Stereoselective Assembly of Complex Oligosaccharides Using Anomeric Sulfonium Ions as Glycosyl Donors

Tao Fang[1,2], **Kai-For Mo**[1], and **Geert-Jan Boons**[*,1,2]

[1]Complex Carbohydrate Research Center, University of Georgia, 315 Riverbend Road, Athens, GA 30602

[2]Department of Chemistry, University of Georgia, Athens, GA 30602

Abstract

The development of selectively protected monosaccharide building blocks that can reliably be glycosylated with a wide variety of acceptors is expected to make oligosaccharide synthesis a more routine operation. In particular, there is an urgent need for the development of modular building blocks that can readily be converted into glycosyl donors for glycosylations that give reliably high 1,2-*cis*-anomeric selectivity. We report here that 1,2-oxathiane ethers are stable under acidic, basic, and reductive conditions making it possible to conduct a wide range of protecting group manipulations and install selectively removable protecting groups such as levulinoyl (Lev) ester, fluorenylmethyloxy- (Fmoc) and allyloxy- (Alloc) carbonates, and 2-methyl naphthyl ethers (Nap). The 1,2-oxathiane ethers could easily be converted into bicyclic anomeric sulfonium ions by oxidization to sulfoxides and arylated with 1,3,5-trimethoxybenzene. The resulting sulfonium ions gave high 1,2-*cis* anomeric selectivity when glycosylated with a wide variety of glycosyl acceptors including properly protected amino acids, primary and secondary sugar alcohols and partially protected thioglycosides. The selective protected 1,2-oxathianes were successfully employed in the preparation of a branched glucoside derived from a glycogen-like polysaccharide isolated form the fungus *Pseudallescheria boydii*, which is involved in fungal phagocytosis and activation of innate immune responses. The compound was assembled by a latent-active glycosylation strategy in which an oxathiane was employed as an acceptor in a glycosylation with a sulfoxide donor. The product of such a glycosylation was oxidized to a sulfoxide for a subsequent glycosylation. The use of Nap and Fmoc as temporary protecting groups made it possible to install branching points.

Keywords

stereoselective glycosylations; modular building blocks; auxiliary; sulfonium ions; glucosides

INTRODUCTION

Complex carbohydrates are involved in a wide range of biological processes such as cell-cell recognition, fertilization, embryogenesis, neuronal development, hormone activities, the proliferation of cells and their organization into specific tissues, viral and bacterial infection, and tumor cell metastasis.[1] Furthermore, carbohydrates are capable of inducing a protective

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[*]**Corresponding Author**gjboons@ccrc.uga.edu..

antibody response, which is a major contributor to the survival of an organism during infection.[2] Oligosaccharides have also been found to control the development and defense mechanisms of plants.[3] The increased appreciation of the role of carbohydrates in the biological and pharmaceutical sciences has resulted in a revival of interest in carbohydrate chemistry.[4]

A major obstacle to advances in glycobiology and glycomedicine is the lack of pure and structurally well-defined carbohydrates and glycoconjugates. These compounds are often found in low concentrations and in microheterogeneous forms, greatly complicating their isolation and characterization. In many cases, well-defined oligosaccharides can only be obtained by chemical or enzymatic synthesis.[5] Unfortunately, no general method is available for the preparation of complex carbohydrates of biological importance.[6] As a result the chemical synthesis of each target compound is a challenging and time-consuming endeavor.

To speed up the process of oligosaccharide synthesis, efforts are underway to identify limited numbers of monosaccharide building blocks that can repeatedly be employed for the synthesis of a wide range of target structures.[7] Key features of such building blocks include modification at key positions with selectively removable protecting groups and providing reliably glycoside products in high yield with excellent anomeric control. In respect to the latter, 1,2-*trans* glycosides can reliably be introduced by employing a glycosyl donor modified at C-2 with a protecting group that can perform neighboring group participation during glycosylation. On the other hand, conventional methods to introduce 1,2-*cis* glycosides require glycosyl donors having a non-assisting functionality at C-2 and in these cases, reaction conditions such as solvent, temperature, and promoter as well as constitution of the glycosyl donor and acceptor (*e.g.* type of saccharide, leaving group at the anomeric center, protection, and substitution pattern) determine anomeric selectivity.[8] 1,2-*Cis* glycosylations give often mixtures of anomers, which requires time-consuming purification protocols resulting in loss of material, as well as limits the use of one-pot multi-step glycosylations[9] and automated polymer-supported synthesis.[10] Recent advances in anomeric control include the use of protecting groups that sterically shield the β-face of galactosyl donors[11] or locking a glycosyl donor in a conformation that allows nucleophilic attack from only one face of an anomeric oxa-carbenium ion.[12]

We have introduced a stereoselective glycosylation approach based on neighboring group participation by a (*S*)-phenylthiomethylbenzyl moiety at C-2 of a glycosyl donor (Scheme 1a).[13–15] Upon formation of an oxacarbenium ion, the nucleophilic thiophenyl moiety of the C-2 functionality participates leading to the formation of an intermediate sulfonium ion. The formation of the *trans*-decalin stereoisomer is strongly favored because of the absence of unfavorable gauche interactions. In addition, the alternative *cis*-decalin system places the phenyl-substituent in an axial position inducing further unfavorable steric interactions. Displacement of the equatorial anomeric sulfonium ion by a sugar alcohol leads to the formation of a 1,2-*cis* glycoside. We have shown that the (*S*)-(phenylthiomethyl)benzyl moiety can readily be introduced by reaction of a sugar alcohol with (*S*)-(phenylthiomethyl)benzyl acetate in the presence of $BF_3 \cdot OEt_2$ and removed by conversion into an acetyl ester by treatment with $BF_3 \cdot OEt_2$ in acetic anhydride. The attractiveness of chiral auxiliary mediated glycosylations has been shown by solid phase synthesis of several branched pentasaccharides having only 1,2-*cis* glycosidic linkages.[16] The proposed participation mechanism is supported by low temperature NMR experiments, which unambiguously identified a β-substituted sulfonium ion as a reaction intermediate. Furthermore, the displacement mechanism is supported by the observation that glycosylations with donors having a C-2 auxiliary with incorrect stereochemistry {(*R*)-(phenylthiomethyl)benzyl} give mixtures of anomers.

