JOC The Journal of Organic Chemistry

Article

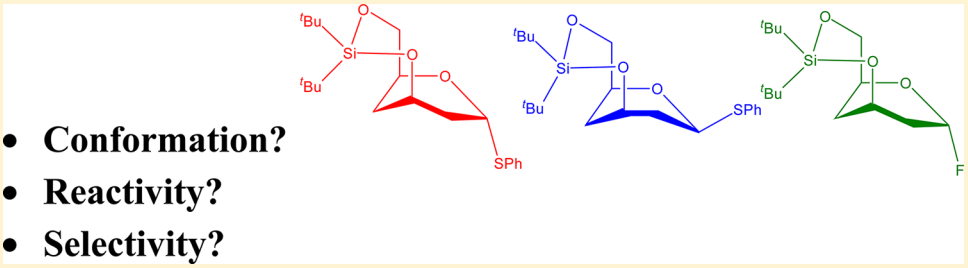
pubs.acs.org/joc

Conformationally Armed 3,6-Tethered Glycosyl Donors: Synthesis, Conformation, Reactivity, and Selectivity

Mads Heuckendorff, Christian Marcus Pedersen,* and Mikael Bols

Department of Chemistry, University of Copenhagen, DK-2100 Copenhagen Ø, Denmark

Supporting Information



ABSTRACT: The reactivity and selectivity of 3,6-tethered glycosyl donors have been studied using acceptors with different steric and electronic characteristics. Eight (four anomeric pairs) 3,6-bridged-glycosyl donors were synthesized in high yields from their common parent sugars. The glycosylation properties were tested using at least three different acceptors and several promoter systems. Thiophenyl 2,4-di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-α-D-glucopyranoside gave α/β mixtures with standard NIS/TfOH mediated activation, whereas the corresponding fluoride was found to be highly β-selective, when using $SnCl_2/AgB(C_6F_5)_4$ as the promoter system. Mannosyl donors were highly α-selective despite the altered conformation. Galactosylations using NIS/TfOH were generally α-selective, but more β-selective using the galactosyl fluoride and depending on the acceptor used. Thiophenyl 2-azido-2-deoxy-4-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-α-D-glucopyranoside was found to be α-selective . The reactivity of the donors was investigated using competition experiments, and some but not all were found to be highly reactive. Generally it was found that the α-thioglycosides were significantly more reactive than the β; this difference in reactivity was not found for 3,6-anhydro-, armed-(benzylated), or the classic super armed (silylated) donors. A mechanism supporting the unusual observations has been suggested.

INTRODUCTION

Carbohydrates structures are of crucial importance in every corner of biology, yet carbohydrates and carbohydrate analogues are underexplored as pharmaceuticals. One of the reasons is undoubtedly the comparatively difficult synthesis and higher complexities of carbohydrates compared to most small molecules. Many intrinsic properties of carbohydrates are also poorly understood as they frequently react widely different than organic molecules with few functionalities.[1]

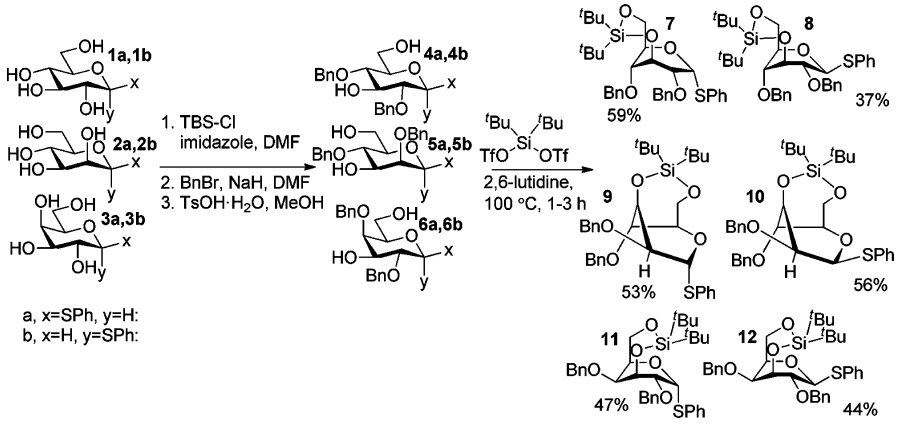
One such phenomenon was the difference in hydrolysis rates of stereoisomeric glycosides,[2] e.g., why do galactosides hydrolyze 5 times faster than glucosides? This was explained by the recent discovery that there is a de facto difference in electron-withdrawing effect from the axial and equatorial OH both in the ground and transition state.[3,4] One of the interesting consequences of this discovery is that it is possible to increase the hydrolysis rate of a gluco-derivative more than 100-fold by forcing it from a $^4C_1$ chair to a $^1C_4$ chair conformation.[5] This has recently been used to enhance the rate of hydrolysis of carbohydrate-based biomass.[6] We and others have subsequently been engaged in studying the influence of stereo electronic effects in the more complicated glycosylation reactions.[7]

The importance of protective groups in glycosylation reactions has been realized for decades and was originally studied by Paulsen,[8] who found that benzylated glycosyl donors are more reactive than acetylated. This was later conceptualized by Fraser-Reid who invented the armed-disarmed concept,[9] which has been of major importance in the development of efficient oligosaccharide synthesis protocols. Using the principles described above of higher reactivity of carbohydrate derivatives with axial O-groups, it is possible to go beyond the reactivity of armed glycosyl donors by forcing the molecule into an axial rich conformation. This can be done by introduction of bulky silyl protective groups trans vicinal to each other.[10] Due to the bulkiness a conformational ring flip is favorable, and partial or completely flipped sugars are obtained.[11] Glycosylation with the all-axial or axial rich donors revealed that they indeed were superior in reactivity compared with the armed derivatives.[12] Trisaccharide donors could be prepared in a one-pot one-addition protocol having three thioglycosides present at the same time competing about the same promoter.[10b] To expand the scope of using super armed donors with access to nonvicinal branching points, tethering of the 3,6-hydroxyl

Received: June 12, 2013
Published: June 20, 2013

dx.doi.org/10.1021/jo4012464 | J. Org. Chem. 2013, 78, 7234−7248

Scheme 1. Synthesis of the 3,6-Tethered Glycosyl Donors[a]



[a]Yields refer to the last step.

groups and the 2,4-hydroxyl groups was investigated using di-*tert*-butyl silylene as the bridging reagent. The initial results demonstrated that the 3,6-tethered donor was highly reactive, whereas the 2,4-tethering was not.[13] Parallel to our investigations of glycosyl donors having a 3,6-tethering, Yamada and co-worker developed a synthesis of 3,6-*O*-(*o*-xylylene)-bridged glycosyl fluoride donor,[14] originally for the synthesis of 3,6-bridged natural products.[15] The synthesis of the donor is rather complicated, since the bridge can only be installed on the open chain form of the sugar and hence 13 steps from glucose are needed. With the donor in hand Yamada and co-workers discovered that complete β-selectivity was obtained when using $SnCl_2/AgB(C_6F_5)_4$ as the promoter system.[16] It was furthermore shown that both anomers initially are formed but epimerize into the strongly favored β, presumable by catalysis performed by HF formed under the conditions. These recent results prompted us to expand the ongoing research on conformationally restricted donors. Herein we presents a thorough study on 3,6-bridged glycosyl donors, covering the most common glycopyranoside donors, i.e., gluco-, manno-, galacto-, and 2-azido-gluco-pyranosides.

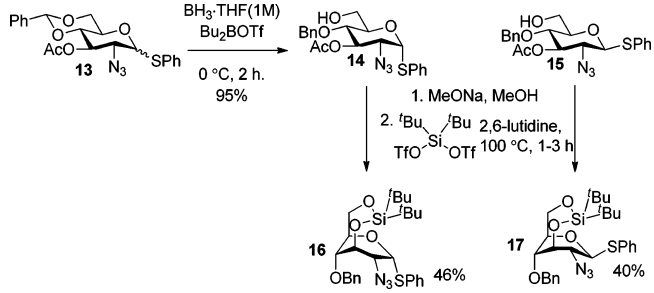
RESULTS AND DISCUSSION

Synthesis of Glycosyl Donors. In preliminary work[13,10d] it was demonstrated that the 3,6-bridging can be installed directly on the readily available phenyl 2,4-di-*O*-benzyl-1-thio-α-D-glucopyranoside.[17] The initial yields were modest but could be significantly improved by raising the reaction temperature, strictly anhydrous conditions, and prolonged reaction time. Scheme 1 shows the general method for direct 3,6-bridge formation from the 3,6-diols. Pleased with the easy introduction and high stability of the di-*tert*-butylsilylene bridge in the α-glucopyranoside, we investigated the substrate scope. The 3,6-diols of the α-[18] and β-anomers of mannoside, galactoside, and glucoside were efficiently synthesized from the corresponding thioglycosides via a selective 3,6-silylation using TBS-Cl together with imidazole in DMF, followed by 2,4-benzylation and subsequent acid-mediated desilylation to the 3,6-diols.[19] The diols were then, without further optimization, reacted with di-*tert*-butylsilylene ditriflate in 2,6-lutidine at 100 °C for 1−3 hours to give the target 3,6-bridged donors in reasonable yields. Both the α- and β-donors of different sugars were prepared effectively, and the configuration of the parent sugars has only little or no effect on the on the outcome of the reactions; hence this method is generally applicable.

Encouraged by the straightforward and efficient bridging using di-*tert*-butyl-silylene ditriflate as the reagent, a number of other alternative bridging reagents were investigated. As a one-carbon bridge, to give a six-membered ring, acid-catalyzed acetal formation was tried using benzaldehyde dimethyl acetal as the reagent. No product was observed. Introduction of the acetal under basic conditions was also investigated using α,α-dibromo toluene as the reagent[20] or Rollins reagent,[21] but with no improvement. Introduction of two-, three-, and four-carbon bridges was also unsuccessfully investigated by using 3,4-dichloro-*cis*-cyclobutene,[22] 3-chloro-2-(chloromethyl)-1-propene, and α,α'-dibromo-*o*-xylene respectively. Finally 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane was tried, but as noticed by Yamada, bridging the glucopyranoside is not straightforward!

The 2-azido-glucosyl donor was synthesized from the known benzylidene **13**[23] via a selective reductive opening using borane−THF complex and dibutylboron triflate as the catalyst (Scheme 2).[24] Separation of the anomers **14** and **15** followed

Scheme 2. Synthesis of 2-Azido 3,6-Tethered Glycosyl Donors



by deacetylation gave the 3,6-diols in high yields. Transformation of the diols into the axial rich bridged compounds **16** and **17** went uneventfully using the standard procedure, giving the donors in reasonable yields and underlining the generality of this approach.

In order to investigate Yamada's method for β-selective glucosylation[14] with this donor system, the corresponding glycosyl fluorides were synthesized by direct conversion of the thio-glycosides using DAST and NBS in CH_2Cl_2.[25] No

dx.doi.org/10.1021/jo4012464 | J. Org. Chem. 2013, 78, 7234−7248

Table 1. Coupling Constants, Optical Rotation, and Retention Factor Values for the Eight Thioglycosyl Donors

	H1	H2	H3	H4	H5	H6	H6	C1-H	[α]	R_f pet. ether/CH_2Cl_2 2:1
7	6.09 (d, 5.9)	4.04 (m)	4.56 (t, 1.4)	4.04 (m	4.50 (br s)	4.24 (d 12.7)	4.04 (m)	84.8 (160.5, 4.4)	65.0	0.38
8	5.14 (d, 9.2)	3.71 (dd, 9.2, 0.7)	4.49−4.42 (m)	4.11 (dd, 3.4, 0.9)	4.04 (m)	4.20−4.08 (m)	3.91 (dd, 12.3, 3.0)	83.8 (160.4, 3.9)	10.8	0.65
9	5.65 (d, 4.9)	3.89 (dd, 4.9, 3.9)	4.52 (m)	4.18−4.13 (m)	4.42 (br s)	4.18−4.13 (m)	3.95 (dd, 12.3, 2.9)	85.5 (165.0, 2.5)	93.1	0.62
10	5.44 (d, 5.1)	3.96 (t, 5.1)	4.63 (t, 4.8)	4.17 (d, 4.3)	4.08 (d, 2.9)	4.25 (dd, 12.4, 0.8)	3.93 (dd, 12.4, 2.9)	85.1 (156.6, 6.0)	6.1	0.73
11	6.17 (d, 3.2)	3.97 (t, 3.0)	4.59 (t, 2.9)	4.33 (dd, 6.7, 3.0)	4.03 (d, 6.6)	4.43 (dd, 13.1, 1.5)	4.23 (dd, 13.1, 2.3)	82.8 (160.2, 5.8)	2.9	0.49
12	4.75 (d, 8.5)	3.79 (dd, 8.5, 0.9)	4.54 (t, 1.3) 1H)	4.10 (dd, 8.2, 1.8)	4.14 (d, 8.2)	4.32 (dd, 12.3, 1.5)	4.19 (dd, 12.3, 2.0)	85.0 (157.1, 3.9)	−31.0	0.70
16	6.06 (d, 4.2)	3.95−3.91(m)	4.55 (ddd, 2.4, 1.1)	3.95−3.91(m)	4.35 (br, s)	4.22 (dd, 13.2, 2.0)	4.03 (dd, 13.2, 3.1)	82.1 (160.8, 5.7)	8.4	0.41
17	5.06 (d, 9.8)	3.67 (d, 9.8)	4.11 (d, 3.4)	4.50 (d, 3.6)	4.16 (d, 3.1)	4.20 (dd, 12.6, 0.9)	3.90 (dd, 12.6, 3.3)	83.4 (160.2, 4.2)	41.9	0.78

degradation of the silylene bridge was observed under these conditions. All of the fluoride donors were obtained with high α-selectivity and in good yields.

Conformation. The 3,6-bridged donors were analyzed in detail to determine their conformation, in order to elaborate the influence of the bridge on the ground state structures. $^3J_{HH}$ coupling constants were obtained from ^{1}H NMR (see Table 1), and the approximate vicinal angles were determined on this basis.[26] With this information the ring could be modeled in Chem3D[27] and the structure determined. The glycosyl donors were all found to resemble a boat conformation, $B_{1,4}$, or a skew conformation, $^3S_1$. Donors with α-gluco-stereochemistry (**7** and **16**) resembled a $^3S_1$ conformation, with a pseudo equatorial thiophenol avoiding flag-pole interactions with the 4-*O*-Bn. The β-anomers (**8** and **17**) on the other hand resembles an almost perfect $B_{1,4}$ with a diaxial $^3J_{H1-H2}$ coupling constant (9.2 Hz). The mannosyl donors, **9** and **10**, were both found to be in a $^3S_1$ conformation, avoiding unfavorable interactions between the silylene bridge and the 2-*O*-benzyl and thiophenol, respectively. This conformation is in agreement with the observed difference (app. 8.5 Hz) in the $^1J_{C1-H1}$ couplings, the chemical shifts, and the $^3J_{H1-H2}$ couplings (4.9 and 5.1 Hz (α and β); see Table 1). The α- and β-galactosyl donors (**11** and **12**) adopts an approximate $B_{1,4}$ conformations, which have minimal strain from steric interactions between the bridge and the now equatorial 4-*O*-Bn and the thiophenol, respectively. The measured optical rotations are consistent with Hudson's rule[28] with the exception of the 2-azido sugars (**16** and **17**). A substantial difference between the retention times (R_f values; see Table 1) were observed with the α-anomer having the smallest in all cases. This suggests an unusually big difference in their respective dipole moments.

The $^1J_{C1-H1}$ couplings are surprisingly similar for all the anomeric pairs with the mannosyl donors (**9** and **10**) being the only pair with a significant difference between them. The donors with gluco-stereochemistry (**7**, **8**, **16**, and **17**) have practically the same $^1J_{CH}$ around 160 Hz and the galacto-pair (**11** and **12**) have couplings within a difference of 3 Hz. The difference usually observed in regular chair conformations between anomers is around 10 Hz, with the α-anomer (equatorial H) giving the larger coupling constant. The small differences observed here suggest a similar C−H bond length and orientation.[29] To eliminate the possibility of having two or more conformations in a rapid equilibrium, ^{1}H NMR of all donors were also recorded at −60 °C. None of the spectra deviated significantly from the ones recorded at 26 °C, and the conformations are therefore considered be in the ground state for the 3,6-bridged system.

