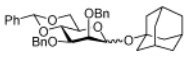
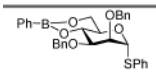
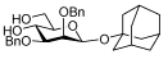
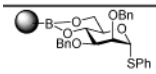
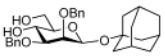
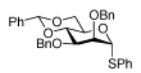
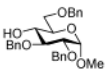
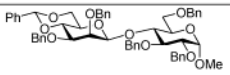
Donor	Acceptor	Conditions	Product (% Yield)	α:β Ratio
				
6	**16**	BSP, Tf_2O, TTBP, -60 °C	**30** (76)	0.27:1
				
6		BSP, Tf_2O, TTBP, -60 °C	**31** (90)	0.83:1
				
6	**32**	BSP, Tf_2O, TTBP, -60 °C	**33** (85)	1.2:1

TABLE 3. Coupling Reactions with Mannosyl Donors

Donor	Acceptor	Conditions	Product (% Yield)	α:β Ratio
				
10	**18**	BSP, Tf_2O, TTBP, -60 °C	**34** (88)[a]	<1:9
10	**18**	Ph_2SO, Tf_2O, TTBP, -60 °C	**34** (96)	1:9
10	**18**	NIS, TMSOTf, rt	**34** (93)	1:1
				
11	**18**	BSP, Tf_2O, TTBP, -60 °C	**35** (72)[b]	β only
				
12	**18**	BSP, Tf_2O, TTBP, -60 °C	**35** (88)[b]	β only
				
10	**25**	Ph_2SO, Tf_2O, TTBP, -60 °C	**36** (79)	β only

[a] From ref 2. [b] From ref 3.

separated ion pair, resulting from the change in hybridization and conformation in the second ring, is manifested by an increased α-selectivity. In other words, in most instances in the galactose series neither the 4,6-*O*-benzylidene acetal, the 4,6-*O*-phenylboronate, nor the 4,6-*O*-polystyrylboronate sufficiently stabilize any intermediate α-galactosyl triflate to permit the S_N2-like *β*-selective process to predominate: this latter process only becomes possible with the more nucleophilic adamantanol and then only for the 4,6-*O*-benzylidene acetal. Looked at in yet another way, differences between the benzylidene- and boronate-protected donors only become apparent in systems that that are on the cusp, i.e., when minor conformational changes can force the selectivity in either direction. In the mannose series, with the greater anomeric effect and more rigid trans-fused nature of the benzylidene acetals and boronate esters, the S_N2-like process always predominates.

Several other couplings were conducted between alcohols of intermediate reactivity and the benzylidene-protected galacostyl donor, as recorded in Table 2 with selectivities clustered either side of the α:*β* threshold, as expected on the basis of the above discussion.

One further point of note again concerns the *β*-selective coupling between the benzylidene-protected donor **6** and adamantanol, when conducted by the NIS/TMSOTf method. The donor in this reaction was a *β*-phenyl thioglycoside, which rules out the possibility of a direct S_N2-like attack on the initial activated thioglycoside. Rather, it seems apparent that even under these condi-

tions there is the formation of another transient intermediate, possibly the α-glycosyl triflate or iodide.

Intrigued by the *β*-selectivity in the NIS/TMSOTf-mediated coupling of adamantanol and **6**, we briefly investigated the same activation system in the mannose series. As recorded in Table 3, the reaction was, however, devoid of selectivity and thereby provided our first sample of an adamantanyl 4,6-*O*-benzylidene-protected α-mannoside. Activation of the thioglycoside **6** with the diphenyl sulfoxide/Tf_2O system of van Boom and coworkers restored the *β*-selectivity with both adamantanol and the much more demanding glucose 4-OH system.

In summary, in the glucose series results obtained with the 4,6-*O*-benzylidene-protected donor cannot be transposed to the corresponding 4,6-*O*-phenylboronate, owing to a general erosion of the α-selectivity. The NIS/TMSOTf method affords significantly different stereoselectivities in the glucose series to either the BSP/Tf_2O or the diphenyl sulfoxide/Tf_2O methods. On the other hand, in the galactose series 4,6-*O*-benzylidene-, 4,6-*O*-phenylboronate-, and 4,6-*O*-polystyrylboronate-protected 2,3-di-*O*-benzyl thioglycosides have all been shown to favor the formation of α-galactosides when activated with either the BSP/Tf_2O, Ph_2SO/Tf_2O, or NIS/TMSOTf systems. The exceptions to this rule involve the more reactive alcohols, especially 1-adamantanol, when moderate *β*-selectivity is observed in the 4,6-*O*-benzylidene series but not with the boronate esters. As was already known, the 4,6-*O*-benzylidene and 4,6-*O*-polystyrylboronates in the mannose series are highly *β*-selective with the BSP/Tf_2O and diphenyl sulfoxide/Tf_2O methods. The NIS/TMSOTf method has, however, been found to afford much reduced *β*-selectivity in the mannose series.

The differences between the glucose, galactose, and mannose series reflect the differences in relative reactivity values and, especially for mannose, those in the anomeric effect and are best interpreted in terms of changes in the relative energetics between the α- and *β*-covalent triflate intermediates and the various contact ion pairs with which they are necessarily in equilibrium.

In closing, we find it somewhat ironic that it is in the mannose series, with its long history of problems necessitating synthesis of the *β*-glycosides by any of a significant number of indirect routes,[24] that the chemistry is most predictable with no significant difference between the benzylidene- and boronate-protected donors noticeable as long as an activating method likely to promote formation of the intermediate α-triflates is selected.

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Note Added after Print Publication: Due to a production error, the structure block on p 8144 was replaced with a duplicate Figure 2 in the version posted on the Web September 26, 2003 (ASAP) and published in the October 17, 2003 issue (Vol. 68, No. 21, pp 8142−8148); the correct electronic version of the paper was published on October 28, 2003, and an Addition and Correction appears in the November 28, 2003 issue (Vol. 68, No. 24).

Supporting Information Available: Full experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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