Published in final edited form as:
J Org Chem. 2010 February 19; 75(4): 1107–1118. doi:10.1021/jo902222a.

Erosion of Stereochemical Control with Increasing Nucleophilicity: *O*-Glycosylation at the Diffusion Limit

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Abstract

Nucleophilic substitution reactions of 2-deoxyglycosyl donors indicated that the reactivity of the oxygen nucleophile has a significant impact on stereoselectivity. Employing ethanol as the nucleophile resulted in a 1:1 (α:β) ratio of diastereomers under S_N1-like reaction conditions. Stereoselective formation of the 2-deoxy-α-*O*-glycoside was only observed when weaker nucleophiles, such as trifluoroethanol, were employed. The lack of stereoselectivity observed in reactions of common oxygen nucleophiles can be attributed to reaction rates of the stereochemistry-determining step that approach the diffusion limit. In this scenario, both faces of the prochiral oxocarbenium ion are subject to nucleophilic addition to afford a statistical mixture of diastereomeric products. Control experiments confirmed that all nucleophilic substitution reactions were performed under kinetic control.

Introduction

The development of new methods for the synthesis of carbohydrates has been particularly challenging because glycosylation reactions often proceed with low or unpredictable selectivity.[1] The problem of low selectivity has been especially difficult to surmount for the synthesis of 2-deoxysugars, which are common structures found in biologically active natural products.[2] Although the use of participating groups at C-2 and their later removal can lead to selective reactions, the direct synthesis of 2-deoxy-α-*O*-glycosides from 2-deoxyglycosyl donors is not generally stereoselective.[3] We have observed that the corresponding reactions with carbon nucleophiles to form 2-deoxy-α-*C*-glycosides, however, occur with high selectivity under comparable S_N1-like conditions (Scheme 1).[4] A similar situation holds for *C*-glycosylations of other glycosyl donors, such as glucose-,[5] mannose-,[6] and ribose-derived systems,[7] where the *C*-glycosylation was selective, but the *O*-glycosylation was not.[8] No explanation has been provided to reconcile the different selectivities observed with the two types of nucleophiles.

Our studies of the reactions of six-membered ring oxocarbenium ions with carbon nucleophiles of varying reactivity suggest a possible explanation.[9] The stereoselectivities of these reactions are generally analyzed by considering stereoelectronic effects. In the absence of participating counterions,[10] both faces of the prochiral oxocarbenium ion can be attacked by a nucleophile (Scheme 2). Nucleophilic addition along the stereoelectronically preferred trajectory would provide the α-product **4** in a chair conformation (Scheme 2, path **a**).[4b,11,12] As the nucleophile becomes more reactive, the rates of nucleophilic addition to the cationic intermediate increase

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Supporting Information Available: Complete experimental procedures, product characterization, stereochemical proofs, details of control experiments, and GC and spectral data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

and approach the diffusion limit.[13] In this case, both paths **a** and **b** result in product formation, affording a statistical mixture of diastereomeric products. We recently provided evidence for this divergence between stereoelectronically controlled and diffusion-controlled diastereoselectivity in *C*-glycosylation reactions.[9] Because of the similar nucleophilicity of alcohols[14] and silyl enol ethers[15] (*C*-nucleophiles that react with oxocarbenium ions at rates approaching the diffusion limit9), the reactions of alcohols should be comparably rapid.[16] In this Article, we provide evidence that the low stereoselectivity of some *O*-glycosylation reactions are the result of reactions of oxocarbenium ion intermediates that approach the diffusion-controlled rate limit.

Results and Discussion

Details of the Experimental Approach

Details of the experimental approach deserve mention prior to discussing the results of nucleophilic substitution:

1. 2-Deoxythioglycosides and related monosubstituted model systems were chosen as substrates for this study. Our previous experience with these systems provided evidence that the reaction pathway (S_N1 versus S_N2) could be controlled with careful choice of leaving group and activation conditions.[9]

2. In all cases, anomeric sulfides were employed as the oxocarbenium ion precursors.[17] *N*-Iodosuccinimide (NIS) was chosen as the thioglycoside activating agent. This combination of C-1 leaving group and activating agent provided results consistent with S_N1-like additions to intermediate oxocarbenium ions.[18,19] Where indicated, 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) was employed as an additive to prohibit the epimerization of the acid-labile *O*-glycosylation products. Rigorous control experiments were conducted to verify that product ratios were obtained under kinetic control (*vide infra*, eq 3, Table 2).

3. Ethanol served as a model nucleophile due to its small size, and because its nucleophilicity could be modified by incorporating electron-withdrawing halogen substituents.[14,20–23] Field inductive effect parameters (*F*) were used as a quantitative measurement of the electron-withdrawing ability of the halogen substituents on the alcohol nucleophiles.[24,25] As the *F*-value increased, the alcohol should be rendered less nucleophilic; competition experiments verified this hypothesis (*vide infra*, eq 4, Table 3).

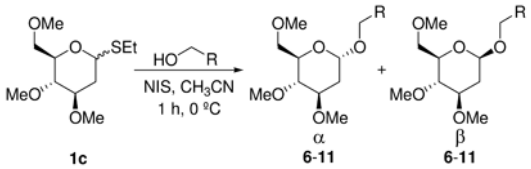
4. Both CH_3CN and CH_2Cl_2 were employed as solvents. Comparable yields and stereochemical trends were observed in either solvent, but CH_3CN generally provided higher diastereoselectivities consistent with stereoelectronically controlled attack on an oxocarbenium ion intermediate.[26]

5. Diastereomeric ratios were obtained by analysis of GC and ^1H NMR spectroscopy of the unpurified reaction mixtures. The product stereochemistry was determined by analysis of ^1H NMR coupling constants and NOE measurements of the purified products.

Nucleophilic Substitution Reactions of 2-Deoxythioglycosides

Experiments using 2-deoxyglucosyl donor **1c** and a range of oxygen nucleophiles demonstrated an erosion of stereoselectivity with increasing nucleophilicity (eq 1, Table 1). For example, substitution with the weakest nucleophile examined, trifluoroethanol,[14] resulted in an 83:17 (α:β) mixture of products (Table 1, entry 1).[27] This stereochemical outcome is consistent with stereoelectronically controlled attack (Scheme 2, path **a**), and the selectivity compares to those

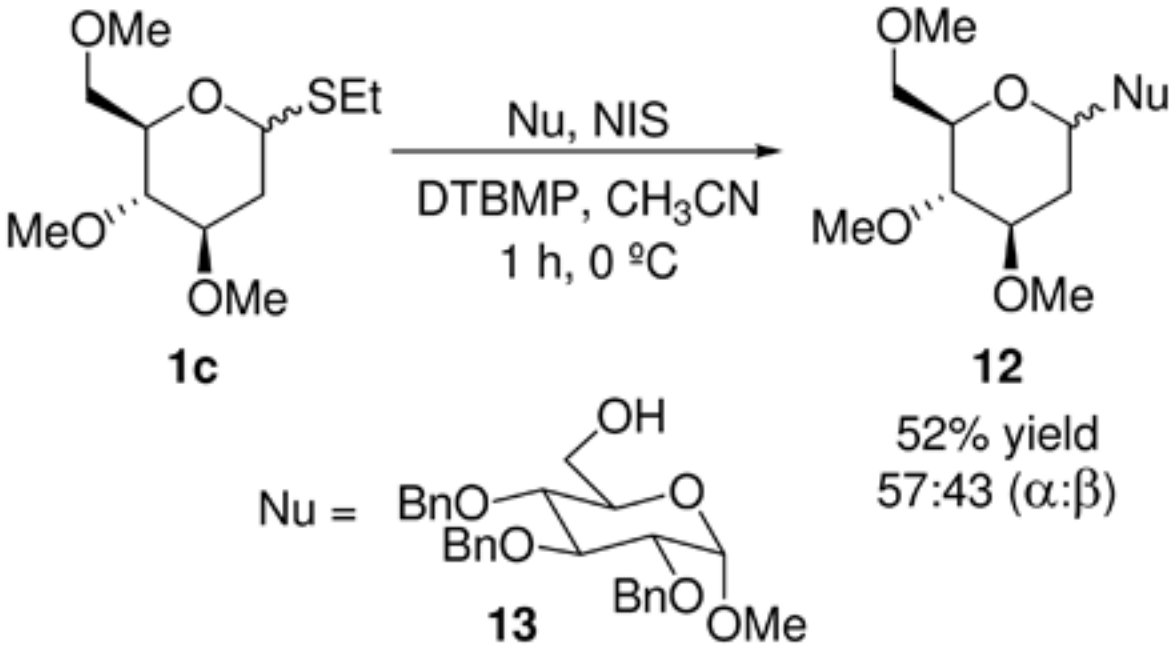
observed for reactions of less reactive carbon nucleophiles (Scheme 1). Nucleophiles with fewer electron-withdrawing groups, which should be more nucleophilic,[14] exhibit lower selectivity. The strongest nucleophile employed, ethanol,[14] afforded the 2-deoxy-α-*O*-glycoside **11** in a 51:49 (α:β) mixture of diastereomers (Table 1, entry 6).[28] The same substitution reaction performed in CH_2Cl_2 resulted in a 52:48 (α:β) mixture of diastereomeric products, suggesting that both reactions proceed through a similar S_N1-like mechanism (*vide infra*). These results clearly indicate that the nucleophilicity of alcohols impacts the stereoselectivity of glycosylation reactions.[29]



(1)

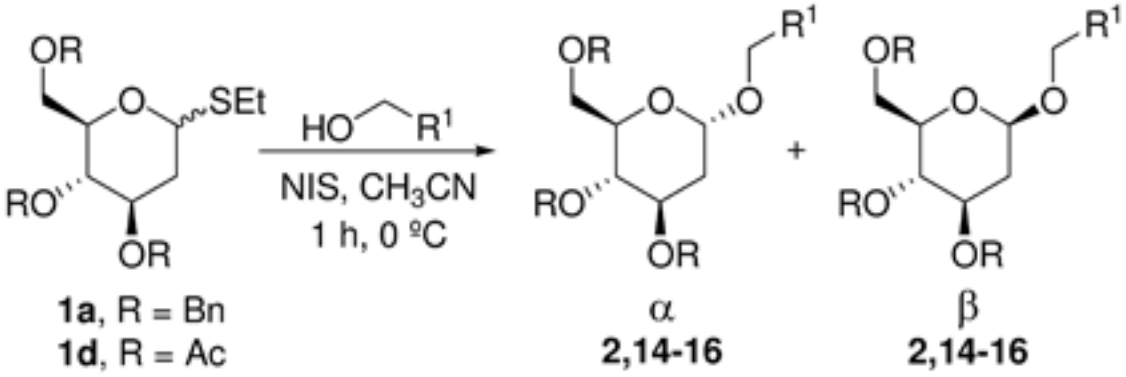
Several factors were considered to explain the trend of decreasing selectivity with increasing reactivity. The mechanism for activation of thioglycoside **1c** involves two types of intermediates. Activation of the sulfur atom occurs to form sulfonium ion **A**, followed by rate-determining ionization of **A** to form oxocarbenium ion **B** (Scheme 3).[19] The low diastereoselectivities observed with strong nucleophiles could result from competitive S_N2-like pathways[9,10,30] involving displacement of the activated starting material **A** (Scheme 3)[31] or analogous compounds, such as the glycosyl iodide.[30c,32] This explanation, however, does not explain the stereochemical data (eq 1′, Table 1), because the β-substitution products expected from direct displacement reactions of thioglycoside **1c**[30] are not the major products in any case observed. Direct displacement of an adduct with CH_3CN (a nitrilium ion), which has been invoked in other glycosylation reactions,[33] also does not satisfactorily explain the observed diastereoselectivities. First, the expected β-glycoside products arising from direct displacement of an α-nitrilium species33 are not favored for any of the substrates examined. Second, invoking an intermediate nitrilium species does not account for the similar selectivity trends observed in CH_2Cl_2 as in CH_3CN. The loss of selectivity with increasing reactivity, however, is consistent with erosion of diastereoselectivity by an S_N1-like pathway involving oxocarbenium ion **B** (Scheme 3), which has been observed for *C*-nucleophiles.[9]

The stronger nucleophiles employed in the substitution reactions of 2-deoxyglycosyl donor **1c** follow the level of stereocontrol observed in a common glycosylation reaction. Substitution using the glucose-derived nucleophile **13**[34] afforded a 57:43 (α:β) mixture of products (**12′**, eq 2), comparable to the diastereoselectivities observed for reactions of alcohols containing a single electron-withdrawing substituent (Table 1, entries 3–5).[23]



(2)

Varying the protecting groups on the 2-deoxyglycosyl donor had a minimal effect on the stereoselectivity of nucleophilic substitution. In all cases, reactions of trifluoroethanol provided the highest level of stereocontrol favoring the stereoelectronically preferred α-product, while use of ethanol as the nucleophile resulted in a near statistical mixture of diastereomers (eq 3, Table 2). The relationship between nucleophilicity and stereoselectivity appears to be a general characteristic of *O*-glycosylation reactions under S_N1-like conditions.[19]



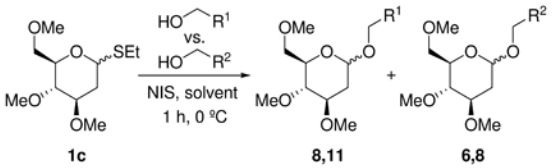
(3)

Competition experiments between select alcohol nucleophiles confirmed the relative reactivities of the ethanol derivatives. Nucleophilic substitution reactions of 2-deoxyglycosyl donor **1c** were performed in the presence of an equimolar mixture of two nucleophiles of differing reactivity (eq 4, Table 3).[35] As expected, increasing the number of electron-withdrawing substituents on the alcohol resulted in a decrease of nucleophilicity. For example,

a competition experiment performed in CH_3CN between ethanol and trifluoroethanol resulted in near complete incorporation of ethanol, reflecting the relative nucleophilicities of the two nucleophiles (Table 3, entry 1).[36,37] Similarly, a competition experiment between fluoroethanol and trifluoroethanol provided incorporation of the more nucleophilic alcohol with nearly complete chemoselectivity (Table 3, entry 3). These results confirm that the stereochemistry-determining step of the substitution reaction of trifluoroethanol with 2-deoxyglycosyl donor **1c** occurs at a rate below the diffusion limit. Lastly, ethanol and fluoroethanol were subjected to a competition experiment in CH_3CN. This experiment afforded the ethanol adduct **11** as the major product, but with diminished chemoselectivity (Table 3, entry 4). This result is consistent with the hypothesis that both nucleophiles react at rates near the diffusion limit, in accord with the stereochemical data (eq 1, Table 1).

