Published in final edited form as:

J Org Chem. 2013 October 4; 78(19): 9677–9688. doi:10.1021/jo4013805.

Regioselective Silyl/Acetate Exchange of Disaccharides Yields Advanced Glycosyl Donor and Acceptor Precursors

Hsiao-Wu Hsieh^{a,b}, Matthew W. Schombs^{a,b}, Mark A. Witschi^a, and Jacquelyn Gervay-Hague^{a,*}

Jacquelyn Gervay-Hague: jgervayhague@ucdavis.edu

^aDepartment of Chemistry, University of California at Davis, One Shields Avenue, Davis, CA 95616, USA

Abstract

Glycoconjugates are comprised of carbohydrate building blocks linked together in a multitude of ways giving rise to diverse biological functions. Carbohydrates are especially difficult to synthetically manipulate due to the similar reactivity of their numerous and largely equivalent hydroxyl groups. Hence, methodologies for both the efficient protection and selective modification of carbohydrate alcohols are considered important synthetic tools in organic chemistry. When per-*O*-TMS protected mono- or disaccharides in a mixture of pyridine and acetic anhydride are treated with acetic acid, regioselective exchange of silicon for acetate protecting groups occurs. Acid concentration, thermal conditions and microwave assistance mediate the silyl/acetate exchange reaction. Regiocontrol is achieved by limiting the equivalents of acetic acid and microwave irradiation hastens the process. We coined the term Regioselective Silyl Exchange Technology (ReSET) to describe this process, which essentially sets the protecting groups anew. To demonstrate the scope of the reaction, the conditions were applied to lactose, melibiose, cellobiose and trehalose. ReSET provided rapid access to a wide range of orthogonally protected disaccharides that would otherwise require multiple synthetic steps to acquire. The resulting bi-functional molecules are poised to serve as modular building blocks for more complex glycoconjugates.

Introduction

In humans, carbohydrates are important constituents of secreted and cell-surface glycoproteins, membrane components in the form of glycolipids and gangliosides as well as

Corresponding Author: Fax: 1-530-754-6915; Tel: 1-530-754-9577, jgervayhague@ucdavis.edu.

^bThese authors contributed equally to this work

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

various types of extracellular matrix molecules.¹ As such, they mediate a wide range of biological processes from embryonic development to differentiation, cell-cell recognition, signaling, host-pathogen interactions, cancer immunology, intracellular trafficking and localization.^{2, 3} The nine common monosaccharides found in mammalian cells can be linked in an astonishing number of ways, resulting in much higher complexity than is possible from amino acids or nucleotides. The development of synthetic methods to generate such complex structures in an efficient and controlled fashion is a cornerstone of glycobiology and glycochemistry research.¹ A major challenge in developing methods for oligosaccharide synthesis is the ability to differentiate between seemingly equivalent hydroxyl groups in order to achieve specific chemical linkages. Often, several protection and deprotection sequences are required, which increases production time and decreases step economy.⁴ Methods that streamline the pathway to selectively protected carbohydrate hydroxyl groups are continually under development and the topic of this report.⁵

Acetyl protecting groups are among the most versatile and widely used because they are easily introduced, robust and can be removed without affecting glycosidic linkages. And because of the numerous methods available for selective saponification of the anomeric acetate,⁶⁻⁹ it can be considered orthogonal to other acetates. Accordingly, significant resources have been dedicated to research focused on the selective acetylation of glycosides both enzymatically and chemically.¹⁰ Enzymatic acylation¹¹ has enabled the preparation of selectively acetylated pyranosides,¹²⁻¹⁵ furanosides,¹⁶ sialosides,¹⁷ oligosaccharides¹⁸⁻²⁰ and natural glycosides.^{21, 22} However, enzyme specificity and substrate solubility often limit the diversity of substrates amenable to modification.^{23, 24} Chemical methods for the selective acylation of sugars have also had limited success.^{10, 25} The main factor hindering progress in this area can be attributed to the insolubility of free sugars in organic solvents. Further complicating matters is anomalous behavior resulting from the hydrogen bonding network present in unprotected carbohydrates.²⁶ In these instances, alkyl glycosides have proved useful and, not surprisingly, selective acetylation of the primary hydroxyl at C-6 can be achieved preferentially.²⁷⁻²⁹ However, hydrolysis of the anomeric acetal (acetolysis) typically requires harsh acidic and thermal conditions.³⁰ Since disaccharides can also be readily hydrolysed under these conditions, this strategy is largely limited to monosaccharides.^{31, 32}