Glycosylations. With the eight thioglycoside donors (**7**−**12**, **16**, and **17**) in hand, their properties as glycosyl donors could be studied. As a standard test three different types of acceptors were chosen (Figure 1): cyclohexanol **22** (a

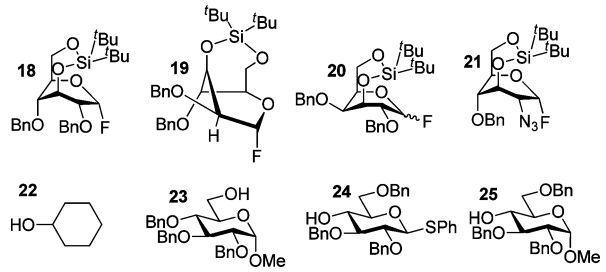
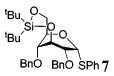
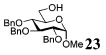
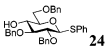
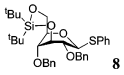
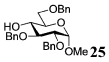
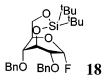
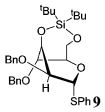
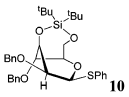
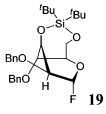
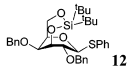
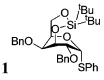
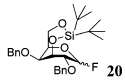
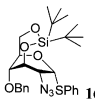
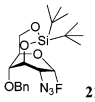


Figure 1. Glycosyl fluorides and acceptors.

secondary nonchiral acceptor), a primary sugar hydroxyl group **23** (methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside), and finally a sterically hindered secondary sugar hydroxyl group on a glycosyl donor **24** (phenyl 2,3,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside) to challenge the reactivity and hence determine whether the new donor is to be considered super armed. When the reactivity test failed, then glycosylation was carried out on a regular 4-hydroxyl acceptor **25** (methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside). All donors are activated at low temperature, in the presence of the acceptor. The reaction mixture was then allowed to slowly warm to 0 °C, where it was quenched by adding triethylamine. As the preferred promoter system NIS/TfOH was chosen due to high yields, clean reactions, and the formation of I_2, which makes it easy to follow the reaction visually (see Table 2). Preactivation (Ph_2SO, Tf_2O, TTBP)[30] and Lemieux conditions[31] were also tried, but decomposition of starting material, together with side products (mainly Friedel−Crafts-type reaction with the 2-*O*-benzyl[32]), and only a small amount of products were observed. The selectivity in the glycosylation reactions was determined by ^{1}H NMR of the crude reaction mixtures, and all products were deprotected to confirm the stereochemistry. Table 2 summerizes the glycosylation reactions. In term of selectivity

dx.doi.org/10.1021/jo4012464 | J. Org. Chem. 2013, 78, 7234−7248

Table 2. Yields and α/β Ratios for the Glycosylations

Donor	Acceptor	Promoter	Solvent	Temperature	Yield	α/β
 **7**	 **22**	NIS/TfOH	CH_2Cl_2	-78 → 0 °C	91 %	1.4/1
7	 **23**	NIS/TfOH	CH_2Cl_2	-78 → 0 °C	98 %	4/1
7	 **24**	NIS/TfOH	CH_2Cl_2	-78 →0 °C	64 %	1.7/1
 **8**	**22**	NIS/TfOH	CH_2Cl_2	-78 →0 °C	99 %	1.8/1
8	**23**	NIS/TfOH	CH_2Cl_2	-78 →0 °C	93 %	3.8/1
8	 **25**	NIS/TfOH	CH_2Cl_2	-78 →0 °C	92 %	1.9/1
 **18**	**22**	$SnCl_2$ $AgB(C_6F_5)_4$	BTF	25 °C	89 %	Only β
18	**23**	$SnCl_2$ $AgB(C_6F_5)_4$	BTF	25 °C	75 %	Only β
18	**25**	$SnCl_2$ $AgB(C_6F_5)_4$	BTF	25 °C	73 %	Only β
 **9**	**22**	NIS/TfOH	CH_2Cl_2	-78 → 0 °C	99 %	Only α
9	**23**	NIS/TfOH	CH_2Cl_2	-78 → 0 °C	99 %	Only α
9	**24**	NIS/TfOH	CH_2Cl_2	-78 → 0 °C	70 %	Only α
 **10**	**22**	NIS/TfOH	CH_2Cl_2	-78 → 0 °C	99 %	Only α
10	**23**	NIS/TfOH	CH_2Cl_2	-78 → 0 °C	96 %	Only α
10	**24**	NIS/TfOH	CH_2Cl_2	-78 → 0 °C	73 %	Only α
 **19**	**22**	$SnCl_2$ $AgB(C_6F_5)_4$	BTF	25 °C	98 %	Only α
19	**23**	$SnCl_2$ $AgB(C_6F_5)_4$	BTF	25 °C	74 %	Only α
19	**25**	$SnCl_2$ $AgB(C_6F_5)_4$	BTF	25 °C	71 %	Only α
 **12**	**22**	NIS/TfOH	CH_2Cl_2	-78 → 0 °C	95 %	10/1
12	**23**	NIS/TfOH	CH_2Cl_2	-78 → 0 °C	99 %	8.5/1
12	**25**	NIS/TfOH	CH_2Cl_2	-78 → 0 °C	99 %	Only α
 **11**	**22**	NIS/TfOH	CH_2Cl_2	-78 → 0 °C	99 %	10:1
11	**23**	NIS/TfOH	CH_2Cl_2	-78 → 0 °C	99 %	7:1
11	**24**	NIS/TfOH	CH_2Cl_2	-78 → 0 °C	51 %	Only α
 **20**	**22**	$SnCl_2$ $AgB(C_6F_5)_4$	BTF	25 °C	96 %	2:1
20	**23**	$SnCl_2$ $AgB(C_6F_5)_4$	BTF	25 °C	95 %	1:2
20	**25**	$SnCl_2$ $AgB(C_6F_5)_4$	BTF	25 °C	93 %	1:2
 **16**	**22**	NIS/TfOH	CH_2Cl_2	-78 → 0 °C	95 %	2.5/1
16	**23**	NIS/TfOH	CH_2Cl_2	-78 → 0 °C	99 %	4/1
16	**25**	NIS/TfOH	CH_2Cl_2	-78 → 0 °C	94 %	3:1
 **17**	**22**	NIS/TfOH	CH_2Cl_2	-78 → 0 °C	30 %	2/1
 **21**	**22**	$SnCl_2$ $AgB(C_6F_5)_4$	BTF	25 °C	95 %	Only β
21	**23**	$SnCl_2$ $AgB(C_6F_5)_4$	BTF	25 °C	84 %	1.2/1
21	**25**	$SnCl_2$ $AgB(C_6F_5)_4$	BTF	25 °C	87 %	2.2/1

no difference between the two anomeric donors was observed; all glucosylations were slightly α-selective and independent of donor stereochemistry. Glucosylation on the armed hindered donor **24** could be performed in a reasonable yield of 64% with the α-donor **7**, but interestingly no glucoside was obtained from the glucosylation using the β-anomer **8**. The β-donor, however, gave an excellent yield (92%) when using the 4-OH acceptor **25**. This demonstrates an unusual big difference in reactivity between the anomers, with the α being the most reactive and super armed and the β not (see Table 2).

dx.doi.org/10.1021/jo4012464 | J. Org. Chem. 2013, 78, 7234−7248

The β-selective procedure developed by Yamada was performed using the glucosyl fluoride **18**, which is obtained in one step from the thioglucoside **7**. Similar to Yamada's xylylene bridged donor[15] a complete β-selectivity was observed with the promoter system $SnCl_2/AgB(C_6F_5)_4$ in benzotrifluoride (BTF). TLC of the reaction progress suggested that the α-anomer is initially formed but in time is anomerized to the thermodynamically more stable β-anomer. This means that the silylene bridge is an easy accessible alternative to Yamada's xylylene bridge. The phenyl 2,3,6-tri-*O*-benzyl-1-thio-β-D-glucopyranoside donor was also tried as acceptor, but the thioglucoside is not compatible the catalytic promoter system.

The mannosyl donors **9** and **10** were investigated in the same way as the glucosyl donors (**7** and **8**) and gave excellent yields and complete α-selectivity with the different acceptors. Coupling with the armed donor gave the disaccharide donor in around 70% for both anomers, i.e., both are highly reactive. Essentially no difference in yields or selectivity was observed between the anomeric set of donors. Encouraged by the great shift in selectivity toward the β-anomer when using Yamada's procedure, the mannosyl fluoride donor **19** was prepared from the corresponding thiomannoside **9**, and the glycosylation on the three acceptors was performed. Disappointingly, no β-product was obtained, but complete α-selectivity and good to excellent yields. Prolonged reaction time or increased temperature did not change the outcome.

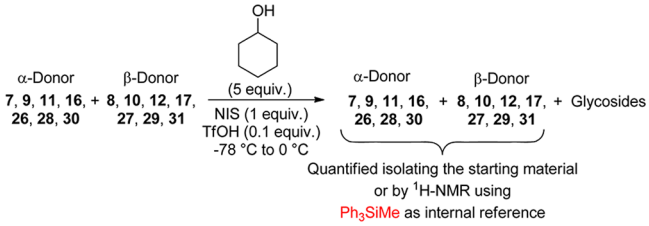
The galactosyl donors **11** and **12** were found to perform similarly to the glucosyl donors, giving excellent yields and α-selectivity, which is slightly higher for these donors and increases with the steric bulk of the acceptor. As with the glucosyl donors (**7** and **8**) only the α-donor was found to be more reactive than an armed donor **24**. The β-donor **12** gave mixtures with an armed donor, but excellent yield and selectivity when coupling to the 4-OH acceptor **25**. Changing to the $SnCl_2/AgB(C_5F_6)_4$ promoter system and the galactosyl fluoride **20** produced a change in product ratios, and a slight β-selectivity was obtained when using carbohydrate based acceptors (**23** and **25**). The equilibrium is however far from the gluco case, and only a 2:1 (β:α) ratio could be achieved (Table 2).

The 2-azido donors **16** and **17** were, as expected, significantly less reactive than the other donors, and therefore no glycoside formation was observed when using the armed donor **24** as acceptor. The selectivity was however found to be close to that observed for the gluco-donors (**7** and **8**). When the α-donor **16** was used, excellent yields were obtained within the temperature frame, despite the higher activation temperature. Changing to the β-donor **17** gave a dramatic decrease in yield, from 99% to 30%, when using the simple cyclohexanol acceptor. This result could not be improved further by using more promoter or higher temperatures; unreacted donor remained the major outcome of the reaction. This again underlines the substantial difference in reactivity between the anomers. The product ratio was found to be essentially the same. Shifting to the glycosyl fluoride **21** and using the $SnCl_2/AgB(C_6F_5)_4$ promotor system, a complete β-selectivity was observed for the cyclohexanol acceptor. The selectivity however decreased when using the carbohydrate acceptors but remained β-selective. The yields ranged from 84% to 95%. This result suggests that the anomerization is taking place in all of the reactions described here, since it is observed with this, the least reactive donor **21**, and therefore the product ratios mirror the thermodynamic equilibrium.

Competition Experiments between Anomers. Due to the unexpected and pronounced difference in the reactivity of the bridged donors, a number of competition experiments were carried out. In order to compare the 3,6-bridged donors with other more common donor systems, three other anomeric pairs were synthesized. Classic α- and β- super armed glucosyl donors (**26** and **27**) (silylated) were included because of their conformational resemblance with the bridged donors, both being close to the $^3S_1$ conformation, but **26** and **27** being unrestricted. A pair of armed glucosyl donors (**28** and **29**) (phenyl 2,3,4,6-tetra-*O*-benzyl-D-thioglucopyranoside), being in the $^4C_1$ chairs representing a standard donor type, and finally a pair of 3,6-anhydro-donors (**30** and **31**), being 3,6 -tethered, but without the bulky bridge, were chosen.

With the 14 donors in hand, each pair was activated under the NIS/TfOH conditions. One equivalent of each donor competes for 1 equiv of promoter; the acceptor **22** is present in 5 equiv. The competition reactions were analyzed by isolating the remaining starting material or by NMR of the crude reaction mixtures. Since the donors have more distinct spectra, compared with the products, the amount of unreacted donor was determined by using methyltriphenylsilane as an internal standard in the NMR spectra (see Scheme 3). In the

Scheme 3. Competition Experiments between Anomeric Pairs of Donors[a]



[a]The reactivity is estimated from the amount of remaining donors isolated or observed and quantified by ^{1}H NMR.

competition experiments with the silylene bridged donors only the α-anomers (**7**, **9**, **11**, **16**) were fully consumed and only a little of the β-anomer (**8**, **10**, **12**, **17**) (Table 3, entries 1−4). In the reaction with the 2-azido donors a trace of remaining α-donor could be observed (see Table 3 for the results).

When the competition experiment was performed between the classic super armed donors (**26** and **27**, Figure 2), an almost 1:1 mixture of remaining donors could be observed after the reaction, i.e., the anomers have similar reactivity in agreement with earlier studies (Table 3, entry 5).[10c] Activation of the per-benzylated (armed) donors gave a 1:3 (α:β) ratio with the α-

Table 3. Ratios of Donor before and after the Competition Reaction

entry	donor x,x	ratio before	ratio after
1	**7,8**	1/1	0/0.84
2	**9,10**	1/1	0/0.97
3	**11,12**	1/1	0/0.93
4	**16,17**	1/1	0.03/0.94
5	**26,27**	1/1	0.52/0.42
6	**28,29**	1/1	0.22/0.66
7	**30,31**	1/1	0.35/0.41
8	**7,26**	1/1	0.18/0.73

dx.doi.org/10.1021/jo4012464 | J. Org. Chem. 2013, 78, 7234−7248

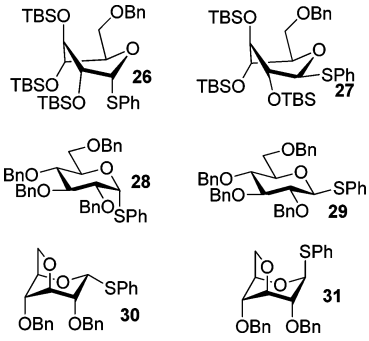


Figure 2. Donors, besides the 3,6-silylene bridged, used in competition experiments.

anomer **28** being slightly more reactive than the β **29** (Table 3, entry 6). Finally the 3,6-anhydro donors gave a 1:1 mixture of unreacted donors, **30** and **31**, mirroring a similar reactivity, despite the 3,6-restricted conformation (Table 3, entry 7). Thus the silylene bridge donors *are* special cases with an unpresented difference in anomeric reactivity.

To clarify whether the bridged super armed donor **7** can compete or even exceed the reactivity of a classic unrestricted silylated donors, such as **26**, a competition between the two types was performed (Table 3, entry 8). The donors (**26** and **7**) were allowed to compete for the promoter, as described above, and to our surprise crude NMR revealed that more of the bridged donor had been consumed. The classic super armed donor **26** is therefore less reactive than bridged donor **7** (see Table 3 for the results and Supporting Information for details and data).

The 3,6-bridged donors (**7**−**12**, **16**, and **17**) demonstrate some unique and surprising properties. Due to the axial rich conformation, it was expected that their reactivity would exceed that of the armed donors, such has been demonstrated with the super armed donors earlier developed by this group.[10] Indeed the reactivity was superior for all the bridged 3,6-bridged α-thioglycosides, but surprisingly only the β-manno donor **10** could compete with a conventional armed donor **24**. The β-galacto-donor **12** and β-gluco-donor **8** gave rise to mixtures, and the reactivity was found to be in the range of that of an armed perbenzylated donor. The difference in anomeric reactivity is clearly related to the silylene bridge and not only the conformation, as demonstrated by the glycosylations with the conventional super armed donors (**26** and **27**) and the 3,6-anhydro-donors (**30** and **31**). None of them show any significant difference between the anomers (see Table 3). The difference observed here can be explained by the conformational limitations introduced by the bulky di-*tert*-butylsilylene, which dictate the conformation for the part of the sugar ring included in the seven-membered tethering. The two *tert*-butyl substituents force the C-1 downward due to steric conflicts, and the conformational freedom is reduced to essentially two conformations, the $^3S_1$ and the $B_{1,4}$. These conformations are close to the intermediate oxo-carbenium ions' $^3H_4$ conformation (see Figure 3),[33] and since it is locked, the reactivity, i.e., the leaving group ability, of the activated thioacetal (sulfonium ion) becomes important. There is not enough flexibility to provide access to a pseudoaxial sulfonium ion from the pseudo equatorial and *vice versa* (see Figure 4).[34]

Upon activation the build-up of positive charge on the sulfur demands electrons to be stabilized. When having the axial/pseudoaxial configuration at C1, the *anti-periplanar* electron pair on O5 can participate as in a classic E1 elimination reaction (Figure 4).[35] This generates the oxocarbenium intermediate and departure of the phenyl hypoiodothionite. Due to inefficient overlap this cannot take place when having the equatorial/pseudoequatorial configuration (Figure 4). The orientation of O6, which is dictated by the bridge, might also contribute additionally to the stability of the oxocarbenium ion.[36] Yang and Woerpel have observed this conformation on dioxocarbenium ions by NMR.[37] These observations have also been supported by theoretical studies.

Release of strain might also be an important contribution to the increased reactivity of the axial configuration. As mentioned above flag-pole interactions with the substituents on C4 generate unfavorable steric interactions. The equatorial isomers on the other hand are in steric conflict with the bridge.

There could be parallels between this proposed mechanism and what is referred to as the ether effect[38] and in some cases the "reverse anomeric effect".[39] In these "effects" a cationic substituent on C1 prefers an equatorial position. The axial

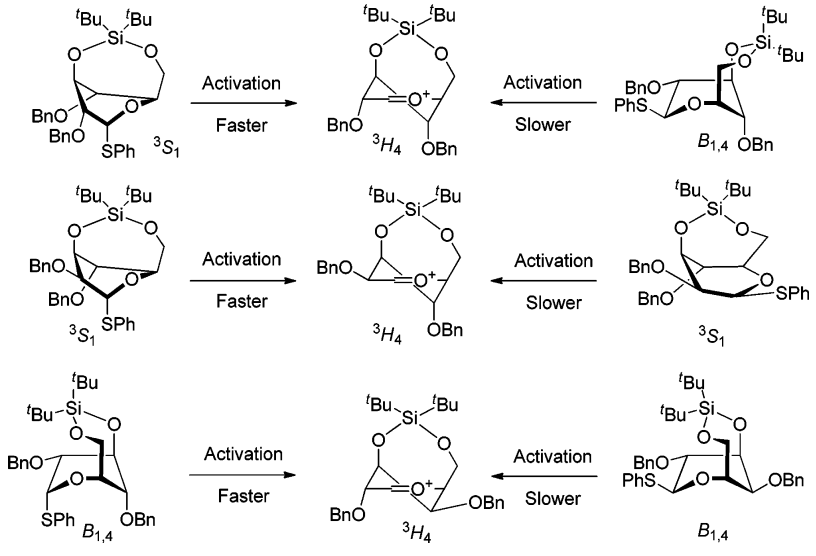


Figure 3. Reaction pathway for the glycosyl donors.

dx.doi.org/10.1021/jo4012464 | J. Org. Chem. 2013, 78, 7234−7248

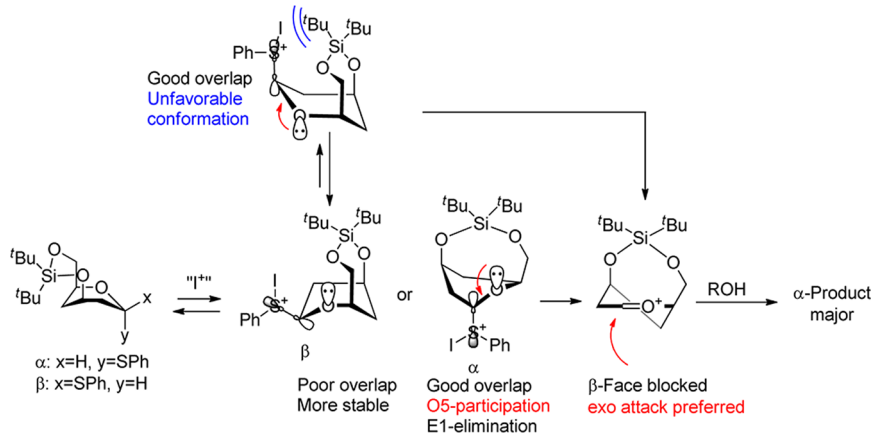


Figure 4. α-Anomer is activated faster than the β-anomer because of the optimal anti periplanar orbital alignment for an E1 elimination. To obtain a similar overlap the β-anomer has to approach the $^1C_4$ conformation, which is sterically highly unfavorable.

aglycon might simply be too reactive[40] and hence will transform into the thermodynamic product, the equatorial isomer. A similar trend has been observed in studies of the related glycosyl sulfonium ions by low temperature NMR; only the equatorial isomers were observed.[41]

The observed stereoselectivity stems from several contributing effects. The bridge itself is very sterically demanding and shields the β-face effectively.[42] The effect is enhanced when the O4 is equatorial and pushes the bridge further toward the anomeric site, i.e., the galacto-donors (**11** and **12**) gives more α-product compared to the donors with gluco-stereochemistry (**7** and **8**). The enhanced effect in the galacto donors is resulting in an increased α-selectivity with increasing acceptor size.