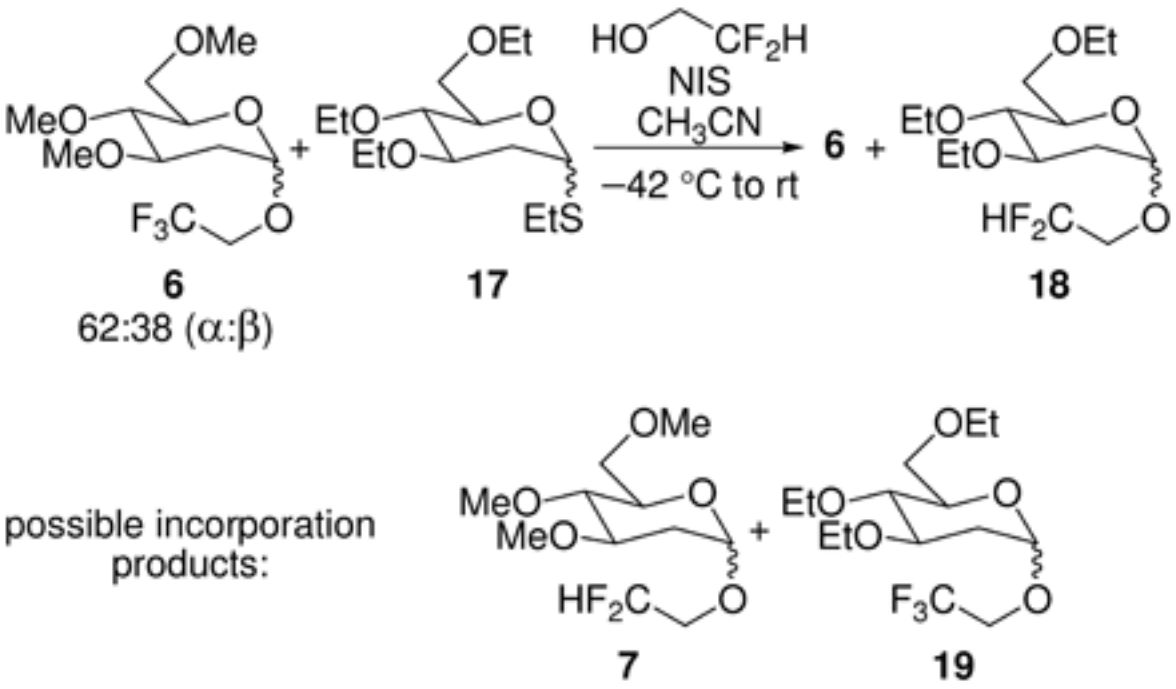
Comparison of the relative rates of reaction (k_{EtOH}/k_{TFE}) to the rates of nucleophilic addition to analogous oxocarbenium ion intermediates supports the transition to diffusion-limited diastereoselectivity with more nucleophilic alcohols. Additions of water to a propionaldehyde-derived oxocarbenium ion occur at rates of approximately 4×10^8 $M^{-1}s^{-1}$, a rate at which diffusional processes begin to be important.[16a,38] The 50-fold decrease in reactivity of trifluoroethanol (Table 3, entry 1) would suggest that the rate of addition to the oxocarbenium ion intermediate is approximately 8×10^6 $M^{-1}s^{-1}$, which is about one thousand-fold slower than the diffusion rate limit.

The competition experiment between ethanol and trifluoroethanol in CH_2Cl_2 resulted in lower chemoselectivity than the identical reaction performed in CH_3CN (Table 3, entry 2). This result can be explained by considering that the rate of addition of trifluoroethanol to oxocarbenium ion **5** (Scheme 2) approaches the diffusion rate limit in CH_2Cl_2.[13] The dependence of chemoselectivity on solvent choice is consistent with the stereochemical data, in which stereoselectivity was greater in CH_3CN than in CH_2Cl_2. Increasing the polarity of the solvent results in the stabilization of the cationic intermediate, and subsequently reduces the rate of nucleophilic addition.[26] As the rate of nucleophilic addition is decreased from the diffusion limit regime, greater facial selectivity for the stereoelectronically preferred product would be observed.



(4)

Control experiments confirmed that the products derived from nucleophilic substitution of 2-deoxythioglycoside **1c** were formed under kinetic control.[39,40] The presence or absence of epimerization could be tested by re-subjecting the products of nucleophilic substitution to the reaction conditions (eq 5, Table 4). For example, acetal **6** and tri-*O*-ethylthioglycoside **17** were subjected to difluoroethanol and *N*-iodosuccinimide in CH_3CN at −42 °C. Of the four possible products, only acetal **6** (which did not undergo epimerization) and nucleophilic substitution product **18** were observed (Table 4, entry 1). Increasing the temperature to 0 °C resulted in neither epimerization nor incorporation of difluoroethanol into acetal **6**. At 25 °C, however, small amounts of epimerization of the trifluoroethanol addition product **6** was observed.[41] Therefore, it was deemed critical to perform all nucleophilic substitution reactions at or below 0 °C. Following this model, control experiments were performed for each pyran system investigated; those results are provided as supporting information.



(5)

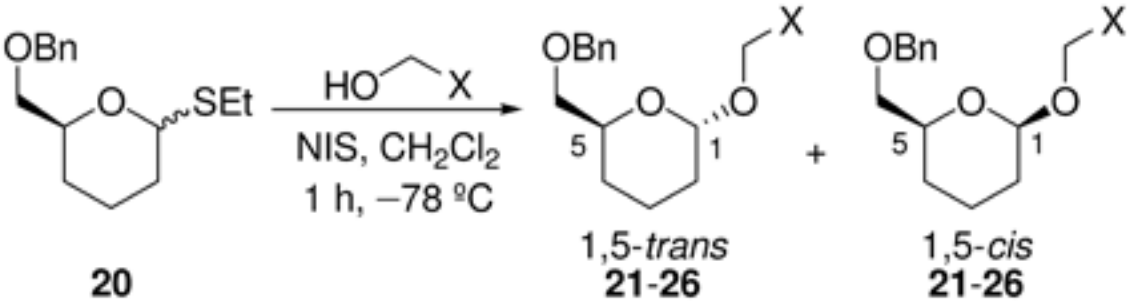
Nucleophilic Substitution Reactions of Monosubstituted Tetrahydropyran Acetals

The inverse relationship between nucleophilicity and selectivity was also observed for the nucleophilic substitution reactions of monosubstituted tetrahydropyran acetals.[17] In all cases examined, reactions of trifluoroethanol provided the highest level of stereocontrol, favoring the stereoelectronically preferred product, while use of ethanol as the nucleophile resulted in a 1:1 mixture of diastereomers. The major products of addition to each model system matched those products previously obtained with allyltrimethylsilane,[42] which has a nucleophilicity parameter comparable to trifluoroethanol.[14,15]

A graphical summary of the nucleophilic substitution data for the monosubstituted tetrahydropyran acetals is presented in Figure 1. Data for the nucleophilic substitution of 2-deoxythioglycosides (eq 1, Table 1) are included for comparison purposes. Clearly, the nucleophilicity-selectivity relationship is not restricted to highly oxygenated carbohydrate systems, but must be considered for any substitution reactions of acetals that proceed through oxocarbenium ion intermediates. Specific details concerning the origin of stereoselectivity (or lack thereof) of these nucleophilic substitutions provide additional insight into the trends depicted in Figure 1.[43]

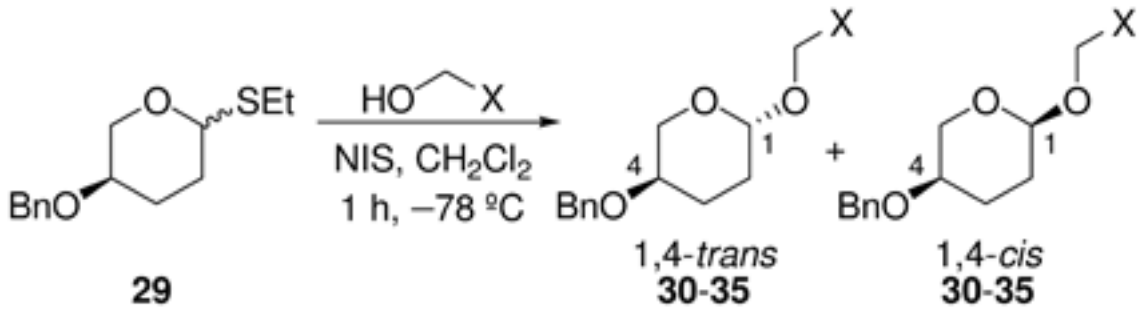
The stereochemical trend observed upon nucleophilic substitution of the C5-benzyloxymethyl-substituted acetal **20** with various nucleophiles was consistent with reaction rates that approach the diffusion limit (eq 6, Table 5). Activation of acetal **20** occurred readily at −78 °C in CH_2Cl_2, and control experiments indicated that these conditions provided kinetic product ratios.[39,44] Formation of the favored 1,5-trans product (**21–26**) is consistent with stereoelectronically controlled addition to the lowest energy oxocarbenium ion conformer **27** (Scheme 4, path **a**).[4b] At reaction rates below the diffusion limit, the minor 1,5-cis product arises from stereoelectronically controlled addition to the higher energy half-chair conformer **28** in which the C-5 substituent resides in a pseudo-axial orientation (Scheme 4, path **c**).[4b] The

erosion of stereoselectivity observed upon substitution with more reactive alcohols can be explained by considering the diffusion-controlled addition to oxocarbenium ions **27** and **28** through paths **b** and **d**.



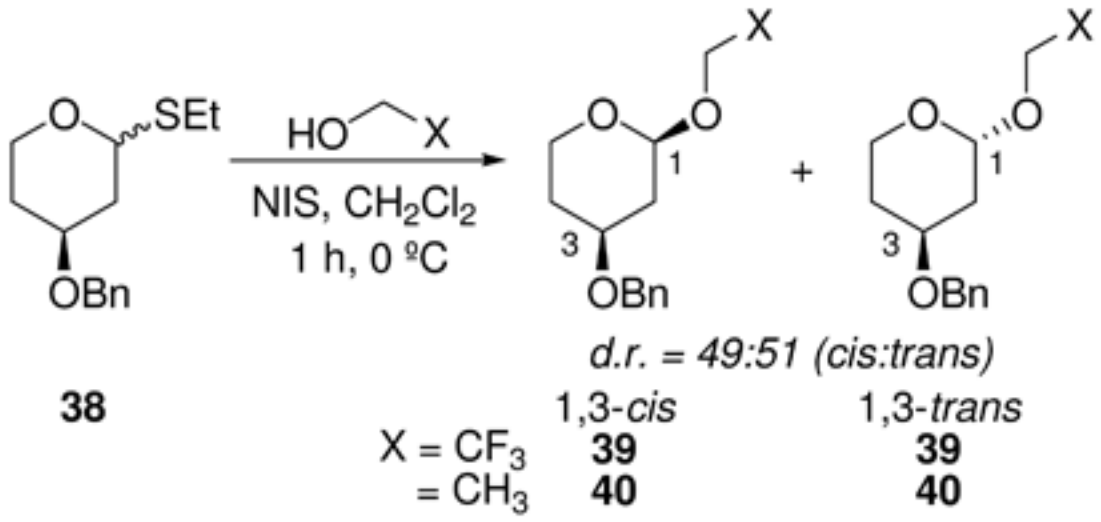
(6)

Nucleophilic substitution reactions of the C4-benzyloxy-substituted acetal **29** proceeded under identical conditions to provide the expected stereochemical trend (eq 7, Table 6). As with the C5-benzyloxymethyl-substituted acetal model system (**20**), CH_2Cl_2 was employed as the solvent because it reliably provided kinetically derived diastereomeric ratios.[39,44] The low-energy oxocarbenium ion **36**, in which the C4-benzyloxy substituent resides in the pseudo-axial position to maximize electrostatic stabilization of the cationic center,[42] is shown in Scheme 4. Upon addition of trifluoroethanol, the major product 1,4-*trans*-**30** arises from addition to the stereoelectronically favored face (Scheme 5, path **a**). The minor product 1,4-*cis*-**30** arises from addition to the higher energy oxocarbenium ion **37** (path **c**) at rates below the diffusion limit. As nucleophilicity increases, reaction rates for addition to oxocarbenium ion **36** approach the diffusion rate limit. In this scenario, path **b** becomes a viable pathway for the formation of the 1,4-cis product. Therefore, the substitution reaction of ethanol results in a statistical mixture of products (**35**, Table 6, entry 6) arising from competing pathways **a–d** (Scheme 5).