As opposed to using either alkyl glycosides or unprotected sugars, we recently reported a complimentary protocol allowing for the direct exchange of trimethylsilyl ethers with acetyl protecting groups (Scheme 1).³³ The methodology begins with a free monosaccharide, which is per-*O*-silylated to confer maximal solubility in organic solvent. Silylation can be carried out on multi-gram quantities in nearly quantitative yield. Subsequent treatment of the per-*O*-silylated sugar with acetic acid in a pyridine acetic anhydride mixture results in regioselective silyl acetate exchange giving rise to selectively acetylated monosaccharides. We refer to this process by the acronym ReSET (Regioselective Silyl Exchange Technology) because silyl protecting groups are being set anew to acetates during the reaction. As illustrated in Scheme 1, when ReSET was applied to galactose four uniquely protected analogs were prepared via a single transformation.³³ Careful monitoring of the reaction revealed that the C-6 trimethylsilyl group was the first to exchange followed by the

anomeric silyl acetal. This order of reactivity held true for all the monosaccharides studied.³³ Upon increasing the concentration of acetic acid from 2 equiv. to 4 equiv., the secondary trimethyl silyl groups began to exchange and the order and rate of exchange varied depending upon the structure of the monosaccharide. In the case of galactose, the C-2 silyl protecting group was more labile than the C-3, which in turn was more reactive than the C-4 position.

The orthogonally protected compounds generated by ReSET can be readily converted to a wide range of glycosyl donors through activation of the anomeric acetate or silyl ether. Alternatively, protodesilylation of the silicon protecting groups reveals selectively acetylated glycosyl acceptors (Scheme 2). In this manner, these bi-functional intermediates are poised to serve as modular building blocks en route to more complex glycoconjugates.

As part of a program targeting the synthesis of complex oligosaccharides, we sought to extend ReSET to disaccharides. We were especially interested in lactose, since a similar reactivity profile to galactose could potentially provide highly diversified building blocks in a single step. One might expect that disaccharides would be bound by the reactivity of the monosaccharides from which they are constructed, however it is not uncommon for disaccharides varying only in connectivity to exhibit remarkably different behaviors. Moreover, unprotected disaccharides are far less soluble in organic solvents than the monosaccharides from which they are composed. Further complicating matters is the susceptibility of the internal glycosidic linkages to hydrolysis under a variety of conditions. For example, Bhat et al. observed rapid cleavage of the internal glycosidic linkages of per-*O*-TMS-melibiose, per-*O*-TMS-cellobiose and per-*O*-TMS-lactose upon addition of TMSI, even at 0 °C.³⁴ In fact microwave conditions, similar to those used for ReSET, have been employed for the degradation of oligosaccharides and polysaccharides.^{35–38} Collectively, these challenges made disaccharides ideal substrates for developing the technology.

We reasoned that in order to apply the silyl exchange reaction to disaccharides, conditions would need to be identified under which acetate exchange occurred more rapidly than glycoside cleavage. It had been shown that the cleavage process can be attenuated through careful selection of protecting groups.^{39–41} Indeed, a significant decrease in the rate of internal glycosidic bond scission has been observed upon replacement of electron donating protecting groups (such as TMS) with electron withdrawing acetates. Herein, is described the results of extending ReSET to both reducing and nonreducing disaccharides including the biologically relevant lactose, melibiose, cellobiose and trehalose substrates.

Results and Discussion

Lactose (D-galp- β (1 $\rightarrow$ 4)-D-glcp) is a key component of several tumor associated carbohydrate antigens (TACA).^{42–46} Thus, it is not surprising that this important structural motif has been incorporated into several carbohydrate based cancer vaccines.^{47–49} Moreover, lactosides have been extensively used to target and image asialoglycoprotein receptors, which are overexpressed on cancer cells.⁵⁰ In 2000, Bruehl and Bertozzi synthesized a series of mono- and disulfated lactose derivatives in order to determine the optimal configuration for L-selectin binding.^{51, 52} Structurally defined multivalent lactose-

containing clusters have also been designed for optimal galectin binding.^{48, 53} As such, there is a need for ready access to differentially protected lactosides to further investigate these biological processes.