Normally the attack on the oxocarbenium ion, which directly produces the chair conformation, is kinetically preferred. Attack from the opposite site gives a twist-boat conformation, which in unrestricted donors has to transit to the thermodynamic more stable chair. In the bridged donor the opposite effect is seen since the more stable ground state conformation is the $^3S_1$ or $B_{1,4}$; both close to the twist boat intermediate. The kinetic product is therefore the α-anomer (Figure 5).

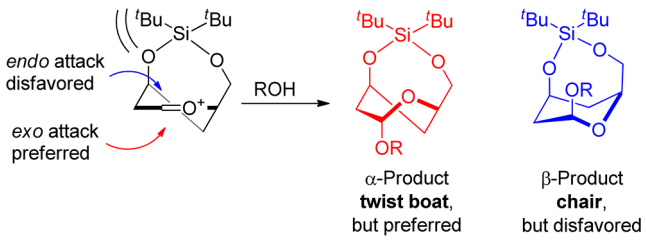


Figure 5. *Exo* attack is favored, and the α-anomer is thereby the major product. The normally disfavored twist boat is the most stable conformation due to the restriction by the 3,6-bridge.

When the glucosyl fluoride **18** was used as the donor, complete β-selectivity (using Yamada's conditions) could be obtained independent of the acceptor used. When the galacto-donor **20** was used, an increase in β-product was observed compared with the NIS/TfOH method, but not to a synthetically useful extent. Despite the lower reactivity of the 2-azido derivative **21**, complete β-selectivity could be obtained with the cyclohexanol acceptor. The complete α-selectivity in the mannosylation (with **19**) was however unaffected by the anomerization conditions. The experiments strongly suggest that the post-glycosylation anomerization is taking place for all of the donors, even the disarmed 2-azido donor **21**, and the obtained product ratios are therefore mirroring the thermodynamic equilibrium between the anomers obtained from glycosylation with the four glycosyl fluoride donors (**18**–**21**) (12 glycosylations), with the two extremes being the strongly favored β-glucosides and α-mannosides. The remarkable β-gluco-selectivity can be explained by the looking at the conformations; the β-anomers prefers a $B_{1,4}$, whereas a $^3S_1$ is more stable for the α due to the flag-pole interactions. As illustrated in Figure 3 there is only little strain in the $B_{1,4}$ conformation, and hence it must be more thermodynamically stable. The galacto stereochemistry reduces the flag-pole interaction and pushes the bridge toward the β-site, and the effect diminishes the difference between the anomers. The α-mannosides are disfavored by the flag-pole interactions, but this effect is overruled by stereoelectronic effects from the neighboring O2 and the O5. The interplay between the anomeric effect and the Δ2 effect[43] is acting and stabilizes the α-anomer. Additionally the $B_{1,4}$ conformation, favoring the β-anomer, is disfavored by the steric clash between the bridge and the 2-*O*-Bn, making the $^3S_1$ conformation the most stable.

In conclusion, it has been shown that 3,6-bridged glycosyl donors indeed are more reactive than conventionally armed glycosyl donors and hence they are super armed. It is now possible to super arm the most common glycosyl donors with a 3,6-tether, making the concept even more attractive for oligosaccharide synthesis, especially when a 2–4 or 3–6 branching is desired. The reactivity is strongly dependent on anomeric configuration, with an axial leaving group being superior. This has been explained by the need of participation from the O5 lone pair. When the overlap is poor, such as for the equatorial isomer, reactivity drops dramatically. The extent of this effect has not been observed earlier due to conformationally flexibility and steric in conventional donors. The effect is for example not seen in a perbenzylated-, 3,6-anhydro, or classic super armed glucosyl donor, so far only in the 3,6-bridged donors. Due to the restriction and bulk of the di-*tert*-butylsilylene only two ground state conformations are observed, the $^3S_1$ and the $B_{1,4}$. Anomerization using $SnCl_2$/$AgB(C_6F_5)_4$ as the catalyst takes place for all glycosides presented here, but only the gluco-stereochemistry, and hence conformation, significantly favors the β-product; α-mannosides

dx.doi.org/10.1021/jo4012464 | J. Org. Chem. 2013, 78, 7234–7248

are still thermodynamically favored despite the conformational changes.

EXPERIMENTAL SECTION

General Methods. All reagents were used as purchased without further purification. Dry solvents were taken from a solvent purification system. Glassware used for water-free reactions was dried for 12 h at 120 °C before use. Columns were packed with silica gel 60 (230−400 mesh) as the stationary phase. TLC plates (Merck, 60, F254) were visualized by 10% H_2SO_4 in EtOH and heating until spots appeared. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer equipped with a cryo probe. Chemical shifts (δ) are reported in ppm relative to the residual solvent signal (δ = 7.26 for ^{1}H NMR and 77.16 for ^{13}C NMR). High-resolution mass spectral (HRMS) data were obtained on an electrospray (ESI) time-of-flight mass spectrometer. Optical rotation data were obtained on a Perkin-Elmer 341 Polarimeter. NMR assignments were based on COSY and HSQC NMR experiments.

Phenyl 3,6-Di-*O*-acetyl-2,4-di-*O*-benzyl-1-thio-α-D-glucopyranoside. 1,3,6-Tri-*O*-acetyl-2,4-di-*O*-benzyl-α/β-D-glucopyranoside (16.6 g, 0.034 mol) and thiophenol (4.4 mL, 0.043 mol) in 200 mL dry DCM was cooled to 0 °C, and $BF_3{\cdot}Et_2O$ (5.26 mL, 0.043 mol) was added. The solution was allowed to reach room temperature and was stirred for 24 h. The reaction was quenched with satd bicarbonate solution. The mixture was extracted with 1 M HCl, satd bicarbonate solution, and brine. The organic layer was dried with $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by flash column chromatography with petroleum ether as eluent with a gradient of EtOAc Recrystallization from methanol gave the product as white crystals. Yield: 6.76, 38%. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.49−7.44 (m, 2H, Ar), 7.38−7.23 (m, 13H, Ar), 5.63 (d, *J* = 5.5 Hz, 1H, H1), 5.49 (t, *J* = 9.4 Hz, 1H, H3), 4.73 (d, *J* = 12.3 Hz, 1H, benzyl), 4.63−4.52 (m, 3H, benzyl), 4.49 (ddd, *J* = 10.0, 5.1, 2.1 Hz, 1H, H5), 4.28 (dd, *J* = 12.0, 5.2 Hz, 1H, H6), 4.20 (dd, *J* = 12.0, 2.2 Hz, 1H, H6), 3.79 (dd, *J* = 9.9, 5.5 Hz, 1H, H2), 3.57−3.50 (m, 1H, H4), 2.02 (s, 3H, Ac), 1.99 (s, 3H, Ac). ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.7(C═O), 169.8(C═O), 137.5(ipso), 137.4(ipso), 133.8(ipso), 132.0(Ar), 129.1(Ar), 128.7(Ar), 128.6(Ar), 128.2(Ar), 128.2(Ar), 128.14(Ar), 128.0(Ar), 127.5(Ar), 86.5(C1), 76.9(C2), 76.2(C3), 74.4(CH_2-benzyl), 73.9(C3), 72.2(CH_2-benzyl), 69.4(C5), 63.1(C6), 21.2(CH_3-Ac), 21.0(CH_3-Ac). Mp 143−144 °C, $[\alpha]^{rt}_D$ 195° (*c* 1.0, CH_2Cl_2), HRMS calcd for $C_{30}H_{32}O_7SNa$ 559.1766, found 559.1771

Phenyl 2,4-Di-*O*-benzyl-1-thio-α-D-glucopyranoside (4b). Phenyl 3,6-di-*O*-acetyl-2,4-di-*O*-benzyl-1-thio-α-D-glucopyranoside (6.7 g, 12.49 mmol) was dissolved in a mixture of 67 mL DCM and 67 mL MeOH. To the solution was added 5 mL of 25% sodium methoxide solution in methanol. The reaction was stirred until TLC showed full conversion. The solution was neutralized by adding Amberlite IR120. The solution was filtered and evaporated to dryness giving the product as a syrup. Yield 5.65 g, 100%. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.47−7.24 (m, 15H, Ar), 5.60 (d, *J* = 5.3 Hz, 1H, H1), 4.94 (d, *J* = 11.3 Hz, 1H, benzyl), 4.79 (d, *J* = 11.4 Hz, 1H, benzyl), 4.72 (d, *J* = 11.3 Hz, 1H, benzyl), 4.61 (d, *J* = 11.4 Hz, 1H, benzyl), 4.20 (dt, *J* = 9.9, 3.4 Hz, 1H, H5), 4.05 (t, *J* = 9.2 Hz, 1H, H3), 3.80−3.72 (m, 2H, H6), 3.69 (dd, *J* = 9.6, 5.4 Hz, 1H, H2), 3.56−3.50 (m, 1H, H4). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.4(ipso), 137.4(ipso), 134.1(ipso), 132.2(Ar), 129.2(Ar), 128.7(Ar), 128.7(Ar), 128.4(Ar), 128.4(Ar), 128.3(Ar), 128.1(Ar), 127.6(Ar), 86.4(C1), 79.3(C2), 76.9(C4), 74.8(CH_2-benzyl), 74.4(C3), 72.4(CH_2-benzyl), 71.5(C5), 62.0(C6). $[\alpha]^{RT}_D$ 185° (*c* 1.0, CH_2Cl_2), HRMS calcd for $C_{26}H_{28}O_5SNa$ 475.1555, found 475.1546

Phenyl 2,4-Di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-1-thio-α-D-glucopyranoside (7). Phenyl 2,4-di-*O*-benzyl-1-thio-α-D-glucopyranoside (0.3 g, 0.663 mmol) was dissolved in 8 mL of dry 2,6-lutidine. The solution was added di-*tert*-butylsilyl ditriflate (0.24 mL, 0.729 mmol) and heated to 100 °C for 4 h. The solution was cooled to rt, and ethyl acetate was added and then extracted 3 times with 1 M HCl solution, one time with satd bicarbonate solution, and one time with brine. The organic layer was dried with $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by flash column chromatography with petroleum ether as eluent with a gradient of DCM, giving the product as a clear oil. Yield 0.231 g, 59%. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.74−7.46 (m, 5H), 7.46−7.13 (m, 10H), 6.09 (d, *J* = 5.9 Hz, 1H, H1), 4.91 (d, *J* = 11.5 Hz, 1H, benzyl), 4.83−4.62 (m, 3H, benzyl), 4.56 (t, *J* = 1.4 Hz, 1H, H3), 4.50 (s, 1H, H5), 4.24 (d, *J* = 12.7 Hz, 1H, H6), 4.04 (m, 3H, H2, H4, H6), 0.95 (d, *J* = 12.4 Hz, 18H, TBS). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2(ipso), 138.0(ipso), 137.4(ipso), 130.6(Ar), 128.8(Ar), 128.5(Ar), 128.4(Ar), 128.0(Ar), 127.8(Ar), 127.7(Ar), 126.5(Ar), 84.8(C1), 78.0, 75.4, 73.6, 73.2(CH_2-benzyl), 71.2(CH_2-benzyl), 70.0, 68.3(C6), 28.4(CH_3), 28.1(CH_3), 21.9(C-Si), 21.2(C-Si). $[\alpha]^{rt}_D$ 65.0° (*c* 1.0, CH_2Cl_2), HRMS calcd for $C_{34}H_{44}O_5SSiNa$ 615.2576, found 615.2570

2,4-Di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-1-fluoro-α-D-glucopyranoside (18). Phenyl 2,4-di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-1-thio-α-D-glucopyranoside (0.0593 g, 0.1 mmol) was dissolved in DCM (2 mL), and the solution was cooled to −15 °C. To the solution was added DAST (0.04 mL, 0.3 mmol), the solution was stirred for 5 min, and then NBS (0.0463 g, 0.26 mmol) was added . The reaction was stirred for 1 h while it was slowly allowed to reach 0 °C. The reaction mixture was then transferred to a separation funnel, washed with satd bicarbonate solution and brine, then dried with $MgSO_4$, filtered, and evaporated to dryness. The crude compound was purified by flash column chromatography with petroleum ether as eluent with a gradient of DCM, giving the product as a clear oil. Yield 0.081 g, 81%, ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.41−7.38 (m, 2H, Ar), 7.37−7.33 (m, 2H, Ar), 7.33−7.30 (m, 1H, Ar), 7.29 (s, 5H, Ar), 5.72 (dd, *J* = 53.2, 5.9 Hz, 1H, H1), 4.80 (d, *J* = 11.8 Hz, 1H, CH-benzyl), 4.73 (d, *J* = 11.7 Hz, 1H, CH-benzyl), 4.68 (d, *J* = 11.5 Hz, 1H, CH-benzyl), 4.51−4.44 (m, 2H), 4.30−4.26 (m, 1H), 4.23 (dd, *J* = 12.7, 1.1 Hz, 1H, H6), 4.06 (s, 1H), 3.97 (ddd, *J* = 12.7, 3.0, 1.9 Hz, 1H, H6), 3.80 (dd, *J* = 22.5, 5.8 Hz, 1H, H2), 1.00 (s, 9H, TBS), 0.92 (s, 9H, TBS). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.1(ipso, Ar), 137.5(ipso, Ar), 128.6(Ar), 128.5(Ar), 128.1(Ar), 128.1(Ar), 127.9(Ar), 127.8(Ar), 109.9 (d, *J* = 212.3 Hz, C1), 83.3 (d, *J* = 23.9 Hz, C2), 81.4 (d, *J* = 4.2 Hz), 74.63−74.62, (broad doublet), 72.7 (d, *J* = 8.4 Hz), 72.7(CH_2-benzyl), 71.9(CH_2-benzyl), 66.7(C6), 28.1(CH_3), 27.8(CH_3), 21.8(C-Si), 21.6(C-Si).^{13}C NMR (126 MHz, chloroform-*d*, CH-coupling) δ 109.9 (dddd, *J* = 212.3, 174.9, 5.2 Hz). ^{19}F NMR (282 MHz, chloroform-*d*) δ −134.9 (dd, *J* = 52.6, 23.1 Hz). $[\alpha]^{rt}_D$ 34.6° (*c* 1.0, $CHCl_3$), HRMS calcd for $C_{28}H_{39}O_5SiFNa$ = 525.2448, found 525.2444

Phenyl 3,6-Di-*O*-TBS-1-thio-β-D-glucopyranoside. To a solution of phenyl-1-thio-β-D-glucopyranoside (8.28 g, 0.0304 mol) in 125 mL DMF at 0 °C were added imidazole (7.25 g, 0.106 mol) and TBSCl (16.0 g, 0.0912 mol). The mixture was stirred overnight at room temperature and was then quenched with MeOH. The mixture was added EtOAc and extracted with 1 M HCl, satd bicarbonate solution, and brine. The organic layer was dried with $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by flash column chromatography with petroleum ether as eluent with a gradient of DCM, giving the known product as a clear oil. Yield 7.89 g, 52%.

Phenyl 2,4-Di-*O*-benzyl-1-thio-β-D-glucopyranoside (4a). To a solution of phenyl 3,6-di-*O*-TBS-1-thio-β-D-glucopyranoside (7.89 g, 0.0158 mol) in 75 mL DMF at 0 °C were added BnBr (5.62 mL, 0.0473 mol) and NaH (1.9 g, 0.0473 mol). The mixture was stirred overnight at room temperature and was then quenched with MeOH. The mixture was added to Et_2O and extracted with water, and brine. The organic layer was dried with $MgSO_4$, filtered, and evaporated to dryness. The crude product was dissolved in 50 mL MeOH, and a catalytic amount of TsOH was added. The mixture was refluxed for 2 h and quenched by adding 3 mL of Et_3N. The mixture was evaporated, and the crude product was purified by flash column chromatography with petroleum ether as eluent with a gradient of EtOAc, giving the product as a clear plastic solid. Yield 5.68 g, 80%. The compound can be crystallized from MeOH giving white crystals. Mp 63−65 °C, ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.56−7.52 (m, 2H, Ar), 7.44−7.31 (m, 13H, Ar), 5.01 (d, *J* = 10.9 Hz, 1H, CH_2-benzyl), 4.85 (d, *J* = 11.3 Hz, 1H, CH_2-benzyl), 4.77−4.69 (m, 3H, CH_2-benzyl, H1), 3.92 (ddd,

dx.doi.org/10.1021/jo4012464 | J. Org. Chem. 2013, 78, 7234−7248

J = 12.0, 6.2, 2.6 Hz, 1H, H6), 3.82 (tt, J = 8.8, 2.6 Hz, 1H, H3), 3.74 (ddd, J = 12.1, 7.4, 4.9 Hz, 1H, H6), 3.52−3.47 (m, 1H, H4), 3.45−3.35 (m, 2H, H5, H2), 2.46 (d, J = 2.6 Hz, 1H, OH-2), 1.93 (dd, J = 7.3, 6.4 Hz, 1H, OH-6). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2(ipso), 138.09(ipso), 133.56(ipso), 131.86(Ar), 129.23(Ar), 128.78(Ar), 128.74(Ar), 128.36(Ar), 128.28(Ar), 128.21(Ar), 128.18(Ar), 127.86(Ar), 87.25(C1), 81.05(C2), 79.18(C5), 78.70(C3), 77.32(C4), 75.44(CH_2-benzyl), 74.90(CH_2-benzyl), 62.41(C6). $[\alpha]^{rt}_D$ −3.6° (c 1.0, $CHCl_3$), HRMS calcd for $C_{26}H_{28}O_5SNa$ 475.1555, found 475.1547

