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Stereocontrolled Formation of β-Glucosides and Related Linkages in the Absence of Neighboring Group Participation: Influence of a *trans*-Fused 2,3-*O*-Carbonate Group

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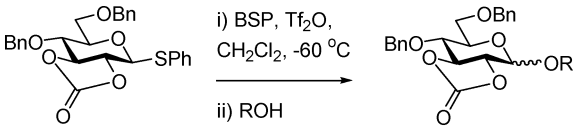

9 Examples. Yield: 47-89%. β:α Selectivity: 3:1 - 100:0

Phenyl 4,6-di-*O*-benzyl-2,3-*O*-carbonyl-β-D-glucothiopyranoside and the regiosiomeric phenyl 2,6-di-*O*-benzyl-3,4-*O*-carbonyl-β-D-glucothiopyranoside were prepared and studied as glucosyl donors at −60 °C in dichloromethane with preactivation by 1-benzenesulfinyl piperidine before addition of the acceptor alcohol. The 2,3-*O*-carbonate protected donor showed moderate to excellent β-selectivity under these conditions depending on the acceptor employed, thereby providing a means for 1,2-*trans*-equatorial glycosidic bonds without recourse to neighboring group participation and its associated problem of ortho ester formation. In contrast, the 3,4-*O*-carbonate protected donor showed moderate to no β-selectivity under the conditions employed. The results obtained in this study with carbonate protected glucopyranosyl donors are contrasted with those obtained previously in the manno- and rhamnopyranosyl series when the 2,3-*O*-carbonate protected is α-selective and the 3,4-*O*-carbonate is β-selective.

Introduction

The synthesis of 1,2-*trans*-equatorial pyranosidic bonds (e.g., the β-glucopyranosides) is dominated by neighboring group participation, as embodied in the use of disarmed, ester-protected glycosyl donors.[1] This extremely widespread methodology suffers from the competing formation of glycosyl ortho esters, particularly when the glycosylation sequence is conducted under basic conditions, and of migration of the 2-*O*-acyl group to both the anomeric center and the glycosyl acceptor.[2] These deleterious side reactions, from which no carboxylate esters, neither the highly hindered pivalates nor the highly electron-deficient perfluoroalkylcarboxylates, are exempt,[3] are consequences of the mechanism and are always potentially problematic.[4] The need for increasingly sophisticated oligosaccharide synthesis, driven by potential biological applications,[5] presents the need for ever-more efficient and selective glycosylation reactions, devoid of such potential yield-reducing side reactions.[6] Nowhere is this more apparent than in the cutting edge fields of polymer-supported automated,[7] and programmed one-pot oligosaccharide synthesis and other iterative one-pot glycosylation protocols,[8] when less than perfect yields lead to deletion sequences and complicate final product isolation and purification. Our laboratory is interested

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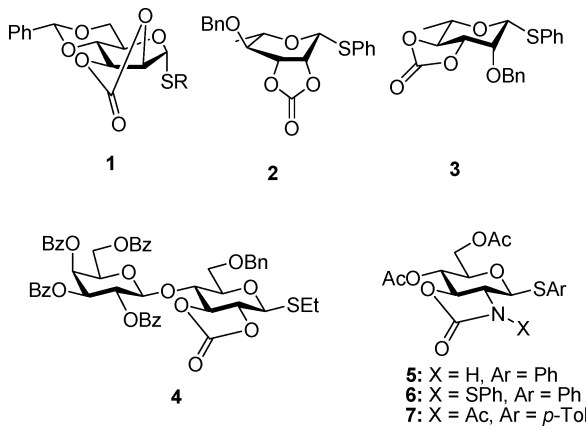
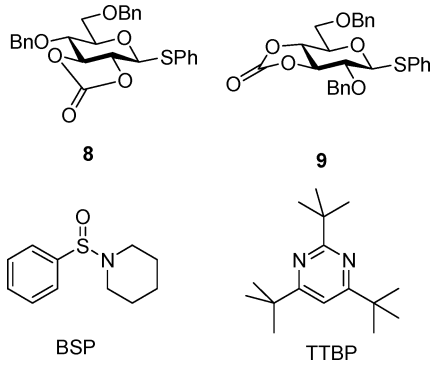
in the development of improved glycosylation methods, such as the low-temperature activation of thioglycosides,[9] and nontraditional methods for the stereocontrolled glycosidic bond formation, as exemplified by β-mannoside synthesis by means of torsionally disarming benzylidene groups.[10] We have shown how the 2,3-*O*-carbonate group in manno- (**1**)[11] and rhamnopyranosyl donors (**2**)[12] is highly α-directing in homogeneous coupling reactions, a phenomenon we attribute to the half-chair conformation imposed by this *cis*-fused, five-membered ring, which lowers the activation barrier to oxacarbenium ion formation.[11,12] In contrast, 3,4-*O*-carbonate protected rhamnosyl donors (**3**) are moderately β-selective, which we ascribe to the electron-withdrawing but nonparticipating effect of this group.[12] If the α-selective nature of the 2,3-*O*-carbonate group in mannosyl and rhamnosyl donors is indeed a function of the conformation imposed on the pyranose ring by the *cis*-fused five-membered ring, it seemed reasonable to expect that in the corresponding glucopyranose systems, with the *trans*-fused ring junctions, the electron-withdrawing, nonparticipating carbonate group might be induced to function as a β-directing group even when spanning the 2,3-diol group. Our intended work in this area was given additional impetus by reports from Boons and Zhu,[13] that donor **4** was α-selective under conditions closely related to our own but in the unusual solvent combination of toluene/1,4-dioxane (1/3). Even more intriguing are the reports of Kerns and co-workers on the α-selectivity of the oxazolidinone **5**, thought to undergo initial in situ sulfenylation to **6**, and of the β-selectivity of the *N*-acetyl derivative **7**, under conditions even more closely related to our own.[14]