Our studies began with the preparation of per-*O*-TMS lactose, which was accomplished in one step from commercially available lactose.³⁴ The conditions developed for the regioselective acetylation of monosaccharides served as the starting point for the disaccharide system (Table 1). As such, per-*O*-silylated lactose was diluted into a mixture of anhydrous pyridine and acetic anhydride followed by addition of 3 equiv. of glacial acetic acid (Table 1, Entry 1).⁵⁴ The homogeneous solution was stirred under argon at rt for 5 d, after which time the solvent was removed and the mixture was purified using flash column chromatography affording the 6,6'-di-*O*-acetyl-lactoside (**1**) in 19% yield, 55% of the 1,6,6'-tri-*O*-acetyl-lactoside (**2**) and 12% of the 1,2,6,6'-tetra-*O*-acetyl-lactoside (**3**). The initial exchange followed the same trend as the monosaccharides in that the primary hydroxyls reacted first followed by anomeric exchange. The formation of **1** was consistent with a recently reported exchange of a per-*O*-TMS protected beta-thio maltoside.⁵⁵

It is worthy of note that the results shown in Table 1 constitute the first example of a silyl exchange reaction on a disaccharide bearing an anomeric silyl acetal. Moreover, both the silyl acetal (**1**) and the anomeric acetate (**2**) can be activated with trimethylsilyl iodide (TMSI) affording the same glycosyl iodide (**2I**, Scheme 3).^{34, 54} The *in situ* convergence of **1** and **2** to the same glycosyl donor (**2I**) can be considered additive. As such, **2I** was obtained in high yield (73% from commercially available lactose, Table 1, Entry 5).

Next, a thermal study was conducted in order to probe the effects of temperature on the reaction rate and selectivity. Similar product mixtures were obtained by increasing the reaction temperature from rt to 60 °C. However, the increased temperature was accompanied by a significant decrease in reaction time (Table 1, Entries 2 and 3). Under thermal conditions, compound **4** containing a single TMS ether at the 4' position was also observed. Recognizing the potential of **4** to serve as a modular building block for many of the more complex tumor associated carbohydrate antigens,^{56–58} we sought to increase its production thermally. After heating at 80 °C for 1 d, the main products recovered were **4** and per-*O*-acetylated lactose (**5**, Table 1, Entry 4). Hence, heating the reaction to 80 °C reduced the reaction time to 1 d and resulted in approximately a five-fold increase in the yield of **4**. Ready access to compounds **1–4** opens the door to a wide range of glycosides with minimal synthetic manipulation. Importantly, all compounds were isolated using column chromatography illustrating the enhanced stability conferred upon the remaining TMS ethers by the newly installed acetates. All structures were unambiguously characterized, with key assignments being identified via NMR (¹H, ¹³C, DEPT, HSQC, HMBC and COSY experiments; see Supporting Information).

The previously results from the microwave studies on silylated monosaccharides suggested a similar strategy with disaccharides may serve to further increase the reaction rate.³³ At the same time, we were mindful of the susceptibility of the glycosidic linkage. Accordingly, per-*O*-TMS lactose was irradiated at 125 °C for 3 cycles of 25 min (Table 1, Entry 5). After each cycle, the reaction progress was monitored via thin layer chromatography (TLC).

These conditions afforded a similar product distribution of **1** and **2** as that obtained under thermal conditions, albeit in a much shorter time. No cleavage or hydrolysis products were observed, which can be attributed to the rapid incorporation of the C-6,6' acetates which confer stability to the glycosidic linkage. Next, the amount of acetic acid was varied to determine its effect on the product distribution and reaction time. Increasing the amount of acetic acid accelerated the reaction and resulted in the exclusive formation of compounds **4** and **5**, (Table 1, Entries 6 and 7). Thus, the orthogonally protected species (**4**) was prepared in 2 steps from commercially available D-lactose and in just under 4 h from per-*O*-TMS lactose.