Phenyl 2,4-Di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-1-thio-β-D-glucopyranoside (8). Phenyl 2,4-di-*O*-benzyl-1-thio-β-D-glucopyranoside (1.0, 2.21 mmol) was dissolved in 10 mL of dry 2,6-lutidine. To the solution was added di-*tert*-butylsilyl ditriflate (0.8 mL, 2.43 mmol), and the mixture was heated to 100 °C for 3 h. The solution was cooled to rt and added to ethyl acetate and was then extracted 5 times with 1 M HCl solution, one time with satd bicarbonate solution, and one time with brine. The organic layer was dried with $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by flash column chromatography with petroleum ether as eluent with a gradient of DCM, giving the product as a clear oil. Yield 0.468 g, 37%. ^{1}H NMR (500 MHz, chloroform-d) δ 7.46−7.41 (m, 5H, Ar), 7.37−7.29 (m, 5H, Ar), 7.25−7.19 (m, 5H, Ar), 5.14 (d, J = 9.2 Hz, 1H, H1), 4.84 (d, J = 11.6 Hz, 1H, CH_2-benzyl), 4.78 (d, J = 11.6 Hz, 1H, CH_2-benzyl), 4.67 (d, J = 11.6 Hz, 1H, CH_2-benzyl), 4.49−4.42 (m, 2H, CH_2-benzyl, H3), 4.20−4.18 (m, 2H, H5, H6), 4.11 (dd, J = 3.4, 0.9 Hz, 1H, H4) 3.91 (dd, J = 12.3, 3.0 Hz, 1H, H6), 3.71 (dd, J = 9.2, 0.7, 1H, H2), 1.00 (s, 9H, TBS), 0.90 (s, 9H, TBS). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.34(ipso), 137.75(ipso), 135.27(ipso), 130.95(Ar), 128.88(Ar), 128.53(Ar), 128.44(Ar), 128.22(Ar), 128.08(Ar), 127.97(Ar), 127.81(Ar), 126.99(Ar), 83.75(C1), 82.73(C2), 81.89, 74.93, 73.37(CH_2-benzyl), 71.76(CH_2-benzyl), 71.71, 67.56(C6), 28.39(CH_3), 27.84(CH_3), 21.81(C-Si), 21.65(C-Si). $[\alpha]^{rt}_D$ 10.8° (c 1.0, $CHCl_3$), HRMS calcd for $C_{34}H_{44}O_5SSiNa$ 615.2576, found 615.2569

Phenyl 2,4-Di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-1-thio-α-D-mannopyranoside (9). Phenyl 2,4-di-*O*-benzyl-1-thio-α-D-mannopyranoside (0.841 g, 1.86 mmol) was dissolved in 10 mL of dry 2,6-lutidine. To the solution was added di-*tert*-butylsilyl ditriflate (0.66 mL, 2.04 mmol), and the mixture was heated to 100 °C for 1 h. The solution was cooled to rt and was then added to ethyl acetate and was then extracted 3 times with 1 M HCl solution, one time with satd bicarbonate solution, and one time with brine. The organic layer was dried with $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by flash column chromatography with petroleum ether as eluent with a gradient of DCM, giving the product as a clear oil. Yield 0.575 g, 53%. ^{1}H NMR (500 MHz, chloroform-d) δ 7.50−7.47 (m, 2H), 7.43−7.40 (m, 2H), 7.39−7.35 (m, 2H), 7.34−7.32 (m, 5H), 7.30−7.26 (m, 4H), 7.23−7.19 (m, 1H), 5.65 (d, J = 4.9 Hz, 1H, H1), 4.70 (d, J = 11.8 Hz, 1H, CH-benzyl), 4.68−4.59 (m, 3H, CH-benzyl, H3), 4.50 (d, J = 12.1 Hz, 1H, CH-benzyl), 4.42 (s, 1H, H5), 4.18−4.13 (m, 2H, H4, H6), 3.95 (dd, J = 12.3, 2.9 Hz, 1H, H6), 3.89 (dd, J = 4.9, 3.9 Hz, 1H, H2), 1.03 (s, 9H, TBS), 0.94 (s, 9H, TBS). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.61(Ar ipso), 137.61(Ar(ipso), 136.42(Ar,ipso), 130.15(Ar), 128.87(Ar), 128.67(Ar), 128.39(Ar), 128.11(Ar), 127.93(Ar), 127.78(Ar), 127.61(Ar), 126.51(Ar), 85.54(C1), 76.95(C2), 74.83(C4), 73.75(C5), 71.88(CH_2-benzyl), 70.92(CH_2-benzyl), 68.67(C3), 68.19(C6), 28.24(CH_3), 28.16(CH_3), 21.95(C-Si), 21.90(C-Si). $[\alpha]^{rt}_D$ 93.1° (c 1.0, $CHCl_3$), HRMS calcd for $C_{34}H_{44}O_5SSiNa$ 615.2576, found 615.2572

2,4-Di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-1-fluoro-α-D-mannopyranoside (19). Phenyl 2,4-di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-1-thio-α-D-mannopyranoside (0.341 g, 0.575 mmol) was dissolved in DCM (6 mL), and the solution was cooled to −15 °C. To the solution was added DAST (0.11 mL, 0.863 mmol), the solution was stirred for 5 min, and then NBS (0.133 g, 0.748 mmol) was added. The reaction was stirred for 1 h while it was slowly allowed to reach 0 °C. The reaction mixture was then transferred to a separation funnel, washed with satd bicarbonate solution and brine, then dried with $MgSO_4$, filtered, and evaporated to dryness. The crude compound was purified by flash column chromatography with petroleum ether as eluent with a gradient of DCM, giving the product as a clear oil. Yield 0.216 g, 75%, ^{1}H NMR (300 MHz, chloroform-d) δ 7.46−7.25 (m, 10H, Ar), 5.71 (d, J = 54.7 Hz, 1H, H1), 4.72 (d, J = 11.8 Hz, 1H, CH-benzyl), 4.66 (d, J = 11.8 Hz, 1H, CH-benzyl), 4.56 (m, 3H), 4.33 (s, 1H), 4.22−4.14 (m, 2H), 4.06−3.95 (m, 1H), 3.92−3.83 (m, 1H), 1.02 (d, J = 1.6 Hz, 9H), 0.94 (d, J = 1.6 Hz, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.21, 137.34, 128.71, 128.48, 128.25, 127.94, 127.83, 127.78, 110.83 (d, J = 222.9 Hz), 76.22 (d, J = 35.0 Hz), 75.51, 73.59, 72.22, 70.81, 68.10, 67.52 (d, J = 6.4 Hz), 28.05, 27.90, 21.92, 21.87. ^{19}F NMR (282 MHz, chloroform-d) δ −121.20 (dd, J = 55.3, 18.3 Hz). $[\alpha]^{rt}_D$ 65.6° (c 1.0, $CHCl_3$), HRMS calcd for $C_{28}H_{39}O_5SiFNa$ 525.2448, found 525.2446

Phenyl 3,6-Di-*O*-TBS-1-thio-β-D-mannopyranoside. To a solution of phenyl-1-thio-β-D-mannopyranoside (6.17 g, 0.0230 mol) in 100 mL DMF at 0 °C were added imidazole (3.32 g, 0.0487 mol) and TBSCl (7.34 g, 0.0487 mol). The mixture was stirred overnight at room temperature and was then quenched with MeOH. The mixture was added to EtOAc and extracted with 1 M HCl, satd bicarbonate solution, and brine. The organic layer was dried with $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by flash column chromatography with petroleum ether as eluent with a gradient of DCM, giving the product as a clear syrup. Yield 7.02 g, 62%. ^{1}H NMR (500 MHz, chloroform-d) δ 7.49 (m, 2H, Ar), 7.30−7.19 (m, 3H, Ar), 4.82 (t, J = 1.4 Hz, 1H, H1), 4.04−3.99 (m, 1H, H2), 3.89 (d, J = 5.8 Hz, 2H, H6), 3.73 (td, J = 9.2, 1.9 Hz, 1H, H4), 3.61 (dd, J = 8.7, 3.6 Hz, 1H, H3), 3.32 (dt, J = 9.4, 5.8 Hz, 1H, H5), 2.81 (d, J = 1.9 Hz, 1H,OH4), 2.68 (t, J = 1.6 Hz, 1H, OH2), 0.90 (s, 9H, $(CH_3)_3$), 0.88 (s, 9H, $(CH_3)_3$), 0.13 (s, 3H, CH_3-Si), 0.11 (s, 3H, CH_3-Si), 0.07 (s, 3H, CH_3-Si), 0.06 (s, 3H, CH_3-Si).^{13}C NMR (126 MHz, $CDCl_3$) δ 135.6(Ar), 130.8(Ar), 129.0(Ar), 127.3(Ar), 86.7(C1), 78.6(C5), 76.3(C3), 73.0(C2), 70.6(C4), 65.2(C6), 26.0($(CH_3)_3$), 25.9($(CH_3)_3$), 18.4(C-Si)1, 18.3(C-Si), −4.3(CH_3-Si), −4.7(CH_3-Si), −5.3(CH_3-Si), −5.4(CH_3-Si). $[\alpha]^{rt}_D$ −59.5 (c 1.0, $CHCl_3$), HRMS calcd for $C_{24}H_{44}O_5Si_2SNa$ 523.2346, found 523.2341

Phenyl 2,4-Di-*O*-benzyl-1-thio-β-D-mannopyranoside (5a). To a solution of phenyl 3,6-di-*O*-TBS-1-thio-β-D-mannopyranoside (7.02 g, 0.0140 mol) in 100 mL DMF at 0 °C were added BnBr (4.2 mL, 0.0350 mol) and NaH (1.4 g, 0.0350 mol). The mixture was stirred overnight at room temperature and was then quenched with MeOH. The mixture was added to Et_2O and extracted with water and brine. The organic layer was dried with $MgSO_4$, filtered, and evaporated to dryness. The crude product was dissolved in 100 mL MeOH, and a catalytic amount of TsOH was added. The mixture was refluxed for 2 h and quenched by adding 5 mL of Et_3N. The mixture was evaporated, and the crude product was purified by flash column chromatography with petroleum ether as eluent with a gradient of EtOAc, giving the product as a clear syrup. Yield 4.56 g, 72%. ^{1}H NMR (500 MHz, chloroform-d) δ 7.52−7.46 (m, 4H), 7.44−7.41 (m, 2H), 7.39−7.28 (m, 9H), 5.01 (d, J = 11.4 Hz, 1H, CH_2-benzyl), 4.90 (d, J = 1.1 Hz, 1H, H1), 4.87−4.80 (m, 2H, CH_2-benzyl), 4.71 (d, J = 11.2 Hz, 1H, CH_2-benzyl), 4.10 (dd, J = 3.2, 1.1 Hz, 1H, H2), 3.95 (dd, J = 12.0, 2.8 Hz, 1H, H6), 3.81 (dd, J = 12.0, 5.4 Hz, 1H, H6), 3.78 (dd, J = 9.3, 3.3 Hz, 1H, H3), 3.76−3.72 (m, 1H, H4), 3.37 (ddd, J = 8.4, 5.3, 2.7 Hz, 1H, H5), 2.12(s, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.1(ipso), 138.0(ipso), 134.9(ipso), 130.8(Ar), 129.3(Ar), 128.7(Ar), 128.7(Ar), 128.5(Ar), 128.3(Ar), 128.3(Ar), 128.2(Ar), 127.6(Ar), 87.8(C1), 80.6(C2), 79.9(C5), 76.4(CH_2-benzyl), 76.1, 75.8, 75.1(CH_2-benzyl), 62.6(C6). $[\alpha]^{rt}_D$ −93.8 (c 1.0, $CHCl_3$), HRMS calcd for $C_{26}H_{28}O_5SNa$ 475.1555, found 475.1548

Phenyl 2,4-Di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-1-thio-β-D-mannopyranoside (10). Phenyl 2,4-di-*O*-benzyl-1-thio-β-D-mannopyranoside (0.858 g, 1.90 mmol) was dissolved in 10 mL of dry 2,6-lutidine. To the solution was added di-*tert*-butylsilyl ditriflate (0.74 mL, 2.28 mmol), and the mixture was heated to 100 °C for 1 h. The solution was cooled to rt, and then ethyl acetate was added and extracted 3 times with 1 M HCl solution, one time with satd bicarbonate solution, and one time with brine. The organic layer was dried with $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by flash column chromatography with petroleum

dx.doi.org/10.1021/jo4012464 | J. Org. Chem. 2013, 78, 7234−7248

ether as eluent with a gradient of DCM, giving the product as a clear oil. Yield 0.626 g, 56%. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.54−7.46 (m, 4H, Ar), 7.42−7.20 (m, 11H, Ar), 5.44 (d, J = 5.1 Hz, 1H, H1), 4.86 (d, J = 12.1 Hz, 1H, CH_2-benzyl), 4.65 (d, J = 12.1 Hz, 1H, CH_2-benzyl), 4.63 (t, J = 4.8 Hz, 1H, H3), 4.57 (d, J = 12.0 Hz, 1H, CH_2-benzyl), 4.51 (d, J = 12.0 Hz, 1H, CH_2-benzyl), 4.25 (dd, J = 12.4, 0.8 Hz, 1H, H6), 4.17 (d, J = 4.3 Hz, 1H, H4), 4.08 (d, J = 2.9 Hz, 1H, H5), 3.96 (t, J = 5.1 Hz, 1H, H2), 3.93 (dd, J = 12.4, 2.9 Hz, 1H, H6), 1.10 (s, 9H, $(CH_3)_3$), 0.97 (s, 9H, $(CH_3)_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.7(ipso), 137.4(ipso), 137.0(ipso), 130.2(Ar), 128.8(Ar), 128.7(Ar), 128.3(Ar), 128.3(Ar), 128.0(Ar), 127.5(Ar), 127.4(Ar), 126.4(Ar), 85.1(C1), 81.4(C5), 74.6(C4), 74.2(C2), 72.5(CH_2-benzyl), 71.5(CH_2-benzyl), 67.9(C6), 67.7(C3), 28.3-(CH_3), 27.9(CH_3), 22.2(C-Si), 21.9(C-Si). $[\alpha]^{rt}_D$ 6.1° (c 1.0, $CHCl_3$), HRMS calcd for $C_{34}H_{44}O_5SSiNa$ 615.2576, found 615.2566

Phenyl 2,4-Di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-1-thio-*β*-D-galactopyranoside (12). Phenyl 2,4-di-*O*-benzyl-1-thio-*β*-D-galactopyranoside (1.24 g, 2.74 mmol) was dissolved in 10 mL of dry 2,6-lutidine. To the solution was added di-*tert*-butylsilyl ditriflate (1 mL, 3.01 mmol), and the mixture was heated to 100 °C for 2 h. The solution was cooled to rt, and was ethyl acetate was added and extracted 3 times with 1 M HCl solution, one time with satd bicarbonate solution, and one time with brine. The organic layer was dried with $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by flash column chromatography with petroleum ether as eluent with a gradient of DCM, giving the product as a clear oil. Yield 0.716 g, 44%. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.47 (dd, J = 8.2, 1.3 Hz, 2H, Ar), 7.42−7.23 (m, 13H. Ar), 4.77 (s, 2H, CH_2-benzyl), 4.75 (d, J = 8.5 Hz, 1H, H1), 4.71 (d, J = 12.3 Hz, 1H, CH_2-benzyl), 4.54 (t, J = 1.3 Hz, 1H, H3), 4.45 (d, J = 12.3 Hz, 1H, CH_2-benzyl), 4.32 (dd, J = 12.3, 1.5 Hz, 1H, H6), 4.19 (dd, J = 12.3, 2.0 Hz, 1H, H6), 4.14 (d, J = 8.2, 1H, H5), 4.10 (dd, J = 8.2, 1.8 Hz, 1H, H4), 3.79 (dd, J = 8.5, 0.9 Hz, 1H, H2), 1.10 (s, 9H), 1.03 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.0(Ar), 137.7(Ar), 135.5(Ar), 130.9(Ar), 128.9(Ar), 128.6(Ar), 128.0(Ar), 127.9(Ar), 127.2(Ar), 85.0(C1), 84.1(C2), 77.7, 75.4, 72.9(CH_2-benzyl), 72.7, 71.5(CH_2-benzyl), 64.8(C6), 28.9(CH_3), 28.5(CH_3), 22.2(C-Si), 21.7(C-Si). $[\alpha]^{rt}_D$ −31.0° (c 1.0, $CHCl_3$), HRMS calcd for $C_{34}H_{45}O_5SSi$ 593.2751, found 593.2748

2,4-Di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-1-fluoro-*α*,*β*-D-galactopyranoside (21). Phenyl 2,4-di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-1-thio-*β*-D-galactopyranoside (0.533 g, 0.9 mmol) was dissolved in DCM (9 mL), and the solution was cooled to −15 °C. To the solution was added DAST (0.2 mL, 1.35 mmol), the solution was stirred for 5 min, and then NBS (0.208 g, 1.17 mmol) was added. The reaction was stirred for 1 h while it was slowly allowed to reach 0 °C. The reaction mixture was then transferred to a separation funnel, washed with satd bicarbonate solution and brine, then dried with $MgSO_4$, filtered, and evaporated to dryness. The crude compound was purified by flash column chromatography with petroleum ether as eluent with a gradient of DCM, giving the product as a clear oil. Yield 0.335 g, 74% (α/β, 30/1), ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.46−7.34 (m, 10H, Ar), 5.82 (dd, J = 53.4, 5.0 Hz, 1H, H1), 4.79 (d, J = 12.0 Hz, 1H), 4.75 (s, 2H), 4.59−4.53 (m, 2H), 4.46−4.38 (m, 2H), 4.29−4.24 (m, 1H), 4.17 (dd, J = 12.6, 2.8 Hz, 1H), 3.94 (dd, J = 22.1, 5.0 Hz, 1H, H2), 1.06 (s, 9H, TBS), 1.00 (s, 9H, TBS). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.5(ipso), 137.4(ipso), 128.6(Ar), 128.5(Ar), 128.5(Ar), 128.1(Ar), 128.0(Ar), 127.9(Ar),110.1 (d, J = 214.3 Hz, H1), 104.3 (d, J = 232.9 Hz, H1), 83.2 (d, J = 25.2 Hz, C2), 79.1 (d, J = 22.3 Hz, C2), 76.0 (d, J = 5.1 Hz), 75.0, 74.6 (d, J = 3.4 Hz), 73.2 (d, J = 1.4 Hz), 73.0 (d, J = 7.7 Hz), 73.0, 72.1, 71.8, 71.6, 71.6, 71.5, 63.78, 63.5, 28.6(CH_3), 28.4(CH_3), 28.4(CH_3), 28.2(CH_3), 22.2(C-Si), 22.2(C-Si), 21.5(C-Si), 21.3(C-Si). ^{19}F NMR (282 MHz, chloroform-*d*) δ −135.3 (dd, J = 52.1, 19.6 Hz), −142.4 (dd, J = 56.0, 18.8 Hz). HRMS calcd for $C_{28}H_{39}O_5SiFNa$ 525.2448, found 525.2442

