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How the Arming Participating Moieties can Broaden the Scope of Chemoselective Oligosaccharide Synthesis by Allowing the Inverse Armed−Disarmed Approach

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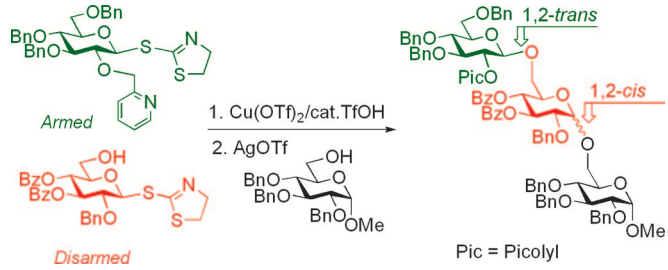

A new method for stereocontrolled glycosylation and chemoselective oligosaccharide synthesis has been developed. It has been determined that complete 1,2-trans selectivity can be achieved with the use of a 2-*O*-picolyl moiety, a novel neighboring group that is capable of efficient participation via a six-membered intermediate. The application of the picolyl concept to glycosidations of thioimidoyl, thioglycosyl, and trichloroacetimidoyl glycosyl donors is demonstrated. The picolyl moiety also retains the glycosyl donor in the armed state, as opposed to conventional acyl participating moieties. We name this new approach the "inverse armed−disarmed" strategy, because it allows for the chemoselective introduction of a 1,2-*trans* glycosidic linkage prior to other linkages. In the context of the oligosaccharide synthesis, the strategy provides *trans*−*trans* and *trans*−*cis* patterned oligosaccharides as opposed to classic Fraser-Reid's armed−disarmed approach leading to *cis*−*trans* and *cis*−*cis* linkages.

Introduction

The involvement of complex glycostructures, polysaccharides and glycoconjugates, in many cellular processes has been directly linked to the progression of many fatal diseases of the 21st century including AIDS, cancer, meningitis, hepatitis, septicemia, etc.[1,2] Elucidation of the exact mechanisms of the disease pathogenesis in many cases would be significantly facilitated if scientists could rely on the comprehensive knowledge of the structure, conformation, and properties of the carbohydrate molecules involved. One of the main drawbacks in studying the biological functions of complex glycostructures is their limited availability in pure form from natural sources. Therefore, there are expectations that efficient chemical or chemo-enzymatic syntheses would make complex carbohydrates more accessible to keep pace with exploding areas of glycosciences.[3] Among possible solutions for this need is the development of reliable methods for stereoselective glycosylation[4] and efficient strategies for expeditious oligosaccharide assembly.[5,6] In spite of significant progress that has already been made in the area of synthetic carbohydrate chemistry, complex glycostructures remain among the most challenging targets of modern synthetic chemistry.[2]

Many known expeditious strategies for oligosaccharide synthesis are based on the selective activation of one leaving group over another, which significantly reduces the number of synthetic steps required for assembly.[5] Among the most efficient procedures developed to date, Fraser-Reid's *armed−disarmed approach* is based on the chemoselectivity principle.[7,8] It was

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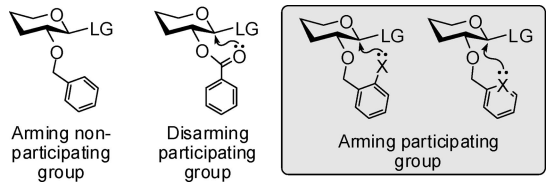

FIGURE 1. Concept of arming participating group.

determined that a benzylated (electronically activated, armed) glycosyl donor can be chemoselectively activated over an acylated (electronically deactivated, disarmed) derivative bearing the same type of leaving group. At this stage, 1,2-*cis*-linked disaccharide is preferentially obtained due to the necessity to use the ether-type substituent (arming nonparticipating group, Figure 1). A key feature of such an approach is the availability of a suitable mild activator (promoter) that would allow for differentiating the reactivity levels between the armed and disarmed building blocks.

Initially being designed for *O*-pentenyl glycosides, this concept was further explored in chemoselective glycosidations of other glycosyl donors, including thioglycosides,[9] selenoglycosides,[10] fluorides,[11] phosphoroamidates,[12] substituted thioformimidates,[13] glycals,[14] S-benzoxazolyl glycosides,[15] and S-thiazolinyl (STaz) glycosides.[16] The obtained 1,2-*cis* linked disaccharides (usually a mixture) can be then used for 1,2-*trans* glycosylation directly in the presence of a more potent promoter, capable of activating the disarmed leaving group. This two-step activation leads to efficient assembly of *cis*−*trans*-patterned oligosaccharide sequences. In the context of the glycoside synthesis in general, the use of an acyl-type disarming participating group (Figure 1) remains virtually the only common approach to achieve excellent 1,2-*trans* stereoselectivity.

The attractive concept of chemoselective oligosaccharide synthesis was further analyzed, summarized and expanded by Ley,[17] Wong,[18] and others.[19] As a result, excellent programmable multistep reactivity-based techniques including highly efficient one-pot approaches have become available. The armed−disarmed strategy thus offers an efficient tool for the synthesis of oligosaccharides with a *cis*−*trans* glycosylation pattern. While the synthesis of *cis*−*cis*-linked derivatives is also possible by means of additional protecting group manipulations,[7,8] this concept is not directly applicable to the synthesis of *trans*−*cis*- or *trans*−*trans*-linked oligosaccharide fragments. This arguably limits its versatility and flexibility in the context of practical oligosaccharide synthesis, whereas the use of other, usually more laborious techniques, such as orthogonal,[20] semi-orthogonal,[21] and two-step activation (or preactivation)[22,23] strategies allow for the synthesis of such patterns.

To overcome this major drawback of chemoselective glycosylations and expand the scope and applicability of this excellent technique to other oligosaccharide sequences (*trans*−*trans* and *trans*−*cis*), we initiated studies of an approach that we call "inverse armed−disarmed strategy". Conceptually, we should be able to perform the chemoselective introduction of 1,2-*trans* linkage prior to another 1,2-*trans* or 1,2-*cis* linkage if a neighboring substituent capable of both activation and participation (arming participating moiety, APG, Figure 1) were available. Our preliminary results related to this approach have already been communicated.[24] Herein we present the full account of these studies and our initial steps toward broadening the concept in the context of its application to other classes of compounds and targets. Other types of moieties that allow for excellent β-stereoselectivities while keeping the glycosyl donor in the armed state have recently been developed.[25]

Results and Discussion

Since the inverse armed−disarmed approach would require the use of a neighboring substituent capable of both activation and participation, we investigated a number of substituents to be used as an APG. We reasoned that since the benzyl substituent has proven to be excellent arming moiety, the investigation of modified benzyls would be a good starting point. It should be appreciated that the modification at the benzylic α-carbon however could result in altering its arming properties; hence, to design a suitable moiety that would be capable of participation, and to investigate its possible influence on the outcome of glycosylations, we decided to focus these studies on the ortho-substituted/modified benzyl ethers.

Investigation of Thioglycosides. This novel concept was first investigated using ethyl thioglycosides, which are known to be common and versatile glycosyl donors.[23,26] The synthesis of the 2-hydroxyl intermediate **4** was achieved from known thioorthoester **1a**,[27] as shown in Scheme 1. Thus, a deacetylation-benzylation sequence followed by opening of the resulting orthoester **2a** afforded 2-acetyl thioglycoside **3**. Deacetylation of the latter compound resulted in the formation of the key intermediate **4**. Subsequently, alkylation of the 2-hydroxyl under typical reaction conditions (alkyl bromide, NaH in DMF) afforded 2-*O*-(*o*-bromobenzyl, BrBn) **6**, 2-*O*-(*o,o*-dimethoxy-

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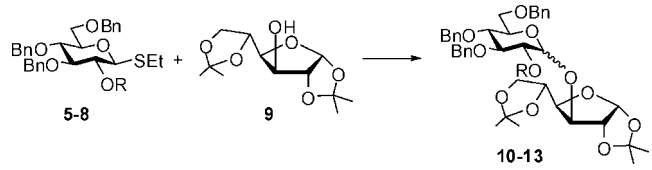
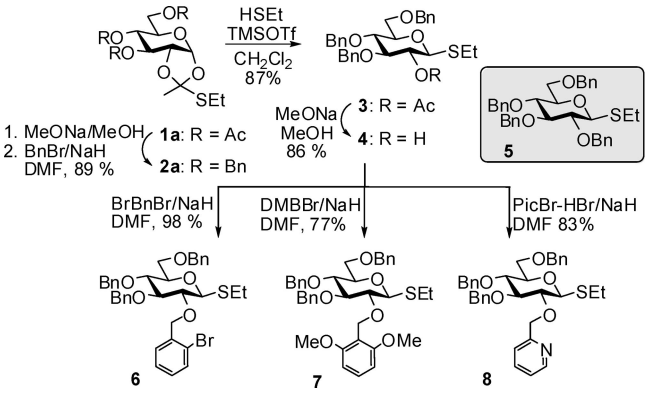
TABLE 1. Investigation of Glycosyl Donors 5−8 Bearing Various Arming Participating Groups



entry	donor	R[a]	promoter	temp.	product	yield	α/β ratio
1	**5**	Bn	IDCP	rt	**10**	80%	2.7/1
2	**6**	BrBn	IDCP	rt	**11**	78%	1.8/1
3	**6**	BrBn	IDCP	−40 °C → rt	**11**	87%	2.3/1
4	**7**	DMB	IDCP	rt	**12**	58%	1.8/1
5	**7**	DMB	IDCP	−35 °C → rt	**12**	87%	2.3/1
6	**7**	DMB	IDCP	−40 °C → rt	**12**	89%	1.8/1
7	**8**	Pic	IDCP	rt	**13**	n.d.[b]	−
8	**8**	Pic	MeOTf	rt	**13**	n.d.	−
9	**8**	Pic	NIS/TfOH	rt	**13**	n.d.	−
10	**8**	Pic	DMTST	rt	**13**	5%	β only
11	**8**	Pic	DMTST	rt → 45 °C	**13**	45%	β only

[a] Bn, benzyl; BrBn, -*o*-bromobenzyl; DMB, *o,o*-dimethoxybenzyl; Pic, picolyl. [b] Not detected.

SCHEME 1



benzyl, DMB) **7**, and 2-*O*-picolyl (2′-pyridylmethyl, Pic) derivatives **8** in 98, 77, and 83%, respectively (Scheme 1).

Preliminary experiments with novel glycosyl donors **6**−**8** were performed in direct comparison with standard glycosidation of per-benzylated glycosyl donor **5**.[28] These couplings were performed using model glycosyl acceptor **9** in the presence of iodonium(di-γ-collidine)perchlorate (IDCP).[9,29] Although glycosyl donors **6** and **7** allowed slightly improved β-stereoselectivity in comparison to that achieved with 2-benzyl donor **5** (Table 1, entries 1−6), it remained uncertain whether this marginally improved β-stereoselectivity should be attributed to the anticipated participation via a seven-membered intermediate (Figure 1) or would rather be a result of the increased steric hindrance of the bottom face of the ring. Not being able to differentiate between these two possible pathways, and being discouraged by the negligibly improved stereoselectivity of the formation of disaccharides **11** and **12** in comparison to that of **10** (Table 1), our subsequent studies refocused on the investigation of the picolylated glycosyl donor **8**. We reasoned that the picolyl moiety would offer a more efficient participation via six-membered cyclic intermediate (Figure 1) while being about the same size as conventional benzyl substituent. Therefore, if the anticipated increase in stereoselectivity takes place, this could be exclusively attributed to the anchimeric participation, but not steric hindrance. The synthesis of the glycosyl donor **8** bearing a picolyl substituent at C-2 was achieved as described in Scheme 1 with the commercial picolyl bromide hydrobromide.