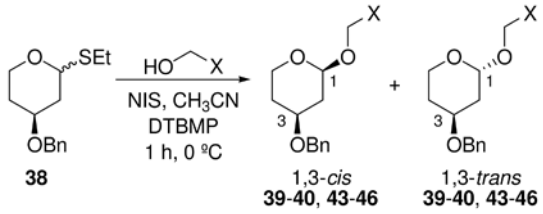
(7)

In stark contrast, the C3-benzyloxy-substituted acetal **38** displayed no stereoselectivity in CH_2Cl_2 for any of the nucleophiles examined (eq 8). Substitution reactions employing both ethanol and trifluoroethanol as the nucleophile resulted in a 49:51 (*cis:trans*) ratio of diastereomers under conditions optimized for the C4- and C5-substituted acetals (**20** and **29**).[45,46]



(8)

Performing the nucleophilic substitution reactions of C3-benzyloxy-substituted acetal **38** in CH_3CN, however, resulted in the stereochemical trend observed for other substrates (eq 9, Table 7).[47] The more polar solvent is expected to stabilize the oxocarbenium ions **41** and **42** (Scheme 6), thus decreasing their electrophilicities and lowering rates of nucleophilic addition from the diffusion-limit regime.[26] Of note, the nucleophilic substitution reaction of bromoethanol resulted in a data point that did not fit the expected trend (Table 7, entry 4). Because the destabilizing steric interactions encountered in the favored transition state are sensitive to nucleophile size,[42] the unexpected erosion of selectivity may be the result of the size of the bromine atom as compared to the other halogen substituents.[48]



(9)

Conclusion

The stereoselectivity of *O*-glycosylation reactions are significantly affected by the nucleophilicity of the glycosyl acceptor. Common oxygen nucleophiles, such as ethanol, result in diastereomeric mixtures of products, regardless of the glycosyl donor. Only upon the addition of weaker nucleophiles, such as trifluoroethanol, is stereoselectivity observed favoring the product of stereoelectronically controlled addition (Figure 1). In many cases, the complete lack of stereocontrol observed for nucleophilic substitution may be attributed to reaction rates of the stereochemistry-determining step at or near the diffusion limit.

Experimental Section

General Procedure for the Nucleophilic Substitution of Acetals 1c, 20, 29, 38

To a cooled (−78 °C or 0 °C) solution of the sulfide in CH_3CN or CH_2Cl_2 (0.10 M) was added a nucleophile (4.0 equiv) and then *N*-iodosuccinimide (2.0 equiv). 2,6-Di-*tert*-butyl-4-methylpyridine (2.0 equiv) was added, where indicated. After 1 h, the cooled solution was washed with 10% aqueous $Na_2S_2O_3$ (1 mL per mL of reaction volume), and the aqueous layer was extracted with two portions of Et_2O (2 mL per mL of reaction volume). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The unpurified product was analyzed by GC and ^{1}H NMR spectroscopy and then purified as indicated.

2-Deoxyglycoside trifluoroethanol substitution product α-6/β-6

The standard procedure for nucleophilic substitution of acetals was followed with thioglycoside **1c** (0.050 g, 0.20 mmol), trifluoroethanol (0.058 mL, 0.80 mmol), and *N*-iodosuccinimide (0.090 g, 0.40 mmol) in CH_3CN at 0 °C. GC and ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 83:17 (α:β) ratio. Purification by flash chromatography (3:1 pentane:Et_2O) afforded an inseparable mixture of diastereomers α-**6**/β-**6** as a colorless oil (0.047 g, 81%): GC t_R(major) 8.4 min, t_R(minor) 8.7 min; $[\alpha]^{22}_D$ + 80.2 (*c* 1.12, $CHCl_3$); IR (thin film) 2934, 2830, 1468, 1267, 1067 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{19}F_3O_5Na$ $(M + Na)^+$ 311.1082, found 311.1086. Anal. Calcd for $C_{11}H_{19}F_3O_5$: C, 45.83; H, 6.64. Found: C, 45.61; H, 6.66.

Major Isomer (α-6)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.01 (d, *J* = 3.4 Hz, 1H), 3.88 (m, 2H), 3.56–3.64 (m, 4H), 3.55 (s, 3H), 3.45 (s, 3H), 3.42 (s, 3H), 3.18 (t, *J* = 9.2 Hz, 1H), 2.31 (ddd, *J* = 13.3, 5.1, 1.2 Hz, 1H), 1.60 (ddd, *J* = 13.2, 11.4, 3.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 123.9 (q, *J* = 278.4 Hz), 98.1, 79.6, 78.1, 71.3, 71.1, 64.1 (q, *J* = 26.0 Hz), 60.57, 59.3, 57.5, 34.4.

Minor Isomer (β-6)

^{1}H NMR (500 MHz, $CDCl_3$, distinctive peaks) δ 4.55 (dd, *J* = 9.8, 1.8 Hz, 1H), 4.13 (dq, *J* = 12.6, 8.9 Hz, 2H), 3.54 (s, 3H), 3.43 (s, 3H), 3.30 (m, 2H), 3.13 (t, *J* = 9.2 Hz, 1H), 2.38 (dd, *J* = 12.7, 5.1, 2.1 Hz, 1H), 1.53 (td, *J* = 11.9, 9.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 123.8 (q, *J* = 278.4 Hz), 99.9, 80.6, 79.2, 75.2, 71.5, 65.5 (q, *J* = 34.7 Hz), 60.61, 59.4, 57.0, 35.5.

2-Deoxyglycoside difluoroethanol substitution product α-7/β-7

The standard procedure for nucleophilic substitution of acetals was followed with thioglycoside **1c** (0.050 g, 0.20 mmol), difluoroethanol (0.050 mL, 0.80 mmol), and *N*-iodosuccinimide (0.090 g, 0.40 mmol) in CH_3CN at 0 °C. GC and ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 66:34 (α:β) ratio. Purification by flash chromatography (3:1 pentane:Et_2O) afforded an inseparable mixture of diastereomers α-**7**/β-**7** as a colorless oil (0.042 g, 78%): GC t_R(major) 9.7 min, t_R(minor) 9.9 min; $[\alpha]^{22}_D$ +58 (*c* 0.80, $CHCl_3$); IR (thin film) 2935, 2832, 1449, 1111 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{20}F_2O_5Na$ $(M + Na)^+$ 293.1176, found 293.1169.

Major Isomer (α-7)

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 (tt, *J* = 55.5, 4.1 Hz, 1H), 4.96 (d, *J* = 3.4 Hz, 1H), 3.76 (dtd, *J* = 15.0, 11.9, 3.7 Hz, 1H), 3.55–3.67 (m, 4H), 3.54 (s, 3H), 3.44 (s, 3H), 3.42 (s, 3H), 3.29 (m, 1H), 3.14 (m, 1H), 2.27 (ddd, *J* = 13.3, 5.1, 1.0 Hz, 1H), 1.58 (ddd, *J* = 13.3, 11.7, 3.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 114.2 (t, *J* = 241.1 Hz), 98.3, 79.7, 78.2, 71.2, 71.0, 66.5 (t, *J* = 28.0 Hz), 60.55, 59.3, 57.4, 34.6.

Minor Isomer (β-7)

^{1}H NMR (500 MHz, $CDCl_3$, distinctive peaks) δ 5.90 (m, 1H), 4.49 (dd, *J* = 9.7, 1.7 Hz, 1H), 3.99 (m, 1H), 3.53 (s, 3H), 3.43 (s, 3H), 3.41 (s, 3H), 2.35 (ddd, *J* = 12.7, 5.0, 1.8 Hz, 1H), 1.51 (td, *J* = 11.9, 9.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 114.4 (t, *J* = 240.7 Hz), 100.2, 80.8, 79.4, 75.1, 71.6, 68.1 (dd, *J* = 30.5, 26.4 Hz), 60.60, 59.4, 57.0, 35.7.

2-Deoxyglycoside fluoroethanol substitution product α-8/β-8

The standard procedure for nucleophilic substitution of acetals was followed with thioglycoside **1c** (0.030 g, 0.12 mmol), fluoroethanol (0.028 mL, 0.48 mmol), and *N*-iodosuccinimide (0.054 g, 0.24 mmol) in CH_3CN at 0 °C. GC and ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 56:44 (α:β) ratio. Purification by flash chromatography (3:1 pentane:Et_2O) afforded an inseparable mixture of diastereomers α-**8**/β-**8** as a colorless oil (0.021 g, 69%): GC t_R(major) 10.4 min, t_R(minor) 10.6 min; $[\alpha]^{22}_D$ +41 (*c* 0.39, $CHCl_3$); IR (thin film) 2934, 2830, 1450, 1110 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{21}FO_5Na$ $(M + Na)^+$ 275.1271, found 275.1266. Anal. Calcd for $C_{11}H_{21}FO_5$: C, 52.37; H, 8.39. Found: C, 52.38; H, 8.35.

Major Isomer (α-8)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.97 (d, *J* = 3.4 Hz, 1H), 4.49–4.61 (m, 2H), 3.81 (m, 2H), 3.56–3.66 (m, 4H), 3.55 (s, 3H), 3.45 (s, 3H), 3.41 (s, 3H), 3.17 (t, *J* = 9.2 Hz, 1H), 2.28 (dd, *J* = 12.8, 5.2 Hz, 1H), 1.58 (ddd, *J* = 13.1, 11.6, 3.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 97.7, 82.7 (d, *J* = 165.3 Hz), 79.9, 78.4, 71.4, 70.6, 66.3 (d, *J* = 19.9 Hz), 60.5, 59.2, 57.4, 34.8.

Minor Isomer (β-8)

^{1}H NMR (500 MHz, $CDCl_3$, distinctive peaks) δ 4.52–4.70 (m, 3H), 4.26 (m, 1H), 4.06 (dddd, *J* = 35.0, 12.1, 4.3, 2.6 Hz, 1H), 3.69 (m, 1H), 3.54 (s, 3H), 3.43 (s, 3H), 3.41 (s, 3H), 3.30 (m, 2H), 3.10 (t, *J* = 9.2 Hz, 1H), 2.81 (dtt, *J* = 21.0, 13.6, 7.5 Hz, 1H), 2.38 (ddd, *J* = 12.6, 5.1, 1.8 Hz, 1H), 1.52 (td, *J* = 12.0, 9.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 100.0, 82.9 (d, *J* = 165.8 Hz), 80.9, 79.6, 75.1, 71.7, 68.1 (d, *J* = 19.9 Hz), 60.6, 59.4, 56.9, 35.9.

2-Deoxyglycoside bromoethanol substitution product α-9/β-9

The standard procedure for nucleophilic substitution of acetals was followed with thioglycoside **1c** (0.030 g, 0.12 mmol), bromoethanol (0.034 mL, 0.48 mmol), and *N*-iodosuccinimide (0.054 g, 0.24 mmol) in CH_3CN at 0 °C. GC and ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 55:45 (α:β) ratio. Purification by flash chromatography (1:1 pentane:Et_2O) afforded an inseparable mixture of diastereomers α-**9**/β-**9** as a colorless oil (0.028 g, 74%): GC t_R(major) 13.2 min, t_R(minor) 13.4 min; $[\alpha]^{22}_D$ +21.8 (*c* 0.805, $CHCl_3$); IR (thin film) 2932, 2830, 1459, 1113 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{21}BrO_5Na$ $(M + Na)^+$ 335.0470, found 335.0464. Anal. Calcd for $C_{11}H_{21}BrO_5$: C, 42.19; H, 6.76. Found: C, 41.94; H, 6.60.

Major Isomer (α-9)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.98 (d, *J* = 3.4 Hz, 1H), 3.92 (dt, *J* = 11.6, 6.1 Hz, 1H), 3.76 (m, 2H), 3.55–3.70 (m, 3H), 3.55 (s, 3H), 3.48 (m, 2H), 3.45 (s, 3H), 3.42 (s, 3H), 3.17 (t, *J* = 9.4 Hz, 1H), 2.26 (ddd, *J* = 13.1, 5.1, 1.0 Hz, 1H), 1.57 (ddd, *J* = 13.1, 11.5, 3.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 97.8, 79.9, 78.4, 75.1, 70.9, 67.4, 60.5, 59.3, 57.4, 34.8, 30.6.

Minor Isomer (β-9)

^{1}H NMR (500 MHz, $CDCl_3$, distinctive peaks) δ 4.49 (dd, *J* = 9.7, 2.1 Hz, 1H), 4.33 (m, 1H), 4.17 (ddd, *J* = 11.6, 6.6, 5.3 Hz, 1H), 3.54 (s, 3H), 3.43 (s, 3H), 3.41 (s, 3H), 3.30 (m, 2H),

3.11 (t, *J* = 9.2 Hz, 1H), 2.82 (m, 1H), 2.35 (ddd, *J* = 12.6, 5.1, 2.0 Hz, 1H), 1.51 (td, *J* = 12.3, 9.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 100.1, 80.9, 79.5, 71.6, 71.3, 69.2, 60.6, 59.4, 57.0, 35.8, 30.4.