Phenyl 2,4-Di-*O*-benzyl-1-thio-*α*-D-galactopyranoside (6b). Thiophenol (0.1 mol, 10.3 mL) in 50 mL of HMPA was cooled to 0 °C, and NaH (0.15 mol, 6 g) was added. The solution was stirred for 5 min. Then 2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranoside chloride (18.34 g, 0.05 mol) in 50 mL HMPA was added slowly. The reaction mixture was stirred for 1 h and then quenched by adding water. The mixture was diluted with EtOAc, washed three times with water and one time with brine, dried with $MgSO_4$, filtered, and evaporated to dryness. The crude compound was subjected to flash column chromatography with petroleum ether as eluent with a gradient of EtOAc, giving the impure product as a mixture of anomers (α/β, 4:1). The crude compound was dissolved in 50 mL of MeOH, and 1 mL of NaOMe solution was added. The mixture was stirred for 4 h and was then neutralized by adding Amberlite IR120. The solution was filtered and evaporated to dryness giving crude phenyl 1-thio-*α*-D-galactopyranoside, in total 7.1 g. The crude phenyl 1-thio-*α*-D-galactopyranoside (7.1 g, 0.0261 mol) was dissolved in 100 mL of dry DMF. The solution was cooled to 0 °C, and then imidazole (3.82 g, 0.0561 mol) and TBSCl (8.45 g, 0.0561 mol) were added. The mixture was stirred overnight, and was then 5 mL of methanol and 100 mL of EtOAc were added. The mixture was washed with water, 1 M HCl solution, satd $NaHCO_3$ solution, and brine, then dried with $MgSO_4$, filtered, and evaporated to dryness. The crude compound was subjected to flash column chromatography with DCM as eluent giving impure phenyl 3,6-*O*-di-*tert*-butylsilyl-1-thio-*α*-D-galactopyranoside, 3.83 g. The crude phenyl 3,6-*O*-di-*tert*-butylsilyl-1-thio-*α*-D-galactopyranoside (3.83 g, 0.00765 mol) was dissolved in 50 mL of DMF and cooled to 0 °C, and first benzylbromide (3.7 mL, 0.0191 mol) and then NaH (0.76 g, 0.0191 mol) were added. The mixture was stirred overnight and then quenched by adding 5 mL of methanol. The mixture was diluted with EtOAc, washed with water and brine, then dried with $MgSO_4$, filtered, and evaporated to dryness. The crude product was dissolved in 50 mL of methanol, and 0.1 g of TsOH was added. The mixture was refluxed for 3 h, and then 1 mL of triethylamine was added. The solution was evaporated, and the crude product was purified by flash column chromatography with petroleum ether as eluent with a gradient of EtOAc The product was further purified by recrystallization from DCM and petroleum ether, giving the product as white crystals. Yield 1.74 g, 7.8%, ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.56−7.25 (m, 15H), 5.82 (d, J = 5.3 Hz, 1H, H1), 4.96 (d, J = 11.6 Hz, 1H, CH_2-benzyl), 4.84 (d, J = 11.2 Hz, 1H, CH_2-benzyl), 4.70 (d, J = 11.6 Hz, 1H, CH_2-benzyl), 4.61 (d, J = 11.1 Hz, 1H, CH_2-benzyl), 4.36−4.30 (m, 1H, H5), 4.23 (dd, J = 10.0, 5.3 Hz, 1H, H2), 4.05 (dd, J = 10.0, 3.1 Hz, 1H, H3), 3.97 (dd, J = 3.1, 1.3 Hz, 1H, H4), 3.77 (dd, J = 11.5, 6.7 Hz, 1H, H6), 3.57 (dd, J = 11.5, 4.9 Hz, 1H, H6), 2.55 (s, 1H, OH), 1.58 (s, 1H, OH). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.2(Ar ipso), 137.5(Ar ipso), 134.0(Ar ipso), 132.1(Ar), 129.2(Ar), 128.7(Ar), 128.7(Ar), 128.6(Ar), 128.5(Ar), 128.4(Ar), 128.2(Ar), 127.5(Ar), 86.7(C1), 76.8(C2), 75.9(C4), 75.1(CH_2-benzyl), 72.3(CH_2-benzyl), 71.6, 71.5, 62.5(C6). Mp 108−109 °C, $[\alpha]^{rt}_D$ 169.2° (c 1.0, $CHCl_3$), HRMS calcd for $C_{26}H_{28}O_5SNa$ 475.1555, found 475.1554

Phenyl 2,4-Di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-1-thio-*α*-D-galactopyranoside (12). Phenyl 2,4-di-*O*-benzyl-1-thio-*α*-D-galactopyranoside (1.00 g, 2.21 mmol) was dissolved in 10 mL of dry 2,6-lutidine. To the solution was added di-*tert*-butylsilyl ditriflate (0.8 mL, 2.43 mmol), and the mixture was heated to 100 °C for 2 h. The solution was cooled to rt, and then added ethyl acetate was added and extracted 3 times with 1 M HCl solution, one time with satd bicarbonate solution, and one time with brine. The organic layer was dried with $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by flash column chromatography with petroleum ether as eluent with a gradient of DCM, giving the product as a clear oil. Yield 0.618 g, 47%. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.51−7.47 (m, 2H, Ar), 7.39−7.26 (m, 12H, Ar), 7.23−7.18 (m, 1H, Ar), 6.17 (d, J = 3.2 Hz, 1H, H1), 4.75 (d, J = 11.4 Hz, 1H, CH_2-benzyl), 4.65 (d, J = 11.4 Hz, 2H, CH_2-benzyl), 4.59 (t, J = 2.9 Hz, 1H, H3), 4.51 (d, J = 12.1 Hz, 1H, CH_2-benzyl), 4.43 (dd, J = 13.1, 1.5 Hz, 1H, H6), 4.33 (dd, J = 6.7, 3.0 Hz, 1H, H4), 4.23 (dd, J = 13.1, 2.3 Hz, 1H, H6), 4.03 (d, J = 6.6 Hz, 1H, H5), 3.97 (t, J = 3.0 Hz, 1H, H2), 1.07 (s, 9H, $(CH_3)_3$), 0.91 (s, 9H, $(CH_3)_3$). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.8(ipso), 137.6(ipso), 135.6(ipso), 130.1(Ar), 128.9(Ar), 128.6(Ar), 128.5(Ar), 128.3(Ar), 128.1(Ar), 128.1(Ar), 128.0(Ar), 126.7(Ar), 82.8(C1), 81.2(C2), 75.5(C5), 74.0(CH_2-benzyl),

dx.doi.org/10.1021/jo4012464 | J. Org. Chem. 2013, 78, 7234−7248

73.8(C4), 71.0(C2), 70.9(CH_2-benzyl), 66.1(C6), 29.4((CH_3)$_3$), 28.3((CH_3)$_3$), 23.2(C-Si), 21.0(C-Si). $[\alpha]^{rt}_D$ 2.9° (*c* 1.0, $CHCl_3$), HRMS calcd for $C_{34}H_{44}O_5SSiNa$ 615.2576, found 615.2571

Phenyl 3-*O*-Acetyl-2-azido-4-*O*-benzyl-2-deoxy-1-thio-α,β-D-glucopyranoside. Phenyl 3-*O*-acetyl-2-azido-4,6-*O*-benzylidene-2-deoxy-1-thio-α,β-D-glucopyranoside (5 g, 0.0117 mol) was dissolved in 121.5 mL of 1 M BH_3·THF at 0 °C. The mixture was stirred for 5 min, and then 12.2 mL of 1 M Bu_2BOTf in DCM was added. The reactions was stirred for 2 h, and then 6 mL Et_3N was added followed by addition of methanol. The reaction mixture was co-distilled with methanol 3 times and then purified by flash column chromatography with petroleum ether as eluent with a gradient of EtOAc giving the known products (β:1.15, α:3.01 g, α/β: 0.589), total 4.75 g, 95%.

Phenyl 2-Azido-4-*O*-benzyl-(di-*tert*-butylsilylene)-2-deoxy-1-thio-α-D-glucopyranoside (16). Phenyl 3-*O*-acetyl-2-azido-4-*O*-benzyl-2-deoxy-1-thio-α-D-glucopyranoside (3.01 g, 7.0 mmol) was dissolved in 50 mL of dry methanol. To the solution was added 2 mL of 25% sodium methoxide solution in methanol. The reaction was stirred until TLC showed full conversion. The solution was neutralized by adding Amberlite IR120. The solution was filtered and evaporated to dryness, giving the product as a white solid. The white solid (1.0 g, 2.58 mmol) was dissolved in 10 mL of dry 2,6-lutidine. To the solution was added di-*tert*-butylsilyl ditriflate (0.92 mL, 2.84 mmol), and the mixture was heated to 100 °C for 2 h. The solution was cooled to rt, and then ethyl acetate was added and extracted 3 times with 1 M HCl solution, one time with satd bicarbonate solution, and one time with brine. The organic layer was dried with $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by flash column chromatography with petroleum ether as eluent with a gradient of DCM, giving the product as a clear oil. Yield: 0.631 g, 46%, ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.58−7.53 (m, 2H, Ar), 7.43−7.25 (m, 8H, Ar), 6.06 (d, *J* = 4.2 Hz, 1H, H1), 4.75 (d, *J* = 12.6 Hz, 1H, CH_2-benzyl), 4.71 (d, *J* = 12.6 Hz, 1H, CH_2-benzyl), 4.55 (ddd, *J* = 2.4, 1.1 Hz, 1H, H3), 4.35 (s, 1H, H5), 4.22 (dd, *J* = 13.2, 2.0 Hz, 1H, H6), 4.03 (dd, *J* = 13.2, 3.1 Hz, 1H, H6), 3.95−3.91 (m, 2H, H2, H4), 0.91 (s, 9H, TBS), 0.89 (s, 9H, TBS). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.4(ipso), 135.3(ipso), 131.3(Ar), 128.0(Ar), 128.7 (Ar), 128.2(Ar), 127.3(Ar), 82.1(C1), 76.4, 72.4, 71.7(CH_2-benzyl), 70.8, 68.3(C6), 61.6(C2), 28.7(CH_3), 28.0(CH_3), 21.9(C-Si), 21.0(C-Si). $[\alpha]^{rt}_D$ 8.4° (*c* 1.0, $CHCl_3$), HRMS calcd for $C_{27}H_{37}N_3O_4SSiNa$ 550.2172, found 550.2172

Phenyl 2-Azido-4-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-2-deoxy-1-thio-β-D-glucopyranoside (17). Phenyl 3-*O*-acetyl-2-azido-4-*O*-benzyl-2-deoxy-1-thio-β-D-glucopyranoside (1.15 g, 2.68 mmol) was dissolved in 50 mL of dry methanol. To the solution was added 2 mL of 25% sodium methoxide solution in methanol. The reaction was stirred until TLC showed full conversion. The solution was neutralized by adding Amberlite IR120. The solution was filtered and evaporated to dryness, giving the product as a white solid. The white solid was dissolved in 10 mL of dry 2,6-lutidine. To the solution was added di-*tert*-butylsilyl ditriflate (0.81 mL, 2.47 mmol), and the mixture was heated to 100 °C for 2 h. The solution was cooled to rt, and then ethyl acetate was added and extracted 3 times with 1 M HCl solution, one time with satd bicarbonate solution, and one time with brine. The organic layer was dried with $MgSO_4$, filtered, and evaporated to dryness. The crude product was purified by flash column chromatography with petroleum ether as eluent with a gradient of DCM, giving the product as a clear oil. Yield: 0.474 g, 40%, ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.56−7.52 (m, 2H, Ar), 7.40−7.30 (m, 8H, Ar), 5.06 (d, *J* = 9.8 Hz, 1H, H1), 4.71 (d, *J* = 12.0 Hz, 1H, CH_2-benzyl), 4.54 (d, *J* = 12.0 Hz, 1H, CH_2-benzyl), 4.50 (d, *J* = 3.6 Hz, 1H, H4), 4.20 (dd, *J* = 12.6, 0.9 Hz, 1H, H6), 4.16 (d, *J* = 3.1 Hz, 1H, H5), 4.11 (d, *J* = 3.4 Hz, 1H, H3), 3.90 (dd, *J* = 12.6, 3.3 Hz, 1H, H6), 3.67 (d, *J* = 9.7 Hz, 1H, H2), 1.01 (s, 9H, TBS), 0.91 (s, 9H, TBS). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.2(ipso), 133.8(ipso), 132.1(Ar), 129.1(Ar), 128.7(Ar), 128.3(Ar), 128.2(Ar), 127.9(Ar), 83.4(C1), 82.0, 73.9, 73.0, 72.2(CH_2-benzyl), 67.4(C6), 65.5(C2), 28.3(CH_3), 27.7(CH_3), 21.8(C-Si), 21.6(C-Si). $[\alpha]^{rt}_D$ 41.9° (*c* 1.0, $CHCl_3$), HRMS calcd for $C_{27}H_{37}N_3O_4SSiNa$ 550.2172, found 550.2167

2-Azido-4-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-2-deoxy-1-fluoro-α-D-glucopyranoside (21). Phenyl 2-azido-4-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-2-deoxy-1-thio-α-D-glucopyranoside (0.570 g, 1.08 mmol) was dissolved in DCM (10 mL), and the solution was cooled to −15 °C. To the solution was added DAST (0.21 mL, 1.62 mmol), the solution was stirred for 5 min, and then NBS (0.256 g, 1.44 mmol) was added. The reaction was stirred for 1 h while it was slowly allowed to reach 0 °C. The reaction mixture was then transferred to a separation funnel, washed with satd bicarbonate solution and brine, then dried with $MgSO_4$, filtered, and evaporated to dryness. The crude compound was purified by flash column chromatography with petroleum ether as eluent with a gradient of DCM, giving the product as a clear oil. Yield 0.246 g, 52%, ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.39−7.30 (m, 5H, Ar), 5.62 (dd, *J* = 53.1, 6.3 Hz, 1H, H1), 4.67 (d, *J* = 11.9 Hz, 1H, CH_2-benzyl), 4.52 (d, *J* = 11.9 Hz, 1H, CH_2-benzyl), 4.40 (t, *J* = 4.1 Hz, 1H), 4.26 (d, *J* = 3.0 Hz, 1H), 4.21 (dd, *J* = 12.8, 1.1 Hz, 1H), 4.03 (t, *J* = 2.8 Hz, 1H), 3.92 (ddd, *J* = 12.8, 3.2, 1.9 Hz, 1H), 3.75 (dd, *J* = 23.0, 6.3 Hz, 1H, H2), 0.99 (s, 9H, TBS), 0.89 (s, 9H, TBS).^{13}C NMR (126 MHz, $CDCl_3$) δ 136.8(ipso), 128.7(Ar), 128.3(Ar), 128.0(Ar), 108.2 (d, *J* = 212.9 Hz, C1), 81.3 (d, *J* = 3.8 Hz), 73.5 (d, *J* = 1.4 Hz), 73.2 (d, *J* = 7.0 Hz), 72.2(CH_2-benzyl), 66.6 (d, *J* = 24.7 Hz, C2), 66.4(C6), 27.9(CH_3), 27.6(CH_3), 21.6(C-Si), 21.4(C-Si). ^{19}F NMR (282 MHz, chloroform-*d*) δ −134.8 (dd, *J* = 52.7, 23.5 Hz). $[\alpha]^{rt}_D$ 59.4° (*c* 1.0, $CHCl_3$), HRMS calcd for $C_{21}H_{32}FN_3O_4SiNa$ 460.2044, found 460.2032

Phenyl 3,6-Anhydro-2,4-di-*O*-benzyl-1-thio-α-D-glucopyranoside (30). Phenyl 2,4-di-*O*-benzyl-1-thio-α-D-glucopyranoside (0.223 g, 0.492 mmol) was dissolved in 5 mL of dry pyridine, and then TsCl (0.10 g, 0.541 mmol) was added. The reaction was stirred for 3 days, then diluted with ethyl acetate, and extracted 3 times with 1 M HCl solution, one time with satd bicarbonate solution, and one time with brine. The organic layer was dried with $MgSO_4$, filtered, and evaporated to dryness. The compound was dissolved in 5 mL of DMF, and NaH (0.022 g, 0.541 mmol) was added. The reaction was stirred for 3 h, quenched with water, and diluted with ethyl acetate. The mixture was washed 3 times with water and one time with brine. The organic layer was dried with $MgSO_4$, filtered, and evaporated to dryness. The crude compound was purified by flash column chromatography with petroleum ether as eluent with a gradient of EtOAc, giving the product as a white solid. Yield: 106 mg, 50%, ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.67−7.55 (m, 2H, Ar), 7.56−7.48 (m, 2H, Ar), 7.47−7.22 (m, 11H, Ar), 5.65 (d, *J* = 3.9 Hz, 1H, H1), 4.90 (d, *J* = 11.6 Hz, 1H, CH_2-benzyl), 4.77 (d, *J* = 12.0 Hz, 1H, CH_2-benzyl), 4.73 (d, *J* = 11.6 Hz, 1H, CH_2-benzyl), 4.65 (d, *J* = 12.0 Hz, 1H, CH_2-benzyl), 4.50 (t, *J* = 2.9 Hz, 1H), 4.37 (t, *J* = 4.7 Hz, 1H), 4.22 (d, *J* = 10.7 Hz, 1H, H6), 3.93 (dd, *J* = 10.7, 3.1 Hz, 1H, H6), 3.90−3.83 (m, 2H, H2). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.0(ipso), 138.0(ipso), 136.2(ipso), 130.5(Ar), 128.9(Ar), 128.4(Ar), 128.3(Ar), 128.0(Ar), 128.0(Ar), 127.8(Ar), 127.6(Ar), 126.9(Ar), 84.3(C1), 78.4, 76.1, 75.1, 74.7(CH_2-benzyl), 72.2(CH_2-benzyl), 71.0, 68.6(C6). Mp 115−117 °C, $[\alpha]^{rt}_D$ 64.2° (*c* 1.0, $CHCl_3$), HRMS calcd for $C_{26}H_{26}O_4SNa$ 457.1449, found 457.1446