Several other studies have shown the usefulness of anomeric sulfonium ions for stereoselective glycosylations. In this respect, a number of donors having an achiral thioether at C-2 have been examined and some of these derivatives gave remarkably good α-anomeric selectivity.[13,17] Another interesting approach for forming bicyclic anomeric sulfonium ions involves arylation of 1,2-oxathiane ketals, which can easily be prepared from a thioglycoside (Scheme 1b).[18–20] The addition of a thioether to traditional glycosylations or alkylation of thioglycosides can also lead to the formation of anomeric sulfonium ions and enhance alpha-anomeric selectivity (Scheme 1c).[21,22]

To advance auxiliary mediated glycosylations for building block based oligosaccharide synthesis, it is critical to establish convenient procedures for the preparation of selective protected anomeric sulfonium ions, which can be employed in glycosylations that allow rapid assembly of complex branched compounds. We report here that 1,2-oxathiane ethers are stable under acidic, basic, and reductive conditions making it possible to conduct a wide variety of protecting group manipulations to give panels of selectively protected compounds. The resulting 1,2-oxathiane ethers can easily be converted into bicyclic anomeric sulfonium ions by oxidization to sulfoxides, followed by arylation with 1,3,5-trimethoxybenzene. It is shown that the latter compounds are appropriate glycosyl donors for highly selective 1,2-*cis* glycosylations provided that they are sufficiently deactivated with electron withdrawing protecting groups. The selective protected 1,2-oxathianes were successfully employed for the preparation of a branched glucoside derived from *Pseudallescheria boydii*,[23] which is involved in fungal phagocytosis and Toll-like receptor activation.

RESULTS AND DISCUSSION

Synthesis and Glycosylations of Oxathiane

We have observed that the (*S*)-(phenylthiomethyl)benzyl ethers are sensitive to moderately strong acidic conditions complicating a number of important protecting group manipulations. We envisaged that this problem could be addressed by using 1,2-oxathiane ethers as precursors of anomeric sulfonium ions. 1,2-Oxathiane ethers were expected to be stable under acidic conditions because their ring structure prevents the sulfur atom of participating in acid catalyzed cleavage of the benzylic ether linkage, and thus should be compatible with a wide variety of protecting group manipulations. These compounds can, however, be readily converted into an anomeric sulfonium ions by oxidative arylation, for stereoselective 1,2-*cis*-glycosylations.[15,20]

To explore the compatibility of 1,2-oxathiane ethers with a range of protecting group manipulations, compounds **9–11** and **13–16** were prepared which differ in the pattern of ether and ester protecting groups (Scheme 2). Furthermore, several of these derivatives are protected with Alloc, Lev or Fmoc protecting groups, which can be selectively removed under mild conditions providing opportunities for further functionalization. The selectively protected 1,2-oxathianes can be oxidized to the corresponding sulfoxides **17–23**, which can then be used for the generation of sulfonium ions for subsequent glycosylations.

Thus, oxathiane **2** was prepared on large scale by a one-pot two-step reaction involving treatment of **1** with TMS$_2$O in the presence of TMSOTf to give an intermediate trimethylsilyl acetal, which was reduced by the addition of Et$_3$SiH. The 4,6-diol of **2** was protected as a benzylidene acetal by treatment with (dimethoxymethyl)benzene in the presence of camphorsulfonic acid (CSA) in DMF under reduced pressure to give **3** in a yield of 87%. The C-3 hydroxyl of compound **3** was protected as an acetyl- and levulinoyl- (Lev) ester,[24] fluorenylmethyloxy- (Fmoc)[25] and allyloxy- (Alloc)[26] carbonate, and benzyl ether using standard conditions to give fully protected **4**, **5**, **6**, and **7**, respectively. The benzylidene acetal of **4** was reductively opened using Et$_3$SiH and triflic acid (TfOH) in

DCM at −78 °C[27] to give compound **8** having a C-4 hydroxyl which was acetylated with Ac$_2$O in pyridine, benzylated under neutral conditions using benzyl bromide and Ag$_2$O in DMF, or treated with FmocCl in a mixture of pyridine and CH$_2$Cl$_2$ to provide selectively protected oxathianes **9**, **10**, and **11**, respectively. Alternatively, the benzylidene acetal of **4** could be opened by treatment with Et$_3$SiH and PhBCl$_2$ at −78 °C[27] to give **12** having a C-6 hydroxyl, which was acetylated to give derivative **13**. The benzylidene acetals of compounds **5** and **6** could also be selectively opened to give derivatives having a C-4 alcohol, which were acetylated using standard conditions to provide compounds **14** and **15**, respectively. Finally, the benzylidene acetal of **7** was removed by treatment with *p*-toluenesulfonic acid in the presence of ethanethiol to give a diol, which was acetylated to provide derivative **16**. The selectively protected oxathianes **9**–**11** and **13**–**16** were oxidized by *m*CPBA at −78 °C to give sulfoxides **17**–**23** as mixtures of diastereoisomers. The successful preparation of these compounds demonstrates that oxathianes can be subjected to a wide variety of protecting group manipulation and withstand acidic, basic and reductive conditions.

Having the sulfoxides **17**–**23** at hand, attention was focused on their conversion into anomeric sulfonium ions for subsequent glycosylations. In this respect, activation of the sulfoxides by triflic anhydride in the presence of trimethoxybenzene will result in arylation of sulfur to give an intermediate sulfonium ion.[15,18] In the first instance, oxathiane **17** was explored as a glycosyl donor for glycosylations with a variety of different glycosyl acceptors (Table 1). Thus, **17** was activated with trifluoromethanesulfonic anhydride (Tf$_2$O) in the presence of 1,3,5-trimethoxybenzene in DCM at −10 °C. After completion of the electrophilic aromatic substitution and formation of the intermediate sulfonium ion, alcohols **24**–**28** were added and after a reaction time of 16 h at room temperature, the disaccharides **29**–**33** were isolated by size exclusion column chromatography and anomeric selectivities determined by careful analysis of ^{1}H NMR spectra. Each glycosylation proceeded with exceptional high alpha-anomeric selectivity, however, in the case of acceptors **24**, **25**, and **27** a trace amount of beta-amomer was detected. The use of primary and secondary sugar alcohols gave the corresponding disaccharides in good to excellent yields. The glycosylation protocol is also compatible with the use of appropriately protected amino acids and for example glycosylated threonine derivative **31** could be prepared in high yield as only the α-anomer. Furthermore, it was also found that thioglycosides can be employed as glycosyl acceptor and for example the use of **27** and **28** led to clean formation of disaccharides **32** and **33**, respectively. The latter type of glycosylation is attractive because it is to be expected that the thioglycosyl products can employed as glycosyl donors in subsequent glycosylations using an appropriate thiophilic reagent thereby offer a rapid strategy for oligosaccharide assembly.