2-Deoxyglycoside chloroethanol substitution product α-10β-10

The standard procedure for nucleophilic substitution of acetals was followed with thioglycoside **1c** (0.030 g, 0.12 mmol), chloroethanol (0.032 mL, 0.48 mmol), and *N*-iodosuccinimide (0.054 g, 0.24 mmol) in CH_3CN at 0 °C. GC and ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 56:44 (α:β) ratio. Purification by flash chromatography (1:1 pentane:Et_2O) afforded an inseparable mixture of diastereomers α-**10**/β-**10** as a colorless oil (0.023 g, 72%): GC t_R(major) 12.3 min, t_R(minor) 12.4 min; $[\alpha]^{22}_D$ +26.5 (*c* 0.900, $CHCl_3$); IR (thin film) 2933, 2831, 1448, 1112 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{21}ClO_5Na$ $(M + Na)^+$ 291.0975, found 291.0975. Anal. Calcd for $C_{11}H_{21}ClO_5$: C, 49.16; H, 7.88. Found: C, 49.12; H, 7.77.

Major Isomer (α-10)

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.97 (d, *J* = 3.4 Hz, 1H), 3.86 (m, 1H), 3.55–3.75 (m, 7H), 3.54 (s, 3H), 3.45 (s, 3H), 3.42 (s, 3H), 3.17 (t, *J* = 9.4 Hz, 1H), 2.26 (ddd, *J* = 13.1, 5.1, 1.1 Hz, 1H), 1.57 (ddd, *J* = 13.1, 11.5, 3.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 97.8, 79.9, 78.4, 71.4, 70.8, 67.5, 60.5, 59.3, 57.4, 43.0, 34.8.

Minor Isomer (β-10)

^{1}H NMR (500 MHz, $CDCl_3$, distinctive peaks) δ 4.49 (dd, *J* = 9.8, 1.8 Hz, 1H), 4.28 (m, 1H), 4.11 (dt, *J* = 10.8, 5.3 Hz, 1H), 3.54 (s, 3H), 3.43 (s, 3H), 3.41 (s, 3H), 3.30 (m, 2H), 3.10 (t, *J* = 9.0 Hz, 1H), 2.82 (m, 1H), 2.35 (ddd, *J* = 12.6, 5.1, 1.8 Hz, 1H), 1.51 (td, *J* = 12.5, 9.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 100.2, 80.9, 79.5, 75.1, 71.7, 69.3, 60.6, 59.4, 57.0, 42.8, 35.8.

2-Deoxyglycoside ethanol substitution product α-11/β-11

The standard procedure for nucleophilic substitution of acetals was followed with thioglycoside **1c** (0.030 g, 0.12 mmol), ethanol (0.028 mL, 0.48 mmol), and *N*-iodosuccinimide (0.054 g, 0.24 mmol) in CH_3CN at 0 °C. GC and ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 51:49 (α:β) ratio. Purification by flash chromatography (1:1 pentane:Et_2O) afforded an inseparable mixture of diastereomers α-**11**/β-**11** as a colorless oil (0.023 g, 82%): GC t_R(major) 9.4 min, t_R(minor) 9.7 min; $[\alpha]^{22}_D$ +1.0 (*c* 0.43, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$, mixture of anomers) δ 4.93 (d, *J* = 3.7 Hz, 1H), 4.44 (dd, *J* = 9.7, 1.8 Hz, 1H), 3.95 (dq, *J* = 9.3, 7.0 Hz, 1H), 3.55–3.70 (m, 9H), 3.55 (s, 3H), 3.54 (s, 3H), 3.45 (s, 3H), 3.42 (s, 3H), 3.41 (s, 6H), 3.30 (m, 2H), 3.16 (t, *J* = 9.2 Hz, 1H), 3.08 (t, *J* = 9.2 Hz, 1H), 2.30 (ddd, *J* = 12.5, 5.0, 1.8 Hz, 1H), 2.21 (dd, *J* = 12.8, 5.2 Hz, 1H), 1.52 (m, 2H), 1.21 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of anomers) δ 99.6, 97.1, 81.1, 80.1, 79.7, 78.7, 75.1, 71.8, 71.5, 70.4, 64.7, 62.6, 60.6, 60.5, 59.4, 59.2, 57.3, 56.9, 36.1, 35.0, 15.13, 15.07; IR (thin film) 2932, 2830, 1446, 1113 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{22}O_5Na$ $(M + Na)^+$ 257.1365, found 257.1361. Anal. Calcd for $C_{11}H_{22}O_5$: C, 56.39; H, 9.46. Found: C, 56.47; H, 9.56.

2-Deoxyglycoside 2,3,4-tri-*O*-benzyl-αα α-D-glucopyranoside substitution product α-12/β-12

The standard procedure for nucleophilic substitution of acetals was followed with thioglycoside **1c** (0.010 g, 0.040 mmol), 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside **13**[34] (0.020 g, 0.044 mmol), *N*-iodosuccinimide (0.018 g, 0.080 mmol), and 2,6-di-*tert*-butyl-4-methylpyridine (0.017 g, 0.080 mmol) in CH_3CN at 0 °C. ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 57:43 (α:β) ratio. Purification by flash

chromatography (1:1 hexanes:EtOAc) afforded an inseparable mixture of diastereomers α-**12**/β-**12** as a colorless oil (0.014 g, 52%): $[\alpha]^{22}_{D}$ +20 (*c* 0.47, $CHCl_3$); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of anomers) δ 138.8, 138.7, 138.5, 138.4, 138.21, 138.18, 128.54, 128.52, 128.51, 128.48, 128.47, 128.44, 128.2, 128.12, 128.07, 127.99, 127.98, 127.97, 127.8, 127.74, 127.70, 127.68, 127.66, 100.1, 98.03, 97.99, 97.9, 82.29, 82.26, 81.0, 80.1, 79.9, 79.8, 79.7, 78.6, 77.8, 77.4, 77.3, 75.9, 75.8, 75.2, 74.9, 74.8, 73.41, 73.37, 71.9, 71.2, 70.7, 69.8, 69.7, 67.6, 65.8, 60.6, 60.5, 59.4, 59.2, 57.3, 56.9, 55.2, 35.8, 34.8; IR (thin film) 3063, 3030, 2930, 2834, 1454, 1097 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{37}H_{48}O_{10}Na$ $(M + Na)^+$ 675.3145, found 675.3151. Anal. Calcd for $C_{37}H_{48}O_{10}$: C, 68.08; H, 7.41. Found: C, 68.09; H, 7.64.

Major Isomer (α-12)

^1H NMR (500 MHz, $CDCl_3$) δ 7.26–7.38 (m, 15H), 4.57–5.00 (m, 8H), 3.99 (m, 1H), 3.83 (dd, *J* = 11.4, 4.2 Hz, 1H), 3.74 (dd, *J* = 10.0, 3.1 Hz, 1H), 3.46–3.62 (m, 7H), 3.50 (s, 3H), 3.42 (s, 3H), 3.37 (s, 3H), 3.34 (s, 3H), 3.20 (m, 1H), 3.15 (t, *J* = 9.4 Hz, 1H), 2.24 (dd, *J* = 13.0, 5.0 Hz, 1H), 1.53 (ddd, *J* = 13.0, 11.6, 3.7 Hz, 1H).

Minor Isomer (β-12)

^1H NMR (500 MHz, $CDCl_3$) δ 7.26–7.38 (m, 15H), 4.57–5.00 (m, 8H), 4.18 (dd, *J* = 9.8, 1.2 Hz, 1H), 4.08 (dd, *J* = 11.0, 1.6 Hz, 1H), 3.99 (m, 1H), 3.46–3.62 (m, 7H), 3.51 (s, 3H), 3.40 (s, 3H), 3.37 (s, 3H), 3.35 (s, 3H), 3.20 (m, 1H), 2.99 (t, *J* = 9.1 Hz, 1H), 2.13 (dd, *J* = 12.5, 4.9 Hz, 1H), 1.47 (td, *J* = 12.2, 9.9 Hz, 1H)

C5-OBn Pyranoside trifluoroethanol substitution product *trans*-21/*cis*-21

The standard procedure for nucleophilic substitution of acetals was followed with thioglycoside **20** (0.050 g, 0.19 mmol), trifluoroethanol (0.050 mL, 0.75 mmol), and *N*-iodosuccinimide (0.084 g, 0.38 mmol) in CH_2Cl_2 at −78 °C. GC and ^1H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 83:17 (trans:cis) ratio. Purification by flash chromatography (3:1 hexane:EtOAc) afforded an inseparable mixture of diastereomers *trans*-**21**/*cis*-**21** as a colorless oil (0.037 g, 65%): GC t_R(major) 12.9 min, t_R(minor) 13.2 min; IR (thin film) 3034, 2940, 1445, 1282, 1156 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{19}F_3O_3Na$ $(M + Na)^+$ 327.1184, found 327.1174. Anal. Calcd for $C_{15}H_{19}F_3O_3$: C, 59.20; H, 6.29. Found: C, 59.50; H, 6.37.

Major Isomer (*trans*-21)

^1H NMR (500 MHz, $CDCl_3$) δ 7.25–7.37 (m, 5H), 4.96 (d, *J* = 2.6 Hz, 1H), 4.57 (m, 2H), 3.82–4.05 (m, 3H), 3.45 (m, 2H), 1.86 (m, 1H), 1.78 (m, 1H), 1.55–1.70 (m, 3H), 1.45 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.33, 128.4, 127.64, 127.59, 124.3 (q, *J* = 278.4 Hz), 97.8, 73.4, 73.2, 68.8, 63.7 (q, *J* = 25.8 Hz), 29.0, 27.19, 17.4.

Minor Isomer (*cis*-21)

^1H NMR (500 MHz, $CDCl_3$, distinctive peaks) δ 4.53 (dd, *J* = 8.8, 2.2 Hz, 1H), 4.14 (dq, *J* = 12.6, 9.2 Hz, 1H), 3.65 (dddd, *J* = 10.8, 6.2, 4.5, 2.0 Hz, 1H), 3.57 (dd, *J* = 10.1, 6.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, distinctive peaks) δ 138.30, 128.5, 127.72, 127.69, 124.0 (q, *J* = 277.9 Hz), 102.1, 75.7, 73.5, 73.1, 65.0 (q, *J* = 34.7 Hz), 30.6, 27.15, 21.3.

C5-OBn Pyranoside difluoroethanol substitution product *trans*-22/*cis*-22

The standard procedure for nucleophilic substitution of acetals was followed with thioglycoside **20** (0.050 g, 0.19 mmol), difluoroethanol (0.048 mL, 0.75 mmol), and *N*-iodosuccinimide (0.084 g, 0.38 mmol) in CH_2Cl_2 at −78 °C. GC and ^1H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in an 74:26 (trans:cis) ratio. Purification

by flash chromatography (5:1 hexane:EtOAc) afforded an inseparable mixture of diastereomers *trans*-**22**/*cis*-**22** as a colorless oil (0.045 g, 79%): GC t_R(major) 14.1 min, t_R(minor) 14.3 min; IR (thin film) 3031, 2943, 2867, 1455, 1075 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{20}F_2O_3Na$ $(M + Na)^+$ 309.1278, found 309.1281. Anal. Calcd for $C_{15}H_{20}F_2O_3$: C, 62.92; H, 7.04. Found: C, 63.20; H, 7.18.

Major Isomer (*trans*-22)

^1H NMR (500 MHz, $CDCl_3$) δ 7.25–7.38 (m, 5H), 5.97 (tt, *J* = 55.8, 8.4 Hz, 1H), 4.91 (d, *J* = 2.3 Hz, 1H), 4.57 (s, 2H), 3.95 (m, 1H), 3.84 (tdd, *J* = 15.8, 12.0, 3.9 Hz, 1H), 3.70 (m, 1H), 3.45 (m, 2H), 1.85 (m, 1H), 1.75 (m, 1H), 1.55–1.70 (m, 2H), 1.43 (m, 1H), 1.25 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.35, 128.4, 127.61, 127.58, 114.6 (t, *J* = 240.7 Hz), 98.3, 73.4, 68.5, 66.5 (t, *J* = 28.0 Hz), 29.3, 27.3, 17.5.

Minor Isomer (*cis*-22)

^1H NMR (500 MHz, $CDCl_3$, distinctive peaks) δ 5.95 (tdd, *J* = 56.0, 5.4, 3.1 Hz, 1H), 4.47 (dd, *J* = 9.4, 1.8 Hz, 1H), 3.56 (dd, *J* = 10.2, 6.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.29, 128.5, 127.72, 127.70, 114.7 (t, *J* = 240.9 Hz), 102.7, 75.6, 73.5, 73.2, 67.8 (dd, *J* = 29.6, 26.8 Hz), 30.7, 27.2, 21.5.

C5-OBn Pyranoside fluoroethanol substitution product *trans*-23/*cis*-23

The standard procedure for nucleophilic substitution of acetals was followed with thioglycoside **20** (0.050 g, 0.19 mmol), fluoroethanol (0.044 mL, 0.75 mmol), and *N*-iodosuccinimide (0.084 g, 0.38 mmol) in CH_2Cl_2 at −78 °C. GC and ^1H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 62:38 (trans:cis) ratio. Purification by flash chromatography (3:1 hexane:EtOAc) afforded an inseparable mixture of diastereomers *trans*-**23**/*cis*-**23** as a colorless oil (0.046 g, 91%): GC t_R(major) 14.7 min, t_R(minor) 14.9 min; IR (thin film) 3030, 2946, 2865, 1453, 1041 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{21}FO_3Na$ $(M + Na)^+$ 291.1372, found 291.1372. Anal. Calcd for $C_{15}H_{21}FO_3$: C, 67.14; H, 7.89. Found: C, 67.44; H, 7.95.