Unfortunately, nearly all of our attempts to glycosidate donor **8** have failed. Thus, common promoters for thioglycoside activation[26] have been screened, but each experiment performed at ambient temperature led to the reaction between the electrophilic promoter and nucleophilic nitrogen in the pyridine moiety in lieu of the anomeric sulfur atom (entries 7−10, Table 1). Mildly electrophilic dimethyl(thiomethyl)sulfonium triflate (DMTST)[30] commonly used as the promoter for thioglycosides,[31] was the most promising in this respect, but even upon prolonged heating at 45 °C (16 h) the reaction provided the disaccharide **13** in a modest yield of 45% (entry 11). The stereoselectivity though exceeded all of our expectations as the reaction was found to be completely β-stereoselective. In this context, although an approach for controlling the anomeric stereoselectivity with a neighboring substituent capable of the six-membered participation is relatively unexplored, a number of moieties for stereoselective α-glycosylation have recently been reported.[32]

Investigation of 2-*O*-Picolylated Glycosyl Donors. Although the latter result could serve as the ultimate proof of the concept, low efficiency would the major burden for subsequent practical applications. To investigate this concept further and with the hopes to avoid the interference of the picolyl group with the leaving group activation we decided to apply these findings to S-thiazolinyl (STaz) glycosyl donors. The rationale for selecting the STaz moiety for subsequent studies was the fact that this type of leaving group can be activated by mildly electrophilic metal salt-based promoters.[33] Another important motivation for selecting the STaz glycosides was related to their excellent glycosyl donor properties and the compatibility with the classic Fraser-Reid's armed−disarmed strategy.[16]

For the purpose of synthesizing picolylated STaz glycosyl donor, the orthoester **2a** was opened with 2-mercaptothiazoline

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SCHEME 2

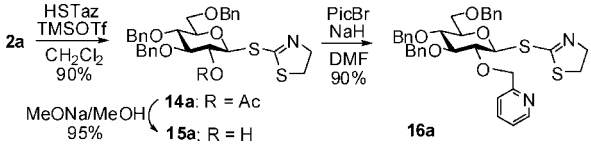

TABLE 2. Synthesis of 1,2-*trans*-Linked Disaccharides 23−28 from 2-*O*-Picolyl Donors

entry	donor	acceptor	promoter	product	yield, %
1	**16a**	**18**	$Cu(OTf)_2$	**23**	80
2	**16a**	**18**	$Cu(OTf)_2$/ TfOH	**23**	84
3	**16a**	**18**	AgOTf	**23**	78
4	**16a**	**19**	$Cu(OTf)_2$	**25**	83
5	**16a**	**19**	$Cu(OTf)_2$/TfOH	**25**	80
6	**16a**	**20**	$Cu(OTf)_2$/TfOH	**26**	85
7	**16a**	**21**	$Cu(OTf)_2$	**27**	69
8	**16a**	**21**	$Cu(OTf)_2$/TfOH	**27**	80
9	**16a**	**21**	AgOTf	**27**	63
10	**16a**	**22a**	$Cu(OTf)_2$	**28a**	56
11	**16a**	**22b**	$Cu(OTf)_2$	**28b**	78
12	**16a**	**22b**	AgOTf	**28b**	72
13	**16b**	**18**	$Cu(OTf)_2$	**24**	76
14	**8**	**18**	DMTST	**23**	70
15	**31**	**18**	TESOTf	**23**	84

(HSTaz) in the presence of TMSOTf to give the intermediate **14a** in 90% yield. The deacetylation of **14a** was carried out over 72 h with NaOMe/MeOH to give compound **15a** (95%). Although the STaz moiety was generally found to be stable in the presence of strong bases,[16] careful optimization of the following transformation allowed us to obtain the target 2-picolylated derivative **16a** in an excellent yield of 90%. Thus, picolyl bromide hydrobromide was first reacted with NaH in DMF to quench the HBr and to exclude possible interference of the STaz group at this stage. Subsequently, the 2-hydroxyl derivative **15a** was added to the resulting mixture at −30 °C followed by further addition of NaH to give the target glycosyl donor **16a** (Scheme 2).

Having synthesized 2-picolyl STaz glycoside **16a**, we turned our attention to studying its glycosyl donor properties. For this purpose, a range of differently protected glycosyl acceptors **18**−**22** was selected (Figure 2).[9,34−37] Per-benzylated STaz glycosyl donor **17**[16] was used as a stereoselectivity/reactivity control. After screening a variety of suitable activators ranging from common activators for the thioglycoside activation to metal salts that are unique for the thioimidates, we chose $Cu(OTf)_2$ to be applied alone or in combination with catalytic TfOH. To our encouragement, all glycosylations summarized in Table 2 proceeded with complete 1,2-*trans* stereoselectivity: no traces of the α-anomer were detected in every reaction. The corresponding disaccharide derivatives **23**−**28** (Figure 3) were isolated in good yields in the range of 56−85%. In comparison, glycosidations of benzylated STaz glycoside **17** provided predominantly α-linked disaccharide with predominant α-stereoselectivity (α/β = 2−4/1).[16]

We have also noticed that glycosidation of **16a** required significantly more time at rt than that of its per-benzylated counterpart **17** (48 h vs 1−3 h, respectively). To enhance the efficiency of this approach and shorten the reaction time, all glycosylations with **16a** were performed in 1,2-dichloroethane

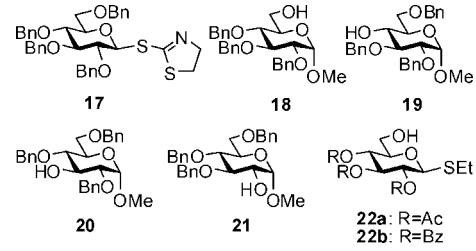

FIGURE 2. Glycosyl donor **17** and glycosyl acceptors **18**−**22**.

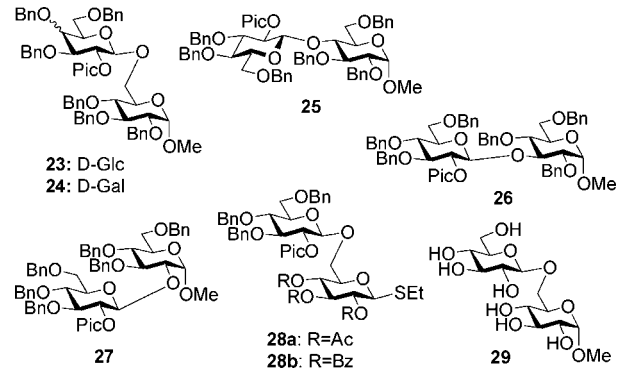

FIGURE 3. Disaccharides **23**−**29**.

at elevated temperature. It was determined that the reaction temperature of 42 °C was optimal in terms of both conversion rate—all couplings were completed in 12−16 h—and yields (see Table 2). While the efficiency of silver(I) triflate was similar to that achieved with $Cu(OTf)_2$ (compare entries 1 and 3), in a variety of cases the use of catalytic TfOH additive along with stoichiometric $Cu(OTf)_2$ resulted in significantly higher reaction yields (e.g., entries 1, 2, 7, and 8). It should be noted that all reactions were performed with each promoter (or promoter combination) mentioned herein, yet only the most representative results are summarized in Table 2. Upon completion, the glycosylations were quenched with an excess of triethylamine (∼20 equiv) to ensure that the copper-pyridinium complex of the product with promoter that could have been formed during the prolonged reactions has been completely decomposed.

Being satisfied with the utilization of an array of structurally diverse glycosyl acceptors, we decided to evaluate whether the developed technique could be applied to other classes of glycosyl donors. First of all, we decided to investigate glycosyl donor of the D-galacto series, which is among the most abundant monosaccharides in nature, thus representing an important target. As in the case of the D-gluco counterpart **16a**, the synthesis of picolylated galactosyl donor **16b** (compound numbers for the D-galacto series are essentially the same as shown for the D-gluco series and designated with index **b** and **a**, respectively) was initiated from the derivatization of the orthoester. Thus, the orthoester **1b** was deacetylated and benzylated without the need for the intermediate purification to give **2b** in 79% yield. The latter orthoester then was opened to give STaz galactoside **14b** in 83% yield, which was deprotected to give 2-hydroxyl derivative **15b** in 95% yield. The picolyl group was then installed to give the desired galactose donor **16b** in 85% yield. As indicated in Table 2, the galactosyl donor **16b** was glycosidated with acceptor **18** to give the desired disaccharide **24** with complete 1,2-*trans* stereoselectivity in 76% yield (entry 13).

Having demonstrated that the picolyl moiety could be simply introduced under conventional alkylation conditions and applied

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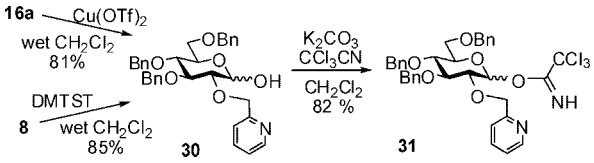
SCHEME 3



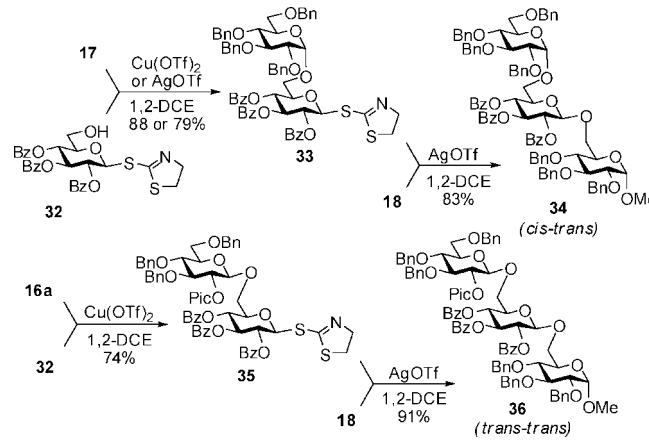
to the successful stereoselective synthesis of 1,2-*trans*-linked disaccharides, we decided to investigate the pathways for its deprotection. Indeed, the development of a novel protecting group would be totally impractical if it could not be removed. Along these lines, the 2-*O*-picolyl moiety could be removed under conventional catalytic hydrogenation conditions (Pd/C).[49] Thus, hydrogenolysis of *O*-picolyl moiety in **23** was achieved along with concomitant removal of benzyls affording a fully unprotected disaccharide **29** (Figure 3) in 98% yield.

Upon establishing the reaction conditions with the STaz glycosides, we decided to investigate the compatibility of the picolyl moiety with other types of glycosylations. First of all, we have reinvestigated the thioglycoside donor by applying a procedure similar to that developed for the STaz glycosides. When 2-picolyl thioglycoside **8** and acceptor **18** were mixed with DMTST at room temperature followed by heating at 42 °C for 18 h, only modest yield of the disaccharide **23** could be obtained (~50%). However, a significantly improved yield was reached by cooling the reaction mixture to −50 °C prior to the addition of promoter followed by slow warming to rt and subsequent heating at 42 °C for 18 h. This modified approach led to the disaccharide **23** in a significantly improved yield of 70% (entry 14, Table 2).

We then turned our attention to the investigation of the trichloroacetimidate approach to glycosylation, arguably the most widespread method of glycosylation.[38] The trichloroacetimidate donor **31** was obtained from the STaz (or SEt) glycoside **16a** (or **8**) via sequential hydrolysis of the anomeric moiety with $Cu(OTf)_2$ (or DMTST) leading to the hemiacetal **30** followed by the introduction of the trichloroacetoimidoyl moiety by reaction with trichloroacetonitrile in the presence of potassium carbonate as a base (Scheme 3). The target trichloroacetimidate **31** was sufficiently stable to be purified by chromatographic column, and the α- and β-isomers could be isolated individually in 48% and 34% yield, respectively. A TESOTf-promoted glycosidation of **31** with glycosyl acceptor **18** led to the formation of disaccharide **23** with complete 1,2-*trans* stereoselectivity in a yield of 84% (entry 15, Table 2).

Novel Applications of Chemoselective 1,2-*trans* Glycosylations in Oligosaccharide Synthesis. Having established general conventions for simple one-step 1,2-*trans* glycosylations, we turned our attention to investigating the applicability of this novel methodology to expeditious oligosaccharide synthesis. As aforementioned, the major motivation for these studies was to invent new chemoselective pathways for the rapid synthesis of various oligosaccharide sequences. As aforementioned, in our previous work we have already established that the STaz glycosides also follow general armed−disarmed strategy.[16] Thus, the armed STaz glycoside donor **17** was chemoselectively activated over the disarmed STaz glycosyl acceptor **32**[16] in the presence of $Cu(OTf)_2$ or AgOTf (Scheme 4). As a result, the disaccharide **33** was obtained in 88% yield (α/β = 1.5/1) and

SCHEME 4



79% yield (α/β = 2.0/1) respectively. The disarmed reducing end of the intermediate **33** could be activated with a more potent promoter AgOTf for the coupling with glycosyl acceptor **18** that resulted in the formation of the *cis*−*trans*-patterned trisaccharide **34** in 83% yield.[16]

Since in our simple glycosylation experiments we have noticed that glycosidation of picolylated glycosyl donors required prolonged experiments in comparison to that of their per-benzylated counterparts, it seemed essential to establish whether the 2-picolyl derivatives could be chemoselectively activated over the disarmed glycosyl acceptors. As a matter of fact, the direct coupling between picolylated glycosyl donor **16a** and the tribenzoylated STaz acceptor **32**[16] clearly demonstrates the proof of concept of the APG and the feasibility of the chemoselective introduction of the 1,2-*trans* glycosidic linkage early in the synthetic sequence prior to other linkages. Thus, disaccharide **35** was obtained in 74% yield as the sole β-anomer (Scheme 4). Subsequently, the activation of the disarmed disaccharide **35** for the reaction with **18** in the presence of AgOTf afforded the *trans*−*trans*-linked trisaccharide **36** in 91% yield. It should be noted that prior to our studies, this type of sequence could not be accessed via chemoselective armed−disarmed activations.