We report here that in line with our initial expectations the glycosyl donor **8** is indeed β-selective with a range of moderately reactive glycosyl acceptors on activation with 1-benzenesulfinyl piperidine (BSP) and triflic anhydride,[9,15] in the presence of the hindered base 2,4,6-tri-*tert*-butylpyrimidine (TTBP),[16] in dichloromethane at −60 °C. On the other hand, in a limited range of experiments, donor **9** showed a disappointing lack of stereoselectivity, which, when taking into consideration the modestly β-selective rhamnosyl donor **3**, serves to highlight the influence of the configuration of C2 on glycopyranosylation reactions.[17]





Results and Discussion

Following the method of Ley,[18] treatment of phenylthio β-D-glucopyranoside[19] with 2,2,3,3-tetramethoxybutane under acid catalysis gave a separable mixture of the bisacetals **10** and **11**. These were individually benzylated giving the fully protected thioglycosides **12** and **13**. Hydrolysis of the bisacetal functionality afforded the diols **14** and **15**, whose phosgenation provided donors **8** and **9**.

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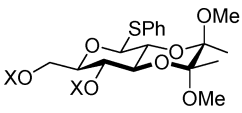

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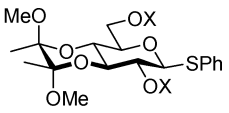
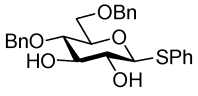
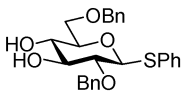


11: X = H
13: X = Bn



14



15

Examination of the ^{1}H NMR spectra of **8** and **9**, especially their anomeric $^1J_{CH}$ coupling constants,[20] revealed that both retained the standard $^4C_1$ chair conformations typical of the D-hexopyranosides. We therefore proceeded to examine the coupling reactions of both donors to a pair of simple, reactive substrates under our standard conditions, with preactivation of the thioglycoside by means of BSP and Tf_2O in the presence of TTBP at −60 °C before addition of the acceptor alcohol. The results of these coupling reactions, set out in Table 1, reveal that the 2,3-*O*-carbonyl protected donor is indeed β-selective with the model alcohols (entries 1 and 4). The 3,4-*O*-carbonate, on the other hand, showed poor selectivity with the simple model alcohol 3β-cholestanol (Table 1, entry 2) and only modest β-selectivity with 1-adamantanol (Table 1, entry 5), whose reactions are usually characterized by a high degree of selectivity in favor of the β-anomer.[21] Also included in Table 1 for ease of comparison are the previous couplings (entries 3 and 6)[12] of the 3,4-*O*-carbonate protected rhamnosyl donor **3** to the same model alcohols.

As expected, the 2,3-*O*-carbonate **8** is highly β-selective with these simple model alcohols. On the other hand, the 3,4-*O*-carbonate **9** performed disappointingly with both 3β-cholestanol and 1-adamantanol. The results with the 3,4-*O*-carbonate **9** are to be contrasted with those obtained with the 3,4-*O*-carbonate protected rhamnosyl donor **3**, which showed significantly better β-selectivity. The contrast in selectivity between **3** and **9**, which, unlike **1** and **2**, and **8**, are predicted to have the same pyranose ring conformation, serves to highlight the fundamental difference in selectivity between glucosyl and mannosyl/rhamnosyl donors in the absence of neighboring group participation on which we have previously commented.[11]

On the basis of these results, our study with the 2,3-*O*-carbonyl protected donor **8** was expanded to include a series of carbohydrate and amino acid based acceptor alcohols (Table 2). These couplings each proceeded with β-selectivity ranging from good to excellent depending on the acceptor alcohol. The better selectivities were generally obtained with the less hindered primary alcohols. However, this was not exclusively the case, and excellent selectivity was obtained with two secondary alcohols, raising the possibility of diastereomeric matching and mismatching situations[22] as are widely appreciated in the broader context of asymmetric synthesis.[23] A final coupling with donor **9** served to confirm the relatively poor selectivity obtained in the 3,4-*O*-carbonate series.