In order to reveal the selectively protected lactosyl acceptor (**6**), compound **4** was simply treated with Dowex[®] acidic resin in methanol. After 10 h at rt, TLC showed complete consumption of the starting material and subsequent formation of the key intermediate (**6**) in 90% yield (Scheme 4). Interestingly, the removal of a single TMS group required stirring with acidic resin in methanol for 10 h. Further investigation revealed that as the number of acetate protecting groups increased, the time required to remove the remaining TMS groups also lengthened providing further evidence of the inductively stabilizing effects of the acetate groups during protodesilylation. As such, the exchange process not only adds stability to the glycosidic linkages, but to the remaining silyl ethers as well.

TMS groups are often used as transient protecting groups due to their labile nature.⁵⁹ When stability is a concern and the orthogonality associated with the use of silyl protection strategies is required, bulky silyl protecting groups such as *tert*-butyldimethylsilyl (TBDMS) or *tert*-butyldiphenylsilyl (TBDPS) are frequently employed. However, conformational changes associated with the steric bulk of these groups are often observed when incorporated into carbohydrates.⁶⁰ The technology disclosed here allows for the extended use of TMS protecting groups in multistep sequences, thereby providing access to silicon bearing carbohydrates without affecting sugar conformation. As far as we are aware, this is the first reported synthesis of compounds **1–4**. Moreover, per-*O*-TMS lactose could be regenerated via a salvage pathway. Simple deacetylation and subsequent re-silylation allows any unwanted derivatives to be recycled in a nearly quantitative manner (Scheme 5).

Having established the optimal conditions for ReSET of per-*O*-TMS lactose, we next explored the effects of shifting the internal glycosidic linkage from the 4-position to the 6-position. Melibiose (D-galp- α (1 $\rightarrow$ 6)-D-glcp) is composed of the same monomeric units as lactose, however in melibiose the glycosidic linkage is α (1 $\rightarrow$ 6) to glucose; so unlike lactose, there is only one C-6 hydroxyl, which is one sugar removed from the anomeric center. There are several natural product based glycolipids containing a macrolactone linkage between the anomeric position of the glucosyl moiety and the C-6' position of the galactosyl residue. These compounds have been isolated from plants and yeast and are of growing commercial interest as biodegradable emulsifiers.^{61, 62} The application of ReSET to melibiose not only provides the opportunity to investigate the reactivity differences between constitutional isomers, but also grants access to a series of orthogonally protected derivatives that can be useful for structure activity relationship studies (Table 2).

As described earlier, per-*O*-TMS melibiose was prepared in one step from commercially available melibiose.³⁴ After co-evaporation with anhydrous benzene, per-*O*-TMS melibiose was subjected to the optimized selective acetylation conditions starting with 2.0 equiv. of glacial acetic acid. The reaction mixture was irradiated at 125 °C for 6 × 25 min cycles. Once TLC revealed the starting material had been consumed, the solvent was removed and the residue was purified using flash column chromatography. The reaction afforded a mixture containing the 6'-mono-*O*-acetate (**7**) in 39% yield and 1,6'-di-*O*-acetate (**8**) in 20% yield as a mixture of α/β anomers (Table 3, Entry 1). This result closely mirrors the lactose case, in that the first groups to exchange are the primary and anomeric silyl ethers.

Next, access to melibiose derivatives with a higher degree of exchange was explored. Based on the results of lactose, further exchange can be achieved either through prolonged microwave irradiation or by increasing the concentration of acetic acid. As microwave irradiation has been used to degrade oligosaccharides, we opted to increase the acetic acid content for our studies (Table 3, Entry 2). Under these conditions, instead of obtaining the mono- and di-*O*-acetylated analogs; the penta-, hexa-, hepta- and per-*O*-acetylated compounds (**9–12**) were isolated in moderate yields. Each analog was found to exist as a mixture of α/β anomers. It is also worthy of note that for lactose a mixture containing approximately 10–15% of unresolved partially acetylated compounds was always obtained, in addition to the major products. However, for melibiose the partially acetylated intermediates were well-resolved via TLC and column chromatography. As such, isolation and characterization of each compound was possible. Assignment of the structures to the corresponding TLC spots observed during the course of the reaction led to the conclusion that acetylation proceeds in a pseudo-stepwise fashion. After the primary and anomeric positions are acetylated, the remaining glucose silyl ethers (2, 3 and 4 positions) appear to exchange non-specifically, followed somewhat sequentially by the 2', 3' and 4' positions of the galactosyl moiety. This two-step process enabled the first reported synthesis of these selectively acetylated melibiose building blocks (**9–12**) that would otherwise require multiple synthetic steps.