Phenyl 3,6-Anhydro-2,4-di-*O*-benzyl-1-thio-β-D-glucopyranoside (31). Phenyl 2,4-di-*O*-benzyl-1-thio-β-D-glucopyranoside (0.211 g, 0.466 mmol) was dissolved in 5 mL of dry pyridine, and then TsCl (0.098 g, 0.513 mmol) was added. The reaction was stirred for 3 days, then diluted with ethyl acetate, and extracted 3 times with 1 M HCl solution, one time with satd bicarbonate solution, and one time with brine. The organic layer was dried with $MgSO_4$, filtered, and evaporated to dryness. The compound was dissolved in 5 mL of DMF, and NaH (0.020 g, 0.513 mmol) was added. The reaction was stirred for 3 h, quenched with water, and diluted with ethyl acetate. The mixture was washed 3 times with water and one time with brine. The organic layer was dried with $MgSO_4$, filtered, and evaporated to dryness. The crude compound was purified by flash column chromatography with petroleum ether as eluent with a gradient of EtOAc, giving the product as a syrup. Yield: 126 mg, 62%, ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.56−7.53 (m, 2H, Ar), 7.45−7.27 (m, 13H, Ar), 5.71 (d, *J* = 5.4 Hz, 1H, H1), 4.82−4.78 (m, 2H, CH_2-benzyl), 4.71 (d, *J* = 11.8 Hz, 1H, CH_2-benzyl), 4.66 (d, *J* = 11.5 Hz,

dx.doi.org/10.1021/jo4012464 | J. Org. Chem. 2013, 78, 7234−7248

1H, CH_2-benzyl), 4.46 (t, J = 2.8 Hz, 1H), 4.37 (dd, J = 5.2, 1.8 Hz, 1H), 4.19 (d, J = 10.0 Hz, 1H, H6), 4.08−4.04 (m, 1H), 3.86−3.81 (m, 2H, H2, H6). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.9(ipso), 137.5(ipso), 134.6(ipso), 131.6(Ar), 128.9(Ar), 128.5(Ar), 128.5(Ar), 128.1(Ar), 128.1(Ar), 128.0(Ar), 127.9(Ar), 127.3(Ar), 82.4(C2), 82.4(C1), 76.7, 73.5, 72.9, 72.9(CH_2-benzyl), 72.5(CH_2-benzyl), 71.6(C6). $[\alpha]^{rt}_D$ −41.1° (c 1.0, $CHCl_3$), HRMS calcd for $C_{26}H_{26}O_4SNa$ 457.1449, found 457.1440

General Glycosylation Procedures. Typical NIS/TfOH-promoted glycosylation procedure: A mixture of glycosyl donor (0.10 mmol), glycosyl acceptor (0.11 mmol), and freshly activated molecular sieves (3 Å, 100 mg) in DCM (4 mL) was stirred under argon for 1 h. The solution was cooled to −78 °C, and NIS (0.11 mmol) and TfOH (0.010 mmol) were added. The reaction was slowly allowed to reach 0 °C. Upon completion, the reaction was quenched by adding triethylamine. The solid was filtered off, and the filtrate was washed with 1 M HCl, satd bicarbonate solution, 10% $Na_2S_2O_3$, and brine. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography to afford the corresponding saccharide. Anomeric ratios were measured by integration of the anomeric protons from ^{1}H NMR of crude product mixtures. The anomeric configuration of conformationally changed sugars was checked by first deprotection of silyl groups with TBAF and then ^{1}H NMR to measure the coupling constants between H1 and H2.

Typical $SnCl_2/AgB(C_6F_5)_4$ promoted glycosylation procedure: A mixture of $SnCl_2$(0.02 mmol), $AgB(C_6F_5)_4$ (0.02 mmol), and molecular sieves (5 Å, 300 mg) was dissolved in 2 mL of BTF. Then the glycosyl donor (0.1 mmol) and the glycosyl acceptor were added (0.11 mmol). The reaction was stirred upon completion and quenched with satd bicarbonate solution. The solids was filtered of and washed with ethyl acetate, and the organic layer was washed with water and brine. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography to afford the corresponding saccharide.

Anomeric ratios were measured by integration of the anomeric protons from ^{1}H NMR of crude product mixtures.

The anomeric configuration of conformationally changed sugars was checked by first deprotection of silyl groups with TBAF and then H NMR to measure the coupling constants between H1 and H2.

Competion Experiments. A mixture of the two glycosyl donors (0.10 mmol each), cyclohexanol (0.50 mmol), and freshly activated molecular sieves (3 Å, 100 mg) in DCM (4 mL) was stirred under argon for 1 h. The solution was cooled to −78 °C, and NIS (0.10 mmol) and TfOH (0.010 mmol) were added. The reaction was slowly allowed to reach 0 °C. The reaction was quenched by adding triethylamine. The mixture was diluted with CH_2Cl_2, the solid was filtered off, and the filtrate was washed with 1 M HCl, satd bicarbonate solution, 10% $Na_2S_2O_3$, and brine. The organic layer was dried with $MgSO_4$ and concentrated *in vacuo*. The donors were isolated by purifying the crude mixture by flash column chromatography. In cases where purification of starting material or products was impossible, then the yields were measured by ^{1}H NMR. This was done by taking the two donors (0.10 mmol each) and 0.10 mmol of Ph_3SiMe as internal standard, which were dissolved in $CDCl_3$, and measuring the ratios of donors compared to Ph_3SiMe by ^{1}H NMR. Then the solvent was evaporated, and the procedure as described above was followed. After workup another ^{1}H NMR was recorded of the crude mixture, and comparison of the ratios of donors before and after gave the yields.

General Deprotection Procedure. The compound (0.10 mmol) was dissolved in 1 mL of THF, and then 1 M TBAF solution in THF (0.2 mL, 0.20 mmol) was added. The solution was stirred until the reaction was finished (checked by TLC). The reaction mixture was subjected to aqueous workup with brine, dried with $MgSO_4$, and concentrated *in vacuo*. The crude compound was purified by flash column chromatography to afford the corresponding deprotected compound.

Cyclohexyl 2,4-Di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-β-D-glucopyranoside. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.45−7.41 (m, 2H), 7.38−7.28 (m, 8H), 4.99 (d, J = 6.5 Hz, 1H), 4.88 (d, J = 11.9 Hz, 1H), 4.75 (d, J = 9.0 Hz, 1H), 4.73 (d, J = 8.7 Hz, 1H), 4.49 (s, 1H), 4.48 (d, J = 8.2 Hz, 1H), 4.19 (dd, J = 12.2, 1.0 Hz, 1H), 4.11 (d, J = 2.0 Hz, 2H), 4.04 (d, J = 2.7 Hz, 1H), 3.95 (dd, J = 12.2, 2.9 Hz, 1H), 3.69 (d, J = 6.5 Hz, 1H), 3.63 (tt, J = 9.3, 3.8 Hz, 2H), 1.92 (s, 2H), 1.76 (s, 2H), 1.55 (s, 1H), 1.49−1.36 (m, 2H), 1.36−1.21 (m, 4H), 1.03 (s, 9H), 0.94 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.2, 138.0, 128.5, 128.3, 128.1, 127.9, 127.7, 127.4, 100.2, 83.5, 80.1, 76.9, 75.2, 72.8, 72.6, 71.7, 67.5, 34.0, 32.4, 28.4, 27.9, 25.9, 24.3, 24.3, 21.9, 21.7. $[\alpha]^{rt}_D$ 8.2° (c 1.0, CH_2Cl_2), HRMS calcd for $C_{34}H_{50}O_6SiNa$ 605.3274, found 605.3278

Cyclohexyl 2,4-Di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-α-D-glucopyranoside. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.31 (m, 4H), 7.26−7.14 (m, 6H), 5.27 (d, J = 5.4 Hz, 1H), 4.75 (d, J = 12.2 Hz, 1H), 4.62 (d, J = 12.5 Hz, 1H), 4.56 (d, J = 12.2 Hz, 1H), 4.51 (d, J = 12.5 Hz, 1H), 4.33 (d, J = 2.9 Hz, 1H), 4.08 (s, 1H), 4.04 (dd, J = 12.4, 1.5 Hz, 1H), 3.83 (d, J = 2.6 Hz, 1H), 3.78 (dd, J = 12.4, 2.8 Hz, 1H), 3.65 (d, J = 5.4 Hz, 1H), 3.58 (tt, J = 9.4, 3.8 Hz, 1H), 1.86 (s, 2H), 1.69 (s, 2H), 1.50−1.41 (m, 2H), 1.31 (q, J = 12.4, 11.0 Hz, 1H), 1.19 (td, J = 28.2, 26.9, 11.1 Hz, 4H), 0.84 (s, 9H), 0.79 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0, 138.6, 128.4, 128.3, 128.0, 127.9, 127.7, 127.4, 93.2, 77.2, 75.4, 74.7, 74.0, 72.4, 71.6, 71.2, 68.4, 33.5, 31.7, 28.3, 28.2, 25.9, 24.5, 24.3, 21.9, 21.3. $[\alpha]^{rt}_D$ 50.3° (c 1.0, CH_2Cl_2), HRMS calcd for $C_{34}H_{50}O_6SiNa$ 605.3274, found 605.3277

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2,4-di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-β-D-glucopyranosyl)-α-D-glucopyranoside. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.41−7.21 (m, 25H), 5.03 (d, J = 10.9 Hz, 1H), 4.97 (d, J = 6.7 Hz, 1H), 4.89−4.80 (m, 4H), 4.75 (d, J = 11.7 Hz, 1H), 4.71−4.66 (m, 2H), 4.64−4.59 (m, 2H), 4.49 (d, J = 3.4 Hz, 1H), 4.44 (d, J = 11.4 Hz, 1H), 4.18 (d, J = 12.7 Hz, 1H), 4.12−4.02 (m, 4H), 3.95 (dd, J = 12.3, 3.0 Hz, 1H), 3.85−3.79 (m, 1H), 3.75 (dd, J = 11.2, 5.6 Hz, 2H), 3.54 (ddt, J = 9.1, 5.9, 2.9 Hz, 2H), 3.36 (s, 3H), 1.02 (s, 9H), 0.96 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0, 138.8, 138.5, 138.3, 137.8, 128.6, 128.5, 128.4, 128.3, 128.2, 128.09, 128.0, 128.0, 127.8, 127.8, 127.7, 127.7, 127.5, 102.3, 98.0, 83.6, 82.3, 80.5, 80.0, 78.2, 75.8, 75.3, 75.0, 73.4, 72.8, 72.3, 71.7, 70.6, 68.6, 67.3, 55.3, 28.3, 27.9, 21.8, 21.7. $[\alpha]^{rt}_D$ 20.9° (c 1.0, CH_2Cl_2), HRMS calcd for $C_{56}H_{70}O_{11}SiNa$ 969.4585, found 969.4591

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2,4-di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-α,β-D-glucopyranosyl)-α-D-glucopyranoside. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.50−7.12 (m, Ar), 5.35 (d, J = 5.8 Hz), 5.04 (d, J = 10.9 Hz), 4.98 (d, J = 7.0 Hz), 4.95 (d, J = 7.0 Hz), 4.89 (d, J = 11.1 Hz), 4.86−4.77 (m), 4.75−4.67 (m), 4.64−4.53 (m), 4.47 (d, J = 11.5 Hz), 4.24−3.86 (m), 3.80−3.68 (m), 3.38 (s), 3.36 (s), 3.31 (dd, J = 9.6, 3.5 Hz), 1.04 (s), 1.01 (s), 0.97 (s), 0.97 (s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.2, 139.1, 139.0, 138.9, 138.7, 138.4, 138.2, 138.0, 137.7, 128.5, 128.4, 128.3, 128.2, 128.2, 128.1, 128.1, 128.0, 128.0, 127.9, 127.8, 127.8, 127.7, 127.7, 127.6, 127.6, 127.5, 127.5, 127.4, 127.3, 127.3, 102.3, 98.2, 97.9, 96.5, 83.5, 82.2, 82.0, 80.4, 80.1, 79.9, 78.1, 77.6, 77.3, 77.2, 77.1, 76.8, 75.7, 75.4, 75.2, 74.9, 74.8, 74.6, 74.3, 73.4, 73.3, 72.7, 72.2, 71.7, 71.5, 70.5, 70.3, 70.2, 68.5, 68.1, 67.6, 67.2, 55.2, 55.1, 28.2, 28.1, 27.8, 21.8, 21.4.

Phenyl 2,3,6-Tri-*O*-benzyl-4-*O*-(2,4-di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.49 (dd, J = 8.1, 1.5 Hz, 2H), 7.39−6.97 (m, 28H), 5.05 (d, J = 7.3 Hz, 1H), 5.02 (d, J = 11.2 Hz, 1H), 4.72 (d, J = 11.7 Hz, 1H), 4.67−4.52 (m, 6H), 4.47 (d, J = 11.9 Hz, 1H), 4.35−4.27 (m, 4H), 4.15 (d, J = 12.0 Hz, 1H), 4.05 (s, 1H), 3.91 (d, J = 12.5 Hz, 1H), 3.84 (dd, J = 14.3, 5.1 Hz, 4H), 3.76 (d, J = 9.0 Hz, 1H), 3.68 (dd, J = 12.6, 3.0 Hz, 1H), 3.62−3.52 (m, 2H), 3.43−3.34 (m, 2H), 0.81 (s, 1H, 9H), 0.78 (s, 1H, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.3, 138.9, 138. 5, 138. 3, 137.7, 133.8, 132.2, 129.0, 128.5, 128.5, 128.4, 128.4, 128.2, 128.0, 128.0, 128.0, 127.8, 127.8, 127.7, 127.5, 127.4, 127.3, 127.2, 101.4, 87.1, 84.8, 84.4, 80.8, 80.4, 79.4, 78.9, 75.7, 75.5, 75.3, 72.8, 72.6, 72.4, 71.7, 68.3, 67.1, 28.2, 28.0, 21.8, 21.2. $[\alpha]^{rt}_D$ 11° (c 1.0, CH_2Cl_2), HRMS calcd for $C_{61}H_{72}O_{10}SSiNa$ 1047.4513, found 1047.4489

Phenyl 2,3,6-Tri-*O*-benzyl-4-*O*-(2,4-di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-α-D-glucopyranosyl)-1-thio-β-D-glucopyranoside. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.60 (dd, J = 7.9, 1.7 Hz, 2H), 7.39−7.06 (m, 28H), 5.96 (d, J = 6.5 Hz, 1H), 4.93 (d, J = 11.3 Hz, 1H), 4.88 (d, J = 10.2 Hz, 1H), 4.72−4.56 (m, 6H), 4.55−

dx.doi.org/10.1021/jo4012464 | J. Org. Chem. 2013, 78, 7234−7248

4.39 (m, 5H), 4.35 (d, J = 3.1 Hz, 1H), 4.20 (s, 1H), 4.11−4.02 (m, 2H), 3.98 (dd, J = 12.4, 1.3 Hz, 1H), 3.91 (d, J = 2.7 Hz, 1H), 3.85 (dd, J = 10.8, 1.8 Hz, 1H), 3.77 (t, J = 8.8 Hz, 1H), 3.73−3.64 (m, 2H), 3.60−3.50 (m, 2H), 0.88 (s, 9H), 0.85 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0, 138.3, 138.2, 138.1, 133.8, 132.1, 129.0, 128.6, 128.5, 128.4, 128.3, 128.3, 128.1, 127.9, 127.7, 127.6, 127.5, 127.4, 127.2, 94.3, 87.5, 87.2, 81.2, 79.1, 75.2, 75.1, 74.4, 74.1, 73.2, 72.4, 72.2, 71.7, 69.5, 69.1, 68.0, 28.2, 28.1, 21.8, 21.4. $[\alpha]^{rt}_D$ 29° (c 1.0, CH_2Cl_2), HRMS calcd for $C_{61}H_{72}O_{10}SSiNa$ 1047.4513, found 1047.4523

Methyl 2,3,6-Tri-*O*-benzyl-4-*O*-(2,4-di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-*β*-D-glucopyranosyl)-*α*-D-glucopyranoside. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.37−7.04 (m, 25H), 5.02 (d, J = 7.2 Hz, 1H), 4.98 (d, J = 11.1 Hz, 1H), 4.71 (m, 2H), 4.68−4.59 (m, 2H), 4.53−4.45 (m, 2H), 4.41 (d, J = 11.9 Hz, 1H), 4.34−4.24 (m, 3H), 4.12 (d, J = 11.9 Hz, 1H), 4.06 (s, 1H), 3.95−3.78 (m, 5H), 3.67 (dd, J = 12.5, 2.9 Hz, 1H), 3.65−3.60 (m, 1H), 3.61−3.56 (m, 1H), 3.51 (dd, J = 10.6, 1.8 Hz, 1H), 3.41 (dd, J = 9.3, 3.8 Hz, 1H), 3.28 (s, 3H), 0.85 (s, 9H), 0.78 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.7, 138.5, 138.5, 138.5, 137.6, 128.4, 128.3, 128.1, 128.0, 128.0, 127.9, 127.8, 127.7, 127.6, 127.2, 127.1, 101.4, 98.3, 84.5, 80.7, 80.2, 79.4, 79.0, 75.6, 75.2, 73.72, 72.8, 72.5, 71.7, 70.3, 67.8, 67.1, 55.3, 28.2, 28.0, 21.8, 21.2. $[\alpha]^{rt}_D$ 33.3° (c 1.0, CH_2Cl_2), HRMS calcd for $C_{56}H_{70}O_{11}SiNa$ 969.4585, found 969.4572

Methyl 2,3,6-Tri-*O*-benzyl-4-*O*-(2,4-di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-*α*,*β*-D-glucopyranosyl)-*α*-D-glucopyranoside. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.40−7.07 (m), 6.00−5.93 (d, J = 6.6), 5.06 (d, J = 7.2 Hz), 5.00 (d, J = 11.0 Hz), 4.75 (dd, J = 11.4, 3.1 Hz), 4.71−4.31 (m), 4.16 (d, J = 11.9 Hz), 4.10 (s), 4.08−4.01 (m,), 3.98−3.96 (m), 3.96−3.91 (m), 3.89−3.84 (m), 3.82 (d, J = 2.3 Hz), 3.79−3.75 (m), 3.72 (dd, J = 12.5, 2.9 Hz), 3.68 (d, J = 6.6 Hz), 3.62 (d, J = 7.3 Hz), 3.60−3.52 (m), 3.45 (dd, J = 9.3, 3.7 Hz), 3.33 (s), 3.33 (s), 0.89 (s), 0.85 (s), 0.82 (s), 0.80 (s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.7, 138.7, 138.7, 138.5, 138.5, 138.5, 138.4, 138.3, 138.1, 137.6, 128.6, 128.5, 128.4, 128.4, 128.3, 128.3, 128.3, 128.2, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.6, 127.5, 127.3, 127.2, 127.1, 127.0, 101.4, 98.3, 97.8, 94.2, 84.5, 82.7, 80.7, 80.2, 79.4, 79.0, 76.9, 75.6, 75.2, 75.1, 74.3, 73.9, 73.7, 73.4, 73.0, 72.8, 72.7, 72.5, 72.4, 72.3, 71.6, 71.6, 70.3, 69.7, 69.7, 68.9, 68.0, 67.8, 67.1, 55.3, 55.1, 28.2, 28.2, 28.1, 28.0, 21.8, 21.8, 21.4, 21.2. HRMS calcd for $C_{56}H_{70}O_{11}SiNa$ 969.4585, found 969.4582