Major Isomer (*trans*-23)

^1H NMR (500 MHz, $CDCl_3$) δ 7.25–7.37 (m, 5H), 4.92 (d, *J* = 2.7 Hz, 1H), 4.50–4.68 (m, 4H), 3.98 (m, 1H), 3.92 (ddd, *J* = 32.3, 5.1, 2.7 Hz, 1H), 3.70 (m, 1H), 3.45 (m, 2H), 1.88 (m, 1H), 1.75 (m, 1H), 1.67 (m, 1H), 1.59 (m, 1H), 1.43 (m, 1H), 1.25 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 128.43, 127.70, 127.60, 97.6, 83.02 (d, *J* = 168.8 Hz), 73.53, 73.3, 68.2, 66.0 (d, *J* = 19.9 Hz), 29.5, 27.5, 17.7.

Minor Isomer (*cis*-23)

^1H NMR (500 MHz, $CDCl_3$, distinctive peaks) δ 4.49 (dd, *J* = 9.4, 1.8 Hz, 1H), 4.07 (ddd, *J* = 33.8, 4.4, 2.7 Hz, 1H), 3.80 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 128.33, 127.66, 127.57, 102.3, 83.04 (d, *J* = 168.8 Hz), 75.5, 73.50, 67.6 (d, *J* = 19.9), 31.0, 21.7.

C5-OBn Pyranoside bromoethanol substitution product *trans*-24/*cis*-24

The standard procedure for nucleophilic substitution of acetals was followed with thioglycoside **20** (0.050 g, 0.19 mmol), bromoethanol (0.053 mL, 0.75 mmol), and *N*-iodosuccinimide (0.084 g, 0.38 mmol) in CH_2Cl_2 at −78 °C. GC and ^1H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 62:38 (trans:cis) ratio. Purification by flash chromatography (3:1 hexane:EtOAc) afforded an inseparable mixture of diastereomers *trans*-**24**/*cis*-**24** as a colorless oil (0.053 g, 85%): GC t_R(major) 17.2 min, t_R(minor) 17.4 min; IR (thin film) 3029, 2942, 2861, 1454, 1124 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{21}BrO_3Na$

$(M + Na)^+$ 351.0572, found 351.0574. Anal. Calcd for $C_{15}H_{21}BrO_3$: C, 54.72; H, 6.43. Found: C, 54.95; H, 6.59.

Major Isomer (*trans*-24)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.35 (m, 5H), 4.93 (d, *J* = 2.3 Hz, 1H), 4.57 (m, 2H), 4.01 (dddd, *J* = 12.0, 6.1, 4.0, 2.6 Hz, 1H), 3.98 (m, 1H), 3.81 (m, 1H), 3.41–3.58 (m, 4H), 1.88 (m, 1H), 1.73 (m, 1H), 1.50–1.69 (m, 2H), 1.42 (m, 1H), 1.25 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.44, 128.4, 127.71, 127.59, 97.7, 73.5, 73.33, 68.5, 67.3, 31.2, 29.5, 27.5, 17.7.

Minor Isomer (*cis*-24)

^{1}H NMR (500 MHz, $CDCl_3$, distinctive peaks) δ 4.48 (dd, *J* = 9.5, 2.0 Hz, 1H), 4.14 (ddd, *J* = 11.3, 7.1, 5.4 Hz, 1H), 3.66 (dddd, *J* = 10.9, 6.4, 4.8, 2.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.37, 128.5, 127.67, 127.57, 102.6, 75.6, 73.28, 68.9, 30.9, 30.7, 27.4, 21.7.

C5-OBn pyranoside chloroethanol substitution product *trans*-25/*cis*-25

The standard procedure for nucleophilic substitution of acetals was followed with thioglycoside **20** (0.050 g, 0.19 mmol), chloroethanol (0.050 mL, 0.75 mmol), and *N*-iodosuccinimide (0.084 g, 0.38 mmol) in CH_2Cl_2 at −78 °C. GC and ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 65:35 (trans:cis) ratio. Purification by flash chromatography (3:1 hexane:EtOAc) afforded an inseparable mixture of diastereomers *trans*-**25**/*cis*-**25** as a colorless oil (0.046 g, 85%): GC t_R(major) 16.4 min, t_R(minor) 16.6 min; IR (thin film) 3030, 2944, 2864, 1353, 1035 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{15}H_{21}ClO_3Na$ $(M + Na)^+$ 307.1077, found 307.1074. Anal. Calcd for $C_{15}H_{21}ClO_3$: C, 63.26; H, 7.43. Found: C, 63.24; H, 7.53.

Major Isomer (*trans*-25)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.36 (m, 5H), 4.93 (d, *J* = 2.3 Hz, 1H), 4.57 (m, 2H), 4.01 (dddd, *J* = 12.0, 6.1, 4.5, 2.3 Hz, 1H), 3.94 (ddd, *J* = 10.9, 6.1, 5.3 Hz, 1H), 3.64–3.80 (m, 3H), 3.45 (m, 2H), 1.88 (m, 1H), 1.74 (m, 1H), 1.50–1.68 (m, 2H), 1.43 (m, 1H), 1.25 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.44, 128.4, 127.71, 127.59, 97.8, 73.5, 73.33, 68.4, 67.3, 43.4, 29.5, 27.5, 17.7.

Minor Isomer (*cis*-25)

^{1}H NMR (500 MHz, $CDCl_3$, distinctive peaks) δ 4.48 (dd, *J* = 9.4, 2.1 Hz, 1H), 4.10 (ddd, *J* = 11.0, 5.9, 5.3 Hz, 1H), 3.56 (dd, *J* = 10.0, 6.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.38, 128.5, 127.67, 127.57, 102.6, 75.6, 73.29, 68.9, 43.0, 30.9, 27.4, 21.7.

C5-OBn Pyranoside ethanol substitution product *trans*-26/*cis*-26

The standard procedure for nucleophilic substitution of acetals was followed with thioglycoside **20** (0.050 g, 0.19 mmol), ethanol (0.043 mL, 0.75 mmol), and *N*-iodosuccinimide (0.084 g, 0.38 mmol) in CH_2Cl_2 at −78 °C. GC and ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 49:51 (trans:cis) ratio. Purification by flash chromatography (3:1 hexane:EtOAc) afforded an inseparable mixture of diastereomers *trans*-**26**/*cis*-**26** as a colorless oil (0.038 g, 81%): GC t_R(major) 13.8 min, t_R(minor) 14.1 min; ^{1}H NMR (500 MHz, $CDCl_3$, mixture of anomers) δ 7.25–7.36 (10H), 4.88 (s, 1H), 4.57 (m, 4H), 4.43 (dd, *J* = 9.4, 2.1 Hz, 1H), 3.97 (m, 2H), 3.76 (ddd, *J* = 14.3, 9.8, 7.3 Hz, 1H), 3.66 (m, 1H), 3.41–3.60 (m, 6H), 1.86 (m, 2H), 1.78 (m, 1H), 1.48–1.69 (m, 7H), 1.41 (m, 2H), 1.23 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of anomers) δ 138.53, 138.49, 128.41, 128.37, 127.7, 127.6, 127.5, 102.0, 97.0, 75.5, 73.7, 73.51, 73.46, 73.3, 67.9, 64.2, 62.2, 31.3, 29.8, 27.7, 27.6, 21.9, 17.8, 15.3, 15.2; IR (thin film) 3029, 2933, 2870, 1450, 1111 cm^{-1};

HRMS (ESI) *m*/*z* calcd for $C_{15}H_{22}O_3Na$ $(M + Na)^+$ 273.1467, found 273.1465. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.22; H, 9.00.

C4-OBn Pyranoside trifluoroethanol substitution product *trans*-30/*cis*-30

The standard procedure for nucleophilic substitution of acetals was followed with thioglycoside **29** (0.050 g, 0.20 mmol), trifluoroethanol (0.057 mL, 0.80 mmol), and *N*-iodosuccinimide (0.089 g, 0.40 mmol) in CH_2Cl_2 at −78 °C. ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in an 88:12 (trans:cis) ratio. Purification by flash chromatography (3:1 hexane:EtOAc) afforded a inseparable mixture of diastereomers *trans*-**30**/*cis*-**30** as a colorless oil (0.046 g, 81%): GC t_R(major and minor) 12.6 min; IR (thin film) 3033, 2928, 1445, 1282, 1156 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{17}F_3O_3Na$ $(M + Na)^+$ 313.1028, found 313.1031. Anal. Calcd for $C_{14}H_{17}F_3O_3$: C, 57.93; H, 5.90. Found: C, 58.19; H, 6.02.

Major Isomer (*trans*-30)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.37 (m, 5H), 4.83 (t, *J* = 2.9 Hz, 1H), 4.57 (m, 2H), 4.00 (dq, *J* = 12.2, 8.9 Hz, 1H), 3.88 (dq, *J* = 12.2, 8.6 Hz, 1H), 3.84 (dd, *J* = 12.0, 2.2 Hz, 1H), 3.66 (dt, *J* = 12.4, 2.5 Hz, 1H), 3.49 (bs, 1H), 2.12 (tt, *J* = 12.6, 3.8 Hz, 1H), 2.00 (tt, *J* = 12.7, 3.7 Hz, 1H), 1.79 (m, 1H), 1.62 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 128.5, 127.7, 127.6, 125.1 (q, *J* = 278.3 Hz), 98.1, 70.8, 70.4, 64.3 (q, *J* = 25.9 Hz), 62.8, 25.0, 22.3.

Minor Isomer (*cis*-30)

^{1}H NMR (500 MHz, $CDCl_3$, distinctive peaks) δ 4.76 (s, 1H), 3.71 (dd, *J* = 10.5, 4.4 Hz, 1H), 3.58 (t, *J* = 10.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, distinctive peaks) δ 138.4, 96.9, 72.0, 70.6, 64.0 (q, *J* = 34.5 Hz), 63.1, 28.2, 24.6.

C4-OBn Pyranoside difluoroethanol substitution product *trans*-31/*cis*-31

The standard procedure for nucleophilic substitution of acetals was followed with thioglycoside **29** (0.050 g, 0.20 mmol), difluoroethanol (0.050 mL, 0.80 mmol), and *N*-iodosuccinimide (0.089 g, 0.40 mmol) in CH_2Cl_2 at −78 °C. ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 82:18 (trans:cis) ratio. Purification by flash chromatography (3:1 pentane:Et_2O) afforded an inseparable mixture of diastereomers *trans*-**31**/*cis*-**31** as a colorless oil (0.037 g, 68%): GC t_R(major and minor) 13.7 min; IR (thin film) 3029, 2935, 2867, 1062 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{18}F_2O_3Na$ $(M + Na)^+$ 295.1122, found 295.1126. Anal. Calcd for $C_{14}H_{18}F_2O_3$: C, 61.75; H, 6.66. Found: C, 62.04; H, 6.76.

Major Isomer (*trans*-31)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.37 (m, 5H), 5.91 (tt, *J* = 55.7, 4.1 Hz, 1H), 4.75 (t, *J* = 3.1 Hz, 1H), 4.57 (m, 2H), 3.86 (m, 2H), 3.70 (m, 1H), 3.62 (ddd, *J* = 12.0, 3.8, 1.6 Hz, 1H), 3.48 (bs, 1H), 2.09 (tt, *J* = 12.3, 3.6 Hz, 1H), 2.00 (tt, *J* = 12.2, 3.7 Hz, 1H), 1.75 (m, 1H), 1.58 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.50, 128.47, 127.7, 127.6, 114.5 (t, *J* = 240.7 Hz), 98.7, 71.0, 70.4, 66.8 (t, *J* = 28.0 Hz), 63.1, 25.6, 22.9.

Minor Isomer (*cis*-31)

^{1}H NMR (500 MHz, $CDCl_3$, distinctive peaks) δ 4.70 (t, *J* = 2.7 Hz, 1H), 1.91 (m, 2H), 1.83 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$, distinctive peaks) δ 138.46, 128.49, 127.8, 127.7, 97.3, 72.1, 70.6, 66.4 (t, *J* = 28.6), 28.3, 24.8.

C4-OBn Pyranoside fluoroethanol substitution product *trans*-32/*cis*-32

The standard procedure for nucleophilic substitution of acetals was followed with thioglycoside **29** (0.10 g, 0.40 mmol), fluoroethanol (0.044 mL, 0.16 mmol), and *N*-iodosuccinimide (0.18 g, 0.79 mmol) in CH_2Cl_2 at −78 °C. ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 71:29 (trans:cis) ratio. Purification by flash chromatography (5:1 hexane:EtOAc) afforded an inseparable mixture of diastereomers *trans*-**32**/*cis*-**32** as a colorless oil (0.072 g, 72%): GC t_R(major and minor) 14.4 min; IR (thin film) 3031, 2952, 2970, 1454, 1041 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{19}FO_3Na$ $(M + Na)^+$ 277.1216, found 277.1217. Anal. Calcd for $C_{14}H_{19}FO_3$: C, 66.12; H, 7.53. Found: C, 66.31; H, 7.59.

Major Isomer (*trans*-32)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25–7.37 (m, 5H), 4.75 (t, *J* = 3.1 Hz, 1H), 4.51–4.64 (m, 4H), 3.90 (dd, *J* = 11.7, 2.4 Hz, 1H), 3.62–3.77 (m, 2H), 3.59 (ddd, *J* = 12.0, 4.3, 1.5 Hz, 1H), 3.48 (bs, 1H), 2.06 (m, 1H), 1.91 (m, 1H), 1.73 (m, 1H), 1.58 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.59, 128.45, 127.6, 98.4, 83.0 (d, *J* = 169.2 Hz), 71.3, 70.4, 66.7 (d, *J* = 19.9 Hz), 63.2, 26.1, 23.4.