Based upon the results with lactose and melibiose, which indicated that the rate of exchange for the glucose silyl ethers is relatively rapid after the primary, C6 and C6' positions exchange, we predicted that cellobiose might pose challenges in terms of achieving regioselective control. Cellobiose (D-glcp- β (1 $\rightarrow$ 4)-D-glcp) is the disaccharide repeat unit of cellulose, which is the most abundant organic material on the planet and a major renewable resource. Research efforts have been dedicated to achieving the selective chemical modification of cellobiose for over twenty-five years.⁶³ It has been used as a model for the development of carbohydrate based sensors.⁶⁴ Cellobiose has also served as the core for synthetic glycolipid based adjuvants and was found to induce a strong immunogenic response when coupled to short peptide antigens.⁶⁵ With applications as a food preservative, conjugation of cellobiose to the aminopolysaccharide chitosan resulted in higher water solubility at neutral pH and conferred increased antibacterial activity against *E. coli*.⁶⁶

With all of its hydroxyls in an equatorial orientation, cellobiose was deemed an interesting substrate for the ReSET reaction. Subsequent studies revealed that as with the other

reducing sugars evaluated, selectivity was achieved for the primary and anomeric positions of cellobiose yielding compounds **13** and **14** (Table 3, Entries 1 and 2). Beyond this initial exchange, both extended reaction times and higher concentrations of acetic acid resulted in inseparable mixtures that quickly converged to per-*O*-acetylated cellobiose. Thus, under the current conditions, selectivity beyond the primary and anomeric positions is not observed for cellobiose.

While all of the substrates described up to this point have been reducing disaccharides, only melibiose contained an internal α -linkage. The silyl exchange reaction on melibiose also proceeded in the most step-wise manner. In order to determine if there is a correlation between the orientation of the internal glycosidic linkage and the order of exchange, we turned our attention to a non-reducing disaccharide of particular biological relevance. Trehalose (D-glcp- α (1 $\rightarrow$ 1)-D-glcp) contains two glucosyl moieties connected by an α,α -1,1 glycosidic bond. Trehalose is utilized by plants, bacteria and all invertebrates^{67,68} for the protection it confers against oxidative stress, desiccation and freezing.⁶⁹ Accordingly, trehalose variants are widely considered potentially powerful therapeutic agents for the treatment of various diseases involving oxidative stress and chronic inflammation. Analogues of trehalose have shown potential as antibiotics and fungicides,⁷⁰ while other derivatives are able to disrupt cell wall biosynthesis and may act as novel agents in the fight against *Mycobacterium tuberculosis*.⁶⁷ For these reasons, ready access to non-symmetrical trehalose analogues is particularly desirable. As such, trehalose was selected as the capstone example for ReSET, as applied to disaccharides.

Being a non-reducing symmetric disaccharide, we expected product isolation and characterization to be simplified by elimination of α/β product mixtures. However, the propensity for glycosidic bond cleavage remained a significant concern. Beginning with the azeotropic distillation of per-*O*-TMS trehalose with anhydrous benzene, subsequent acetylation was evaluated with 2.0 equiv. of glacial acetic under microwave conditions (Table 4, Entry 1). The reaction afforded the mono-acetylated (**15**) and di-acetylated (**16**) compounds after 1.5 h. When the amount of acetic acid was increased to 4.0 equiv. only 30 mins was required for the complete consumption of starting material. After purification, mono-acetylated (**15**) and di-acetylated (**16**) compounds were isolated in 22% and 56% yields respectively (Table 4, Entry 2). In order to access a higher degree of acetylation, the acetic acid was increased to 8 equiv. under the same microwave conditions and after 1.5 h, the reaction afforded a product distribution of penta-acetate **17** in 14% yield, hexa-acetate **18** in 9% yield, and per-acetate **19** in 44% yield (Table 4, Entry 2). Interestingly, NMR analysis revealed that penta-acetate **17** and hexa-acetate **18** were intermediates in which one glucose ring had fully exchanged (acetylated). A similar proximal activation was observed with melibiose suggesting that exchange of one secondary TMS group activates neighboring ethers towards exchange; but further studies are needed to understand the underlying stereoelectronic effects of neighboring activation. Compound **18** has two secondary silyl ethers remaining (2'- and 3'-positions) indicating that the 4'-position is slightly more reactive than the 2'- and 3'-positions, a fact that may be of use for further regioselective reactions. Most importantly, ReSET offers an efficient methodology for breaking the symmetry of trehalose as evidenced by the formation of **15**, **17** and **18**.