The anomeric stereochemistry in each of the above couplings was assigned on the basis of the $^3J_{H1,H2}$ coupling constants in the usual manner when sufficient resolution was available; otherwise the assignments were based on the $^1J_{CH}$ coupling constants.[24] To guard against the possibility that the $^1J_{CH}$ anomeric couplings were influenced by the cyclic carbonate, as is the case with both the α- and the β-glycosides with their half-chair conformations arising from coupling to **1** and **2**,[11,12] selected examples were saponified and the spectral data of the products examined. As is clear from Table 3, in all systems there is a reduction in the $^1J_{C1H1}$ coupling constant on removal of the carbonate in the β-series, suggesting a minor change in conformation, either of the pyranose ring or of the exocyclic glycosidic C−O bond.[25] Nevertheless, all hydrolyses confirmed the original stereochemical assignments. Self-evidently these hydrolyses, which were conducted with lithium hydroxide in aqueous THF, also serve to confirm the ease with which the cyclic carbonates can be removed.

In an attempt to shed more light on the influence of the 2,3-*O*- and 3,4-*O*-carbonates in both the *gluco*- and the *rhamno*-(*manno*-) manifolds, a series of low-temperature experiments were conducted in which selected donors were converted to the corresponding anomeric triflates in CD_2Cl_2 at −60 °C whose decomposition temperatures were then determined by variable-temperature NMR spectroscopy (Table 4). The four triflate decomposition temperatures recorded exhibited a range of 45 °C, with the most stable being the 3,4-*O*-carbonate protected rhamnose derivative **51** (Table 4, entry 4) and the lowest the 2,3-*O*-carbonate protected rhamnosyl triflate **50** (Table 4, entry 3). Interestingly, the two glucosyl triflates **47** and **48** had the same decomposition temperature (Table 4, entries 1 and 2), which was midway between that of the mannosyl and rhamnosyl donors. The wide spread in decomposition temperatures between triflates **50** and **51** shadows the selectivity profile with the 3,4-*O*-carbonates in the rhamnosyl series, giving good β-selectivity consistent with the notion of a relatively stable anomeric triflate (**51**) and a correspondingly short lifetime for the transient contact ion pair with which it is in equilibrium.[26] The 2,3-*O*-carbonate protected rhamnosyl triflate **50**, on the other hand, has the lowest decomposition temperature recorded in this study in accordance with the high α-selectivity observed with this series of compounds. The correlation between triflate decomposition temperatures and β-selectivity observed in the rhamnose series, which mirrors that seen previously with mannosyl triflates,[27] obviously does not extend to the glucose series. Presumably, this is because triflate decomposition is a two-step process and is not governed

(20) Key NMR data for **8**: $J_{H1,H2}$ 9.5 Hz, $J_{H2,H3}$ 11.2 Hz, $J_{H3,H4}$ 9.5 Hz, $^1J_{C1,H1}$ 152.6 Hz. Key NMR data for **9**: $J_{H1,H2}$ 8.8 Hz, $J_{H2,H3}$ 9.5 Hz, $J_{H3,H4}$ 11.3 Hz, $^1J_{C1,H1}$ 157.8 Hz.

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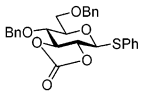
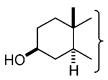
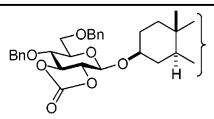
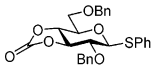
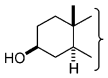
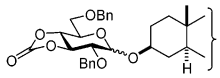
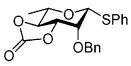
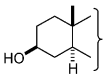
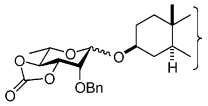
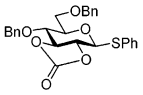
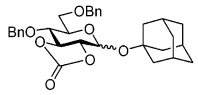
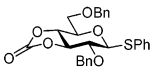
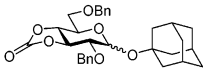
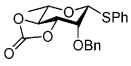
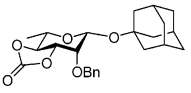
TABLE 1. Comparative Glycosylation Reactions with Donors 8 and 9

Entry	Donor	Acceptor	Product (% yield, α:β selectivity)[a]
1			
	8	**16**	**17** (70), β-only
2			
	9	**16**	**18** (72), α:β = 1:1
3			
	3	**16**	**19** (62), α:β = 1:6
4			
	8	**20**	**21** (69), α:β = 1:10[b]
5			
	9	**20**	**22** (78), α:β = 1:5
6			
	3	**20**	**23** (56), β-only