Minor Isomer (*cis*-32)

^{1}H NMR (500 MHz, $CDCl_3$, distinctive peaks) δ 4.71 (t, *J* = 3.2 Hz, 1H), 3.97 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.56, 128.47, 127.7, 96.9, 82.9 (d, *J* = 169.2 Hz), 72.3, 70.5, 66.2 (d, *J* = 19.9 Hz), 62.9, 28.5, 24.9.

C4-OBn Pyranoside bromoethanol substitution product *trans*-33/*cis*-33

The standard procedure for nucleophilic substitution of acetals was followed with thioglycoside **29** (0.10 g, 0.40 mmol), bromoethanol (0.11 mL, 1.6 mmol), and *N*-iodosuccinimide (0.18 g, 0.80 mmol) in CH_2Cl_2 at −78 °C. GC and ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in n 61:39 (trans:cis) ratio. Purification by flash chromatography (5:1 hexane:EtOAc) afforded an inseparable mixture of diastereomers *trans*-**33**/*cis*-**33** as a colorless oil (0.10 g, 83%): GC t_R(major) 17.1 min, t_R(minor) 17.2 min; IR (thin film) 3030, 2935, 2868, 1456, 1027 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{19}BrO_3Na$ $(M + Na)^+$ 337.0415, found 337.0415. Anal. Calcd for $C_{14}H_{19}BrO_3$: C, 53.35; H, 6.08. Found: C, 53.45; H, 6.11.

Major Isomer (*trans*-33)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (m, 5H), 4.75 (t, *J* = 3.1 Hz, 1H), 4.57 (m, 2H), 3.99 (m, 1H), 3.93 (dd, *J* = 12.0, 2.3 Hz, 1H), 3.79 (m, 1H), 3.60 (ddd, *J* = 11.9, 4.0, 1.7 Hz, 1H), 3.50 (m, 3H), 2.06 (m, 1H), 1.91 (m, 1H), 1.75 (m, 1H), 1.57 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 128.4, 127.653, 127.646, 98.4, 71.2, 70.4, 67.7, 63.4, 31.0, 26.0, 23.4.

Minor Isomer (*cis*-33)

^{1}H NMR (500 MHz, $CDCl_3$, distinctive peaks) δ 4.71 (t, *J* = 2.6 Hz, 1H), 4.57 (m, 2H), 3.74 (m, 1H), 3.66 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 128.5, 127.7, 97.0, 72.2, 70.6, 67.3, 63.2, 30.7, 28.5, 24.9.

C4-OBn Pyranoside chloroethanol substitution product *trans*-34/*cis*-34

The standard procedure for nucleophilic substitution of acetals was followed with thioglycoside **29** (0.10 g, 0.40 mmol), chloroethanol (0.11 mL, 1.6 mmol), and *N*-iodosuccinimide (0.18 g, 0.80 mmol) in CH_2Cl_2 at −78 °C. ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 67:33 (trans:cis) ratio. Purification by flash

chromatography (5:1 hexane:EtOAc) afforded an inseparable mixture of diastereomers *trans*-**34**/*cis*-**34** as a colorless oil (0.085 g, 79%): GC t_R(major) 16.2 min, t_R(minor) 16.3 min; IR (thin film) 3031, 2937, 2869, 1454, 1038 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{19}ClO_3Na$ $(M + Na)^+$ 293.0920, found 293.0925. Anal. Calcd for $C_{14}H_{19}ClO_3$: C, 62.10; H, 7.07. Found: C, 61.86; H, 7.08.

Major Isomer (*trans*-34)

^1H NMR (500 MHz, $CDCl_3$) δ 7.25–7.37 (m, 5H), 4.75 (t, *J* = 3.1 Hz, 1H), 4.57 (m, 2H), 3.95 (m, 1H), 3.92 (m, 1H), 3.73 (m, 1H), 3.67 (m, 2H), 3.59 (ddd, *J* = 11.9, 4.0, 1.6 Hz, 1H), 3.48 (bs, 1H), 2.06 (m, 1H), 1.91 (m, 1H), 1.75 (m, 1H), 1.57 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 128.45, 127.653, 127.646, 98.5, 71.2, 70.4, 67.9, 63.4, 43.2, 26.0, 23.4.

Minor Isomer (*cis*-34)

^1H NMR (500 MHz, $CDCl_3$, distinctive peaks) δ 4.71 (t, *J* = 2.6 Hz, 1H), 4.57 (m, 2H), 3.49 (m, 1H), 1.85 (m, 1H), 1.67 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$,) δ 138.5, 128.48, 127.7, 97.0, 72.2, 70.6, 67.4, 63.1, 43.0, 28.5, 24.9.

C4-OBn Pyranoside ethanol substitution product *trans*-35/*cis*-35

The standard procedure for nucleophilic substitution of acetals was followed with thioglycoside **29** (0.050 g, 0.20 mmol), ethanol (0.046 mL, 0.80 mmol), and *N*-iodosuccinimide (0.089 g, 0.40 mmol) in CH_2Cl_2 at −78 °C. GC and ^1H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 51:49 (trans:cis) ratio. Purification by flash chromatography (3:1 hexane:EtOAc) afforded an inseparable mixture of diastereomers *trans*-**35**/*cis*-**35** as a colorless oil (0.033 g, 70%): GC t_R(major) 13.5 min, t_R(minor) 13.6 min; ^1H NMR (500 MHz, $CDCl_3$, mixture of anomers) δ 7.25–7.37 (m, 10H), 4.66 (bs, 2H), 4.57 (m, 4H), 3.91 (dd, *J* = 11.7, 2.4 Hz, 1H), 3.71–3.83 (m, 2H), 3.65 (m, 2H), 3.40–3.56 (m, 5H), 2.04 (m, 2H), 1.80–1.94 (m, 3H), 1.67 (m, 2H), 1.58 (m, 1H), 1.22 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of anomers) δ 138.64, 138.63, 128.45, 128.44, 127.66, 127.65, 127.64, 127.63, 98.4, 96.4, 72.4, 71.6, 70.50, 70.47, 63.8, 63.3, 62.9, 62.6, 28.8, 26.9, 25.1, 24.2, 15.3, 15.2; IR (thin film) 3030, 2934, 2872, 1364, 1090 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{20}O_3Na$ $(M + Na)^+$ 259.1310, found 259.1311. Anal. Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.35; H, 8.47.

C3-OBn Pyranoside trifluoroethanol substitution product *cis*-39/*trans*-39

The standard procedure for nucleophilic substitution of acetals was followed with thioglycoside **38** (0.030 g, 0.12 mmol), trifluoroethanol (0.034 mL, 0.48 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (0.049 g, 0.24 mmol), and *N*-iodosuccinimide (0.054 g, 0.24 mmol) in CH_3CN at 0 °C. GC and ^1H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in an 86:14 (cis:trans) ratio. Purification by flash chromatography (3:1 pentane:Et_2O) afforded a separable mixture of diastereomers *cis*-**39**/*trans*-**39** as a colorless oil (0.024 g, 69%). IR, mass spectrometry, and combustion analysis data was obtained for major isomer (*cis*-**39**) and minor isomer (*trans*-**39**) as a mixture of diastereomers: GC t_R(major) 12.5 min, t_R(minor) 12.1 min; IR (thin film) 3029.8, 2954, 2861, 1280, 1162 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{17}F_3O_3Na$ $(M + Na)^+$ 313.1028, found 313.1027.

Major Isomer (*cis*-39)

^1H NMR (500 MHz, $CDCl_3$) δ 7.26–7.38 (m, 5H), 4.58 (m, 2H), 4.56 (dd, *J* = 7.5, 2.2 Hz, 1H), 4.10 (m, 2H), 3.92 (m, 1H), 3.64 (tt, *J* = 8.9, 4.2 Hz, 1H), 3.40 (ddd, *J* = 12.2, 9.9, 2.8 Hz, 1H), 2.23 (m, 1H), 1.94 (m, 1H), 1.61–1.73 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 128.5, 127.7, 127.6, 124.0 (q, *J* = 278.4 Hz), 99.9, 71.9, 69.9, 65.0 (q, *J* = 25.9 Hz), 60.8, 36.3, 31.3.

Minor Isomer (*trans*-39)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22–7.39 (m, 5H), 5.01 (t, *J* = 2.8 Hz, 1H), 4.55 (m, 2H), 3.80–4.00 (m, 3H), 3.76 (m, 2H), 2.19 (ddt, *J* = 13.1, 4.5, 2.3 Hz, 1H), 2.0 (d, *J* = 12.2 Hz, 1H), 1.69 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 128.5, 127.7, 127.6, 124.0 (q, *J* = 278.4 Hz), 98.8, 70.4, 70.1, 64.1 (q, *J* = 34.2 Hz), 59.4, 36.3, 31.9.

C3-OBn Pyranoside difluoroethanol substitution product *cis*-43/*trans*-43

The standard procedure for nucleophilic substitution of acetals was followed with thioglycoside **38** (0.030 g, 0.12 mmol), difluoroethanol (0.030 mL, 0.48 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (0.054 g, 0.24 mmol), and *N*-iodosuccinimide (0.049 g, 0.24 mmol) in CH_3CN at 0 °C. GC and ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 84:16 (cis:trans) ratio. Purification by flash chromatography (3:1 pentane:Et_2O) afforded a separable mixture of diastereomers *cis*-**43**/*trans*-**43** as a colorless oil (0.022 g, 68%). IR, mass spectrometry, and combustion analysis data was obtained for major isomer (*cis*-**43**) and minor isomer (*trans*-**43**) as a mixture of diastereomers: GC t_R(major) 13.7 min, t_R(minor) 13.3 min; IR (thin film) 3029, 2931, 2851, 1359, 1072 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{18}F_2O_3Na$ $(M + Na)^+$ 295.1122, found 295.1120.

Major Isomer (*cis*-43)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24–7.37 (m, 5H), 5.93 (tdd, *J* = 55.7, 5.4, 3.1 Hz, 1H), 4.58 (m, 2H), 4.47 (dd, *J* = 8.2, 2.6 Hz, 1H), 4.08 (dt, *J* = 12.4, 4.1 Hz, 1H), 3.95 (m, 1H), 3.75 (m, 1H), 3.61 (tt, *J* = 9.4, 4.3 Hz, 1H), 3.38 (ddd, *J* = 12.0, 10.9, 2.7 Hz, 1H), 2.24 (ddt, *J* = 12.7, 4.2, 2.1 Hz, 1H), 1.94 (m, 1H), 1.62 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.4, 128.5, 127.7, 127.6, 114.5 (t, *J* = 240.9 Hz), 100.5, 72.3, 69.8, 67.7 (t, *J* = 28.5 Hz), 61.1, 36.9, 31.4.

Minor Isomer (*trans*-43)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24–7.36 (m, 5H), 5.90 (tdd, *J* = 55.6, 4.6, 3.7 Hz, 1H), 4.96 (t, *J* = 3.2 Hz, 1H), 4.55 (m, 2H), 3.88 (tt, *J* = 9.2, 4.2 Hz, 1H), 3.82 (m, 1H), 3.76 (m, 2H), 3.66 (m, 1H), 2.14 (dddd, *J* = 13.0, 4.5, 2.8, 2.0 Hz, 1H), 1.98 (m, 1H), 1.71 (ddd, *J* = 13.3, 10.0, 3.4 Hz, 1H), 1.64 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.8, 128.7, 127.81, 127.76, 114.6 (t, *J* = 241.0 Hz), 99.2, 70.8, 70.2, 66.8 (t, *J* = 28.0 Hz), 59.5, 36.7, 32.0.

C3-OBn Pyranoside fluoroethanol substitution product *cis*-44/*trans*-44

The standard procedure for nucleophilic substitution of acetals was followed with thioglycoside **38** (0.030 g, 0.12 mmol), fluoroethanol (0.028 mL, 0.48 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (0.049 g, 0.24 mmol), and *N*-iodosuccinimide (0.054 g, 0.24 mmol) in CH_3CN at 0 °C. GC and ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 74:26 (cis:trans) ratio. Purification by flash chromatography (3:1 pentane:Et_2O) afforded a separable mixture of diastereomers *cis*-**44**/*trans*-**44** as a colorless oil (0.019 g, 63%). IR, mass spectrometry, and combustion analysis data was obtained for major isomer (*cis*-**44**) and minor isomer (*trans*-**44**) as a mixture of diastereomers: GC t_R(major) 14.3 min, t_R(minor) 14.0 min; IR (thin film) 3028, 2959, 2864, 1359, 1058 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{19}FO_3Na$ $(M + Na)^+$ 277.1216, found 277.1215.

Major Isomer (*cis*-44)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.38 (m, 5H), 4.50–4.69 (m, 4H), 4.45 (dd, *J* = 8.7, 2.4 Hz, 1H), 4.07 (m, 1H), 3.71–3.85 (m, 2H), 3.60 (tt, *J* = 9.9, 4.3 Hz, 1H), 3.37 (td, *J* = 11.7, 2.5 Hz, 1H), 2.29 (ddt, *J* = 12.4, 4.2, 2.1 Hz, 1H), 1.94 (m, 1H), 1.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 128.5, 127.7, 127.6, 100.4, 83.0 (d, *J* = 169.2 Hz), 72.8, 69.8, 67.7 (d, *J* = 19.4 Hz), 61.5, 37.4, 31.7.