Cyclohexyl 2,4-Di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-*α*-D-mannopyranoside. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.47−7.43 (m, 2H, Ar), 7.39−7.28 (m, 8H, Ar), 5.23 (d, J = 4.1 Hz, 1H, H1), 4.76 (d, J = 12.0 Hz, 1H, CH-benzyl), 4.72 (d, J = 12.0 Hz, 1H, CH-benzyl), 4.60 (d, J = 12.4 Hz, 1H, CH-benzyl), 4.58 (t, J = 3.9 Hz, 1H, H3), 4.55 (d, J = 12.4 Hz, 1H, CH-benzyl), 4.18−4.13 (m, 2H), 4.09 (d, J = 4.2 Hz, 1H, H4), 3.92−3.88 (m, 1H, H6), 3.78 (t, J = 3.9 Hz, 1H, H2), 3.66 (td, J = 9.4, 4.7 Hz, 1H, H5), 1.99−1.90 (m, 2H), 1.83−1.72 (m, 2H), 1.61−1.53 (m, 1H), 1.53−1.19 (m, 6H), 1.07 (s, 9H, TBS), 0.95 (s, 9H, TBS). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.2(ipso, Ar), 138.0(ipso, Ar), 128.6(Ar), 128.3(Ar), 128.0(Ar), 127.9(Ar), 127.6(Ar), 127.4(Ar), 98.7(C1), 77.4(C2), 75.5(C5), 75.0(C4), 74.2, 71.7(CH_2-benzyl), 71.2(CH_2-benzyl), 69.6(C3), 68.5(C6), 33.8, 32.0, 28.3(CH_3), 28.3(CH_3), 25.89, 24.5, 24.2, 21.9(C-Si), 21.7(C-Si). $[\alpha]^{rt}_D$ 58.3° (c 1.0, $CHCl_3$), HRMS calcd for $C_{34}H_{50}O_6SiNa$ 605.3274, found 605.3267

Cyclohexyl 2,4-Di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-*α*/*β*-D-mannopyranoside. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.47−7.26 (m), 5.22 (d, J = 4.1 Hz), 5.11 (d, J = 3.4 Hz), 4.83 (d, J = 12.2 Hz), 4.75 (d, J = 12.0 Hz), 4.73−4.69 (m), 4.64 (d, J = 11.8 Hz), 4.61−4.52 (m), 4.15 (dd, J = 6.4, 1.6 Hz), 4.15−4.11 (m), 4.08 (d, J = 4.2 Hz), 3.92−3.84 (m), 3.77 (t, J = 3.9 Hz), 3.64 (td, J = 9.4, 4.7 Hz), 1.93 (b,s), 1.77 (b,s), 1.56 (b, s), 1.45−1.23 (m), 1.06 (s), 1.02 (s), 0.94 (s), 0.94 (s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.2, 138.9, 138.0, 137.8, 128.6, 128.6, 128.4, 128.3, 128.3, 128.0, 128.0, 127.9, 127.7, 127.6, 127.6, 127.5, 127.4, 100.5, 98.7, 77.5, 77.3, 75.5, 75.0, 74.7, 74.2, 72.0, 71.7, 71.2, 71.0, 69.6, 69.5, 68.9, 68.5, 68.4, 33.8, 32.1, 28.3, 28.3, 28.2, 28.2, 25.9, 24.5, 24.3, 21.9, 21.9, 21.9, 21.8.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2,4-di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-*α*-D-mannopyranosyl)-*α*-D-glucopyranoside. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.47−7.43 (m, 2H, Ar), 7.42−7.25 (m, 21H, Ar), 7.22−7.19 (m, 2H, Ar), 5.10 (d, J = 3.5 Hz, 1H), 5.03 (d, J = 10.9 Hz, 1H), 4.87−4.80 (m, 3H), 4.74−4.67 (m, 4H), 4.66 (d, J = 3.5 Hz, 1H), 4.60 (t, J = 3.9 Hz, 1H), 4.50 (d, J = 12.1 Hz, 1H), 4.46 (d, J = 12.1 Hz, 1H), 4.10−4.01 (m, 5H), 3.85 (t, J = 3.6 Hz, 1H), 3.84−3.80 (m, 1H), 3.77 (td, J = 12.0, 11.3, 2.1 Hz, 2H), 3.68−3.62 (m, 1H), 3.56 (dd, J = 9.6, 3.5 Hz, 1H), 3.37 (s, 3H, OMe), 1.07 (s, 9H, TBS), 0.96 (s, 9H, TBS).^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0, 138.8, 138.8, 138.4, 137.7, 128.5, 128.4, 128.3, 128.1, 128.0, 128.0, 128.0, 127.8, 127.6, 127.5, 127.5, 101.4, 98.0, 82.2, 80.2, 78.0, 76.7, 75.7, 74.8, 74.8, 74.4, 73.4, 71.9, 70.7, 70.0, 68.8, 68.3, 66.6, 55.1, 28.3, 28.2, 21.9, 21.8. $[\alpha]^{rt}_D$ 50.6° (c 1.0, $CHCl_3$), HRMS calcd for $C_{56}H_{70}O_{11}SiNa$ 969.4585, found 969.4543

Phenyl 2,3,6-Tri-*O*-benzyl-4-*O*-(2,4-di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-*α*-D-mannopyranosyl)-1-thio-*β*-D-glucopyranoside. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.65−7.63 (m, 2H, Ar), 7.47−7.20 (m, 28H, Ar), 5.66 (d, J = 2.8 Hz, 1H), 4.93−4.90 (m, 2H), 4.85 (d, J = 10.1 Hz, 1H), 4.74 (d, J = 9.9 Hz, 2H), 4.69 (d, J = 11.6 Hz, 1H), 4.62−4.56 (m, 4H), 4.58−4.48 (m, 3H), 4.17 (s, 1H), 4.14 (d, J = 4.7 Hz, 1H), 4.09−4.04 (m, 1H), 4.01 (d, J = 11.5 Hz, 1H), 3.91−3.85 (m, 4H), 3.80 (t, J = 8.8 Hz, 1H), 3.73 (dd, J = 12.1, 2.8 Hz, 1H), 3.62−3.56 (m, 2H), 0.99 (s, 9H, TBS), 0.94 (s, 9H, TBS). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.8, 138.7, 138.2, 138.1, 137.7, 133.9, 132.0, 129.0, 128.6, 128.5, 128.4, 128.3, 128.3, 128.2, 128.2, 128.1, 127.9, 127.8, 127.87, 127.5, 127.5, 127.4, 127.3, 100.8, 87.6, 87.4, 81.0, 79.3, 78.0, 75.5, 75.4, 74.4, 74.3, 73.5, 72.1, 71.1, 70.5, 69.5, 68.6, 67.3, 28.2, 27.9, 21.9. $[\alpha]^{rt}_D$ 43.3° (c 1.0, $CHCl_3$), HRMS calcd for $C_{61}H_{72}O_{10}SSiNa$ 1047.4513, found 1047.4522

Methyl 2,3,6-Tri-*O*-benzyl-4-*O*-(2,4-di-*O*-benzyl-(di-*tert*-butylsilylene)-*α*-D-mannopyranosyl)-*α*-D-glucopyranoside. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.39−7.20 (m, 25H), 5.68 (d, J = 2.8 Hz, 1H), 4.92 (d, J = 10.0 Hz, 1H), 4.84 (d, J = 10.0 Hz, 1H), 4.79 (d, J = 12.0 Hz, 1H), 4.69−4.59 (m, 6H), 4.56−4.42 (m, 7H), 4.09−3.97 (m, 6H), 3.94 (d, J = 11.9 Hz, 1H), 3.88−3.81 (m, 4H), 3.76−3.69 (m, 1H), 3.65−3.57 (m, 2H), 3.43 (s, 3H), 0.96 (s, 9H), 0.90 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.8, 138.6, 138.65, 137.8, 128.6, 128.5, 128.4, 128.4, 128.3, 128.3, 128.1, 1287.0, 127.8, 127.5, 127.4, 127.3, 127.2, 100.9, 98.1, 82.7, 80.4, 78.0, 75.4, 74.4, 74.3, 73.5, 73.4, 72.1, 71.6, 70.6, 70.0, 69.5, 68.6, 67.5, 55.3, 28.2, 27.9, 21.9. $[\alpha]^{rt}_D$ 42.0° (c 1.0, $CHCl_3$), HRMS calcd for $C_{56}H_{70}O_{11}SiNa$ 969.4585, found 969.4582

Cyclohexyl 2,4-Di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-*β*-D-galactopyranoside. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.41−7.27 (m, 10H, Ar), 4.74−4.65 (m, 3H, benzyl), 4.63 (d, J = 6.0 Hz, 1H, H1), 4.41 (d, J = 12.3 Hz, 2H), 4.30 (dd, J = 12.1, 1.4 Hz, 1H, H6), 4.11 (dd, J = 12.1, 2.3 Hz, 1H, H6), 4.03 (d, J = 8.1 Hz, 1H), 3.97 (dd, J = 8.2, 1.9 Hz, 1H), 3.70 (dd, J = 6.0, 0.9 Hz, 1H, H2), 3.56 (tt, J = 9.1, 3.8 Hz, 1H), 1.84 (m), 1.72 (m), 1.41−1.16 (m), 1.01 (s, 9H), 0.97 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.6, 137.9, 128.5, 128.5, 127.9, 127.8, 127.7, 127.6, 100.2(C1), 84.2(C2), 76.5, 76.00, 75., 73.3, 72.2(CH_2-benzyl), 71.4(CH_2-benzyl), 64.6(C6), 33.7 32.0, 28.8, 28.6, 25.9, 24.2, 24.1, 22.2, 21.7. $[\alpha]^{rt}_D$ −4.7° (c 1.0, $CHCl_3$), HRMS calcd for $C_{34}H_{50}O_6SiNa$ 605.3274, found 605.3260

Cyclohexyl 2,4-Di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-*α*-D-galactopyranoside. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.42−7.29 (m, 10H), 5.25 (d, J = 5.2 Hz, 1H, H1), 4.78−4.70 (m, 2H), 4.63 (d, J = 12.0 Hz, 1H), 4.54−4.46 (m, 5H), 4.39 (dd, J = 12.4, 1.0 Hz, 1H, H6), 4.09 (dd, J = 12.4, 2.7 Hz, 1H, H6), 3.97 (d, J = 6.6 Hz, 1H), 3.87 (dd, J = 5.3, 0.9 Hz, 1H, H2), 3.68−3.58 (m, 2H), 1.93 (d, J = 10.8 Hz, 1H), 1.84 (d, J = 13.3 Hz, 1H), 1.75 (s, 1H), 1.56 (s, 0H), 1.47−1.18 (m, 6H), 1.02 (s, 7H), 0.96 (s, 8H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.3, 138.2, 128.5, 128.4, 128.0, 128.0, 127.8, 127.7, 93.8(C1), 79.7(C2), 76.0, 75.3, 72.9, 72.7, 71.8, 71.3, 64.6(C6), 33.4, 31.9, 28.8, 28.4, 25.8, 24.5, 24.2, 22.5, 21.3. $[\alpha]^{rt}_D$ 15.5° (c 1.0, $CHCl_3$), HRMS calcd for $C_{34}H_{50}O_6SiNa$ 605.3274, found 605.3273

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2,4-di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-*α*,*β*-D-galactopyranosyl)-*α*-D-glucopyranoside. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.40−7.23 (m), 5.25 (d, J = 5.1 Hz, 1H), 5.00 (d, J = 10.9 Hz, 1H), 4.83 (d, J = 10.9 Hz), 4.80−

dx.doi.org/10.1021/jo4012464 | J. Org. Chem. 2013, 78, 7234−7248

4.68 (m), 4.60 (dd, J = 22.2, 11.9 Hz), 4.55−4.51 (m), 4.50−4.44 (m), 4.42 (dd, J = 7.5, 2.6 Hz), 4.35 (d, J = 11.6 Hz), 4.08 (dd, J = 12.5, 2.6 Hz), 4.03 (d, J = 4.4 Hz), 4.02−3.99 (m), 3.99−3.94 (m), 3.92 (dd, J = 5.1, 1.2 Hz), 3.80−3.73 (m), 3.58−3.52 (m), 3.39 (dd, J = 9.6, 3.6 Hz), 3.36 (s), 3.32 (s), 1.04 (s), 1.03 (s), 1.02 (s), 0.99 (s). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.9, 138.8, 138.4, 138.4, 138.2, 138.2, 137.6, 128.5, 128.4, 128.4, 128.3, 128.3, 128.0, 127.9, 127.9, 127.7, 127.7, 127.6, 127.6, 127.5, 102.32, 97.9, 97.0, 96.4, 84.0, 82.1, 82.0, 80.1, 79.9, 79.5, 78.2, 77.9, 75.8, 75.7, 75.6, 75.3, 75.0, 74.9, 74.8, 73.3, 72.7, 72.5, 72.2, 72.1, 71.7, 71.3, 70.9, 70.3, 70.0, 68.5, 67.6, 64.5, 64.3, 55.1, 55.1, 28.7, 28.6, 28.4, 28.3, 22.4, 21.2. HRMS calcd for $C_{56}H_{70}O_{11}SiNa$ 969.4585, found 969.4578

Methyl 2,3,6-Tri-*O*-benzyl-4-*O*-(2,4-di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-*β*-D-galactopyranosyl)-*α*-D-glucopyranoside. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.48 (d, J = 7.1 Hz, 2H), 7.41−7.23 (m, 21H), 7.20−7.16 (m, 2H), 5.03 (d, J = 10.7 Hz, 1H), 4.82 (d, J = 10.7 Hz, 1H), 4.78 (d, J = 12.2 Hz, 1H), 4.74 (d, J = 11.4 Hz, 1H), 4.70 (d, J = 6.9 Hz, 1H), 4.62 (d, J = 3.0 Hz, 1H), 4.59 (d, J = 1.9 Hz, 1H), 4.58−4.55 (m, 1H), 4.40 (d, J = 2.3 Hz, 1H), 4.36 (d, J = 12.1 Hz, 1H), 4.32 (d, J = 12.1 Hz, 1H), 4.27 (d, J = 12.1 Hz, 1H), 4.20 (d, J = 11.2 Hz, 1H), 4.05−3.98 (m, 2H), 3.95 (d, J = 3.5 Hz, 1H), 3.93−3.91 (m, 1H), 3.89 (d, J = 9.1 Hz, 1H), 3.86−3.81 (m, 1H), 3.79 (dd, J = 8.1, 2.3 Hz, 1H), 3.77 (s, 1H), 3.75 (s, 1H), 3.72 (ddd, J = 9.9, 3.3, 1.6 Hz, 1H), 3.58 (dd, J = 10.6, 1.6 Hz, 1H), 3.52 (dd, J = 9.3, 3.6 Hz, 1H), 3.40 (s, 3H), 1.02 (s, 9H), 1.00 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.5, 138.5, 138.4, 138.0, 137.5, 128.5, 128.5, 128.3, 128.3, 128.2, 128.1, 128.0, 127.9, 127.4, 127.3, 101.5, 98.3, 84.7, 80.1, 79.9, 79.2, 75.8, 75.6, 75.3, 73.7, 73.0, 72.6, 71.9, 71.5, 70.1, 68.2, 63.6, 55.4, 28.7, 28.6, 22.4, 21.2. $[\alpha]^{rt}_D$ 6.0° (c 1.0, $CHCl_3$), HRMS calcd for $C_{56}H_{70}O_{11}SiNa$ 969.4585, found 969.4592

Methyl 2,3,6-Tri-*O*-benzyl-4-*O*-(2,4-di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-*α*-D-galactopyranosyl)-*α*-D-glucopyranoside. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.40−7.26 (m, 25H), 5.97 (d, J = 5.9 Hz, 1H), 5.06 (d, J = 11.2 Hz, 1H), 4.76 (d, J = 12.0 Hz, 1H), 4.70 (dd, J = 11.7, 5.4 Hz, 3H), 4.65−4.61 (m, 2H), 4.54 (s, 2H), 4.50−4.42 (m, 4H), 4.38 (d, J = 12.0 Hz, 1H), 4.31 (dd, J = 7.5, 2.6 Hz, 1H), 4.20 (d, J = 12.0 Hz, 1H), 4.10−3.92 (m, 5H), 3.86−3.82 (m, 1H), 3.76 (dt, J = 9.6, 2.7 Hz, 2H), 3.63−3.56 (m, 3H), 3.41 (s, 3H), 1.02 (s, 9H), 0.97 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.6, 138.1, 137.9, 137.9, 137.8, 128.5, 128.4, 128.4, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.5, 127.4, 127.3, 127.1, 97.7, 95.1, 82.3, 80.4, 79.8, 74.9, 74.6, 73.3, 72.9, 72.0, 71.7, 71.5, 70.7, 69.5, 69.1, 64.1, 55.2, 28.6, 28.4, 22.3, 21.2. $[\alpha]^{rt}_D$ 14.7.0° (c 1.0, $CHCl_3$), HRMS calcd for $C_{56}H_{70}O_{11}SiNa$ 969.4585, found 969.4584

Phenyl 2,3,6-Tri-*O*-benzyl-4-*O*-(2,4-di-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-*α*-D-galactopyranosyl)-1-thio-*β*-D-glucopyranoside. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.63−7.58 (m, 2H), 7.40−7.19 (m, 26H), 7.15 (dd, J = 7.2, 2.2 Hz, 2H), 5.89 (d, J = 5.9 Hz, 1H, H1), 4.92 (d, J = 11.3 Hz, 1H), 4.88 (d, J = 10.2 Hz, 1H), 4.71−4.59 (m, 4H), 4.55−4.42 (m, 6H), 4.29 (dd, J = 7.6, 2.7 Hz, 1H), 4.25 (d, J = 12.0 Hz, 1H), 4.09−4.02 (m, 2H), 3.98 (dd, J = 12.4, 2.6 Hz, 1H), 3.82−3.79 (m, 1H), 3.72−3.65 (m, 2H), 3.57−3.51 (m, 2H), 3.48 (ddd, J = 9.6, 4.2, 1.9 Hz, 1H), 1.01 (s, 9H), 0.94 (s, 9H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.5, 138.3, 138.0, 138.0, 137.9, 132.1, 129.1, 128.6, 128.5, 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.9, 127.9, 127.6, 127.6, 127.6, 127.4, 127.2, 95.2, 87.2, 87.1, 80.9, 79.9, 78.8, 75.2, 74.8, 74.4, 73.5, 72.6, 72.2, 71.7, 71.5, 70.8, 69.2, 64.3, 28.7, 28.4, 22.4, 21.2. $[\alpha]^{rt}_D$ 3.6° (c 1.0, $CHCl_3$), HRMS calcd for $C_{61}H_{72}O_{10}SSiNa$ 1047.4513, found 1047.4511