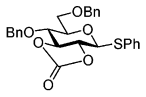
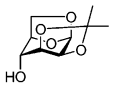
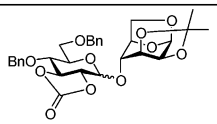
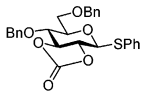
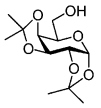
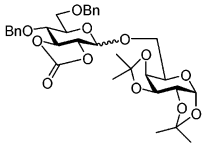
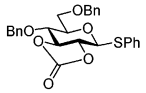
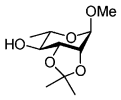
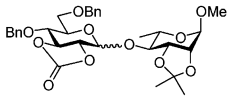
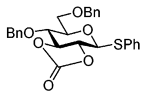
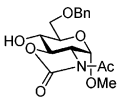
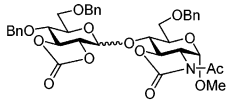
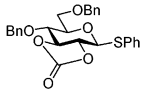
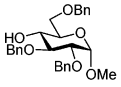
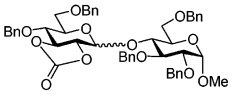
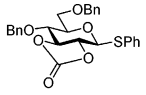
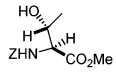
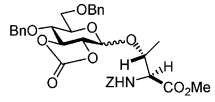
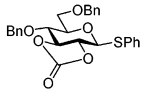
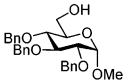
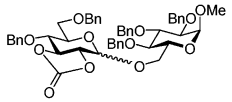
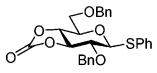
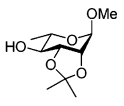
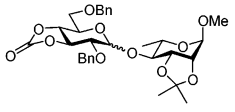
[a] Yields refer to isolated compounds unless otherwise stated. [b] Anomeric ratio determined by integration of the ^{1}H NMR spectrum of the crude reaction mixture.

exclusively by the position of the covalent anomeric triflate/contact ion pair equilibrium. Thus, in the absence of nucleophiles to capture the transient contact ion pair, the ease of decomposition is also governed, among other factors, by the overlap of the C2−H2 bond with the C-1 π-orbital of the oxacarbenium ion, which is dependent on both configuration (*gluco* vs *rhamno*/*manno*) and subtle conformational factors arising from the protecting group array. Interestingly, the VT NMR study also revealed the influence of protecting groups on the initial thioglycoside activation. Thus, while thioglycosides **3**, **7**, and **9** were activated by the BSP/Tf_2O couple in minutes at −60 °C, the 2,3-*O*-carbonate protected rhamnosyl thioglycoside **49** was converted in approximately 15 min at −60 °C to a complex mixture containing at least four anomeric signals, which was only converted completely to a clean anomeric triflate on warming to between −15 and −10 °C, by which time slow decomposition had set in. This scenario, in which a series of moderately stable intermediates is observed prior to the triflate formation, is somewhat analogous to the observations of Lowary on the activation of thioglycosides and glycosyl sulfoxides in the 2,3-anhydrofuranose series.[28] The seeming disparity between the relatively slow activation for **49** and the facile decomposition of the corresponding triflate **50** reflects the different requirements of the two processes with thioglycoside activation being dependent on the nucleophilicity of the sulfur atom toward the thiophilic species, which is reduced in the presence of strongly electron-deficient protecting groups. A final thioglycoside studied in this context was the 4,6-*O*-benzylidene-2,3-*O*-carbonate protected thioglucoside **52**, which was not activated by the BSP/Tf_2O combination below room temperature.

Finally, having demonstrated that 2,3-*O*-carbonate protected glucopyranosyl donors are moderately β-selective under our standard conditions with preactivation by BSP and triflic anhydride in CH_2Cl_2 at low temperature, we return to apparent contrast with the work of Boons with the closely related donor **4** and of Kerns with the glucosamine analogues **5**−**7**. The discrepancy with the work of Boons can most probably be explained by either the different activation conditions[29] or, especially, the use

(28) Callam, C. S.; Gadikota, R. R.; Krein, D. M.; Lowary, T. L. *J. Am. Chem. Soc.* **2003**, *125*, 13112.

TABLE 2. Further Glycosylation Reactions with Donors 8 and 9

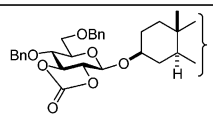
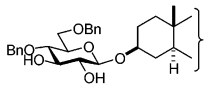
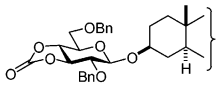
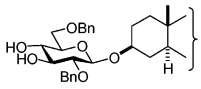
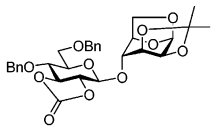
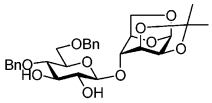
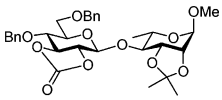
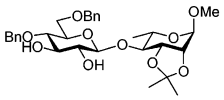
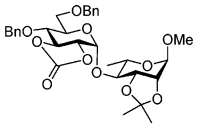
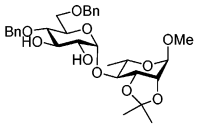
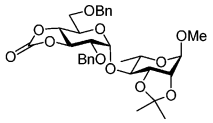
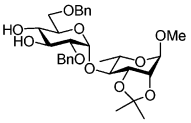
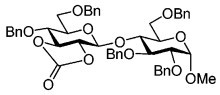
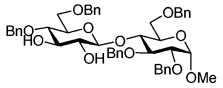
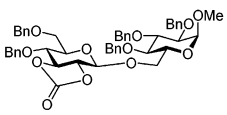
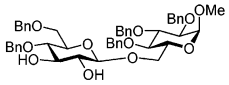
Entry	Donor	Acceptor	Product (% yield, α:β selectivity)[a]
1			
	8	**24**	**25** (69), α:β = 1:10[b]
2			
	8	**26**	**27** (84), α:β = 1:9[b]
3			
	8	**28**	**29** (68), α:β = 1:8
4			
	8	**30**	**31** (47), α:β = 1:4
5			
	8	**32**	**33** (71), α:β = 1:3
6			
	8	**34**	**35** (84), α:β = 1:3
7			
	8	**36**	**37** (89), α:β = 1:20[b]
8			
	9	**28**	**38** (72), α:β = 1:1