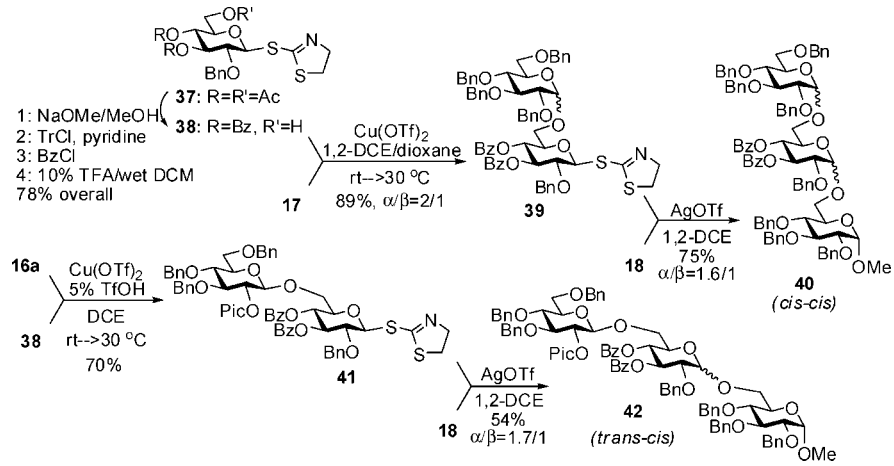
After successfully obtaining both the *cis*−*trans* and *trans*−*trans* oligosaccharide sequences we turned our focus to the investigation of the other sequences i.e. *cis*−*cis* and *trans*−*cis*, the latter being "inverse oligosaccharide pattern" as opposed to that achieved by the classic Fraser-Reid approach (*cis*−*trans*). In this context, although the synthesis of the *cis*−*cis* pattern does not require the use of APG, its exploration herein seemed essential as it would complete the comprehensive toolkit for synthesizing all types of sequences using a simple set of building blocks requiring only one type of anomeric moiety. Recently we demonstrated the two-step synthesis of the *cis*−*cis* linked oligosaccharide by exploring a new effect that we call O-2/O-5 cooperative effect in glycosylation,[15] yet its application to the STaz methodology had not been explored. Alternatively, the same concept could be realized by using the so-called disarming nonparticipating moieties in the glycosyl acceptor unit.[39]

Utilizing the general principle of the cooperative effect we obtained 3,4-di-*O*-benzoyl-2-*O*-benzyl protected STaz glycosyl acceptor **38** from known derivative **37**[16] via conventional

(38) Schmidt, R. R.; Jung, K. H. In *Carbohydrates in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinay, P., Eds.; Wiley-VCH: Weinheim, NY, 2000; Vol. 1, pp 5−59.

(39) Crich, D.; Hutton, T. K.; Banerjee, A.; Jayalath, P.; Picione, J. *Tetrahedron: Asymmetry* **2005**, *16*, 105–119.

SCHEME 5

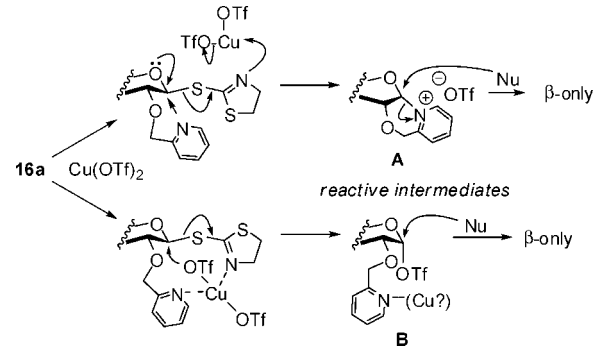


tritylation-acylation-detritylation sequence (78% overall yield, Scheme 5). Performing direct chemoselective activations substantiated our anticipation that the building block **38**, bearing the remote electron-withdrawing acyl groups, would be less reactive than the per-benzylated derivative **17**. The reaction of glycosyl donor **17** with glycosyl acceptor **38** was performed in the presence of $Cu(OTf)_2$ in 1,2-dichloroethane/dioxane to give predominantly α-linked disaccharide **39** in 89% yield (α/β = 2/1, Scheme 5). The disarmed disaccharide **39** was then glycosidated with standard glycosyl acceptor **18** in the presence of AgOTf to give the desired *cis*−*cis*-linked trisaccharide **40** in 75% yield (α/β = 1.6/1).

Lastly, we needed to combine the *trans*-directing picolyl functionality of glycosyl donor **16a** and the *cis*-directing functionality of the cooperative glycosyl acceptor **38** that could potentially lead to the inverse *trans*−*cis* glycosylation pattern. To achieve this, glycosyl donor **16a** was coupled with glycosyl acceptor **38** in the presence of stoichiometric $Cu(OTf)_2$ and catalytic TfOH at 30 °C for 18 h to give the disaccharide **41** in 70% yield (Scheme 5). The yield could be further increased by executing the preactivation of the glycosyl donor **16a** followed by the addition of the glycosyl acceptor **38**. Although deemed unnecessary, the latter modification allows one to significantly reduce the impact of the major competing side reaction of the intramolecular self-condensation of the glycosyl acceptor leading to formation of the 1,6-anhydro derivative. The disaccharide **41** was then coupled to the glycosyl acceptor **18** in the presence of AgOTf to give the desired trisaccharide **42** in 54% yield (α/β = 1.7/1).

Mechanistic Investigations. Being encouraged by the complete 1,2-*trans* stereoselectivity achieved in all glycosidations of 2-*O*-picolylated glycosyl donors, we decided to investigate whether this remarkable selectivity is actually due to the anticipated anchimeric participation. We also had hoped that the in depth mechanistic studies would help to answer other questions that have surfaced during the preliminary experimentations. These include relatively slow glycosidation reaction, partial complexation/salt formation, and good, yet not exceptional yields in glycosylations. Among these, low reactivity was particularly intriguing because while the direct chemoselective activation of **16a** over benzoylated acceptor **32** was possible, the stand alone glycosylations with per-benzoylated STaz glycoside were significantly faster (1−20 h at rt)[33] than those with **16a** (24−48 h at rt). Therefore, this discrepancy could not

SCHEME 6



be simply rationalized by the lower reactivity of 2-*O*-picolylated glycosyl donors.

As aforementioned, our working hypothesis for these studies was based on the anticipation that upon promoter-assisted leaving group departure, the oxocarbenium ion is converted into a stable intermediate of the six-membered cyclic structure **A** (Scheme 6). Although this pathway involving formal participation of the nitrogen atom on the O-2 protecting moiety via the anomeric center seemed very credible, we could not entirely eliminate other possibilities. For example, an alternative explanation exploring the possibility of the intramolecular promoter complexation of the two nitrogen atoms of the glycosyl donor has also come to our attention. We believed that the bidentate complex depicted in Scheme 6 would cause sufficient disturbance to the leaving group to stimulate its departure followed by the formation of the anomeric α-triflate **B** (Scheme 6). Since glycosyl triflates are known to allow for the concerted bimolecular nucleophilic substitution,[40] the second pathway also deemed as a viable explanation to the stereoselective formation of the 1,2-*trans*-linked products.

At this stage it seemed impossible to differentiate between the two plausible intermediates **A** and **B**, therefore, to clarify this we decided to undertake mechanistic studies. We anticipated that if it were possible to trap the reaction intermediate, this would provide sufficient information to clarify the reaction

(40) Crich, D. *J. Carbohydr. Chem.* **2002**, *21*, 667–690.
(41) (a) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217–11223. (b) Callam, C. S.; Gadikota, R. R.; Krein, D. M.; Lowary, T. L. *J. Am. Chem. Soc.* **2003**, *125*, 13112–13119. (c) Rencurosi, A.; Lay, L.; Russo, G.; Caneva, E.; Poletti, L. *Carbohydr. Res.* **2006**, *341*, 903–908. (d) Nokami, T.; Shibuya, A.; Tsuyama, H.; Suga, S.; Bowers, A. A.; Crich, D.; Yoshida, J. *J. Am. Chem. Soc.* **2007**, *129*, 10922–10928.

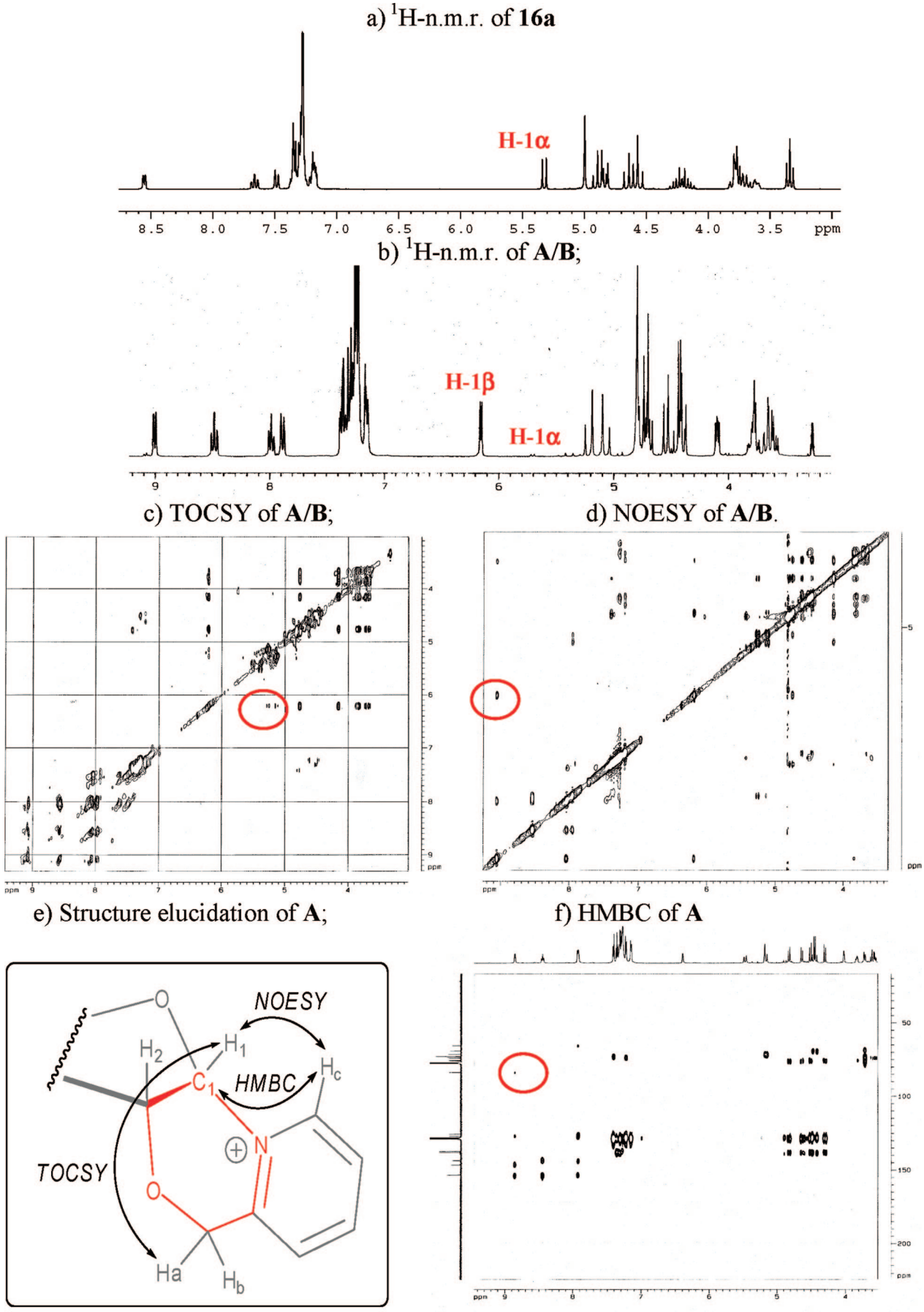


FIGURE 4. Spectral characterization of the reaction intermediates.

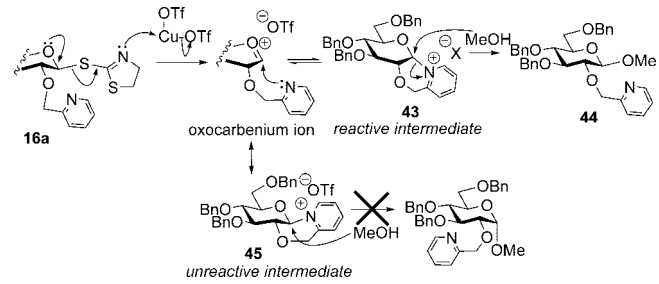
pathway. A number of recent reports described the spectral properties of the anomeric triflates,[41] hence we thought that if our reaction were proceeding via the intermediate **B**, it could be easily detected by recording a simple proton NMR spectrum. The spectral properties of the previously reported glycosyl triflates differ based on their chemical structure, but what they all had in common is small coupling constant doublet (or even a singlet) corresponding to the anomeric proton (H-1) in a relatively low field (between 6.0−6.3 ppm).[41]

Having recorded the proton spectrum of the glycosyl donor **16a** (Figure 4a), we noted that no signals were present between 5.5 and 7.0 ppm. This would significantly facilitate the monitoring of the formation of plausible glycosyl triflate species by avoiding undesirable signal overlaps that is often an unavoidable burden in complex molecules. Subsequently, AgOTf (2 equiv) was added to the standard 5 mm NMR tube containing **16a** and $CDCl_3$, and upon complete disappearance of the glycosyl donor (1 h, TLC analysis) the spectrum was recorded again. Indeed, as can be seen in Figure 4b, no starting material remained at this stage; as a matter of fact, we determined that **16a** gets entirely consumed in about 1 h regardless of the temperature (studied range 0−50 °C). At this stage, the ^{1}H NMR spectrum clearly shows the anomeric signals of two compounds: (major, 6.15 ppm, J = 4.6 Hz) and H-1α (minor, 5.75 ppm, J = 8.2 Hz), corresponding to the α- and β-glycosyl linkage, respectively. The anomeric ratio, determined by comparison of the integral intensities of the corresponding signals in proton spectra, varied depending on the reaction conditions from 5/1 (50 °C) to 20/1 (rt or 0 °C).