As a basis for expanding ReSET in the future, we are interested in understanding the mechanism of this reaction. Two important experimental outcomes emerged from the studies thus far: silyl exchange is facilitated by proximal acetate groups, while at the same time protodesilylation becomes more difficult with increasing numbers of acetate protecting groups. To help explain these results we looked to the recent work of Wu and co-workers. In 2011, they published a proposed mechanism for the direct esterification of TBDMS ethers under strongly acidic conditions.⁷¹ Inspired by this report, we propose a mechanism for regioselective silyl exchange (Figure 1). The reaction first involves the formation of pyridinium-acetate salt upon addition of a stoichiometric amount of AcOH to a mixture containing Ac₂O and pyridine. Recall that AcOH plays a crucial role in the reaction sequence and is necessary for the exchange to proceed. Once a per-*O*-TMS protected disaccharide is introduced, the acetate ion is poised to attack silicon leading to Si-O bond cleavage and subsequent acetylation. Which silicon is attacked is likely a consequence of both its steric and electronic environments. Studies indicate thus far that the primary hydroxyls are always the first to exchange suggesting that sterics are a primary factor. A similar selectivity was recently reported for the step-wise selective desilylation of the primary TMS ethers on a panel of monosaccharides and subsequent acetylation of the resulting free hydroxyls.^{72, 73} Among the remaining TMS ethers, the anomeric position would be most stabilized upon removal of the silicon group putting it next in line for exchange. Incorporation of the acetate at the anomeric center places an inductively withdrawing group in close proximity to the C-2 position making this trimethylsilyl group most susceptible; and for the most part the trend continues around the ring i.e. C-3 is next to exchange and so on. Although at times sterics may interfere. For example, in the formation of **3** there is no discrimination between the C-3 position and the C-2' and C-3' positions. The data for both melibiose and trehalose follow this trend quite well. For trehalose, one entire ring is fully acetylated before any of the secondary TMS ethers are exchanged on the second ring. In general, the secondary OTMS groups in a glucosyl moiety are less selective than the secondary OTMS groups in a galactosyl moiety, presumably due to steric differences between axial and equatorial substituents.

An alternative mechanism worthy of consideration could involve pyridinium acetate catalysing protodesilylation giving selectively deprotected alcohols, which then react with acetic anhydride. To test this possibility, the ReSET reaction was performed in the absence of acetic anhydride. Under these conditions, the reaction was orders of magnitude slower and selectivity was not observed. This finding lends support to the hypothesis that the acylpyridinium rather than pyridinium acetate is attacked by the TMS ether oxygen and also demonstrates the need to incorporate acetate protecting groups to confer selectivity.

On the matter of protodesilylation, the mechanism begins with protonation of the silyl ether oxygen atom (Figure 2). An increased number of acetate groups around the sugar ring would concomitantly decrease the basicity of the ether oxygen atoms thus slowing the reaction. The basicity of acetal oxygen would be similarly affected which explains the increased stability of the glycosidic linkage with incorporation of acetate protecting groups. The addition of a single acetate group confers remarkable stability as observed in the formation of **15**.