[a] Yields refer to isolated compounds unless otherwise stated. [b] Anomeric ratio determined by integration of the ^{1}H NMR spectrum of the crude reaction mixture.

of the considerably more polar solvent combination of toluene/dioxane (1/3). Kerns reported that the *N*-acetyl oxazolidinone-protected glycosyl donor **7** was *β*-selective with less hindered, more reactive alcohols but α-selective with less reactive alcohols, a trend which at least qualitatively parallels the results obtained here with donor **8**.[14c,30] On the other hand, the donor derived from **5/6** was shown to be highly α-selective, pointing to a significant influence of the *N*-substituent on glycosylation stereoselectivity for which we have no explanation at

(29) Unfortunately, donor **8** was not activated by the BSP/Tf_2O system when it was premixed with acceptor alcohols. Rather, the promoter system reacted preferentially with the alcohol, because of the disarmed nature of **8**.

TABLE 3. Selected Deprotections and Key NMR Data

Entry	Substrate	$^1J_{CH}$ (Hz);[a] $^3J_{H1,H2}$ (Hz)[a]	Product (% Yield)	$^1J_{CH}$ (Hz);[a] $^3J_{H1,H2}$ (Hz)[a]
1	 **17β**	164.7; 7.8	 **39**	158.0; 7.8
2	 **18β**	162.5; 5.8	 **40**	158.0; 7.8
3	 **25β**	164.0; 7.7	 **41**	158.4; 7.7
4	 **29β**	169.3; 7.8	 **42**	159.8; 7.7
5	 **29α**	173.6; 2.7	 **43**	170.2; 4.0
6	 **38α**	177.5; 3.6	 **44**	170.7; 3.5
7	 **33β**	167.8, 7.8	 **45**	161.6, 8.3
8	 **37β**	165.9; 7.6	 **46**	159.5, 7.8

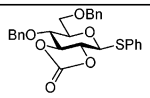
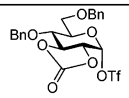
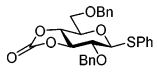
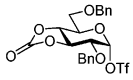
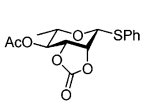
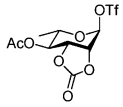
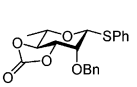
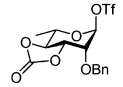
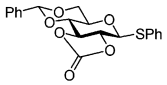
[a] For disaccharides, only the $^1J_{CH}$ and $^3J_{H1,H2}$ coupling constants for the newly formed glucosidic bond are given: assignments were made by ^1H,^{13}C correlated spectroscopy.

present, other than perhaps the bulk of the *S*-phenyl substituent on the oxazolidinone nitrogen, which may lead to a considerably more hindered anomeric center and retard β-face attack.[31]

(30) Neighboring group participation by the *N*-acetyl group in **7** was excluded as the reason for β-selectivity on the basis of the inspection of molecular models.[14]

(31) Recent work from our laboratory has highlighted the influence of protecting group bulk on anomeric selectivity. Crich, D.; Jayalath, P. *Org. Lett.* **2005**, *7*, 2277.

TABLE 4. Anomeric Triflates Chemical Shifts and Decomposition Temperatures

Entry	Donor	Triflate	δ H_1 (CD_2Cl_2)	Decomp Temp (°C)
1	 **8**	 **47**	6.41 (d, J = 1.5 Hz)	~+ 5
2	 **9**	 **48**	6.19 (d, J = 3.3 Hz)	~+5
3	 **49**	 **50**	6.51 (br s)	~-15
4	 **3**	 **51**	6.07 (d, J = 1.2 Hz)	+30
5	 **52**[a]	–	–	–

[a] No activation was observed between −78 and 25 °C.

Conclusion

We have demonstrated that 2,3-*O*-carbonate protected glucopyranosyl donors show moderate to excellent β-selectivity in glycosylations conducted at low temperature in dichloromethane by our two-stage protocol with preactivation before addition of the nucleophile. These reactions, which proceed through the intermediacy of covalent glucosyl triflates, are β-selective in the complete absence of neighboring group or solvent participation and serve additionally to underline the importance of conformational factors apparent from a comparison with similarly protected mannosyl and rhamnosyl donors.