Next, we explored whether protecting groups commonly employed in oligosaccharide synthesis are compatible with the glycosylation protocol. Thus, glycosyl donors **17**, **18**, **20**–**23**, **34**, and **35** were activated by triflic anhydride in the presence of 1,3,5-trimethoxybenzene to give intermediate sulfonium ions, which were glycosylated with acceptors **36** and **37**. As can be seen in Table 2, the expected disaccharides **38**–**54** were isolated in good to excellent yields. Furthermore, glycosyl donors modified with electron withdrawing protecting groups at C-3, 4, and 6 gave the corresponding disaccharides as only the alpha-anomer (entry 1–4). Glycosyl donors that had an ether function at C-4 or C-6 (entries 5–11) gave exceptional high alpha anomeric selectivities (α:β > 15:1). Highly reactive donors having multiple ether type protecting groups gave in some case disaccharides with modest anomeric selectivities (entries 13 and 17). These observations are in agreement with previous finding[15] that highly reactive anomeric sulfonium ions can react through an oxacarbenium ion resulting in loss of α-anomeric selectivity.

Characterization of Sulfonium Ions by NMR

To ascertain that glycosylations of oxathianes proceed through a sulfonium ion intermediates, compound **17**, trimethoxybenzene, and DTBMP were dissolved in CDCl$_3$, activated with triflic anhydride and ^{1}H, gCOSY, gHSQC, and HMBC spectra were recorded (Figure 1). As expected, the chemical shift of H-1 of the newly formed product shifted down field (δ = 4.31 and δ = 4.15 to δ = 5.60) and exhibited $J_{1,2}$ = 9 Hz, which is consistent with a β-anomeric configuration. Full assignment of proton and carbon signals could be made by gCOSY and gHSQC. Careful analysis of proton coupling constants indicated that no conformational distortion of the saccharide ring had occurred. The presence of a carbon-sulfur linkage of the sulfonium ion was established by an HMBC experiment, which allows the determination of three-bond proton-carbon couplings. In particular, a strong correlation was observed between C-1 and H8eq, confirming the presence of a *trans*-decalin system. Furthermore, the smaller geminal-coupling constant between H8eq and H8ax (12 Hz) indicates that the trimethoxyphenyl substituent of sulfur adopts an equatorial orientation. Comparing chemical shifts of the trimethoxyphenyl (H8eq 3.98, H8ax 4.28 ppm) and phenyl (H8eq 4.32, H8ax 3.66 ppm) substituted sulfonium ion indicates that their aromatic rings adopt different conformations and in particular deshielding of H8ax of the trimethoxylbenzene substituted system indicates that the trimethoxybenzene group is perpendicular to the plane of the sugar ring (see SI for further details).

Interestingly, sulfonium **55** was stable at room temperature for 9 h, while subsequent incubation at 45°C for 5 min resulted in complete decomposition. It was also noticed that the excess of trimethoxylbenzene was further consumed after complete formation of the sulfonium ion, and was no longer present after an incubation time of 9 h.

A number of additional sulfonium ions (**56–61**) were generated and their structure and reactivity studied by NMR. Thus, compounds **55–58** were prepared by arylation of the corresponding sulfides and differ in the pattern of protecting groups at C-3, C-4, and C-6. Compounds **59–61** were prepared by methylation of the corresponding sulfides with methyl triflate and also differ in hydroxyl protection. Finally, acyclic sulfonium ion **62** was formed by methylation of the corresponding ethyl thioglycoside with methyl triflate.

As expected sulfonium ions **55–58** are stable at room temperature but readily react with alcohols to give mainly or exclusively α-glucosides. Interestingly, exposure of sulfonium ion **59** to an excess of methanol did not lead to glucoside formation and this compound was unaltered after a reaction time of 24 h. Benzylated sulfonium ion **61** was slightly more reactive and exposure to an excess of **24** gave the corresponding glucoside in a low yield of 21% as a mixture of anomers. These results clearly demonstrate that the nature of the sulfonium ion is a major determinant of anomeric reactivity. It was also found that the cyclic nature of sulfonium ions influences anomeric reactivity and for example within 15 min acyclic sulfonium ion **62** reacted with excess methanol to give a methyl glycoside whereas the corresponding cyclic sulfonium ion **59** is unreactive under these conditions.[22]

It is well known that carbon chemical shifts are mainly determined by local electronic environment.[29] Interestingly, it was observed that the chemical shift of C-1 of the arylated and alkylation sulfonium ions differ by approximately 2 ppm indicating a lower electronic density at C-1 of alkylated sulfonium ion, which surprisingly did not result a higher reactivity towards alcohols. Probably, the higher reactivity of the arylated sulfonium corresponds to its better leaving group ability. In this respect, a weaker base constitutes in general a better leaving group. Furthermore, it has been established that the relative stabilities of sulfonium ions corresponds with the relative basicities of the corresponding leaving group.[30] The fact that thioanisol is a weaker base than dimethyl sulfide[30,31] would

indicate that arylated sulfonium ion are less stable and provide a better leaving. This is in agreement with the observations described above.

Chemical Synthesis of an Immuno-active Glycogen-like Component

Having established a range of selective protected oxathiane building blocks suitable for selective 1,2-*cis*-glycosylations, attention was focused on the preparation of tetraglucoside **79**, which is derived from the cell wall polysaccharide of the fungus *Pseudallescheriaboydii*.[23] This fungus is found in soil and polluted water and can cause infections in immuno-compromised and immuno-competent hosts. Recent structural studies have shown that the cell wall of *P. boydii* contains a glycogen like component that is composed of a α(1–4)-linked glucopyranoside backbone modified at C-6 with α-Glc*p* moieties.[32] A soluble form of the polysaccharide could inhibit phagocytosis in a dose dependent manner and furthermore enzymatic degradation of the glycogen-like component of *P. boydii* could reduce the phagocytic index demonstrating that it plays a key role in phagocytosis. It has also been shown that the α-glucan can induce cytokine secretion in a TLR2-dependent manner. The minimal structural motif that can induce these properties is difficult to establish due to structural heterogeneity of the polysaccharide. However, it is to be expected that this problem can be addressed by chemically synthesizing a library of glucans differing in C-6 branching patterns.