Conclusion

ReSET provides a robust platform for the synthesis of orthogonally protected mono- and disaccharides in a rapid and efficient manner. Per-*O*-TMS lactose was selected as the model system for the systematic evaluation of the effects of acetic acid equivalents as well as identification of optimal thermal and microwave conditions. Acetic acid was found to be an essential component of the reaction mixture, resulting in increased exchange rates and the formation of more highly substituted derivatives. A mechanism for the silyl/acetate exchange reaction is also proposed. The remaining TMS ethers appended to the reaction products were found to be remarkably stable. As such, ReSET allows these TMS groups to be used in multi-step reaction sequences, which would otherwise preclude the use of transient TMS groups. This stability also allows for their extended storage and subsequent unmasking without concern for trans-acetylation or trans-silylation. These orthogonally protected advanced intermediates are poised for selective deprotection and subsequent conversion to a wide range of biologically relevant modifications including sulfation and phosphorylation. The products generated by this technology can be readily converted to a wide range of glycosyl donors. Alternatively, selective deprotection reveals their potential as glycosyl acceptors. In this way, these bi-functional intermediates are groomed to serve as modular building blocks en route to more complex glycoconjugates. ReSET also allows one to tune the reactivity of the resulting glycosides based on the degree of silyl/acetate exchange.⁷⁴ The optimal conditions established for lactose translated seamlessly to other biologically relevant disaccharides such as melibiose, cellobiose and trehalose. Importantly, when applied to trehalose ReSET led to facile desymmetrization. This process not only occurs with respect to the primary hydroxyls, but also by virtue of the fact that one ring becomes completely acetylated before the secondary hydroxyls of the other ring exchange. In addition to ReSET being time- and step-economical, high value starting materials can be easily recycled in a nearly quantitative manner. A motivation of this work is the application of these selectively acetylated disaccharides to the assembly and functionalization of a wide variety of complex glycoconjugates. As such, applications to the synthesis of biologically relevant complex glycosides are on-going and will be reported in due course.

Experimental Section

General procedure for regioselective silyl exchange of per-*O*-TMS disaccharides (Table 1 – Table 4)

In a 10 mL microwave reactor vessel or 25 mL round bottom flask, per-*O*-TMS disaccharide (lactose, melibiose, cellobiose or trehalose) (500 mg, 0.54 mmol or 230 mg, 0.25 mmol) was dissolved in anhydrous benzene (3 mL). The solvent was removed under rotary evaporation with argon backfilling. The azeotropic distillation was repeated two additional times to dryness affording viscous syrup. To the reaction flask was added a dry stirring bar, anhydrous pyridine (2.0 mL/per mmol TMS sugar), acetic anhydride (1.5 mL/per mmol TMS sugar), and glacial acetic acid (2–8 equiv.). The reaction vessel was either placed under room temperature or was heated by conventional oil bath or was subjected to microwave irradiation (standard mode, 100 W, 125 °C or 110 °C, ~40 psi) for various time intervals. Once TLC showed the reaction was complete, the reaction mixture was transferred

into a 50 mL round bottom flask where it was azeotroped with copious amounts of anhydrous benzene to dryness. The crude foam was immediately purified by flash column chromatography (hexanes/ethyl acetate/5% triethylamine) to afford the partially acetylated products.

General procedure for per-OTMS-substrate recycling (Scheme 5)

Compound **5** (1.00g, 1.46 mmol) was dissolved in dry MeOH (5 mL) and treated with wt 25% NaOMe in MeOH solution (0.3 mL) at 0 °C ice bath. After 10 min, H₂O (~3 mL) was added to dissolve the forming white precipitate and continued stirring at rt. After 1 h, the reaction mixture was added Dowex H⁺ resin until pH 7, filtered and concentrated under reduced pressure. The resulting residue was then dissolved in dry pyridine (6 mL), follow by addition of TMSCl (1.8 mL, 14.1 mmol) and catalytic amount of DMAP (18 mg, 0.15 mmol). After 5 h, the reaction mixture was diluted with EA/Hex (v/v=1/1) solution and washed with water and brine. The organic layer was dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to afford per-OTMS-lactose as (1.25 g, 92%) a light yellow oil.