Experimental Section

Phenyl 2,3-Di-*O*-(2,3-dimethoxybutane-2,3-diyl)-1-thio-β-D-glucopyranoside (10) and Phenyl 3,4-Di-*O*-(2,3-dimethoxybutane-2,3-diyl)-1-thio-β-D-glucopyranoside (11). A suspension of phenyl 1-thio-β-D-glucopyranoside[19] (8.0 g, 29.4 mmol) in a solution of 2,2,3,3-tetramethoxybutane (1.2 equiv), trimethyl orthoformate (4 equiv), and methanol (120 mL) was treated with camphorsulfonic acid (0.05 equiv), and then refluxed under Ar for 18 h. The cooled reaction mixture was treated with powdered $NaHCO_3$ and concentrated under reduced pressure. The crude product was purified by flash column chromatography on silica gel (hexane:ethyl acetate, 3:2) to afford **10** and **11** in a 1:1 ratio (28.0 mmol, 94% combined yield). **10**: $[\alpha]^{25}_D$ −156.9 (*c*, 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.32 and 1.33 (2s, 6H), 3.20 and 3.27 (2s, 6H), 3.42 (m, 1H), 3.59 (t, J = 9.6 Hz, 1H), 3.7−3.8 (m, 3H), 3.88 (dd, J = 3.0, 12.0 Hz, 1H), 4.82 (d, J = 9.9 Hz, 1H), 7.23−7.27 (m, 3H), 7.46−7.48 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.6, 17.7, 48.0, 48.2, 62.3, 67.5, 68.0, 74.3, 80.0, 85.2, 99.6, 100.1, 127.4, 128.9, 131.4, 133.3. ESIHRMS calcd for $C_{18}H_{26}O_7S$ $[M + Na]^+$: 409.1297. Found: 409.1291. **11**: $[\alpha]^{25}_D$ +100.4 (*c*, 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.26 and 1.3 (2s, 6H), 3.20 and 3.27 (2s, 6H), 3.48 (t, J = 9.0 Hz, 1H), 3.56 (m, 1H), 3.59 (t, J = 9.5 Hz, 1H), 3.7 (m, 2H), 3.86 (dd, J = 3.0, 12.0 Hz, 1H), 4.56 (d, J = 9.5 Hz, 1H), 7.28 (m, 3H), 7.5 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.6, 17.7, 47.9, 61.3, 65.4, 69.3, 73.3, 78.0, 88.3, 99.5, 99.8, 128.32, 129.0, 131.4, 133.0. Anal. Calcd for $C_{18}H_{26}O_7S$: C, 55.94; H, 6.78. Found: C, 55.58; H, 6.62.

Phenyl 4,6-Di-*O*-benzyl-2,3-di-*O*-(2,3-dimethoxybutane-2,3-diyl)-1-thio-β-D-glucopyranoside (12). Sodium hydride (60%, 1.62 g, 40 mmol) was added to a cooled solution of **10** (4.87 g, 12.5 mmol) in DMF (20 mL). After the mixture was stirred for 10 min, benzyl bromide (4 mL, 34 mmol) was added and stirring was continued for 6 h at room temperature. The solvents were removed under reduced pressure, and the resulting mixture was diluted with dichloromethane (40 mL) and washed with sat. $NaHCO_3$. The organic layer was separated and dried (anhydrous Na_2SO_4) and concentrated in vacuo. Purification was done by flash column chromatography on silica gel (hexane:ethyl acetate; 4:1) to yield **12** as a white solid (6.97 g, 98%). Mp 117 °C; $[\alpha]^{25}_D$ −108 (*c*, 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.34 and 1.36 (s, 6H), 3.2 and 3.3 (2s, 6H), 3.55 (ddd, J = 2.0, 5.0, 9.5 Hz, 1H), 3.69−3.75 (m, 3H), 3.77 (dd, J = 2.0, 11.0 Hz, 1H), 3.9 (t, J = 9.5 Hz, 1H), 4.51 (d, J = 12.0 Hz, 1H), 4.57 (d, J = 8.5 Hz, 1H), 4.59 (d, J = 9.0 Hz, 1H), 4.75 (d, J = 10.0 Hz, 1H), 4.93 (d, J = 11.0 Hz, 1H), 7.2−7.5 (m, 13H), 7.56−7.57 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.6, 17.8, 47.9, 48.1, 68.0, 69.0, 73.4, 74.6, 75.0, 75.5, 79.5, 84.8, 99.5, 100.1, 127.2, 127.5, 127.6, 127.8, 128.0, 128.3, 128.4, 128.8, 131.6, 133.5, 138.3. Anal. Calcd for $C_{32}H_{38}O_7S$: C, 67.82; H, 6.76. Found: C, 67.90; H, 6.67.