α-Glucans represent a considerable synthetic challenge due to the presence of multiple 1,2-*cis* glycosidic linkages, the low reactivity of C-4 hydroxyls of glucosyl acceptors and the branched nature of the compound. Therefore, this component offered an exciting opportunity to examine the usefulness of oxathianes for the preparation of complex and biological important compounds.

We envisaged that a-glucans such as **79** can be assembled by a latent-active glycosylation strategy[33] in which a sulfoxide donor is coupled with an oxathiane acceptor to give a product that can be oxidized to a sulfoxide for further glycosylations (Schemes 3 and 4). To establish the feasibility of such a latent-active glycosylation strategy, sulfoxides **17**, **19**, and **20** were treated with Tf_2O in the presence of 1,3,5-trimethoxybenzene to form an intermediate sulfonium ion, which was glycosylated with oxathiane **63** to give disaccharide **64–66** as mainly alpha-glucosides. These results demonstrate that oxathianes are stable under the condition used for arylation of sulfoxides to give sulfonium ion.

It was expected that disaccharide **65** would be a suitable substrate for the preparation of target compound **79**. In this respect, the anomeric oxathiane can be oxidized to a sulfoxide and then converted into a sulfonium ion for glycosylation with a properly protected aminopropyl spacer. Furthermore, the Nap[34] ether at C-6 and Fmoc carbonate at C-4 are fully orthogonal and will allow glucosylations at these positions to give after deprotection the expected tetrasaccharide **79**.

First, the C-2 auxiliary of **65** was converted into an acetyl ester to give **67** using a standard procedure. This additional step was required to avoid oxidation of the (2,4,6-trimethoxyphenyl)sulfane moiety of the non-reducing glucoside during the subsequent oxidation step to convert the oxathiane moiety into a sulfoxides. As expected, compound **67** could be cleanly oxidized to the corresponding sulfoxides, which was activated with Tf_2O/1,3,5-trimethoxybenzene to give an anomeric sulfonium ion that was glycosylated with alcohol **69** to provide spacer-containing **70** as only the alpha-anomer. The C-2 auxiliary of **70** was converted into an acetyl ester and the Fmoc group of the resulting compound **71** was cleaved by treatment with *N*-methyl-2-pyrrolidone (NMP) in DMF to give glucosyl acceptor **72**. Next, glycosyl acceptor **72** was coupled with the sulfonium ion derived from sulfoxide **17** using standard conditions to give trisaccharide **73** as mainly the alpha glucoside. The

trace amount of unwanted b-anomer could easily be removed by silica gel column chromatography. The C-2 auxilairy of **73** was converted into an acetyl ester by standard procedures to give compound **74**, which was converted into glycosyl acceptor **75** by oxidative removal of the Nap ether using 5,6-dicyano-1,4-benzoquinone (DDQ) in a mixture of DCM and water. A $Tf_2O/1,3,5$-trimethoxybenzene mediated glycosylation of **17** with **75** gave tetrasaccharide **77** as an 8/1 mixture of alpha/beta anomers. In order to improve the anomeric selectivity, the glycosylation was repeated with glycosyl donor **20** having an acetyl esters at C-3 and C-6 and a benzyl ether at C-4 and gratifyingly the use of this compound gave tetrasaccharide **76** in a yield of 70% as only the alpha anomer. Deprotection could easily be accomplished by a three-step procedure involving treatment with TFA in DCM to remove the C-2 auxiliary, saponification of the acetyl esters with sodium methoxide in methanol and catalytic hydrogenolysis of the benzyl ether and the reduction of azide using $Pd(OH)_2/C$. The structural identity of α-glucan **77** was confirmed by homo- and heteronuclear two dimensional NMR (gCOSY and gHSQC) experiments and in particular the chemical shifts and coupling constants of the anomeric protons confirmed (1→4) and (1→6)-linked alpha-glucosidic linkages.[35]

CONCLUSIONS

Modular building blocks that can readily be converted into glycosyl donors and acceptors have the potential to speedup the process of oligosaccharide assembly. The potential of such a strategy will, however, only be realized when building blocks will be developed that reliably give high 1,2-*cis*-anomeric selectivities. Previously, we introduced a stereoselective 1,2-*cis*-glycosylation approach based on neighboring group participation by a (*S*)-phenylthiomethylbenzyl moiety at C-2 of a glycosyl donor to give a bicyclic b-sulfonium ion intermediate that can readily be displaced by sugar alcohol leading to the formation of 1,2-*cis*-glycosides. Although the auxiliary mediated approach has many attractive features, the acid sensitivity of the (*S*)-phenylthiomethylbenzyl moiety complicates certain protecting group manipulation, which in turn makes it difficult to develop robust modular building blocks. We describe here that monosaccharides protected as 1,2-oxathiane ethers are stable to commonly employed protecting groups manipulations making it possible to install a variety of selectively removable protecting groups such as Lev ester, Fmoc and Alloc carbonates, and Nap ether. Furthermore, the 1,2-oxathiane ether could easy be installed by a novel one-pot two-step procedure and it was found that protection of the 1,2-diol facilitated modification of the C-3, C-4 and C-6 alcohols. The resulting 1,2-oxathianes could be employed as glycosyl donors for highly selective 1,2-*cis*glycosylation by oxidation to sulfoxides followed by arylation with 1,3,5-trimethoxybenzene to give a bicyclic anomeric sulfonium ion. The attractiveness of the new building blocks has been demonstrated by the preparation of a biologically important branched a-glucan, which was assembled by a latent-active glycosylation strategy.

EXPERIMENTAL SECTION

Full experimental is available in Supporting Information. Compounds **1**,[18] **24**,[36] **25**,[37] **26**,[38] **27**,[39] **34**,[15] **35**,[15] and **37**[40] were prepared following literature procedures.

General Procedure for the Preparation of Sulfoxide Donors 17 – 23 from their Corresponding Oxathianes 9 – 11 and 13 – 16

m-CPBA (77%, l.1 eq.) was dissolved in DCM and slowly injected into a cooled (-–78 °C) solution of oxathiane in DCM. The mixture was stirred at –78 °C for 30 min, diluted with DCM (50 mL) and then poured into 10% $Na_2S_2O_3$ aqueous solution. The organic layer was washed with saturated $NaHCO_3$, dried ($MgSO_4$), filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography.