Minor Isomer (*trans*-44)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21–7.40 (m, 5H), 4.96 (t, *J* = 3.1 Hz, 1H), 4.56 (dt, *J* = 47.6, 4.3 Hz, 2H), 4.55 (m, 2H), 3.92 (m, 2H), 3.85 (m, 1H), 3.72 (m, 2H), 2.16 (ddd, *J* = 13.1, 4.6, 2.2 Hz, 1H), 1.99 (m, 1H), 1.56–1.75 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 128.5, 127.7, 127.6, 98.5, 82.9 (d, *J* = 169.2 Hz), 70.9, 70.0, 66.4 (d, *J* = 19.9 Hz), 59.1, 36.7, 32.0.

C3-OBn Pyranoside bromoethanol substitution product *cis*-45/*trans*-45

The standard procedure for nucleophilic substitution of acetals was followed with thioglycoside **38** (0.030 g, 0.12 mmol), bromoethanol (0.033 mL, 0.48 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (0.049 g, 0.24 mmol), and *N*-iodosuccinimide (0.054 g, 0.24 mmol) in CH_3CN at 0 °C. GC and ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 60:40 (cis:trans) ratio. Purification by flash chromatography (3:1 pentane:Et_2O) afforded a separable mixture of diastereomers *cis*-**45**/*trans*-**45** as a colorless oil (0.017 g, 46%). IR, mass spectrometry, and combustion analysis data was obtained for major isomer (*cis*-**45**) and minor isomer (*trans*-**45**) as a mixture of diastereomers: GC t_R(major) 17.1 min, t_R(minor) 16.8 min; IR (thin film) 3030, 2930, 2858, 1362, 1097 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{19}BrO_3Na$ $(M + Na)^+$ 337.0415, found 337.0410.

Major Isomer (*cis*-45)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22–7.40 (m, 5H), 4.55 (m, 2H), 4.44 (dd, *J* = 8.6, 2.4 Hz, 1H), 4.06 (m, 1H), 3.82 (m, 1H), 3.75 (m, 1H), 3.59 (tt, *J* = 9.6, 4.3 Hz, 1H), 3.51 (m, 2H), 3.36 (td, *J* = 11.6, 2.6 Hz, 1H), 2.25 (ddt, *J* = 12.5, 4.2, 2.0 Hz, 1H), 1.92 (m, 1H), 1.58–1.72 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 128.5, 127.6, 127.6, 100.5, 72.7, 69.8, 68.9, 61.4, 37.3, 31.6, 30.6.

Minor Isomer (*trans*-45)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22–7.40 (m, 5H), 4.97 (t, *J* = 3.1 Hz, 1H), 4.55 (m, 2H), 4.07 (m, 1H), 3.96 (m, 1H), 3.90 (tt, *J* = 9.4, 4.2 Hz, 1H), 3.82 (td, *J* = 11.2, 3.2 Hz, 1H), 3.74 (m, 1H), 3.49 (m, 2H), 2.12 (m, 1H), 1.98 (m, 1H), 1.70 (ddd, *J* = 13.0, 9.7, 3.1 Hz, 1H), 1.64 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 128.5, 127.7, 127.6, 98.5, 70.9, 70.0, 67.5, 59.3, 36.7, 31.9, 30.8.

C3-OBn Pyranoside chloroethanol substitution product *cis*-46/*trans*-46

The standard procedure for nucleophilic substitution of acetals was followed with thioglycoside **38** (0.030 g, 0.12 mmol), chloroethanol (0.032 mL, 0.48 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (0.049 g, 0.24 mmol), and *N*-iodosuccinimide (0.054 g, 0.24 mmol) in CH_3CN at 0 °C. GC and ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 75:25 (cis:trans) ratio. Purification by flash chromatography (3:1 pentane:Et_2O) afforded a separable mixture of diastereomers *cis*-**46**/*trans*-**46** as a colorless oil (0.021 g, 64%). IR, mass spectrometry, and combustion analysis data was obtained for major isomer (*cis*-**46**) and minor isomer (*trans*-**46**) as a mixture of diastereomers: GC t_R(major) 16.2 min, t_R(minor) 15.9 min; IR (thin film) 3030, 2929, 2856, 1454, 1065 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{19}ClO_3Na$ $(M + Na)^+$ 293.0920, found 293.0919.

Major Isomer (*cis*-46)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24–7.38 (m, 5H), 4.58 (m, 2H), 4.45 (dd, *J* = 8.4, 2.4 Hz, 1H), 4.07 (m, 2H), 3.75 (m, 1H), 3.67 (m, 2H), 3.60 (tt, *J* = 9.8, 4.4 Hz, 1H), 3.37 (td, *J* = 11.6, 2.6 Hz, 1H), 2.26 (ddt, *J* = 12.5, 4.2, 2.0 Hz, 1H), 1.93 (m, 1H), 1.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 128.5, 127.7, 127.6, 100.5, 72.7, 69.8, 69.0, 61.4, 43.0, 37.3, 31.6.

Minor Isomer (*trans*-46)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23–7.38 (m, 5H), 4.96 (t, *J* = 3.1 Hz, 1H), 4.57 (m, 2H), 3.90 (m, 2H), 3.81 (td, *J* = 11.1, 2.8 Hz 1H), 3.74 (m, 1H), 3.66 (m, 3H), 2.13 (m, 1H), 1.97 (m, 1H), 1.71 (ddd, *J* = 13.2, 10.2, 3.5 Hz, 1H), 1.59 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 128.5, 127.7, 127.6, 98.6, 70.9, 70.0, 67.6, 59.3, 43.1, 37.7, 31.9.

C3-OBn Pyranoside ethanol substitution product *cis*-40/*trans*-40

The standard procedure for nucleophilic substitution of acetals was followed with thioglycoside **38** (0.030 g, 0.12 mmol), ethanol (0.028 mL, 0.48 mmol), 2,6-di-*tert*-butyl-4-methylpyridine (0.049 g, 0.24 mmol), and *N*-iodosuccinimide (0.054 g, 0.24 mmol) in CH_3CN at 0 °C. GC and ^{1}H NMR spectroscopic analysis of the unpurified product indicated a pair of diastereomers in a 52:48 (cis:trans) ratio. Purification by flash chromatography (3:1 pentane:Et_2O) afforded a separable mixture of diastereomers *cis*-**40**/*trans*-**40** as a colorless oil (0.027 g, 89%). IR, mass spectrometry, and combustion analysis data was obtained for major isomer (*cis*-**40**) and minor isomer (*trans*-**40**) as a mixture of diastereomers: GC t_R(major) 13.6 min, t_R(minor) 13.2 min; ^{1}H NMR (500 MHz, $CDCl_3$, mixture of anomers) δ 7.25–7.37 (m, 10H), 4.92 (t, *J* = 3.2 Hz, 1H), 4.56 (m, 4H), 4.35 (dd, *J* = 9.0, 2.3 Hz, 1H), 4.05 (ddd, *J* = 12.1, 4.7, 2.6 Hz, 1H), 3.90 (m, 2H), 3.70–3.80 (m, 3H), 3.57 (ddd, *J* = 14.8, 9.8, 4.4 Hz, 1H), 3.52 (dq, *J* = 9.4, 7.0 Hz, 1H), 3.44 (dq, *J* = 9.9, 7.1 Hz, 1H), 3.35 (td, *J* = 11.9, 2.4 Hz, 1H), 2.24 (ddt, *J* = 12.2, 4.0, 2.0 Hz, 1H), 2.07 (m, 1H), 1.89–1.98 (m, 2H), 1.71 (ddd, *J* = 13.1, 9.8, 3.3 Hz, 1H), 1.61 (m, 2H), 1.53 (m, 1H), 1.22 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$, mixture of anomers) δ 138.8, 138.5, 128.5, 128.4, 127.66, 127.65, 127.59, 127.56, 100.2, 97.9, 73.2, 71.2, 70.0, 69.7, 64.4, 62.9, 61.7, 59.0, 38.0, 37.0, 32.0, 31.9, 15.3, 15.2; IR (thin film) 3030, 2930, 2871, 1361, 1070 cm^{-1}; HRMS (ESI) *m*/*z* calcd for $C_{14}H_{20}O_3Na$ $(M + Na)^+$ 259.1310, found 259.1317.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by the National Institutes of Health, National Institute of General Medical Science (GM-61066). M.G.B thanks Eli Lilly for a graduate fellowship. K.A.W. thanks Amgen and Eli Lilly for generous support for research. We thank Dr. John Greaves and Ms. Shirin Sorooshian (UCI) for mass spectrometric data, and Dr. Phil Dennison (UCI) for assistance with NMR spectroscopy.

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35. Competition experiments were performed in the presence of either four or ten equivalents of each nucleophile. Comparable results were obtained regardless of the excess of nucleophile employed. Using DTBMP as an additive did not affect the outcome of the competition experiments.
36. For comparison, the differences in reactivity between ethanol and trifluoroethanol is approximately 220,000 for reactions with benzhydryl carbocations that occur at rates much below the diffusion rate limit (ref 14).
37. Secondary benzylic carbocations exhibit selectivities for k_{EtOH}/k_{TFE} from 17 for the less stable carbocations to 140 for the most stable (ref 28). The k_{EtOH}/k_{TFE} values (2.4–5.4) for reactions involving simple acyclic oxocarbenium ions (ref 16a) in water differ significantly from the 50-fold selectivity reported in this Article for 2-deoxyglucosyloxocarbenium ion in CH_3CN, but are similar to the 6.7-fold selectivity observed in CH_2Cl_2. Given the differences in substrates and conditions, it is not possible to reconcile these values.
38. These rate data provide a conservative estimate of the nucleophilicity of ethanol, as the reactivity of ethanol appears to be greater than that of water in additions to oxocarbenium ion intermediates (ref 28).
39. Details of control experiments are provided as supporting information.
40. Thermodynamic product ratios were obtained for select substrates, and these results do not account for the observed selectivity trends. Details are provided as supporting information.
41. Control experiments performed in the presence of (±)-camphorsulfonic acid resulted in significant epimerization of starting material 6 and product 15 at 0 °C. The incorporation product 7 was also observed at this temperature, indicating complete ionization of the acetal center.
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to the cationic intermediate, but no clear trends in β_{nuc} can be discerned. Details are provided as supporting information.

44. Control experiments indicated that the identical substitution reactions performed in CH_3CN resulted in rapid epimerization of the acetal product.
45. Nucleophilic addition to the lowest energy oxocarbenium ion (41) results in destabilizing steric interactions with the axially oriented C3-benzyloxy substituent (ref 42). In addition, electronic repulsion between the oxygen atoms of the substrate and the nucleophile destabilize the transition state leading to the 1,3-cis product: (a) Smith GD, Jaffe RL, Yoon DY. 1996;100:13439–13446. (b) de Oliveira PR, Rittner R. Spectrochim Acta, Part A 2005;61:1737–1745. (c) de Oliveira PR, Rittner R. J Mol Struct 2005;743:69–72.
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47. Control experiments indicated that the nucleophilic substitution products of C3-benzyloxy-substituted acetal 38 were susceptible to epimerization. DTBMP was employed as an additive to prohibit epimerization of the acetal center.
48. The halogen substituent influences the ground-state conformation of the alcohol nucleophile, which may change its effective size: (a) Thomassen H, Samdal S, Hedberg K. J Phys Chem 1993;97:4004–4010. (b) Durig JR, Shen S, Guirgis GA. J Mol Struct 2001;560:295–314. (c) Trindle C, Crum P, Douglass K. J Phys Chem A 2003;107:6236–6242.