Apparently, experimental data acquired at this stage has not yet provided sufficient information to distinguish whether the obtained reaction intermediate is postulated **A**, **B**, or neither. In principle, both anomeric triflate and α-*N*-glycoside could display H-1 signals in the observed region. Therefore, the NMR studies were continued by using advanced two-dimensional techniques. These NMR determinations we found to be very informative and allowed for the unambiguous structure elucidation of the reaction intermediate. Thus, correlations in the NOESY experiment between protons H-1 (δ 6.15 ppm) and the aromatic proton adjacent to the picolyl nitrogen atom (H_c, δ 9.00 ppm) indicated that these two protons were situated in close proximity (Figure 4d). This has become good, yet not explicit indication on the reaction intermediate being the proposed six-membered cyclic intermediate **A** (Figure 4e). Also, the TOCSY data revealed that H-1 and the benzylic protons of the picolyl group (H_a and H_b, δ 5.15 ppm) are a part of the same spin system (Figure 4c and e), another indication on the ring system. Also from the 1D data (Figure 4a and b), it was evident that the α-benzylic protons underwent significant modifications reflected in their spectral properties (singlet in **16a** vs double of doublets in **A/B**). This was another indication on the ring system and the equivalent protons $H_{a,b}$ have become "fixed" in a more rigid cyclic substructure and thus could be differentiated in the proton spectrum. Finally, by determining the long-range coupling between C-1 (δ 84.89 ppm) and H_c in the HMBC spectrum (Figure 4f) we confirmed that the C-1 and H_c atoms are positioned three bonds apart.[42]

Based on the experimental spectral data presented herein, we conclude that there is a solid evidence for the α-*N*-picolyl glycosidic linkage, as in **A** (Figure 4e), a clear indication for the cyclic intermediate that has formed as a result of the anchimeric assistance of the 2-*O*-picolyl participatory moiety.

SCHEME 7. Proposed Reaction Mechanism



Furthermore, the bicyclic intermediate **A** (**43**) could be isolated in the pure form from the reaction of **16a** with $Cu(OTf)_2$ (1 h, rt) followed by conventional postglycosylation workup and flash column chromatography on silica gel. Although we do not yet have experimental evidence regarding the counteranion of **43**, the isolated intermediate was found to be reactive with potent nucleophiles such as NaOMe, to allow glycoside **44** (Scheme 7), even in the absence of the promoter. Similarly, we determined that compound **43** could be obtained from glycosyl donor **16a** by reaction with bromine.

It was also determined that minor NMR signals (e.g., doublet at 5.75 ppm) seen in the spectrum of **A/43** (Figure 4b) correspond to the β-linked cyclic intermediate **45** (Scheme 7). It is noteworthy that ^{1}H and ^{13}C NMR data of **43** and **45** are in good correlation with those recorded for α- and β-*N*-pyridinium salts.[43] Interestingly, while **43** was found to be reactive leading to 1,2-trans glycosides, the β-intermediate **45** remained completely inert and could be typically isolated from the final reaction mixture. Even purposeful prolonged reactions performed with potent charged nucleophiles in refluxing DMF did not stimulate compound **45** to react. It is possible that this stability is to be attributed to the reverse anomeric effect that favors charged β-*N*-glycosidic species,[44] although no direct experimental data clarifying this high stability of **45** is yet available.

Conclusions

In conclusion, a new method for stereocontrolled and chemoselective glycosylation has been developed. It has been demonstrated that complete 1,2-*trans* selectivity can be achieved with the use of a 2-*O*-picolyl moiety, a novel neighboring group that is capable of efficient participation via a six-membered intermediate while retaining the glycosyl donor in the armed state, as opposed to the conventional acyl participating moieties. Initially developed for the S-thiazolinyl glycosides, this approach was also proven compatible with the most common glycosylation methodologies developed to date based on thioglycosides and glycosyl trichloroacetimidates. The application of a novel arming participating moiety to complement chemoselective oligosaccharide synthesis has been also developed. This new armed−disarmed glycosylation strategy allows for chemoselective introduction of a 1,2-trans glycosidic linkage prior to other linkages, as opposed to the classic Fraser-Reid approach. Based on our chemoselective studies, we conclude that the developed technique, along with the classic armed−disarmed

(42) Bock, K.; Pedersen, C. *J. Chem. Soc., Perkin Trans. 2* **1974**, 293–297.

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

(44) Tvaroska, I.; Bleha, T. *Adv. Carbohydr. Chem. Biochem.* **1989**, *47*, 45–123.

approach, allows for expeditious access to any oligosaccharide sequence (*cis*−*cis, cis*−*trans, trans*−*trans*, and *trans*−*cis*) from only one type of a leaving group. Thorough mechanistic studies led to the discovery that the picolyl-assisted 1,2-trans stereoselective glycosylations proceed via the formal six-membered cyclic intermediate.

Experimental Section

Preparation of Glycosyl Donors Containing APG. Ethyl 3,4,6-Tri-*O*-benzyl-2-*O*-(*o*-bromobenzyl)-1-thio-β-D-glucopyranoside (6). To a solution of the thioglycoside **4** (50 mg, 0.101 mmol) in DMF (1.0 mL) NaH (60% in mineral oil, 8.1 mg, 0.203 mol) and 2-bromobenzyl bromide (30 μL, 0.122 mmol) were added at rt. The reaction mixture was stirred for 20 min, then poured into ice−water (20 mL), stirred for 30 min, and extracted with EtOAc/Et_2O (1/1, v/v, 3 × 15 mL). The combined organic extract was washed with cold water (3 × 20 mL), separated, dried with $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/toluene gradient elution) to allow the title compound as a white amorphous solid in 98% yield. Analytical data for **6**: $R_f = 0.49$ (ethyl acetate−hexane, 1/4, v/v); $[\alpha]_D^{27} = -11.7°$ (c = 1, $CHCl_3$); ^{1}H NMR: δ, 1.34 (t, 3H, SCH_2CH_3), 2.78 (m, 2H, SCH_2CH_3), 3.50−3.57(m, 2H, H-1, 5), 3.63−3.85 (m, 5H, H-2, 3, 4, 6a, 6b), 4.51 (d, 1H, CH_2Ph), 4.56−4.65 (m, 2H, CH_2Ph), 4.82−5.03 (d, 5H, CH_2Ph), 7.11−7.37 (m, 17H, aromatic) 7.53 (d, 1H, aromatic), 7.63 (dd, 1H, aromatic) ppm; ^{13}C NMR: δ, 15.4, 25.1, 69.3, 73.6, 74.4, 75.2, 75.9, 78.2, 79.3, 82.1, 85.0, 86.8, 122.3, 127.5, 127.8, 127.8, 127.9, 128.0, 128.0, 128.1, 128.5, 128.6, 129.0, 129.5, 132.5, 138.0, 138.2, 138.4, 138.5 ppm; HR-FAB MS calc for $C_{36}H_{40}BrNO_5S$ [M + H]$^+$: 663.1780, found 663.1802.

Ethyl 3,4,6-Tri-*O*-benzyl-2-*O*-(*o*,*o*-dimethoxybenzyl)-1-thio-β-D-glucopyranoside (7). To a solution of the thioglycoside **4** (150 mg, 0.304 mmol) and 2,6-dimethoxybenzyl bromide (105 mg, 0.456 mmol) were dissolved in DMF (1.5 mL) and NaH (60% in mineral oil, 24 mg, 0.609 mmol) was added at rt. The reaction mixture was stirred for 2 h, then quenched with ice (5 g) and extracted with EtOAc/Et_2O (1/1, v/v, 3 × 25 mL). The combined organic extract was washed with cold water (3 × 20 mL), separated, dried with magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/toluene gradient elution) to afford the title compound as colorless syrup (77%). Analytical data for **7**: R_f = 0.48 (ethyl acetate−hexane, 1/3, v/v); $[\alpha]_D^{27} = -9.1°$ (c = 1, $CHCl_3$); ^{1}H NMR: δ, 1.31 (t, 3H, J = 7.1, SCH_2CH_3), 2.75 (m, 2H, SCH_2CH_3), 3.45 (m, 1H, H-2), 3.58−3.86 (m, 5H, H- 3, 4, 5, 6a, 6b), 3.76 (s, 6H, OMe), 3.93 (m, 1H, NCH_2CH_3), 4.45 (d, 1H, $J_{1,2}$= 9.1 Hz, H-1), 4.70 (d, 1H, CH_2Ph), 4.76 (d, 1H, CH_2Ph), 5.01−5.06 (m, 3H, CH_2Ph), 6.51 (d, 2H, aromatic), 7.11 (m, 2H, aromatic), 7.18−7.34 (m, 14H, aromatic) ppm. ^{13}C NMR: δ, 15.3, 25.0, 29.9, 55.8, 63.6, 69.6, 73.6, 75.2, 75.4, 77.4, 78.2, 79.2, 82.0, 85.5, 87.0, 103.9, 114.6, 127.4, 127.7, 127.8, 127.9, 128.2, 128.4, 128.5, 130.0, 138.4, 138.5, 139.4, 159.6 ppm; HR-FAB MS calc for $C_{38}H_{44}O_7SNa$ [M + Na]$^+$: 667.2705 found 667.2700 *m*/*z*.

Ethyl 3,4,6-Tri-*O*-benzyl-2-*O*-picolyl-1-thio-β-D-glucopyranoside (8). To a solution of the thioglycoside **4** (150 mg, 0.304 mmol) in DMF (4 mL) NaH (60% in mineral oil, 36 mg, 0.912 mmol) and picolyl bromide hydrobromide (231 mg, 0.365 mmol) were added at rt. The reaction mixture was stirred for 30 min, then quenched with ice (5 g) and extracted with EtOAc/Et_2O (1/1, v/v, 3 × 25 mL,). The combined organic extract was washed with cold water (3 × 20 mL), separated, dried with magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (EtOAc/hexane gradient) to give the title compound as off-white amorphous solid (83%). Analytical data for **8**: R_f = 0.20 (ethyl acetate−hexane, 1/4, v/v); $[\alpha]_D^{27} = +7.0°$ (c = 1, $CHCl_3$); ^{1}H NMR: δ, 1.44 (t, 3H, SCH_2CH_3), 2.77 (m, 2H, SCH_2CH_3), 3.47−3.55 (m, 2H, H-2, 5), 3.60−3.79 (m, 4H, H-3, 4, 6a, 6b), 4.40 (d, 1H, $J_{1,2}$ = 9.7, H-1) 4.53−4.64 (m, 3H, CH_2Ph), 4.83 (d, 1H, CH_2Ph), 4.93 (d, 1H, CH_2Ph), 4.94 (d, 1H, CH_2Ph), 7.28−7.47 (m, 16H, aromatic) 7.60 (d, 1H, aromatic), 7.76 (dt, 1H, aromatic), 8.65 (d, 1H, aromatic) ppm. ^{13}C NMR: δ, 15.3, 25.0, 69.3, 73.6, 75.2, 75.9, 76.2, 78.1, 79.3, 82.4, 85.0, 86.6, 121.9, 122.5, 127.8, 127.8, 127.9, 128.0, 128.1, 128.1, 128.5, 128.6, 128.6 136.6, 138.2, 138.4, 138.5, 149.2, 158.4, ppm; HR-FAB MS calc for $C_{35}H_{39}NO_5S$ [M + H]$^+$: 586.2549 found 586.2548 *m*/*z*.