General Glycosylation Procedure for Oxathiane Donors with Various Acceptors

A mixture of sulfoxide donor (1 eq.), 1,3,5-trimethoxybenzene (1.5 eq.), 2,6-di-*tert*-butyl-4-methyl pyridine (2 eq.), and activated molecular sieves (4 Å) in DCM (adjusted donor concentration to 0.15 M) was stirred for 1 h under an atmosphere of argon. After cooling to −10 °C, trifluoromethanesulfonic anhydride (1.1 eq.) was added. After 30 min, the reaction mixture was cooled (−40 °C), and a solution of acceptor (0.8 eq.) in DCM (adjusted donor concentration to 0.1 M) was added slowly. The temperature of the reaction mixture was kept at −40 °C for another 60 min before allowed to warm to room temperature. After 15 h, the reaction mixture was diluted with DCM (10 mL), filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography or sephadex® LH20 size exclusion chromatography (DCM/MeOH = 1/1, 0.2 mL/min).

General Procedure for the Removal of C-2 Auxiliary

Trifluoroacetic acid was added dropwise to a solution of glucoside in DCM at 0 °C adjusting the final concentration to 10% (v/v). The reaction mixture was stirred for 0.5–3 h until TLC indicated complete consumption of starting material. The reaction mixture was diluted with DCM and poured into saturated $NaHCO_3$. The organic layer was dried ($MgSO_4$), filtered, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography.

Procedures for NMR Study of Sulfonium ions

S-(2,3,5-trimethoxylphenyl)-oxathianium triflate: A mixture of R/S sulfoxides (10 μmol), 1,3,5-trimethoxybenzene (16 μmol), 2,6-di-*tert*- butyl-4-methyl pyridine (21 μmol), and activated molecular sieves (4 Å, pellets) in $CDCl_3$ (1 mL) was shaken for 30 min under an atmosphere of argon. Then 0.5 mL of the solution was transferred to a 5 mm NMR tube and sealed. After cooling to 0 °C, a trifluoromethanesulfonic anhydride stock solution (25 μL, 0.23 M in $CDCl_3$) was added and NMR spectra for **55–58** were recorded at room temperature. *S*-methyl-oxathianium triflate: Sulfide (10 μmol) was dissolved in dry $CDCl_3$ (1 mL), methyl triflate (0.1 mmol) was added under the atmosphere of argon at room temperature. The reaction mixture was stirred for 2–16 h and monitored by TLC. After the consumption of sulfide, 0.5 mL of the reaction mixture was transferred to a 5 mm NMR tube and sealed. NMR spectra for **59–61** were recorded at room temperature.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

REFERENCES

(1). Brockhausen I. EMBO Rep. 2006; 7:599–604. [PubMed: 16741504] Ohtsubo K, Marth JD. Cell. 2006; 126:855–867. [PubMed: 16959566] Slawson C, Hart GW. Nat. Rev. Cancer. 2011; 11:678–684. [PubMed: 21850036]

(2). Crocker PR, Paulson JC, Varki A. Nat. Rev. Immunol. 2007; 7:255–266. [PubMed: 17380156] van Vliet SJ, Garcia-Vallejo JJ, van Kooyk Y. Immunol. Cell Biol. 2008; 86:580–587. [PubMed: 18679407] Astronomo RD, Burton DR. Nat. Rev. Drug Discov. 2010; 9:308–324. [PubMed: 20357803] Morelli L, Poletti L, Lay L. Eur. J. Org. Chem. 2011:5723–5777.

(3). Montesano M, Brader G, Palva ET. Mol. Plant Pathol. 2003; 4:73–79. [PubMed: 20569365] Silipo A, Erbs G, Shinya T, Dow JM, Parrilli M, Lanzetta R, Shibuya N, Newman MA, Molinaro A. Glycobiology. 2010; 20:406–419. [PubMed: 20018942]

(4). Brown JR, Crawford BE, Esko JD. Crit. Rev. Biochem. Mol. Biol. 2007; 42:481–515. [PubMed: 18066955] Liang PH, Wu CY, Greenberg WA, Wong CH. Curr. Opin. Chem. Biol. 2008; 12:86–92. [PubMed: 18258211] Buskas T, Thompson P, Boons GJ. Chem. Commun. 2009:5335–5349.Ernst B, Magnani JL. Nat. Rev. Drug Discov. 2009; 8:661–677. [PubMed: 19629075] Laremore TN, Zhang F, Dordick JS, Liu J, Linhardt RJ. Curr. Opin. Chem. Biol. 2009; 13:633–640. [PubMed: 19781979] Stallforth P, Lepenies B, Adibekian A, Seeberger PH. J. Med. Chem. 2009; 52:5561–5577. [PubMed: 19702275]

(5). Zhu XM, Schmidt RR. Angew. Chem. Int. Ed. 2009; 48:1900–1934.Schmaltz RM, Hanson SR, Wong CH. Chem. Rev. 2011; 111:4259–4307. [PubMed: 21749134]

(6). Boltje TJ, Buskas T, Boons GJ. Nat. Chem. 2009; 1:611–622. [PubMed: 20161474]

(7). Wong CH, Ye XS, Zhang Z. J. Am. Chem. Soc. 1998; 120:7137–7138.Zhu T, Boons GJ. Tetrahedron: Asymmetry. 2000; 11:199–205.Werz DB, Ranzinger R, Herget S, Adibekian A, von der Lieth CW, Seeberger PH. ACS Chem. Biol. 2007; 2:685–691. [PubMed: 18041818] Arungundram S, Al-Mafraji K, Asong J, Leach FE 3rd, Amster IJ, Venot A, Turnbull JE, Boons GJ. J. Am. Chem. Soc. 2009; 131:17394–17405. [PubMed: 19904943] Adibekian A, Stallforth P, Hecht ML, Werz DB, Gagneux P, Seeberger PH. Chem. Sci. 2011; 2:337–344.

(8). Demchenko AV. Curr. Org. Chem. 2003; 7:35–79.Cai F, Wu B, Crich D. Adv. Carbohydr. Chem. Biochem. 2009; 62:251–309. [PubMed: 19501707] Guo J, Ye XS. Molecules. 2010; 15:7235–7265. [PubMed: 20966873]

(9). Boons GJ. Tetrahedron. 1996; 52:1095–1121.Codee JDC, Litjens R, van den Bos LJ, Overkleeft HS, van der Marel GA. Chem. Soc. Rev. 2005; 34:769–782. [PubMed: 16100617] Tanaka H, Yamada H, Takahashi T. Trends Glycosci. Glycotechnol. 2007; 19:183–193.