Cyclohexyl 2-Azido-4-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-2-deoxy-1-thio-*α*-D-glucopyranoside. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.41−7.30 (m, 5H, Ar), 5.60−5.58 (d, J = 4.8, 1H, H1), 4.72 (d, J = 12.6 Hz, 1H, CH_2-benzyl), 4.65 (d, J = 12.6 Hz, 1H, CH_2-benzyl), 4.43−4.41 (m, 1H), 4.22 (br s, 1H), 4.19 (dd, J = 12.7, 1.7 Hz, 1H, H6), 3.94 (dd, J = 12.7, 2.9 Hz, 1H, H6), 3.89 (d, J = 2.8 Hz, 1H), 3.76 (tt, J = 8.7, 3.7 Hz, 1H), 3.54 (d, J = 4.8 Hz, 1H, H2), 1.92 (m, 2H), 1.80 (m, 2H), 1.54 (m, 2H), 1.45 (m, 1H), 1.31 (m, 5H), 0.99 (s, 9H, TBS), 0.89 (s, 9H, TBS). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.8(ipso), 128.6(Ar), 128.1(Ar), 128.0(Ar), 93.2(C1), 75.8, 75.2, 72.8, 71.8, 71.5(CH_2-benzyl), 68.3(C6), 60.9, 33.3, 31.5, 28.5(CH_3), 28.1(CH_3), 25.8, 24.0, 23.8(C-Si), 21.9(C-Si), 21.6. $[\alpha]^{rt}_D$ 56.6° (c 1.0, $CHCl_3$), HRMS calcd for $C_{27}H_{43}N_3O_5SiNa$ 540.2870, found 540.2870

Cyclohexyl 2-Azido-4-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-2-deoxy-1-thio-*β*-D-glucopyranoside. ^{1}H NMR (500 MHz, chloroform-*d*) 7.38−7.28 (m, 5H, Ar), 4.94 (d, J = 7.1 Hz, 1H, H1), 4.68 (d, J = 11.9 Hz, 1H, CH_2-benzyl), 4.49 (d, J = 11.9 Hz, 1H, CH_2-benzyl), 4.30 (d, J = 3.5 Hz, 1H, H3), 4.14 (dd, J = 12.3, 1.1 Hz, 1H, H6), 4.08 (d, J = 2.5 Hz, 1H, H5), 3.95 (d, J = 3.2 Hz, 1H, H4), 3.86 (dd, J = 12.3, 3.0 Hz, 1H, H6), 3.65 (d, J = 7.1 Hz, 1H, H2), 3.61 (td, J = 9.4, 4.7 Hz, 2H), 1.94−1.83 (m, 2H), 1.79−1.70 (m, 2H), 1.56−1.47 (m, 2H), 1.47−1.36 (m, 2H), 1.30−1.20 (m, 3H), 0.98 (s, 9H, TBS), 0.88 (s, 9H, TBS). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.5, 128.7, 128.2, 128.1, 98.7, 80.3, 77.4, 74.5, 72.7, 72.1, 67.3, 66.3, 33.9, 32.3, 28.3, 27.8, 25.8, 24.4, 24.4, 21.8, 21.7:$[\alpha]^{rt}_D$ 23.6° (c 1.0, $CHCl_3$), HRMS calcd for $C_{27}H_{43}N_3O_5SiNa$ 540.2870, found 540.2861

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(2-azido-4-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-2-deoxy-*α*,*β*-D-glucopyranosyl)-*α*-D-glucopyranoside. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.45−7.24 (m, Ar), 5.50 (d, J = 5.0 Hz), 5.05−4.98 (m), 4.94 (d, J = 11.1 Hz), 4.92−4.80 (m), 4.78 (d, J = 11.2 Hz), 4.73−4.67 (m), 4.65 (d, J = 6.5 Hz), 4.63−4.56 (m), 4.49 (d, J = 11.9 Hz), 4.43 (s), 4.38 (d, J = 3.5 Hz), 4.22−4.00 (m), 3.91−3.72 (m), 3.69 (d, J = 7.1 Hz), 3.59 (d, J = 3.5 Hz), 3.56 (dd, J = 7.3, 4.4 Hz), 3.53−3.47 (m), 3.41 (s, OMe), 3.39 (s, OMe), 1.00 (s, TBS), 0.96 (s, TBS), 0.92 (s, TBS), 0.88 (s, TBS). ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.9, 138.8, 138.4, 138.3, 138.2, 137.4, 137.2, 128.5, 128.5, 128.5, 128.4, 128.4, 128.4, 128.4, 128.3, 128.2, 128.1, 128.1, 128.0, 127.9, 127.9, 127.7, 127.7, 127.6, 127.5, 127.5, 100.9, 98.2, 97.9, 96.0, 82.1, 82.0, 80.4, 90.0, 79.9, 78.1, 77.6, 75.7, 75.6, 75.4, 74.9, 74.8, 74.2, 73.5, 73.3, 72.9, 72.6, 72.0, 71.5, 71.2, 70.4, 70.1, 68.7, 67.9, 67.4, 67.0, 66.6, 60.3, 55.1, 28.3, 28.1, 28.0, 27.7, 21.8, 21.7, 21.5, 21.0. HRMS calcd for $C_{49}H_{63}N_3O_{10}SiNa$ 904.4180, found 904.4183

Methyl 2,3,6-Tri-*O*-benzyl-4-*O*-(2-azido-4-*O*-benzyl-3,6-*O*-(di-*tert*-butylsilylene)-2-deoxy-*α*,*β*-D-glucopyranosyl)-*α*-D-glucopyranoside. ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.49−7.26 (m, Ar), 5.96 (d, J = 6.4 Hz,), 5.13 (d, J = 11.1 Hz), 5.05−5.03 (m), 5.01 (d, J = 11.4 Hz), 4.89 (d, J = 11.4 Hz), 4.82 (d, J = 11.1 Hz), 4.78 (d, J = 12.1 Hz), 4.74 (d, J = 12.2 Hz), 4.71−4.64 (m), 4.64−4.45 (m), 4.42−4.38 (m), 4.33 (d, J = 3.2 Hz), 4.12 (m), 4.05 (dd, J = 10.8, 3.8 Hz), 4.02−3.82 (m), 3.78 (dd, J = 10.8, 1.7 Hz), 3.72 (dd, J = 10.7, 1.9 Hz), 3.70−3.64 (m), 3.64−3.58 (m), 3.55 (dd, J = 9.2, 3.6 Hz), 3.42 (s, OMe), 3.41 (s, OMe), 3.35 (d, J = 6.4 Hz), 0.94 (s, TBS), 0.87 (s, TBS), 0.86 (s, TBS), 0.84 (s, TBS).^{13}C NMR (126 MHz, $CDCl_3$) δ 139.5, 138.7, 138.5, 138.3, 138.2, 138.1, 137.5, 137.0, 128.5, 128.5, 128.4, 128.2, 128.2, 128.1, 128.0, 128.0, 128.0, 128.9, 128.8, 127.8, 127.6, 127.4, 127.4, 127.3, 127.3, 127.1, 127.0, 100.3, 98.1, 97.8, 95.5, 82.3, 80.5, 80.3, 79.9, 79.6, 78.4, 75.5, 74.9, 74.5, 74.3, 74.1, 73.7, 73.5, 73.2, 73.2, 73.0, 72.4, 71.7, 70.8, 69.8, 69.7, 68.8, 68.3, 67.7, 67.5, 66.8, 60.3, 55.3, 28.0, 28.0, 27.7, 21.7, 21.6, 21.2, 21.1. HRMS calcd for $C_{49}H_{63}N_3O_{10}SiNa$ 904.4180, found 904.4185

■ ASSOCIATED CONTENT

Supporting Information

Copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: cmp@chem.ku.dk.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank FTP for supporting this work and Christian Tortzen for help with low temperature NMR.

REFERENCES

(1) Bols, M. *Carbohydrate Building Blocks*; John Wiley Science Publishers: New York, 1996.

(2) Namchuk, M. N.; McCarter, J. D.; Becalski, A.; Andrews, T.; Withers, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 1270−1277.

(3) In the transition state: (a) Romero, J. A. C.; Tabacco, S. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 168−169. (b) Woods, R. J.; Andrews, C. W.; Bowen, J. P. *J. Am. Chem. Soc.* **1992**, *114*, 859. (c) Jensen, H. H.; Lyngbye, L.; Bols, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3447−3449. (d) Smith, D. M.; Woerpel, K. A. *Org. Biomol. Chem.* **2006**, *4*, 1195−1201.

(4) In the ground state: (a) Jensen, H. H.; Bols, M. *Acc. Chem. Res.* **2006**, *39*, 259−265. (b) Heuckendorff, M.; Pedersen, C. M.; Bols, M. *Chem.—Eur. J.* **2010**, *16*, 13982−13994.

(5) McDonnell, C.; López, O.; Murphy, P.; Bolaños, J. G. F.; Hazell, R.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 12374−12385.

(6) Jadhav, V.; Pedersen, C. M.; Bols, M. *Org. Biomol. Chem.* **2011**, *9*, 7525−7534.

(7) Recently reviewed: (a) Walvoort, M. T. C.; Dinkelaar, J.; van den Bos, L. J.; Lodder, G.; Overkleeft, H. S.; Codée, J. D. C.; van der Marel, G. A. *Carbohydr. Res.* **2010**, *345*, 1252−1263. (b) Pedersen, C. M.; Marinescu, L. G.; Bols, M. *C. R. Chim.* **2011**, *14*, 17−43.

(8) Paulsen, H.; Richter, A.; Sinnwell, V.; Stenzel, W. *Carbohydr. Res.* **1978**, *64*, 339−364.

(9) (a) Mootoo, D. R.; Konradson, P.; Udodong, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583. (b) Fraser-Reid, B.; Wu, Z.; Udodong, U.; Ottoson, H. *J. Org. Chem.* **1990**, *55*, 6068. (c) Fraser-Reid, B.; Wu, Z.; Andrews, C. W.; Skowrinski, E. *J. Am. Chem. Soc.* **1991**, *113*, 1434−1435.

(10) (a) Pedersen, C. M.; Nordstrøm, L. U.; Bols, M. *J. Am. Chem. Soc.* **2007**, *129*, 9222−9235. (b) Jensen, H. H.; Pedersen, C. M.; Bols, M. *Chem.—Eur. J.* **2007**, *13*, 7576−7582. (c) Pedersen, C. M.; Marinescu, L. G.; Bols, M. *Chem. Commun.* **2008**, 2465−2467. (d) Heuckendorff, M.; Pedersen, C. M.; Bols, M. J. *Org. Chem.* **2012**, *77*, 5559−5568.

(11) (a) Broddefalk, J.; Bergquist, K.-E.; Kihlberg, J. *Tetrahedron* **1998**, *54*, 12047−12070. (b) Yamada, H.; Tanigakiuchi, K.; Nagao, K.; Okajima, K.; Mukae, T. *Tetrahedron Lett.* **2004**, *45*, 5615−5618. (c) Yamada, H.; Nakatami, M.; Ikeda, T.; Marumoto, Y. *Tetrahedron Lett.* **2004**, *45*, 5615−5618. (d) Okada, Y.; Nagata, O.; Taira, M.; Yamada, H. *Org. Lett.* **2007**, *9*, 2755−2758. (e) Okada, Y.; Mukae, T.; Okajima, K.; Taira, M.; Fujita, M.; Yamada, H. *Org. Lett.* **2007**, *9*, 1573−1576.

(12) The use of axial-rich glycosyl donors have recently been reviewed: Yamada, H. *Trends Glycosci. Glycotechnol.* **2011**, *23*, 122−133.

(13) Pedersen, C. M. Super Armed Glycosyl Donors: The Best Aid for a Better Reaction Rate; Radical Azidonation: Novel Safe Methodologies. Ph.D. thesis, University of Aarhus, 2007.

(14) (a) Yamada, H.; Nagao, K.; Dokei, K.; Kasai, Y.; Michihata, N. *J. Am. Chem. Soc.* **2008**, *130*, 7566−7567. (b) Okada, Y.; Asakura, N.; Bando, M.; Ashikaga, Y.; Yamada, H. *J. Am. Chem. Soc.* **2012**, *134*, 6940−6943.

(15) Ikeda, Y.; Nagao, K.; Tanigakiuchi, K.; Tokumaru, G.; Tsuchiya, H.; Yamada, H. *Tetrahedron Lett.* **2004**, *45*, 487−489.

(16) Mukaiyama, T.; Maeshima, H.; Jona, H. *Chem. Lett.* **2001**, 388−389.

(17) (a) Koto, S.; Takebe, Y.; Zen, S. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 291−293. (b) Cao, Y.; Okada, Y.; Yamada, H. *Carbohydr. Res.* **2006**, *341*, 2219−2223.

(18) (a) Ibatullin, F. M.; Selivanov, S. I. *Tetrahedron Lett.* **2002**, *43*, 9577−9580. (b) Crich, D.; Picione, J. *Org. Lett.* **2003**, *5*, 781−784.

(19) (a) van den Bos, L. J.; Litjens, R. E. J. N.; van den Berg, R. J. B. H. N.; Overkleeft, H. S.; van der Marel, G. A. *Org. Lett.* **2005**, *7*, 2007−2010. (b) van den Bos, L. J.; Dinkelaar, J.; Overkleeft, H. S.; van der Marel, G. A. *J. Am. Chem. Soc.* **2006**, *128*, 13066−13067. (c) Christina, A. E.; van den Bos, L. J.; Overkleeft, H. S.; van der Marel, G. A.; Codée, J. D. C. *J. Org. Chem.* **2011**, *76*, 1692−1706. (d) Ikeda, Y.; Furukawa, K.; Yamada, H. *Carbohydr. Res.* **2002**, *337*, 1499−1501.

(20) Crich, D.; Pedersen, C. M.; Bowers, A. A.; Wink, D. J. *J. Org. Chem.* **2007**, *72*, 1553−1565.

(21) Chéry, F.; Rollin, P.; De Lucchi, O.; Cossu, S. *Synthesis* **2001**, *2*, 286−292.

(22) Nicolaou, K. C.; Vega, J. A.; Vassilikogiannakis, G. *Angew. Chem., Int. Ed.* **2001**, *40*, 4441−4445.

(23) (a) Gouin, S. G.; Bultel, L.; Falentin, C.; Kovensky, J. *Eur. J. Org. Chem.* **2007**, *7*, 1160−1167. (b) Emmadi, M.; Kulkarni, S. S. *J. Org. Chem.* **2011**, *76*, 4703−4709.

(24) Jiang, L.; Chan, T.-H. *Tetrahedron Lett.* **1998**, *39*, 355−358.

(25) Nicolaou, K. C.; Dolle, R. E.; Papahatjis, D. P.; Randall, J. L. *J. Am. Chem. Soc.* **1984**, *106*, 4189−4192.

(26) The angles were calculated using the program available at http://www.stenutz.eu/conf/haasnoot.php according to Haasnoot, C. A. G.; DeLeeuw F. A. A. M.; Altona C. *Tetrahedron* **1980**, *36*, 2783−2792

(27) *Chem3D Ultra*, Version 12.0.2.1076, part of ChemOffice package from Cambridgesoft.

(28) Hudson, C. S. *J. Am. Chem. Soc.* **1916**, *38*, 1566.

(29) The Perlin effect might be less reliable when having thioglycosides: Alabugin, I. V. *J. Org. Chem.* **2000**, *65*, 3910−3919.

(30) Codee, J. D. C.; Litjens, R.; den Heeten, R.; Overkleeft, H. S.; van Boom, J. H.; van der Marel, G. A. *Org. Lett.* **2003**, *5*, 1519−1522.

(31) Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056−4062.

(32) Suzuki, K.; Maeta, H.; Suzuki, T.; Matsumoto, T. *Tetrahedron Lett.* **1989**, *30*, 6879−6882.

(33) Calculations have suggested different preferred conformations of the oxocarbenium intermediate depending on counterion, solvents and protective group patterns. See: (a) Satoh, H.; Hansen, H. S.; Manabe, S.; van Gunsteren, W. F.; Hünenberger, P. H. *J. Chem. Theory Comput.* **2010**, *6*, 1783−1797. (b) Whitfield, D. M. *Carbohydr. Res.* **2012**, *356*, 180−190.

(34) The difference in reactivity could also be connected with the difference in the dipole moments of the respective donors as indicated by their R_f values (Table 1).

(35) Similar explanation has been presented by Miljkovic et al. to explain the greater rate of acetolysis of α-anomers: Miljkovic, M.; Habash-Marino, M. *J. Org. Chem.* **1983**, *48*, 855−860.

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

(37) Yang, M. T.; Woerpel, K. A. *J. Org. Chem.* **2009**, *74*, 545−553.

(38) (a) Lemieux, R. U. *Pure Appl. Chem.* **1971**, *25*, 527−548. (b) Wulff, G.; Schröder, U.; Wichelhaus. *J. Carbohydr. Res.* **1979**, *72*, 280−284.

(39) Lemieux, R. U.; Morgan, A. R. *Can. J. Chem.* **1965**, *43*, 2205−2213.

(40) Buckley, N.; Oppenheimer, N. J. *J. Org. Chem.* **1996**, *61*, 8048−8062.

(41) Nokami, T.; Nozaki, Y.; Saigusa, Y.; Shibuya, A.; Manabe, S.; Ito, Y.; Yoshida, J.-I. *Org. Lett.* **2011**, *13*, 1544−1547.

(42) The steric bulk of a 4,6-di-*O*-di-*tert*-butylsilylene bridge has been used in α-selective galactosylations. Reviewed in: Imamura, A.; Ando, H.; Ishida, H.; Kiso, M. *Curr. Org. Chem.* **2008**, *12*, 675−689.

(43) Reeves, R. E. *J. Am. Chem. Soc.* **1950**, *72*, 1499−1506.