Thiazolinyl 3,4,6-Tri-*O*-benzyl-2-*O*-picolyl-1-thio-β-D-glucopyranoside (16a). A solution of **15a** (1.40 g, 2.55 mmol) in DMF (22 mL) was added to a stirred suspension of NaH (0.32 g, 7.90 mmol) and picolyl bromide hydrobromide (1.94 g, 7.65 mmol) in DMF (22 mL) at −25 °C. Additional NaH (60% in mineral oil, 0.20 g, 5.01 mmol) was added, the reaction mixture was stirred 30 min and then allowed to warm to rt over 90 min. Upon completion, the reaction was quenched by adding crushed ice (10 g), stirred until cessation of H_2 evolution, and then extracted with ethyl acetate/diethyl ether (1/1 v/v, 3 × 80 mL). The combined organic phase was washed with water (3 × 40 mL), separated, dried with $MgSO_4$, and evaporated in vacuo. The residue was and purified by column chromatography on silica gel (ethyl acetate−hexane gradient elution) to afford the title compound as colorless syrup (1.39 g, 90%). Analytical data for **16a**: R_f = 0.37 (ethyl acetate−hexane, 2/1, v/v); $[\alpha]_D^{24} = +13.2°$ (c = 1, $CHCl_3$); ^{1}H NMR: δ, 3.34 (t, 2H, SCH_2), 3.62 (m, 1H, H-5), 3.65−3.83 (m, 5H, H-2, 3, 4, 6a, 6b), 4.21 (m, 2H, CH_2N), 4.60 (dd, 2H, J2 = 12.0 Hz, CH_2Ph), 4.70 (dd, 2H, J = 10.8 Hz, CH_2Ph), 4.87 (dd, 2H, J = 10.8 Hz, CH_2Ph), 5.00 (s, 2H, CH_2Ph), 5.32 (d, 1H, $J_{1,2}$ = 9.7 Hz, H-1), 7.15−7.38 (m, 16H, aromatic) 7.48 (d, 1H, aromatic), 7.66 (m, 1H, aromatic), 8.55 (br. d, 1H, aromatic) ppm; ^{13}C NMR: δ, 35.2, 64.5, 68.8, 73.6, 75.2, 75.9, 76.2, 77.4, 79.7, 81.6, 84.7, 86.6, 122.0, 122.6, 127.8, 127.9, 128.0, 128.1, 128.1, 128.2, 128.5, 128.6, 136.8, 138.3, 138.4, 149.1, 158.1, 163.9, ppm; HR-FAB MS [M + H]$^+$ calcd for $C_{36}H_{39}N_2O_5S_2$ 643.2300, found 643.2293.

Thiazolinyl 3,4,6-Tri-*O*-benzyl-2-*O*-picolyl-1-thio-β-D-galactopyranoside (16b). was prepared as yield off-white amorphous solids (85%) as described for the synthesis of **16a**. Analytical data for **16b**: R_f = 0.29 (ethyl acetate−hexane, 3/2, v/v); $[\alpha]_D^{24} = +11.9°$ (c = 1, $CHCl_3$); ^{1}H NMR: δ, 3.32 (t, 2H, $J_{CH2CH2N}$ = 8.0, SCH_2CH_2), 3.62−3.75 (m, 4H, H-3, 5, 6a, 6b), 3.95 (d, 1H, H-2), 4.02 (m, 1H, H-4), 4.07−4.28 (m, 2H, CH_2N), 4.41 (d, 1H, CH_2Ph), 4.50 (d, 1H, CH_2Ph) 4.60 (d, 1H, CH_2Ph), 4.71 (s, 1H, CH_2Ph), 4.91−5.05 (m, 3H, CH_2Ph), 5.37 (d, 1H, $J_{1,2}$ = 9.8 Hz, H-1), 7.17 (m, 1H, aromatic), 7.22−7.39 (m, 15H, aromatic) 7.46 (d, 1H, aromatic), 7.62 (dt, 1H, aromatic), 8.54 (d, 1H, aromatic) ppm; ^{13}C NMR: δ, 35.3, 64.5, 68.5, 72.8, 73.7, 73.7, 74.9, 76.6, 77.4, 77.8, 78.6, 83.9, 85.2, 122.0, 122.4, 127.8, 127.9, 128.0, 128.2, 128.3, 128.4, 128.6, 128.6, 136.6, 138.1, 138.2, 138.8, 149.1, 158.6, 164.2, ppm; HR-FAB MS calc for $C_{36}H_{37}N_2O_5S_2Na$ [M + Na]$^+$: 665.2120, found 665.2124.

3,4,6-Tri-*O*-benzyl-1-thio-α and β-D-Glucopyranosyl Trichloroacetimidate (α- and β-31). To a suspension of the hemiacetal **α,β-30** (51 mg, 0.094 mmol), in dry CH_2Cl_2 (1.5 mL) trichloroacetonitrile (95 μL, 0.942mmol) was added followed by the addition of K_2CO_3 (26 mg, 0.1885 mmol). The reaction mixture was stirred for 30 min at rt, then diluted with CH_2Cl_2 (10 mL) and washed with water (2 × 20 mL). The organic phase was separated, dried and concentrated in vacuo. The residue was purified by column chromatography on silica gel (ethyl acetate/hexane gradient elution) to yield **β−31** as colorless syrup (34%) and **α−31** as light brown syrup (48%). Analytical data for **β−31**: R_f = 0.32 (ethyl acetate−hexane, 1/2, v/v); $[\alpha]_D^{26} = +11.5°$ (c = 1, $CHCl_3$); ^{1}H NMR: δ, 3.69 (m, 1H, H-5), 3.76−3.83 (m, 5H, H-2, 3, 4, 6a, 6b), 4.56 (d, 1H, J = 15.4 Hz, CH_2Ph), 4.64 (d, 1H, J = 12.2 Hz, CH_2Ph), 4.81 (d, 1H, J = 12.3 Hz, CH_2Ph), 4.83 (d, 1H, J = 10.9 Hz, CH_2Ph), 4.89 (d, 1H, J = 10.8 Hz, CH_2Ph), 4.92 (d, 1H, J = 13.0 Hz, CH_2Ph), 5.01 (d, 1H, J = 13.0 Hz, CH_2Ph), 5.84 (dd, 1H, $J_{1,2}$ = 8.4 Hz, H-1), 7.13−7.21 (m, 3H, aromatic), 7.26−7.34 (m,

13H, aromatic), 7.43 (d, 1H, aromatic), 7.57 (dt, 1H, aromatic), 8.53 (d, 1H, aromatic), 8.68 (s, 1H, NH), ppm; ^{13}C NMR; δ, 29.9, 68.4, 73.6, 75.2, 75.1, 76.2, 77.4, 77.5, 81.9, 84.6, 91.1, 98.5, 121.4, 122.5, 127.8, 128.0, 128.1, 128.1, 128.2, 128.6, 128.6, 136.7, 138.2, 138.3, 138.5, 149.2, 158.5, 161.5 ppm; FAB MS $[M + H]^+$ HR-FAB MS calc for $C_{35}H_{35}Cl_3N_2O_6Na$ $[M + Na]^+$: 707.1458 found 707.1412. Analytical data for **α−31**: $R_f = 0.14$ (ethyl acetate−hexane, 1/2, v/v); $[\alpha]_D^{25} = +47.7°$ ($c = 1$, $CHCl_3$); ^{1}H NMR: δ, 3.64 (dd, 1H, $J = 10.9$ Hz, H-6a), 3.74−3.82 (m, 3H, H-2, 4, 6b), 3.87 (m, 1H, H-5), 4.56 (dd, 1H, $J_{2,3} = 9.3$ Hz, H-3), 4.42−4.60 (m, 3H, CH_2Ph), 4.78−4.93 (m, 3H, CH_2Ph), 6.57 (d, 1H, $J_{1,2} = 3.4$ Hz, H-1), 7.10−7.29 (m, 16H, aromatic), 7.40 (d, 1H, aromatic), 7.55 (dt, 1H, aromatic), 8.47 (d, 1H, aromatic), 8.52 (s, 1H, NH) ppm; ^{13}C NMR; δ, 29.9, 68.2, 73.5, 73.7, 73.9, 75.6, 75.9, 77.1, 77.4, 80.1, 81.5, 91.5, 94.5, 121.3, 122.5, 127.8, 127.9, 128.1, 128.2, 128.3, 128.6, 128.6, 128.6, 136.8, 138.1, 138.2, 138.7, 149.1, 158.5, 161.4 ppm; FAB MS $[M + H]^+$ HR-FAB MS calc for $C_{35}H_{35}Cl_3N_2O_6Na$ $[M + Na]^+$: 707.1458 found 707.1412.

Preparation of Di- and Trisaccharides. Method A: Typical Cu(OTf)$_2$-Promoted Glycosylation Procedure (Activation of the STaz Glycosides). A mixture the glycosyl donor (0.13 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4 Å, 200 mg) in DCE (1.6 mL) was stirred under an atmosphere of argon for 1 h followed by the addition of freshly conditioned $Cu(OTf)_2$ (0.39 mmol). The reaction mixture was stirred for 16 h at 40 °C, then quenched with TEA and stirred 30 min. The mixture was then diluted with CH_2Cl_2, the solid was filtered-off and the residue was washed with CH_2Cl_2. The combined filtrate (30 mL) was washed with water, the organic phase was separated, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate−hexane gradient elution).

Method B: Typical Cu(OTf)2/TfOH-Promoted Glycosylation Procedure (Activation of the STaz Glycosides). A mixture the glycosyl donor (0.13 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4 Å, 200 mg) in DCE (1.6 mL) was stirred under an atmosphere of argon for 1 h. TfOH (0.08 mmol) was then added and stirred at rt until donor was fully complexed. Freshly conditioned $Cu(OTf)_2$ (0.26 mmol) was added and the reaction mixture was stirred for 16 h at 40 °C. The reaction was quenched with TEA, stirred for additional 30 min, then diluted with CH_2Cl_2, the solid was filtered-off and the residue was washed with CH_2Cl_2. The combined filtrate (30 mL) was washed with water (4 × 10 mL), the organic phase was separated, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate−toluene gradient elution).

Method C: Typical AgOTf-Promoted Glycosylation Procedure (Activation of the STaz Glycosides). A mixture the glycosyl donor (0.13 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (3 Å, 200 mg) in DCE (1.6 mL) was stirred under an atmosphere of argon for 1 h. Freshly conditioned AgOTf (0.26 mmol) was added and the reaction mixture was stirred for 16 h. at rt, then quenched with TEA and stirred 30 min. The mixture was then diluted with CH_2Cl_2, the solid was filtered-off and the residue was washed with CH_2Cl_2. The combined filtrate (30 mL) was washed with water (4 × 10 mL), the organic phase was separated, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate−toluene gradient elution).

Method D: Typical DMTST-Promoted Glycosylation Procedure (Activation of the SEt Glycosides). A mixture the glycosyl donor (0.13 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4 Å, 200 mg) in CH_2Cl_2 (1.6 mL) was stirred under an atmosphere of argon for 1 h. The mixture was chilled to −50 °C (or started at rt) and DMTST (0.39 mmol) was added. The reaction mixture was allowed to warm to rt over 1 h and stirred for additional 16 h at 42 °C, then quenched with TEA and stirred 30 min. The mixture was then diluted with CH_2Cl_2, the solid was filtered-off and the residue was washed with CH_2Cl_2. The combined filtrate (30 mL) was washed with water (4 × 10 mL), the organic phase was separated, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate−hexane gradient elution).

Method E: Typical TESOTf-Promoted Glycosylation Procedure (Activation of the Glycosyl Trichloroacetimidates). A mixture the glycosyl donor (0.13 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4 Å, 200 mg) in DCE (1.6 mL) was stirred under an atmosphere of argon for 1 h. TESOTf (0.065 mmol) was added and the reaction mixture was stirred for 16 h at 40 °C. The reaction was quenched with TEA, stirred for additional 30 min, diluted with CH_2Cl_2, the solid was filtered-off and the residue was washed with CH_2Cl_2. The combined filtrate (30 mL) was washed with water (4 × 10 mL), the organic phase was separated, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate−hexane gradient elution).

Method F: Typical IDCP-Promoted Glycosylation Procedure (Activation of the SEt Glycosides). A mixture the glycosyl donor (0.13 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4 Å, 200 mg) in CH_2Cl_2 (1.6 mL) was stirred under an atmosphere of argon for 1 h. The mixture was chilled to −40 °C (or started directly at rt, see Table 1) and IDCP (0.39 mmol) was added. The reaction mixture was allowed to warm to rt over 1 h and stirred for additional 16 h at 42 °C, then quenched with TEA and stirred 30 min. The mixture was then diluted with CH_2Cl_2, the solid was filtered-off and the residue was washed with CH_2Cl_2. The combined filtrate (30 mL) was washed with water (4 × 10 mL), the organic phase was separated, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate−hexane gradient elution).

Method G: Typical MeOTf-Promoted Glycosylation Procedure (Activation of the SEt Glycosides. A mixture the glycosyl donor (0.13 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4 Å, 200 mg) in CH_2Cl_2 (1.6 mL) was stirred under an atmosphere of argon for 1 h. MeOTf (0.39 mmol) was added, the reaction mixture was allowed to warm to rt over 1 h and stirred for additional 16 h at 42 °C, then quenched with TEA and stirred 30 min. The mixture was then diluted with CH_2Cl_2, the solid was filtered-off and the residue was washed with CH_2Cl_2. The combined filtrate (30 mL) was washed with water (4 × 10 mL), the organic phase was separated, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate−hexane gradient elution).

Method H: Typical NIS/TfOH-Promoted Glycosylation Procedure (Activation of the SEt Glycosides). A mixture the glycosyl donor (0.13 mmol), glycosyl acceptor (0.10 mmol), and freshly activated molecular sieves (4Å, 200 mg) in CH_2Cl_2 (1.6 mL) was stirred under an atmosphere of argon for 1 h. NIS (0.26 mmol) and TfOH (0.013 mmol) were added, the reaction mixture was allowed to warm to rt over 1 h and stirred for additional 16 h at 42 °C, then quenched with TEA and stirred 30 min. The mixture was then diluted with CH_2Cl_2, the solid was filtered-off and the residue was washed with CH_2Cl_2. The combined filtrate (30 mL) was washed with water (4 × 10 mL), the organic phase was separated, dried with $MgSO_4$ and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (ethyl acetate−hexane gradient elution).