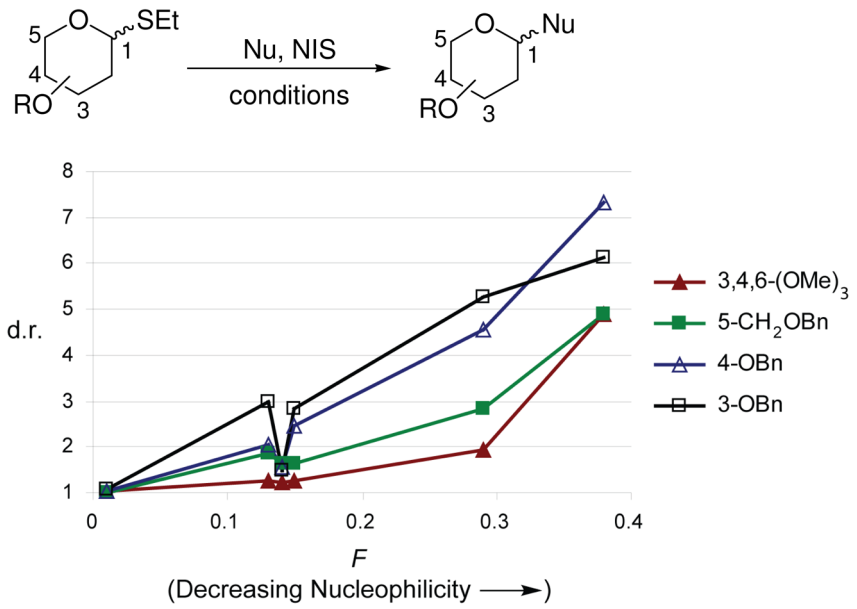
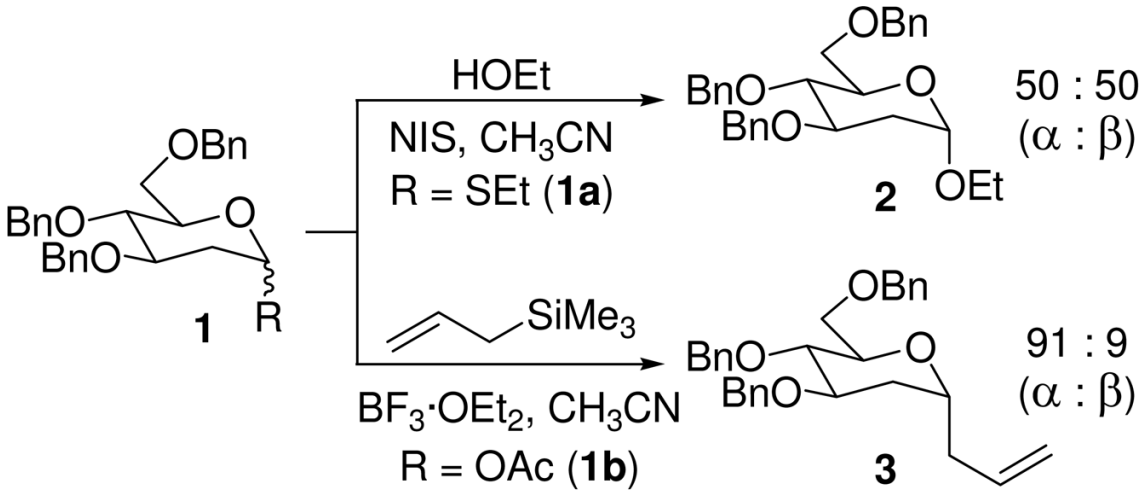
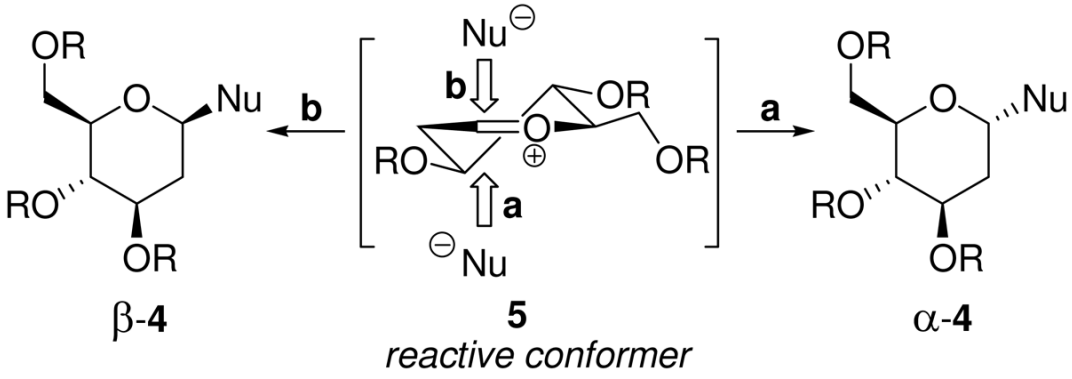


Figure 1.
Stereoselectivity (d.r.) vs. Nucleophilicity (*F*)[24] in Pyran Systems

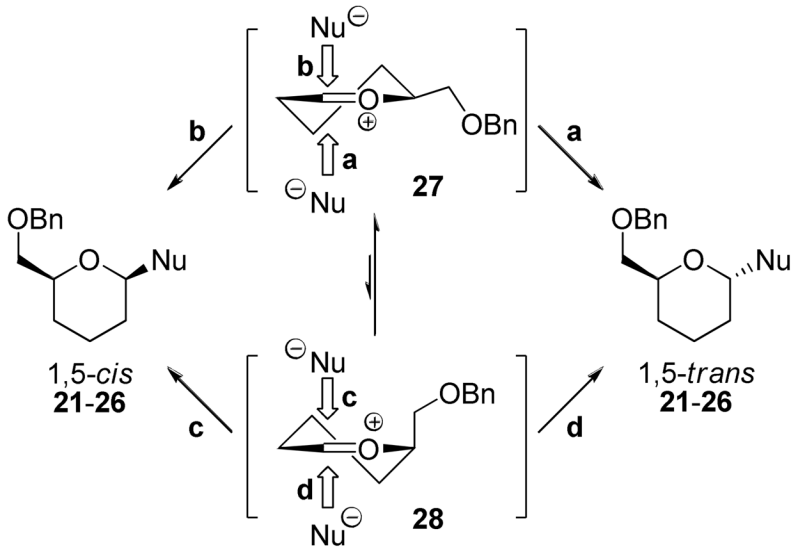


Scheme 1.
Nucleophilic Substitutions of 2-Deoxyglycoside **1**

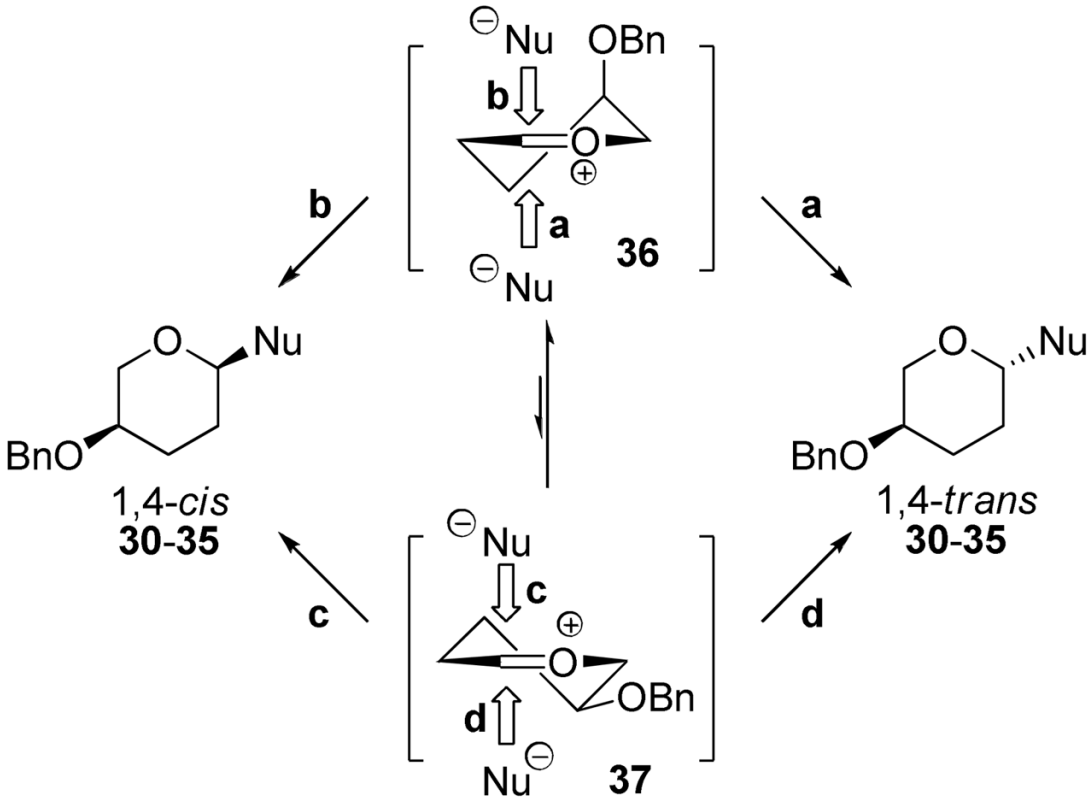


Scheme 2.
Modes of Addition to the 2-Deoxyglucose-Derived Oxocarbenium Ion **5**

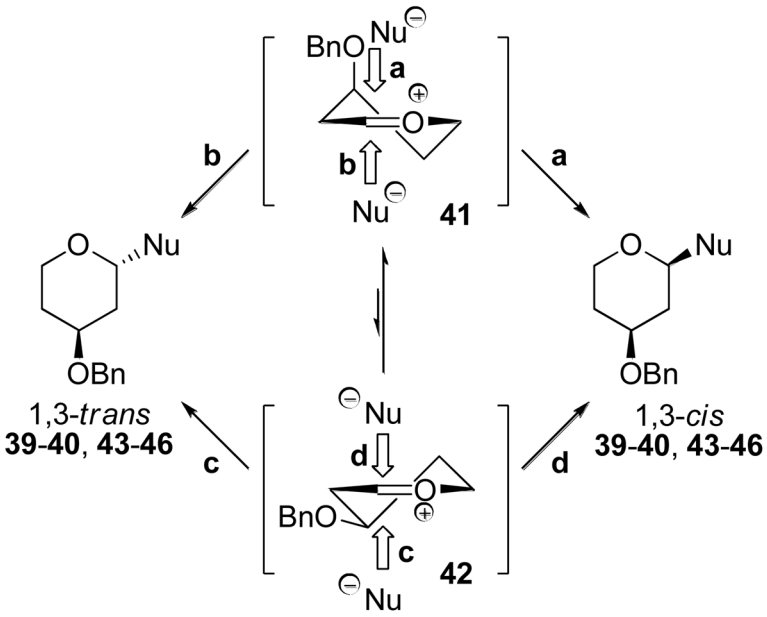
Scheme 3.
Reactive Intermediates Involved in Nucleophilic Substitutions



Scheme 4.
Modes of Addition to the 5-CH_2OBn-Substituted Oxocarbenium Ions **27** and **28**



Scheme 5.
Modes of Addition to the 4-OBn-Substituted Oxocarbenium Ions **36** and **37**



Scheme 6.
Modes of Addition to the 3-OBn-Substituted Oxocarbenium Ion

Table 1

Effect of Nucleophile Strength on Substitution Reactions of 2-Deoxythioglycoside **1c**

entry	compound	R	F^a	d.r. (α:β)^b	yield (%)^c
1	**6**	CF_3	0.38	83:17	80
2	**7**	CF_2H	0.29	67:33	78
3	**8**	CH_2F	0.15	56:44	69
4	**9**	CH_2Br	0.14	55:45	72
5	**10**	CH_2Cl	0.13	56:44	72
6	**11**	CH_3	0.00	51:49	82

[a] Field inductive effect parameter, see ref 24.

[b] Determined by GC and ^{1}H NMR spectroscopy of the unpurified reaction mixture.

[c] Isolated yield.

J Org Chem. Author manuscript; available in PMC 2011 February 19.

Table 2

Effect of the Glycosyl Donor Protecting Group

entry	compound	R	R^1	d.r. (α:β)[a]	yield (%)[b]
1	**14**	Bn	CF_3	81:19	68
2	**2**	Bn	CH_3	50:50	80
3	**15**	Ac	CF_3	75:25	69
4	**16**	Ac	CH_3	56:44	80

[a] Determined by ^{1}H NMR spectroscopy of the unpurified reaction mixture.

[b] Isolated yield.

Table 3

Competition Experiments Confirm the Relative Reactivities of the Alcohol Nucleophiles

entry	solvent	R^{1a}	R^{2a}	product ratio (R^1:R^2)
1	CH_3CN	CH_3	CF_3	98:2 (**11:6**)
2	CH_2Cl_2	CH_3	CF_3	87:13 (**11:6**)
3	CH_3CN	CH_2F	CF_3	97:3 (**8:6**)
4	CH_3CN	CH_3	CH_2F	70:30 (**11:8**)

[a] 10 equiv of nucleophile.

[b] Determined by GC analysis of the unpurified reaction mixture.

Table 4

Control Experiments Confirm Kinetic Product Formation

entry	Temp (°C)	6 (α:β)[a]	18 (α:β)[a]	Incorporation Products (7, 19)
1	−42	61:39	58:42	none
2	0	62:38	59:41	none
3	25	71:29	59:41	none

[a]Determined by GC analysis of the unpurified reaction mixture.

Table 5

Effect of Nucleophile Strength on Substitution Reactions of 5-CH_2OBn-Substituted Acetal **20**

entry	compound	X	F^a	d.r. (*trans:cis*)^b	yield (%)^c
1	**21**	CF_3	0.38	83:17	65
2	**22**	CF_2H	0.29	74:26	79
3	**23**	CH_2F	0.15	62:38	91
4	**24**	CH_2Br	0.14	62:38	85
5	**25**	CH_2Cl	0.13	65:35	85
6	**26**	CH_3	0.00	49:51	81

[a] Field inductive effect parameter, see ref 24.

[b] Determined by GC and ^{1}H NMR spectroscopy of the unpurified reaction mixture.

[c] Isolated yield.

Table 6

Effect of Nucleophile Strength on Substitution Reactions of 4-OBn-Substituted Acetal **29**

entry	compound	X	F^a	d.r. (*trans*:*cis*)[b]	yield (%)[c]
1	**30**	CF_3	0.38	88:12	81
2	**31**	CF_2H	0.29	82:18	68
3	**32**	CH_2F	0.15	71:29	72
4	**33**	CH_2Br	0.14	61:39	83
5	**34**	CH_2Cl	0.13	67:33	79
6	**35**	CH_3	0.00	51:49	70

[a] Field inductive effect parameter, see ref 24.

[b] Determined by GC and ^{1}H NMR spectroscopy of the unpurified reaction mixture.

[c] Isolated yield.

J Org Chem. Author manuscript; available in PMC 2011 February 19.

Table 7

Effect of Nucleophile Strength on Substitution Reactions of 3-OBn-Substituted Acetal **38**

entry	compound	X	F^a	d.r. (*cis*:*trans*)[b]	yield (%)[c]
1	**39**	CF_3	0.38	86:14	69
2	**43**	CF_2H	0.29	84:16	68
3	**44**	CH_2F	0.15	74:26	63
4	**45**	CH_2Br	0.14	60:40	46
5	**46**	CH_2Cl	0.13	75:25	64
6	**40**	CH_3	0.00	52:48	89

[a] Field inductive effect parameter, see ref 24.

[b] Determined by GC and ^{1}H NMR spectroscopy of the unpurified reaction mixture.

[c] Isolated yield.

J Org Chem. Author manuscript; available in PMC 2011 February 19.