(10). Plante OJ, Palmacci ER, Seeberger PH. Science. 2001; 291:1523. [PubMed: 11222853] Seeberger PH. Chem. Soc. Rev. 2008; 37:19–28. [PubMed: 18197330]

(11). Imamura A, Ando H, Korogi S, Tanabe G, Muraoka O, Ishida H, Kiso M. Tetrahedron Lett. 2003; 44:6725–6728.

(12). Zhu XM, Kawatkar S, Rao Y, Boons GJ. J. Am. Chem. Soc. 2006; 128:11948–11957. [PubMed: 16953636]

(13). Kim JH, Yang H, Park J, Boons GJ. J. Am. Chem. Soc. 2005; 127:12090–12097. [PubMed: 16117550]

(14). Park J, Boltje TJ, Boons GJ. Org. Lett. 2008; 10:4367–4370. [PubMed: 18763796]

(15). Boltje TJ, Kim JH, Park J, Boons GJ. Org. Lett. 2011; 13:284–287. [PubMed: 21158475]

(16). Boltje TJ, Kim JH, Park J, Boons GJ. Nat. Chem. 2010; 2:552–557. [PubMed: 20571573]

(17). Cox DJ, Fairbanks AJ. Tetrahedron: Asymmetry. 2009; 20:773–780.

(18). Fascione MA, Adshead SJ, Stalford SA, Kilner CA, Leach AG, Turnbull WB. Chem. Commun. 2009:5841–5843.

(19). Fascione MA, Turnbull WB. Beilstein J. Org. Chem. 2010; 6:19. [PubMed: 20485601]

(20). Fascione MA, Kilner CA, Leach AG, Turnbull WB. Chem. Eur. J. 2012; 18:321–333. [PubMed: 22140005]

(21). West AC, Schuerch C. J. Am. Chem. Soc. 1973; 95:1333–1335.Lundt I, Skelbæk-Pedersen B. Act. Chem. Scand. 1981; B35:637–642.Park J, Kawatkar S, Kim JH, Boons GJ. Org. Lett. 2007; 9:1959–1962. [PubMed: 17432867] Nokami T, Shibuya A, Mgnabe S, Ito Y, Yoshida J. Chem. Eur. J. 2009; 15:2252–2255. [PubMed: 19156648] Nokami T, Nozaki Y, Saigusa Y, Shibuya A, Manabe S, Ito Y, Yoshida J. Org. Lett. 2011; 13:1544–1547. [PubMed: 21323371]

(22). Mydock LK, Kamat MN, Demchenko AV. Org. Lett. 2011; 13:2928–2931. [PubMed: 21563800]

(23). Lopes LC, da Silva MI, Bittencourt VC, Figueiredo RT, Rollin-Pinheiro R, Sassaki GL, Bozza MT, Gorin PA, Barreto-Bergter E. Mycoses. 2011; 54:28–36. [PubMed: 21995660]

(24). van Boom JH, Burgers PMJ. Tetrahedron Lett. 1976:4875–4878.

(25). Gioeli C, Chattopadhyaya JB. Chem. Commun. 1982:672–674.

(26). Adinolfi M, Barone G, Guariniello L, Iadonisi A. Tetrahedron Lett. 2000; 41:9305–9309.

(27). Sakagami M, Hamana H. Tetrahedron Lett. 2000; 41:5547–5551.

(28). Lambert JB, Featherman SI. Chem. Rev. 1975; 75:611–626.

(29). Martin GJ, Martin ML, Odiot S. Organic Magnetic Resonance. 1975; 7:2–17.

(30). Juri S, Denegri B, Kronja O. J. Phys. Org. Chem. 2012; 25:147–152.

(31). Laurence C, Berthelot M, Evain K, Illien B. Can. J. Chem. 2005; 83:138–145.

(32). Bittencourt VC, Figueiredo RT, da Silva RB, Mourao-Sa DS, Fernandez PL, Sassaki GL, Mulloy B, Bozza MT, Barreto-Bergter E. J. Biol. Chem. 2006; 281:22614–22623. [PubMed: 16766532] Figueiredo RT, Fernandez PL, Dutra FF, Gonzalez Y, Lopes LC, Bittencourt VC, Sassaki GL, Barreto-Bergter E, Bozza MT. J. Biol. Chem. 2010; 285:40714–40723. [PubMed: 20959459]

(33). Roy R, Andersson FO, Letellier M. Tetrahedron Lett. 1992; 33:6053–6056.Boons GJ, Isles S. Tetrahedron Lett. 1994; 35:3593–3596.Hasty SJ, Kleine MA, Demchenko AV. Angew. Chem. Int. Ed. 2011; 50:4197–4201.

(34). Fuwa H, Fujikawa S, Tachibana K, Takakura H, Sasaki M. Tetrahedron Lett. 2004; 45:4795–4799.Szabo ZB, Borbas A, Bajza I, Liptak A. Tetrahedron: Asymmetry. 2005; 16:83–95.

(35). Zang LH, Howseman AM, Shulman RG. Carbohydr. Res. 1991; 220:1–9. [PubMed: 1667378] Dinadayala P, Lemassu A, Granovski P, Cerantola S, Winter N, Daffe M. J. Biol. Chem. 2004; 279:12369–12378. [PubMed: 14715664]

(36). Ziegler T, Kovac P, Glaudemans CP. Carbohydr. Res. 1989; 194:185–198. [PubMed: 2620299]

(37). Deninno MP, Etienne JB, Duplantier KC. Tetrahedron Lett. 1995; 36:669–672.

(38). Mo KF, Fang T, Stalnaker SH, Kirby PS, Liu M, Wells L, Pierce M, Live DH, Boons GJ. J. Am. Chem. Soc. 2011; 133:14418–14430. [PubMed: 21812486]

(39). Ellervik U, Grundberg H, Magnusson G. J. Org. Chem. 1998; 63:9323–9338.