Phenyl 4,6-Di-*O*-benzyl-1-thio-β-D-glucopyranoside (14). A solution of compound **12** (5.98 g, 10.5 mmol) in dichlo-

romethane (20 mL) was added to a mixture of TFA and water (10 mL, 19:1). The mixture was stirred for 2 h at room temperature until all of the starting material was consumed as confirmed by TLC. The mixture was neutralized with sat. $NaHCO_3$, and the organic layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure. The product was purified by flash column chromatography on silica gel (hexane: ethyl acetate; 3:2) to give **14** as a white solid (4.42 g, 93%). Mp 78 °C. $[\alpha]^{25}_D$ +5.2 (*c*, 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 3.0 (bs, 2H), 3.38 (t, J = 9.0 Hz, 1H), 3.51−3.53 (m, 2H), 3.68−3.82 (m, 3H), 4.52 (d, J = 9.6 Hz, 1H), 4.57 (d, J = 12.0 Hz, 1H), 4.63 (d, J = 11.2 Hz, 1H), 4.64 (d, J = 12.0 Hz, 1H), 4.8 (d, J = 11.2 Hz, 1H), 7.26−7.37 (m, 13H), 7.5−7.6 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 69.0, 72.2, 73.5, 74.7, 76.8, 78.2, 79.0, 87.7, 127.7, 127.8, 127.9, 128.0, 128.4, 128.5, 129.0, 132.0, 132.7, 138.17, 138.21. Anal. Calcd for $C_{26}H_{28}O_5S$: C, 69.00; H, 6.24. Found: C, 69.16; H, 6.25.

Phenyl 4,6-Di-*O*-benzyl-2,3-carbonyl-1-thio-*β*-D-glucopyranoside (8). To a stirred solution of **14** (2.33 g, 5.15 mmol) and triethylamine (2.15 mL, 15.4 mmol) in dichloromethane (20 mL) at 0 °C was added a 20% solution of phosgene in toluene (5 mL, 10.3 mmol) dropwise, and stirring was continued for 2 h at room temperature. The mixture was diluted with dichloromethane (20 mL) and washed with sat. $NaHCO_3$. The organic layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel (hexane: ethyl acetate; 3:1) to give **8** as a white solid (2.39 g, 97%). Mp 96 °C. $[\alpha]^{25}_D$ +10.2 (*c*, 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 3.6 (m, 1H), 3.75−3.80 (m, 2H), 3.82 (dd, J = 9.5, 11.2 Hz, 1H), 3.9 (t, J = 9.0 Hz, 1H), 4.35 (dd, J = 9.6, 11.2 Hz, 1H), 4.52 (d, J = 11.2 Hz, 1H), 4.53 (d, J = 12.5 Hz, 1H), 4.6 (d, J = 12.0, Hz, 1H), 4.78 (d, J = 11.4 Hz, 1H), 4.85 (d, J = 9.5 Hz, 1H), 7.26−7.35 (m, 13H), 7.6 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 68.2, 72.9, 73.5, 73.6, 76.2, 80.2, 82.4, 85.4, 127.6, 127.7, 128.0, 128.2, 128.4, 128.5, 129.1, 129.2, 134.7, 136.8, 137.9, 153.0. Anal. Calcd for $C_{27}H_{26}O_6S$: C, 67.76; H, 5.48. Found: C, 67.55; H, 5.62.

Phenyl 2,6-Di-*O*-benzyl-2,3-di-*O*-(2,3-dimethoxybutane-2,3-diyl)-1-thio-*β*-D-glucopyranoside (13). Sodium hydride (60%, 1.54 g, 38 mmol) was added to a cooled solution of **11** (4.29 g, 11.1 mmol) in DMF (20 mL). After the mixture was stirred for 10 min, benzyl bromide (3.43 mL, 28 mmol) was added, and stirring was continued for 6 h at room temperature. The solvents were evaporated off under reduced pressure, and the resulting mixture was diluted with dichloromethane (40 mL) and then washed with sat. $NaHCO_3$. The organic layer was separated and dried (anhydrous Na_2SO_4) and concentrated in vacuo. Purification was done by flash column chromatography on silica gel (hexane:ethyl acetate; 4:1) to yield **13** as a white solid (6.2 g, 99%). Mp 92 °C. $[\alpha]^{26}_D$ +70.5 (*c*, 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 1.29 and 1.35 (2s, 6H), 3.2 and 3.3 (2s, 6H), 3.5 (t, J = 9.3 Hz, 1H), 3.64−3.67 (m, 1H), 3.73−3.78 (m, 2H), 3.82 (dd, J = 2.0, 11.5 Hz, 1H), 3.89 (t, J = 9.6 Hz, 1H), 4.57 (d, J = 11.8 Hz, 1H), 4.62 (d, J = 11.9 Hz, 1H), 4.64 (d, J = 9.4 Hz, 1H), 4.73 (d, J = 10.6 Hz, 1H), 4.82 (d, J = 10.6 Hz, 1H), 7.2−7.3 (m, 11H), 7.34−7.44 (m, 2H), 7.57−7.59 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 17.6, 17.8, 47.9, 48.0, 65.7, 68.4, 74.8, 75.4, 76.7, 77.2, 77.7, 87.0, 99.5, 99.6, 127.3, 127.4, 127.7, 127.75, 128.2, 128.25, 128.3, 128.8, 132.8, 132.83, 138.4, 138.5. Anal. Calcd for $C_{32}H_{38}O_7S$: C, 67.82; H, 6.76. Found: C, 67.94; H, 6.71.