***O*-(2,3,4,6-Tetra-*O*-benzyl-D-glucopyranosyl)-(1→3)-1,2:5,6-di-*O*-isopropylidine-α-D-glucofuranoside (10).** The title compound was obtained from donor **5** and acceptor **9** by Method F in 80% yield. The spectroscopic and analytical data for **10** were in good agreement with those reported previously.[45]

***O*-[3,4,6-Tri-*O*-benzyl-2-*O*-(*o*-bromobenzyl)-D-glucopyranosyl]-(1→3)-1,2:5,6-di-*O*-isopropylidine-α-D-glucofuranoside (11).** The title compound was obtained as a colorless syrup from donor **5**

and acceptor **9** by Method F in 78% (α/β = 1.8/1, rt) or 87% (α/β = 2.3/1, −40 °C → rt) yield. Analytical data for **α−11**: R_f = 0.37 (ethyl acetate−hexane); ^{1}H-NMR data: δ, 1.09 (s, 3H, Me), 1.28 (s, 3H, Me), 1.42 (s, 3H, Me), 1.49 (s, 3H, Me), 2.61−3.69 (m, 2H, H-2′, 3′), 3.72−3.75 (m, 2H, H-6a′, 6b′), 3.84 (m, 1H, H-5′), 3.92 (dd, 1H, $J_{6a,6b}$ = 8.7 Hz, H-6a), 3.99−4.07 (m, 2H, H-4′, 6b), 4.12 (dd, 1H, J = 8.0 Hz, H-4), 4.26 (dd, 1H, J = 2.8 Hz, H-3), 4.39−4.66 (m, 7H, H-2, 5, CH_2Ph), 4.71 (dd, 1H, $J_{1,2}$ = 6.3 Hz, H-2), 4.79−4.87 (m, 3H, CH_2Ph), 4.95 (d, 1H, CH_2Ph), 5.35 (d, 1H, $J_{1',2'}$ = 3.5 Hz, H-1′), 5.90 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 7.13−7.36 (m, 20H, aromatic), 7.44−7.63 (m, 2H, aromatic) ppm. ^{13}C NMR: δ, 1.2, 14.3, 22.9, 25.2, 25.3, 26.4, 26.7, 26.9, 27.0, 27.2, 29.6, 29.9, 31.2, 32.2, 67.1, 68.9, 71.6, 72.4, 72.6, 80.6, 81.7, 83.9, 98.2, 101.6, 105.5, 109.2, 112.0, 127.6, 127.8, 128.0, 128.1, 129.0, 132.5, 137.9, 138.0, 138.1, 138.2, 138.4, 138.6, 138.7 ppm; HR-FAB MS calc for $C_{46}H_{53}BrO_{11}$ [M + H]$^+$: 860.2771 found 860.2777.

***O*-[3,4,6-Tri-*O*-benzyl-2-*O*-(*o*,*o*-dimethoxybenzyl)-D-glucopyranosyl]-(1→3)-1,2:5,6-di-*O*-isopropylidine-α-D-glucofuranose (12).** The title compound was obtained as a colorless semisolid from donor **7** and acceptor **9** by Method F in 58−89% yield (α/β = 1.8−2.3/1). Analytical data for **12**: R_f = 0.43 (ethyl acetate−hexane, 2/3, v/v); ^{1}H-NMR data: δ, 1.23, (s, 3H, Me), 1.26 (s, 3H, Me), 1.40 (s, 3H, Me), 1.49 (s, 3H, Me), 3.50 (dd, 1H, $J_{2,3}$ = 9.7, H-3′), 3.62 (dd, 1H, $J_{2,3}$ = 9.7 Hz, H-2′), 3.67−3.84 (m, 4H, H-4′, 5′, 6a′, 6b′), 3.75 (s, 6H, OMe), 4.03 (dd, 1H, $J_{3,4}$ = 8.6 Hz, H-4), 4.15 (dd, 1H, $J_{6a,6b}$ = 9.8 Hz, H-6a), 4.25 (dd, 1H, $J_{5,6}$ = 6.0 Hz, H-6b), 4.35−4.52 (m, 4H, H-3, 5, CH_2Ph), 4.57−4.65 (m, 2H, CH_2Ph), 4.73 (dd, 1H, $J_{2,3}$ = 3.6 Hz, H-2), 4.78−4.90 (m, 3H, CH_2Ph), 5.02 (d, 1H, $J_{1',2'}$ = 3.57, H-1′), 5.89 (d, 1H, $J_{1,2}$ = 3.6 Hz, H-1), 6.54 (d, 2H, aromatic), 7.09−7.34 (m, 18H, aromatic) ppm. ^{13}C NMR: δ, 24.9, 25.5, 26.4, 26.8, 27.0, 29.9, 36.8, 55.9, 60.7, 66.7, 69.3, 71.1, 73.3, 72.7, 75.3, 75.4, 77.4, 80.3, 80.3, 81.4, 81.5, 81.9, 83.75, 98.6, 103.9, 105.5, 108.8, 111.8, 114.5, 127.4, 127.9, 128.0, 128.1, 128.3, 128.4, 128.6, 130.1, 138.21, 138.4, 159.5 ppm; HR-FAB MS calc for $C_{48}H_{58}O_{13}$ [M + H]$^+$: 842.3877 found 842.3881.

***O*-(3,4,6-Tri-*O*-benzyl-2-*O*-picolyl-β-D-glucopyranosyl)-(1→3)-1,2:5,6-di-*O*-isopropylidine-α-D-glucofuranose (13).** The title compound was obtained as a colorless syrup from donor **8** and acceptor **9** by Method D in 45% yield. Analytical data for **13**: R_f = 0.48 (ethyl acetate−hexane, 1/1, v/v); ^{1}H-NMR data: δ, 1.26, (s, 3H, Me), 1.28 (s, 3H, Me), 1.32 (s, 3H, Me), 1.44 (s, 3H, Me), 3.46−3.54 (m, 2H, H-4,5′), 3.60−3.72 (m, 5H, H-5, 3′, 4′, 6a′, 6b′), 3.81 (m, 1H, H-6a), 4.15−4.24 (m, 3H, H-6b, 1′, 2′), 4.49−4.58 (m, 4H, H-2, 3, CH_2Ph), 4.63 (d, 1H, CH_2Ph), 4.78−4.95 (m, 4H, CH_2Ph), 5.17 (d, 1H, CH_2Ph), 5.97 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 7.15 (m, 3H, aromatic), 7.26−7.35 (m, 13H, aromatic), 7.59 (d, 1H, aromatic), 7.60 (dt, 1H, aromatic), 8.54 (d, 1H, aromatic) ppm. ^{13}C NMR: δ, 24.0, 24.1, 26.8, 27.4, 29.9, 69.1, 70.7, 71.8, 73.8, 75.1, 75.2, 75.8, 77.4, 78.0, 79.7, 82.7, 84.2, 84.6, 101.2, 104.3, 106.6, 112.4, 121.7, 122.3 127.8, 127.8, 128.0, 128.0, 128.2, 128.5, 128.6, 138.4, 138.8 ppm; HR-FAB MS calc for $C_{45}H_{53}NO_{11}$ [M + H]$^+$: 783.3619 found 783.3618 *m*/*z*.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-picolyl-β-D-glucopyranosyl)-α-D-glucopyranoside (23). The title compound was obtained from **16a** and methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside[34] (**18**) by Methods A, B and C as white amorphous solid in 80, 84, and 78% yield, respectively. Alternatively, the title compound was obtained from **8** and **18** by Method D and from **α,β−31** and **18** by Method E in 70 and 84%, respectively. Analytical data for **23**: Rf = 0.36 (ethyl acetate−hexane, 2/3, v/v); $[\alpha]_D^{24}$ = +14.3° (c = 1, $CHCl_3$); ^{1}H NMR: δ, 3.28 (s, 3H, OCH_3), 3.39−3.70 (m, 9H, H-2, 2′, 3′, 4, 4′, 5′, 6b, 6a′, 6b′), 3.76 (m, 1H, $J_{5,6a}$ = 1.6 Hz, H-5), 3.92 (dd, 1H, $J_{3,4}$ = 9.2 Hz, H-3), 4.14 (dd, 1H, $J_{6a,6b}$ = 11.0 Hz, H-6a), 4.37 (d, 1H, $J_{1',2'}$ = 7.7 Hz, H-1′), 4.42−5.15 (m, 14H, CH_2Ph), 4.54 (d, 1H, H-1), 6.96−7.43 (m, 33H, aromatic), 8.42 (d, 1H, aromatic) ppm; ^{13}C NMR: δ, 55.3, 69.2, 69.9, 73.6, 73.6, 75.0, 75.2, 75.3, 75.5, 75.8, 75.9, 77.4, 78.1, 78.1, 82.2, 82.5, 98.2, 103.8, 121.5, 122.3, 127.7, 127.7, 127.8, 127.8, 127.9, 127.9, 128.0, 128.1, 128.3, 128.5, 128.5, 128.6, 128.6, 138.3, 138.4, 138.4, 138.5, 138.6, 158.5 ppm; HR-FAB MS calcd for $C_{61}H_{66}NO_{11}$ [M + H]$^+$: 988.4636, found 988.4630.

Methyl 2,3,4-Tri-*O*-benzyl-6-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-picolyl−β-D-glucopyranosyl)-α-D-galactopyranoside (24). The title compound was obtained from **16b** and **18** via Method A as off-white amorphous solid in 76% yield (β-only). Analytical data for **24**: R_f = 0.44 (ethyl acetate−hexane, 2/3, v/v); $[\alpha]_D^{24}$ = −9.3° (c = 1, $CHCl_3$); ^{1}H NMR: δ, 3.21 (s, 3H, OMe), 3.29−3.57 (m, 7H, H-2, 4, 6a, 3′, 4′, 6a′, 6b′), 3.71 (m, 1H, H-5), 3.77−3.89 (m, 3H, H-3, 2′, 5′), 4.05 (dd, 1H, $J_{6a,6b}$ = 10.7 Hz, H-6b), 4.27 (d, 1H, $J_{1',2'}$ = 7.6 Hz, H-1′), 4.34−4.53 (m, 4H, CH_2Ph), 4.50 (d, 1H, $J_{1,2}$ = 7.6 Hz, H-1), 4.57−4.70 (d, 6H, CH_2Ph), 4.81−4.90 (m, 3H, CH_2Ph), 5.03 (d, 1H, CH_2Ph), 6.96 (m, 1H, aromatic), 7.07−7.26 (m, 31H, aromatic), 7.38 (d, 2H, aromatic), 8.38 (d, 1H, aromatic) ppm. ^{13}C NMR: δ, 55.4, 68.7, 68.8, 70.0, 72.9, 73.5, 73.6, 73.7, 74.8, 74.9, 75.8, 77.4, 78.3, 79.9, 80.1, 82.2, 82.4, 98.1, 104.2, 122.1, 122.5, 127.7, 127.7, 127.8, 127.9, 128.0, 128.0, 128.1, 128.2, 128.4, 128.4, 128.5, 128.6, 138.1, 138.4, 138.6, 138.6, 138.9, 139.1 ppm; HR-FAB MS calc for $C_{61}H_{65}NO_{11}Na$ [M + Na]$^+$: 1010.4455 found 1010.4467.

Methyl 2,3,6-Tri-*O*-benzyl-4-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-picolyl-β-D-glucopyranosyl)-α-D-glucopyranoside (25). The title compound was obtained from **16a** and methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside[35] (**19**) by Method A or B as white amorphous solid in 83 and 80% yield. Analytical data for **25**: Rf = 0.29 (ethyl acetate/hexane, 2/3, v/v); $[\alpha]_D^{22}$ = +12.5° (c = 1, $CHCl_3$); ^{1}H NMR: δ, 3.28−4.02 (m, 12H, H-2, 2′, 3, 3′, 4, 4′, 5, 5′, 6a, 6a′, 6b, 6b′), 3.36 (s, 3H, OCH*3*), 4.37−5.12 (m, 14H, CH_2Ph), 4.45 (d, 1H, $J_{1',2'}$ = 9.2 Hz, H-1′), 4.57 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1), 7.11−7.68 (m, 33H, aromatic) 8.53 (d, 1H, aromatic) ppm; ^{13}C NMR: δ, 29.9, 55.5, 69.3, 70.1, 73.6, 73.8, 75.0, 75.5, 75.6, 75.6, 75.8, 78.3, 79.1, 80.5, 83.2, 85.0, 98.7, 102.7, 121.5, 122.4, 127.3, 127.5, 127.7, 127.8, 127.9, 127.9, 128.0, 128.0, 128.2, 128.2, 128.2, 128.3, 128.4, 128.5, 128.7, 138.1, 138.6, 138.8, 139.8, 149.1, 158.9 ppm; HR-FAB MS calcd for $C_{61}H_{66}NO_{11}$ [M + H]$^+$: 988.4636, found 988.4609.