(40). Garegg PJ, Hultberg H. Carbohydr. Res. 1981; 93:C10–C11.
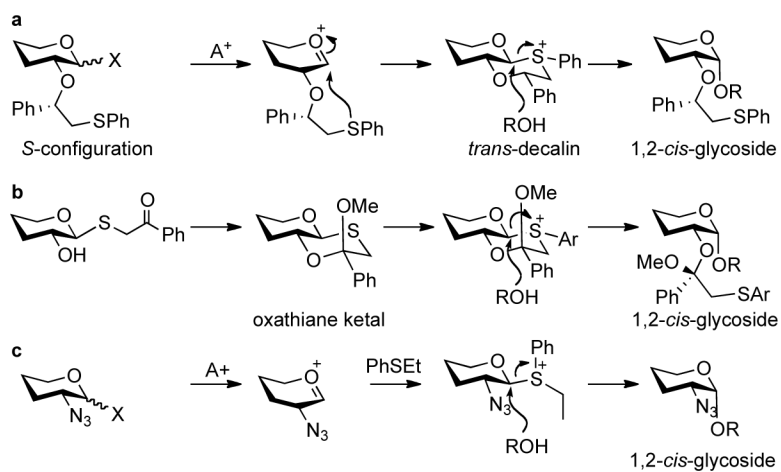
Scheme 1.
Sulfonium-ion promoted 1,2-*cis* glycosylations

a) Neighboring group participation by C-2 (*S*)-auxiliary leading to 1,2-*cis* glycosides; b) β-sulfonium ion formation from precyclized oxathiane ketal. In these reactions, hydrolysis of the C-2 auxiliary is a major side product; c) sulfonium ion formation in the presence of a thioether.
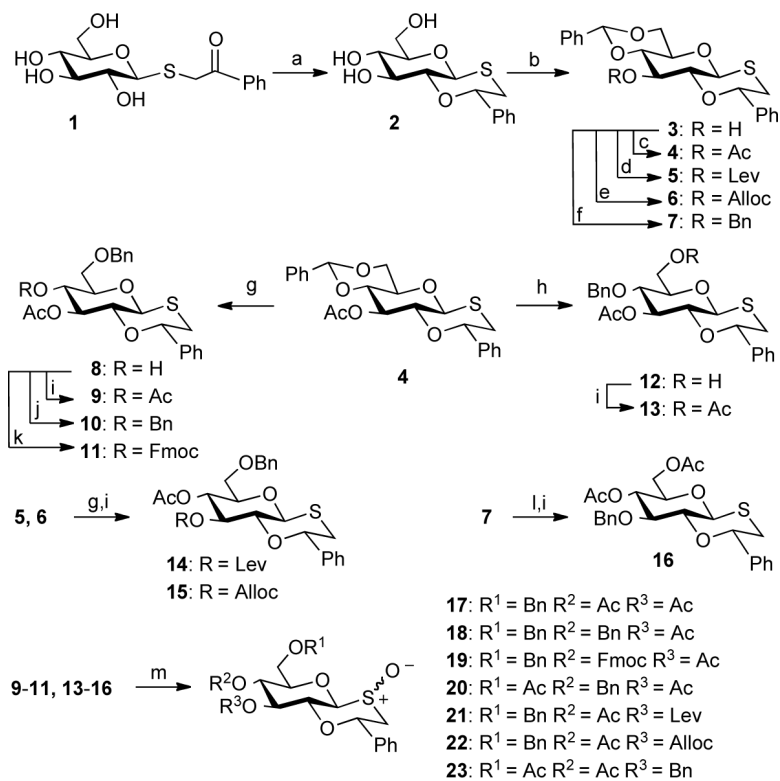
Scheme 2.
Synthesis of 1,4-oxathiane protected donors

a) TMS$_2$O, TMSOTf, 0 °C, 30 min, then Et$_3$SiH, 3 h (74%); b) PhCH(OMe)$_2$, CSA, reduced pressure, DMF, 50 °C,18 h (87%); c) Ac$_2$O, Py; d) Levulinic acid, DCC, DMAP, DCM (79%); e) AllocCl, TMEDA, DMAP, DCM (87%); f) BnBr, NaH, DMF (79%); g) Et$_3$SiH, TfOH, DCM, −78 °C; h) Et$_3$SiH, PhBCl$_2$, −78 °C; i) Ac$_2$O, Py(**9**: 85%, g, i 2 steps; **13**: 78%, h, i 2 steps; **14**: 79%, g, i 2 steps; **15**: 92%, g, i 2 steps; **16**: 84%, l, i 2 steps); j) Ag$_2$O, BnBr (**10**: 55%, g, j 2 steps); k) FmocCl, Py/DCM = 1/1 (v/v) (**11**: 66%, g, k 2 steps); l) EtSH, TsOH, DCM; m) *m*CPBA, DCM, −78 °C (**17**: 92%; **18**: 96%; **19**: 98%; **20**: 93%; **21**: 98%; **22**: 82%; **23**: 96%).
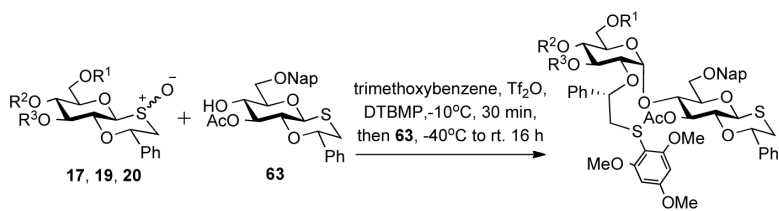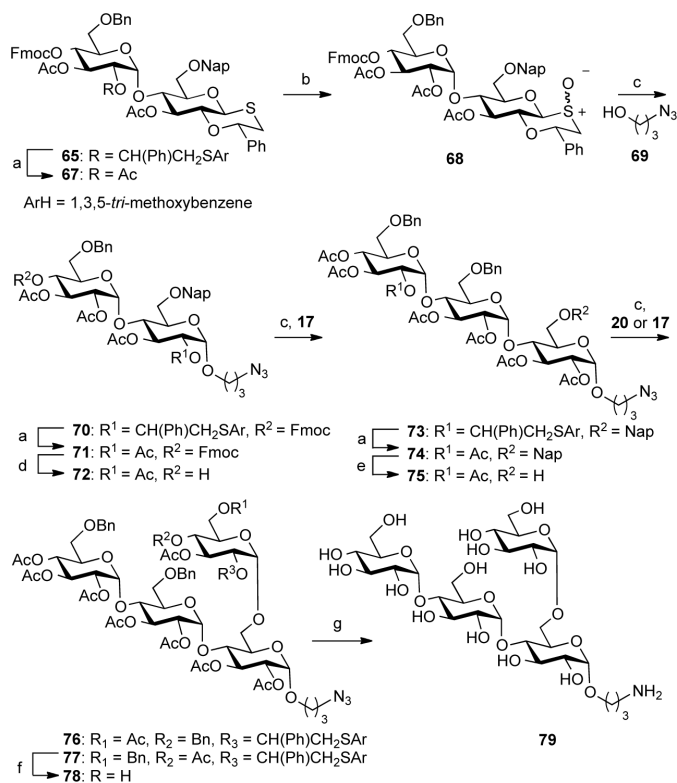
64: R^1 = Bn, R^2 = Ac, R^3 = Ac; α/β>15:1, 68%[a]
65: R^1 = Bn, R^2 = Fmoc, R^3 = Ac; α/β>15:1, 55%[a]
66: R^1 = Ac, R^2 = Bn, R^3 = Ac; α/β>25:1, 55%[a]

Scheme 3.
Latent-active glycosylation strategy
a The α/β ratios were determined by the integration of key signals in the ^{1}H NMR spectra of the disaccharide products after purification by LH-20 size exclusion chromatography.