Phenyl 2,6-Di-*O*-benzyl-1-thio-*β*-D-glucopyranoside (15). A solution of compound **13** (4.95 g, 8.7 mmol) in dichloromethane (20 mL) was added to a mixture of TFA and water (10 mL, 19:1). The mixture was stirred for 2 h at room temperature until all of the starting material was consumed as confirmed by TLC. The mixture was neutralized with sat. $NaHCO_3$, and the organic layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure. The product was purified by flash column chromatography on silica gel (hexane: ethyl acetate; 3:2) to give **15** as a white solid (3.59, 91%). Mp 105 °C. $[\alpha]^{25}_D$ −27.5 (*c*, 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 2.7 (bs, 2H), 3.35 (t, J = 9.6 Hz, 1H), 3.47−3.51 (m, 1H), 3.56−3.63 (m, 2H), 3.75−3.81 (m, 2H), 4.57 (d, J = 11.9 Hz, 1H), 4.60 (d, J = 11.9 Hz, 1H), 4.66 (d, J = 9.7 Hz, 1H), 4.7 (d, J = 10.0 Hz, 1H), 4.97 (d, J = 10.9 Hz, 1H), 7.26−7.39 (m, 13H), 7.55−7.6 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 70.3, 71.5, 73.6, 75.1, 77.7, 78.2, 80.0, 87.3, 127.5, 127.7, 127.8, 128.1, 128.2, 128.4, 128.6, 128.9, 131.7, 133.7, 137.8, 137.9. Anal. Calcd for $C_{26}H_{28}O_5S$: C, 69.00; H, 6.24. Found: C, 68.88; H, 6.28.

Phenyl 2,6-Di-*O*-benzyl-3,4-carbonyl-1-thio-*β*-D-glucopyranoside (9). To a stirred solution of **15** (1.98 g, 4.3 mmol) and triethylamine (1.45 mL, 10.4 mmol) in dichloromethane (20 mL) at 0 °C was added a 20% solution of phosgene in toluene (4.3, 8.8 mmol) dropwise, and stirring was continued for 2 h at room temperature. The mixture was diluted with dichloromethane (20 mL) and washed with sat. $NaHCO_3$. The organic layer was separated, dried (Na_2SO_4), and concentrated under reduced pressure. The crude was purified by flash column chromatography on silica gel (hexane: ethyl acetate; 3:1) to give **9** as a white solid (1.95 g, 94%). Mp 74 °C. $[\alpha]^{24}_D$ −35 (*c*, 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ: 3.68 (t, J = 9.0 Hz, 1H), 3.70 (dd, J = 4.8, 11.2 Hz, 1H), 3.8 (dd, J = 2.5, 11.2 Hz, 1H), 3.91−3.94 (m, 1H), 4.13 (dd, J = 9.6, 11.3 Hz, 1H), 4.32 (dd, J = 9.5, 11.3 Hz, 1H), 4.59 (s, 2H), 4.7 (d, J = 8.8 Hz, 1H), 4.81 (d, J = 11.2 Hz, 1H), 7.24−7.40 (m, 13H), 7.5−7.6 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 68.6, 73.4, 73.7, 75.2, 76.3, 77.0, 84.9, 87.3, 127.7, 127.9, 128.3, 128.4, 128.5, 128.6, 129.0, 131.9, 133.2, 136.7, 137.6, 153.5. Anal. Calcd for $C_{27}H_{26}O_6S$: C, 67.76; H, 5.48. Found: C, 67.77; H, 5.50.

General Procedure for Glycosylation with 8 and 9 Using the BSP/TTBP/Tf_2O System. To a stirred solution of donor (1 equiv), BSP (1.1 equiv), TTBP (1.5 equiv), and 4 Å molecular sieves in CH_2Cl_2 (0.05 M in substrate), at −60 °C under an Ar atmosphere, was added Tf_2O (1.2 equiv). After 30 min of stirring at −60 °C, a solution of the glycosyl acceptor (1.5 equiv) in CH_2Cl_2 (0.02 M in acceptor) was slowly added. The reaction mixture was stirred for further 2 h at −60 °C and was allowed to reach room temperature. The reaction mixture was diluted with dichloromethane (10 mL), and molecular sieves were filtered off and washed with saturated $NaHCO_3$. The organic layer was separated, dried, and concentrated. Purification by flash column chromatography on silica gel, eluting with hexane/ethyl acetate mixtures, afforded the corresponding α- and β-glucopyranosides.

General Procedure for Deprotection of 2,3- and 3,4-*O*-Carbonates. To a solution of substrate (20 mg) in THF (2 mL) was added five drops of 1 M LiOH in water solution. The reaction mixture was stirred until all of the starting material was consumed as confirmed by TLC (∼2 h). The solvent was removed under reduced pressure, and residue was dissolved in CH_2Cl_2 (5 mL) and washed thoroughly with water. The organic layer was separated, dried (Na_2SO_4), and concentrated to give corresponding diols in quantitative yield.

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

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