Methyl 2,4,6-Tri-*O*-benzyl-3-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-picolyl-β-D-glucopyranosyl)-α-D-glucopyranoside (26). The title compound was obtained from **16a** and methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside[36] (**20**) by Method B as white amorphous solid in 85% yield. Analytical data for **26**: Rf = 0.45 (ethyl acetate/hexane, 2/3, v/v); $[\alpha]_D^{23}$ = +20.1° (c = 1, $CHCl_3$); ^{1}H NMR: δ, 3.28 (s, 3H, OCH_3), 3.39−3.71 (m, 10H, H-2, 2′, 3′, 4, 4′, 5′, 6a, 6a′, 6b, 6b′), 3.76 (m, 1H, H-5), 3.92 (dd, 1H, $J_{6a,6b}$ = 9.2 Hz, H-3), 4.37 (d, 1H, $J_{1',2'}$ = 7.7 Hz, H-1′), 4.42−5.11 (m, 14H, CH_2Ph), 6.96−7.43 (m, 33H, aromatic) 8.42 (d, 1H, aromatic) ppm; ^{13}C NMR: δ 29.7, 35.7, 63.0, 64.0, 66.4, 71.2, 72.6, 76.8, 77.2, 82.0, 128.3, 128.4, 128.4, 128.6, 128.8, 129.0, 129.8, 129.8, 130.0, 133.0, 133.3, 133.5, 133.6, 162.5, 165.2, 165.5, 166.1 ppm; HR-FAB MS calcd for $C_{61}H_{66}NO_{11}$ [M + H]$^+$: 988.4636, found 988.4652.

Methyl 3,4,6-Tri-*O*-benzyl-2-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-picolyl-β-D-glucopyranosyl)-α-D-glucopyranoside (27). The title compound was obtained from **16a** and methyl 3,4,6-tri-*O*-benzyl-α-D-glucopyranoside[46] (**21**) by Method A, B and C as white amorphous solid in 69, 80, and 63% yield. Analytical data for **27**: R_f = 0.27 (ethyl acetate−hexane, 2/3, v/v); $[\alpha]_D^{23}$ = +31.7° (c = 1, $CHCl_3$); ^{1}H NMR: δ, 3.44 (s, 3H, OCH_3), 3.46 (m, 1H, H-5), 3.60−3.85 (m, 10H, H-2′, 3′, 4, 4′, 5, 5′, 6a, 6a′, 6b, 6b′), 3.88 (dd, 1H, $J_{2,3}$ = 9.8 Hz, H-2), 4.06 (dd, 1H, $J_{3,4}$ = 9.6 Hz, H-3), 4.46−4.70 (m, 8H, CH_2Ph), 4.75−25 (m, 6H, CH_2Ph), 4.77 (d, 1H, $J_{1',2'}$ = 9.8 Hz, H-1′), 5.01 (d, 1H, $J_{1,2}$ = 3.5 Hz, H-1), 7.02−7.46 (m, 33H,

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aromatic) 8.49 (d, 1H, aromatic) ppm; ^{13}C NMR: δ, 55.4, 68.8, 69.0, 70.1, 73.7, 73.8, 75.0, 75.1, 75.2, 75.3, 75.8, 77.4, 78.0, 78.4, 79.3, 81.9, 82.5, 85.1, 100.0, 104.3, 121.5, 122.1, 127.57, 127.8, 127.9, 127.9, 128.0, 128.0, 128.1, 128.2, 128.3, 128.5, 128.6, 128.6, 136.5, 138.2, 138.3, 138.3, 38.5, 138.7, 138.9, 148.94, 158.7 ppm; HR-FAB MS calcd for $C_{61}H_{66}NO_{11}$ [M + H]$^+$: 988.4636, found 988.4620.

Ethyl 2,3,4-Tri-*O*-acetyl-6-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-picolyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (28a). The title compound was obtained from **16a** and ethyl 2,3,4-tri-*O*-acetyl-1-thio-β-D-glucopyranoside (**22a**)[47] by Method A as white amorphous solid in 56% yield. Analytical data for **28**: R_f = 0.28 (ethyl acetate/hexane, 1/1, v/v); ^{1}H NMR: δ, 1.12 (t, 3H, SCH_2CH_3), 2.00 (s, 3H, OAc), 2.00 (s, 3H, OAc), 2.05 (s, 3H, OAc), 2.54 (q, 2H, SCH_2CH_3), 3.48 (m, 2H, H-2′, 3′), 3.61−3.72 (m, 5H, H-4′, 5′, 6a, 6b, 6a′), 3.79 (m, 1H, H-5), 3.92 (dd, 1H, $J_{6a,6b}$ = 10.9 Hz, H-6b), 4.46−4.55 (m, 4H, H-1, 1′, CH_2Ph), 4.63 (d, 1H, CH_2Ph), 4.78−5.00 (m, 6H, H-2, 3, CH_2Ph), 5.13 (d, 1H, CH_2Ph), 5.21 (dd, 1H, $J_{3,4}$ = 9.4 Hz, H-4), 7.11−7.18 (m, 3H, aromatic), 7.25−7.34 (m, 13H, aromatic), 7.49 (d, 1H, 1H, aromatic), 7.61 (dt, 1H, aromatic), 8.55 (d, 1H, aromatic) ppm; ^{13}C NMR: δ, 14.9, 20.9, 24.2, 29.9, 70.0, 69.5, 70.4, 73.7, 74.2, 75.1, 75.2, 75.6, 76.8, 77.4, 77.9, 82.9, 83.3, 84.7, 103.9, 127.8, 128.0, 128.0, 128.6, 128.6, 138.3, 138.3, 138.7, 169.6, 169.9, 170.4 ppm; HR-FAB MS calc for $C_{47}H_{56}NO_{13}S$ [M + H]$^+$ 874.3472, found 874.3453.

Ethyl 2,3,4-Tri-*O*-benzoyl-6-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-picolyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (28b). The title compound was obtained from **16a** and ethyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside[9] (**22b**) by Method A and C as white amorphous solid in 78 and 72% yield. Analytical data for **28**: R_f = 0.36 (ethyl acetate/hexane, 2/3, v/v); $[\alpha]_D^{23}$ = +2.1° (c = 1, $CHCl_3$); ^{1}H NMR: δ, 1.10 (t, 3H, SCH_2CH_3), 2.63 (q, 2H, SCH_2CH_3), 3.40−3.68 (m, 6H, H-2′, 3′, 4′, 5′, 6a′, 6b′), 3.85 (dd, 1H, $J_{5,6b}$ = 7.7 Hz, $J_{6a,6b}$ = 11.4 Hz, H-6b), 4.00−4.16 (m, 2H, H-5, 6a), 4.40−5.20 (m, 8H, CH_2Ph), 4.55 (d, 1H, $J_{1',2'}$ = 8.8 Hz, H-1′), 4.79 (d, 1H, $J_{1,2}$ = 10.0 Hz, H-1), 5.41 (dd, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 5.49 (dd, 1H, $J_{2,3}$ = 9.7 Hz, H-2), 5.89 (dd, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 7.09−7.95 (m, 33H, aromatic) 8.59 (d, 1H, aromatic) ppm; ^{13}C NMR: δ, 14.3, 32.2, 68.8, 69.1, 70.2, 73.7, 74.4, 75.1, 75.2, 75.9, 77.4, 77.9, 78.6, 82.9, 84.7, 104.0, 127.8, 128.0, 128.0, 128.2, 128.5, 128.6, 128.6, 128.6, 129.0, 129.1, 129.5, 129.9, 130.1, 133.4, 133.4, 133.7, 138.3, 138.7, 165.4, 165.7, 166.0 ppm; HR-FAB MS [M + H]$^+$ calc for $C_{62}H_{62}NO_{13}S$ 1060.3942, found 1060.3932.

Thiazolinyl 2,3,4-Tri-*O*-benzoyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (33). The title compound was obtained from **17** and thiazolinyl 2,3,4-tri-*O*-benzoyl-1-thio-β-D-glucopyranoside[16] (**32**) via Method A or C as white amorphous solid in 88% (α/β = 1.5/1) or 79% (α/β = 2.0/1) yields, respectively. The spectroscopic and analytical data for **33** were in good agreement with those reported previously.[16]

Methyl *O*-(2,3,4,6-Tetra-*O*-benzyl-α/β-D-glucopyranosyl)-(1→6)-*O*-(2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (34). The title compound was obtained from **33** and **18** by Method C as white foam in 83% yield. The spectroscopic and analytical data for **34** were in good agreement with those reported previously.[7]

Thiazolinyl 2,3,4-tri-*O*-benzoyl-6-*O*-(3,4,6-tri-*O*-benzyl-2-*O*-picolyl-β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (35). The title compound was obtained from **16a** and **32** by Method B as white amorphous solid in 74% yield. Analytical data for **35**: R_f = 0.40 (acetone-toluene, 1/4, v/v); $[\alpha]_D^{24}$ = +31.5° (c = 0.71, CHCl3); ^{1}H NMR: δ, 3.13 (m, 2H, SCH_2), 3.38−3.46 (m, 2H, H-2′, 4′), 3.57−3.67 (m, 4H, H-3′, 5′, 6a′, 6b′), 3.87 (dd, 1H, $J_{5,6b}$ = 7.4 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6b), 4.00 (m, 2H, NCH_2), 4.11 (dd, 1H, $J_{5,6a}$ = 1.8 Hz, H-6a), 4.21 (m, 1H, H-5), 4.41−4.58 (m, 4H, $J_{1',2'}$ = 7.6 Hz, H-1′, CH_2Ph), 4.72−4.90 (m, 3H, CH_2Ph), 4.92 (d, 1H, J = 10.9 Hz, CH_2Ph), 5.10 (d, 1H, J = 12.3 Hz, CH_2Ph), 5.49 (dd, 1H, $J_{4,5}$ = 9.7 Hz, H-4), 5.60 (dd, 1H, $J_{2,3}$ = 10.0 Hz, H-2), 5.80 (d, 1H, $J_{1,2}$ = 10.3 Hz, H-1), 5.94 (dd, 1H, $J_{3,4}$ = 9.4 Hz, H-3), 7.12−7.46 (m, 26H, aromatic), 7.63 (m, 1H, aromatic), 7.79 (d, 2H, aromatic), 7.92 (t, 4H, aromatic), 8.55 (d, 1H, aromatic) ppm; ^{13}C NMR: δ, 35.4, 64.2, 68.8, 69.9, 70.5, 73.7, 74.3, 75.1, 75.2, 75.7, 75.9, 77.4, 78.6, 83.0, 83.3, 84.5, 103.6, 122.5, 122.7, 127.8, 127.9, 128.0, 128.1, 128.3, 128.5, 128.5, 128.6, 128.7, 129.0, 129.1, 129.9, 130.1, 130.2, 133.6, 133.7, 136.7, 138.4, 138.8, 149.2, 162.7, 165.4, 165.5, 165.9 ppm; HR-FAB MS calcd for $C_{63}H_{62}N_2O_{13}S_2$ [M + H]$^+$: 1117.3615, found 1117.3625.

Methyl *O*-(3,4,6-Tri-*O*-benzyl-2-*O*-picolyl-β-D-glucopyranosyl)-(1→6)-*O*-(2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (36). The title compound was obtained from **35** and **18** by Method C as white foam in 91% yield. Analytical data for **36**: R_f = 0.60 (acetone-toluene, 1/4, v/v); $[\alpha]_D^{23}$ = +3.0° (c = 1, $CHCl_3$); ^{1}H NMR: δ, 3.12 (s, 3H), 3.30−3.52 (m, 4H), 3.55−3.67 (m, 4H), 3.81 (dd, 1H, J = 9.2 Hz), 3.86 (dd, 1H, J = 8.2 Hz), 4.12−4.17 (m, 4H), 4.31 (d, 1H, J = 11.0 Hz, CH_2Ph), 4.44 (d, 1H, J = 12.0 Hz, CH_2Ph), 4.48−4.90 (m, 14H, CH_2Ph), 5.16 (d, 1H, J = 12.6 Hz, CH_2Ph), 5.38 (dd,1H, J = 9.8 Hz), 5.54 (dd, 1H, J = 7.9, 9.9 Hz), 5.86 (dd, 1H, J = 9.4, H-3), 6.90−7.54 (m, 42H, aromatic), 7.75−7.93 (m, 6H, aromatic), 8.50 (d, 1H) ppm; ^{13}C NMR: δ, 55.4, 68.7, 68.9, 69.6, 70.1, 72.1, 73.2, 73.6 (×2), 73.7 (×2), 74.8, 74.8, 75.1, 75.2, 75,2, 75.6, 76.0, 77.4, 79.8, 82.0, 84.6, 84.7, 98.3, 101.0, 104.1, 127.6, 127.7, 127.8, 127.9, 128.0, 128.0, 128.1, 128.1, 128.2, 128.3, 128.4, 128.5, 128.6, 128.6, 129.0, 129.4, 129.8, 129.9, 130.1, 133.2, 133.4, 133.7, 138.3, 138.4, 138.5, 138.7, 139.1, 165.1, 166.0 ppm; HR-FAB MS calc for $C_{88}H_{88}NO_{19}$ [M + H]$^+$: 1462.5951, found 1462.5951.