Scheme 4.

Synthesis of the glycogen-like glucan isolated from *P. boyii*

a) i. 10% TFA in DCM, 0 °C, 1 h; ii. Ac$_2$O, Py (**67**: 89%, 2 steps; **71**: 98%, two steps; **74**: 76%, 2 steps); b) *m*CPBA, DCM, −78 °C (98%); c) general glycosylation condition (**70**: 86%, α only; **73**: 65%, α/β>15:1; **76**: 70%, α only; **77**: 73%, α/β=8:1); d) 20% NMP in DMF, 30 min (91%); e) DDQ, H$_2$O:DCM=1:10 (92%); f) 10% TFA in DCM, 0 °C, 1 h (85%); g) i. NaOMe, MeOH; ii. H$_2$, Pd(OH)$_2$/C, *t*BuOH-H$_2$O-AcOH=40:1:1 (83%, 2 steps).
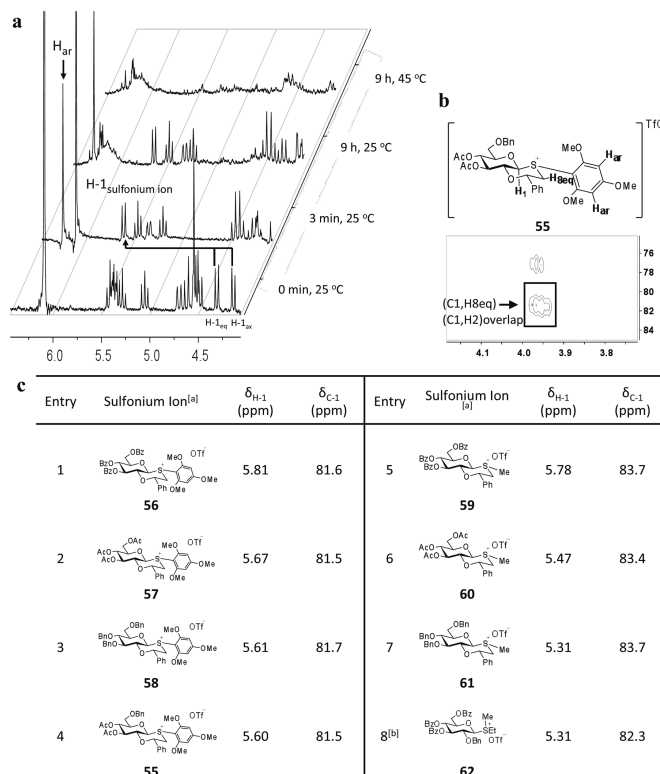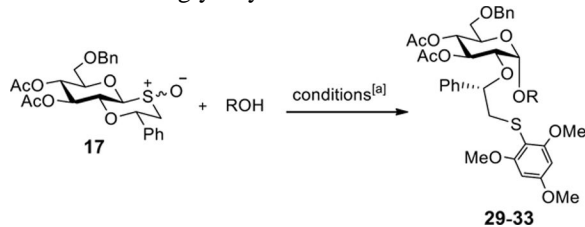
Figure 1.
NMR study of sulfonium ions. a) thermostability of sulfonium ion 55; b) HMBC spectrum of sulfonium ion 55. c) Comparison of electronic properties of different sulfonium ions by NMR chemical shift (all chemical shifts were referred to TMS).

[a]Stereochemistry at sulfur was assigned by empirical rules using H-8ax,eq geminal coupling.[28]

[b]Cited data.[22]

Table 1

Stereoselective glycosylations between donor 17 and various acceptors

29-33

Entry	ROH	Product	Yield[b]	α:β[c]
1	**24**	**29**	91%	>15:1
2	**25**	**30**	62%	>25:1
3	**26**	**31**	89%	α only
4	**27**	**32**	67%	>15:1
5	**28**	**33**	72%	α only

[a] 1,3,5-Trimethoxybenzene, Tf₂O, DTBMP, molecular sieves 4 Å, −10 °C, 30 min, then add acceptor, −40 °C to room temperature, 16 h.

[b] Isolated yields of the α/β mixture of disaccharide products.

[c] The α/β ratios were determined by the integration of key signals in the ¹H NMR spectra of the disaccharide products after purification by LH-20 size exclusion chromatography.

Table 2

Protecting group pattern effect on stereoselectivity

Entry	Donor	R¹	R²	R³	ROH	Product	Yield[a]	α/β ratio[c]
1	34	Ac	Ac	Ac	36	38	80%	α only
2	34	Ac	Ac	Ac	24	39	59%	α only
3	34	Ac	Ac	Ac	37	40	48%	α only
4	20	Ac	Bn	Ac	36	41	84%	α only
5	20	Ac	Bn	Ac	37	42	59%	>15:1
6	17	Bn	Ac	Ac	36	43	94%	α only
7	17	Bn	Ac	Ac	37	44	67%	>25:1
8	22	Bn	Ac	Alloc	36	45	67%	α only
9	22	Bn	Ac	Alloc	24	46	78%	>15:1
10	21	Bn	Ac	Lev	36	47	85%	>15:1
11	21	Bn	Ac	Lev	37	48	64%	>15:1
12	23	Ac	Ac	Bn	36	49	98%	α only
13	23	Ac	Ac	Bn	37	50	46%	7:1
14	18	Bn	Bn	Ac	36	51	95%	>15:1
15	18	Bn	Bn	Ac	37	52	66%	10:1
16	35	Bn	Bn	Bn	36	53	98%	>15:1
17	35	Bn	Bn	Bn	37	54	57%	1.5:1

[a]1,3,5-Trimethoxybenzene, Tf$_2$O, DTBMP, molecular sieves 4 Å, −10 °C, 30 min, then add acceptor, −40 °C to r.t., 16 h.

[b]Isolated yields of the α/β mixture of disaccharide products.

[c]The α/β ratios were determined by the integration of key signals in the ^{1}H NMR spectra of the disaccharide products after purification by LH-20 size exclusion chromatography.