Thiazolinyl 3,4-*O*-Benzoyl-2-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzyl-α/β-D-glucopyranosyl)-1-thio-β-D-glucopyranoside (39). The title compound was obtained from **17** and **38** by Method A as white amorphous solid in 89% yield (α/β = 2.0/1). Analytical data for **39**: R_f = 0.42 (acetone-toluene, 1/2, v/v); ^{1}H NMR: δ, 3.42−3.61 (m, 6H, H-2, 6a, 2′, 4′, 5′, 6a′), 3.68 (dd, 1H, $J_{6a,6b}$ = 11.2 Hz, H-6b), 3.73−3.92 (m, 4H, H-3′, 6a′, CH_2N), 3.96−4.08 (m, 3H, H-5, CH_2S), 4.31−4.38 (m, 3H, C*H*2Ph), 4.48−4.61 (m, 3H, CH_2Ph), 4.66−4.70 (m, 3H, CH_2Ph), 4.75 (d, 1H, J = 10.4 Hz, CH_2Ph), 4.91 (d, 1H, CH_2Ph), 5.32 (dd, 1H, J = 9.8 Hz, H-4), 5.41 (d, 1H, J = 10.1 Hz, H-1), 5.63 (dd, 1H, J = 9.3 Hz, H-3), 7.03−7.31 (m, 29H, aromatic), 7.41 (t, 2H, aromatic), 7.82 (m, 4H, aromatic) ppm; ^{13}C NMR: δ, 22.9, 24.9, 29.2, 31.3, 31.8, 35.0, 36.9, 64.3, 67.1, 68.5, 69.4, 70.3, 73.2, 73.6, 75.3, 75.4, 75.9, 76.2, 77.4, 77.7, 78.3, 80.6, 82.0, 84.6, 97.3, 99.8, 127.8, 127.8, 127.9, 128.0, 128.1, 128.1, 128.2, 128.4, 128.5, 128.6, 128.6, 128.6, 129.9, 130.1, 133.4, 133.6, 137.1, 138.3, 138.6, 138.78, 139.2, 165.5, 165.7 ppm; HR-FAB MS calcd for $C_{64}H_{63}NO_{12}S_2Na$ [M + Na]$^+$: 1124.3689, found 1124.3668.

Methyl *O*-(2,3,4,6-Tetra-*O*-benzyl-α/β-D-glucopyranosyl)-(1→6)-*O*-(3,4-*O*-benzoyl-2-*O*-benzyl-α/β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (40). The title compound was obtained from **39** and **18** by Method C as white amorphous solid in 75% yield (α/β = 1.6/1). Analytical data for **40**: R_f = 0.36 (acetone-hexane, 3/7, v/v); ^{1}H NMR: δ, 3.16 (s, 3H, OMe), 3.39 (m, 1H, H-2), 3.48−4.00 (m, 13H, H-3, 4, 5, 6a, 2′, 6a′, 6b′, 2″, 3″, 4″, 5″, 6a″, 6b″), 4.12 (m, 1H, H-5′), 3.82−4.57 (m, 9H, H-1, CH_2Ph), 4.61−4.84 (m, 9H, H-1″, CH_2Ph), 5.10 (m, 1H, H-1′), 5.31 (m, 1H, H-4′), 5.61 (dd, 1H, H-3′), 6.95−7.35 (m, 44H, aromatic), 7.49 (m, 2H, aromatic), 7.88 (m, 4H, aromatic) ppm; ^{13}C NMR: δ, 30.0, 55.3, 55.5, 66.1, 66.1, 66.6, 67.0, 68.3, 68.6, 68.6, 68.9, 68.9, 67.0, 69.1, 70.9, 71.0, 72.1, 72.2, 72.3, 72.5, 72.9, 73.1, 73.4, 73.6, 73.6, 74.6, 74.8, 74.9, 75.1, 75.2, 75.4, 75.8, 75.9, 77.5, 78.0, 78.0, 79.2, 80.0, 80.4, 82.0, 82.2, 82.4, 82.5, 84.8, 84.8, 96.9, 97.1, 97.4, 97.5, 98.2, 98.4, 103.5, 104.2, 127.8, 127.9, 127.9, 128.0, 128.1, 128.1, 128.1, 128.2, 128.2, 128.3, 128.3, 128.4, 128.5, 128.6, 128.7, 128.7, 129.4, 129.6, 129.8, 130.0, 130.1, 133.1, 133.2, 133.3, 133.4, 133.5, 137.8, 137.9, 138.0, 138.2, 138.4, 138.4, 138.7,

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138.8, 138.8, 139.1, 139.2, 165.5, 165.8, 166.0, 166.0 ppm; HR-FAB MS calcd for $C_{89}H_{90}O_{18}$ [M + Na]$^+$: 1469.6025, found 1469.6023.

Thiazolinyl 3,4-*O*-Benzoyl-2-*O*-benzyl-6-*O*-(3,4,6-tetra-*O*-benzyl-2-*O*-picolyl-β-D-glucopyranosyl)-1-thio-α/β-D-glucopyranoside (41). The title compound was obtained from **16a** and **38** by Method B as white amorphous solid in 70% yield. Analytical data for **41**: R_f = 0.42 (acetone−toluene, 2/3, v/v); ^{1}H NMR: δ, 3.17 (m, 2H, SCH_2), 3.28−3.41 (m, 3H, H-2′, 3′), 3.45−3.62 (m, 4H, H-4′, 5′, 6a′, 6b′), 3.63−3.79 (m, 2H, H-2, 6a), 3.91−4.13 (m, 4H, H-5, 6b, NCH_2), 4.32−4.49 (m, 6H, CH_2Ph, H-1′), 4.64−4.84 (m, 5H, CH_2Ph), 5.06 (d, 1H, CH_2Ph), 5.27 (dd, 1H, $J_{3,4}$ = 9.9 Hz, H-4), 5.43 (d, 1H, $J_{1,2}$ = 10.0 Hz, H-1), 5.66 (dd, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 7.04−7.30 (m, 25H, aromatic), 7.41 (m, 3H, aromatic), 7.59 (t, 1H, aromatic), 7.79 (m, 4H, aromatic), 8.48 (d, 1H, aromatic) ppm; ^{13}C NMR: δ, 29.5, 29.9, 35.3, 54.0, 64.4, 68.,7 68.8, 69.9, 73.8, 75.1, 75.1, 75.2, 75.7, 76.0, 76.7, 77.5, 78.1, 78.3, 82.9, 84.4, 84.8, 127.7, 127.8, 127.9, 128.0, 128.1, 128.1, 128.29, 128.4, 128.5, 128.6, 128.6, 129.1, 129.6, 129.9, 130.1, 137.1, 138.3, 138.8, 142.4, 165.7 ppm; HR-FAB MS calcd for $C_{63}H_{62}N_2O_{12}S_2Na$ [M + Na]$^+$: 1125.3641, found 1125.3661.

Methyl *O*-(3,4,6-Tri-*O*-benzyl-2-*O*-picolyl-β-D-glucopyranosyl)-(1→6)-*O*-(3,4-*O*-benzoyl-2-*O*-benzyl-α/β-D-glucopyranosyl)-(1→6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (42). The title compound was obtained from **41** and **18** by Method C as white amorphous solid in 54% yield (α/β = 1.7/1). Analytical data for **42**: R_f = 0.43 (acetone−hexane, 2/3, v/v); ^{1}H NMR: δ, 3.18, 3.29 (s, 3H, OMe), 3.19−3.42 (m, 3H, H-4, 2″, 3″), 3.46−3.71 (m, 9H, H-2, 5, 5′, 6a′, 6b′, 4″, 5″, 6a″, 6b″), 3.76−4.08 (m, 4H, H-3, 2′, 6a′, 6b′), 4.15 (m, 1H, H-5′), 4.32−4.89 (m, 17H, H-1, 1″, CH_2Ph), 4.99 (d, 1H, $J_{1',2'}$ = 3.6 Hz, H-1′), 5.03 (m, 2H, H-4′, CH_2Ph), 5.84 (dd, 1H, $J_{2',3'}$ = 9.5 Hz, H-3), 6.86−7.26 (m, 44H, aromatic), 7.78 (m, 5H, aromatic), 8.40 (m, 1H, aromatic) ppm; ^{13}C NMR: δ, 30.0, 55.4, 66.3, 68.3, 68.8, 70.0, 70.3, 71.0, 72.2, 73.6, 74.4, 74.8, 75.2, 75.6, 75.8, 77.4, 79.0, 80.0, 80.1, 82.2, 82.9, 84.7, 96.9, 98.3, 98.4, 103.4, 104.1, 121.6, 121.8, 122.3, 122.3, 127.9, 127.9, 128.2, 128.3, 128.6, 129.4, 130.0, 130.1, 133.1, 133.1, 133.5, 133.6, 136.6, 137.6, 138.0, 138.4, 138.9, 139.1, 139.2, 149.2, 149.3, 159.2, 165.9 ppm; HR-FAB MS calcd for $C_{88}H_{89}NO_{18}Na$ [M + Na]$^+$: 1470.5977, found 1470.5945.

Methyl 3,4,6-Tri-*O*-benzyl-2-*O*-picolyl-β-D-glucopyranoside (44). was obtained from **16a** and dry MeOH by method A as white amorphous solid in 65% yield. Analytical data for **44**: R_f = 0.40 (acetone/toluene, 1/4, v/v); $[\alpha]_D^{24}$ = +31.5 (c = 0.71, $CHCl_3$); ^{1}H NMR: δ, 3.42 (s, 3H, CH_3), 3.58−3.82 (m, 5H, H-2, 4, 5, 6a, 6b), 4.03 (dd, 1H, $J_{3,4}$ = 9.0 Hz, H-3), 4.46−5.03 (m, 8H, CH_2Ph), 4.83 (d, 1H, $J_{1,2}$ = 8.9 Hz, H-1), 7.10−7.40 (m, 16H, aromatic), 7.53 (d, 1H, aromatic), 7.64 (t, 1H, aromatic), 8.54 (d, 1H, aromatic) ppm; ^{13}C NMR: δ, 55.4, 68.7, 70.4, 73.7, 75.3, 75.9, 77.4, 78.0, 80.8, 82.1, 97.9, 127.8, 127.9, 128.0, 128.1, 128.1, 128.6, 138.2, 138.4, 139.0 ppm; HR-FAB MS calcd for $C_{34}H_{38}NO_6$ [M + H]$^+$: 556.2699, found 556.2704. If the reaction mixture was quenched after 1 h, expected intermediate **43** could be isolated as a sole product in 80% yield. Analytical data for **43**: Rf = 0.4 (MeOH /CH_2Cl_2, 1/4, v/v); $[\alpha]_D^{27}$ = +20.9 (c = 1, $CHCl_3$); ^{1}H NMR: δ, 3.60 (dd, 1H, $J_{5,6b}$ = 4.5 Hz, H-6b), 3.67 (dd, 1H, $J_{6a,6b}$ = 11.0 Hz, H-6a), 3.76 (dd, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 3.81 (m, 1H, H-5), 4.10 (dd, 1H, $J_{3,4}$ = 3.7 Hz, H-3), 4.43 (dd, 2H, J = 11.9 Hz, CH_2Ph), 4.47 (dd, 2H, J = 11.4 Hz, CH_2Ph), 4.72 (dd, 1H, $J_{2,3}$ = 5.7 Hz, H-2), 4.47 (dd, 2H, J = 11.6 Hz, CH_2Ph), 5.15 (dd, 2H, J = 12.0 Hz, CH_2Ph), 6.15 (d, 1H, $J_{1,2}$ = 4.6 Hz, H-1), 7.14−7.36 (m, 18H, aromatic), 7.88 (d, 1H, aromatic), 8.00 (m, 1H, aromatic), 8.48 (m, 1H, aromatic), 9.00 (d, 1H, aromatic) ppm; ^{13}C NMR: δ, 64.8, 70.1, 73.2, 74.1, 74.2, 74.5, 75.2, 77.0, 77.2, 77.7, 78.5, 84.9, 126.5, 128.1, 129.0, 129.2, 129.3, 129.4, 129.5, 129.6, 129.6, 129.7, 139.1, 139.2, 139.3, 144.2, 147.7, 154.4 ppm; HR-FAB MS calcd for $C_{33}H_{34}NO_5$ [M + H]$^+$: 524.2431, found 524.2442.

Methyl 6-*O*-(β-D-Glucopyranosyl)-α-D-glucopyranoside (29). Pd (10% on charcoal, 100 mg) was added to a stirred solution of **23** (20 mg, 0.093 mmol) and concentrated aq. HCl (50 μL) in ethanol/ethyl acetate (1/1, v/v, 3 mL). The reaction mixture was then purged with H_2 and stirred for 4 h at rt. Upon completion, the solid was filtered off and the filtrate was concentrated under reduced pressure and dried to give the title compound as colorless film in 98% yield. The spectroscopic and analytical data for **29** were in agreement with those reported previously.[12,48]

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Supporting Information Available: Experimental procedures for the synthesis of **2a**, **3**, **4**, **14a**, **15a**, **30**, **38**, and spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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