(6-O-Acetyl-2,3,4-tri-O-trimethylsilyl-β-D-galactopyranosyl)-(1-4)-O-(6-O-acetyl-1,2,3-tri-O-trimethylsilyl)-D-glucopyranoside (1)

Following the general procedure described above, per-O-TMS lactose (500 mg, 0.54 mmol) was acetylated using Ac₂O/pyridine and glacial acetic acid (93 μL, 1.62 mmol, 3.0 equiv.). The reaction mixture was stirred under rt for 5d until the starting material was completely consumed. The reaction mixture was purified using flash column chromatography (EA/Hex/NEt₃ = 5:85:10 – 14:85:1 – 29:70:1) to afford compounds **1**, **2** and **3** (Table 1, Entry 1). Di-acetylated compound **1** (94 mg, 19%) was obtained as a white amorphous foam. TLC (EA/Hex = 30:70) R_f 0.70. ¹H NMR (800 MHz, CDCl₃) δ 4.99 (d, *J* = 3.1 Hz, 1H, H-1), 4.37 – 4.33 (m, 2H, H-6ab), 4.24 (dd, *J* = 5.8, 10.7 Hz, 1H, H-6'a), 4.08 (dd, *J* = 7.8, 10.7 Hz, 1H, H-6'b), 4.04 (d, *J* = 7.5 Hz, 1H, H-1'), 4.02 – 3.97 (m, 1H, H-5), 3.74 (t, *J* = 8.8 Hz, 1H, H-3), 3.71 (d, *J* = 2.3 Hz, 1H, H-4'), 3.63 (app t, *J* = 7.5, 9.2 Hz, 1H, H-2'), 3.50 – 3.45 (m, 2H, H-4, H-5'), 3.41 (dd, *J* = 3.2, 9.0 Hz, 1H, H-2), 3.32 (dd, *J* = 2.5, 9.2 Hz, 1H, H-3'), 2.09 (s, 3H), 2.05 (s, 3H), 0.13 (m, 54H). ¹³C NMR (200 MHz, CDCl₃) δ 170.90, 170.62, 103.0, 93.8, 77.0, 75.1, 74.0, 72.3, 71.93, 71.79, 71.51, 68.9, 63.28, 62.73, 21.1, 20.95, 0.91, 0.87, 0.60, 0.53, 0.49, 0.16. ESI-HRMS (*m/z*) calcd. for C₃₄H₇₄O₁₃Si₆ [M + NH₄]⁺: 876.4089; found: 876.4090.

(6-O-Acetyl-2,3,4-tri-O-trimethylsilyl-β-D-galactopyranosyl)-(1-4)-O-(1,6-di-O-acetyl-2,3-di-O-trimethylsilyl)-D-glucopyranoside (2)

Compound **2** (228 mg, 55%) was obtained as a white amorphous foam (Table 1, Entry 1; see compound **1** for reaction and purification condition). Compound **2** can be separated into two single anomers **2α**; and **2β** by gradient flash column chromatography (EA/Hex/NEt₃ = 5:90:5 to EA/Hex = 10:90 – 20:80). **2α**: TLC (EA/Hex = 2:8) R_f 0.36. ¹H NMR (800 MHz, CDCl₃) δ 6.07 (d, *J* = 3.7, 1H, H-1), 4.41 (dd, *J* = 12.1, 2.0 Hz, 1H, H-6a), 4.30 (dd, *J* = 12.1, 5.0 Hz, 1H, H-6b), 4.25 (dd, *J* = 10.7, 5.8 Hz, 1H, H-6'a), 4.08 (dd, *J* = 10.7, 7.8 Hz, 1H, H-6'b), 4.06 (d, *J* = 7.5 Hz, 1H, H-1'), 3.86 (ddd, *J* = 10.1, 4.9, 1.9 Hz, 1H, H-5), 3.72

(d, $J = 2.1$ Hz, 1H, H-4'), 3.69 (t, $J = 8.9$ Hz, 1H, H-2'), 3.64 (dd, $J = 9.1, 7.5$ Hz, 1H, H-2), 3.60 (dd, $J = 9.0, 3.7$ Hz, 1H, H-4), 3.55 (dd, $J = 10.1, 8.8$ Hz, 1H, H-5'), 3.49 (dd, $J = 7.3, 6.2$ Hz, 1H, H-5'), 3.32 (dd, $J = 9.2, 2.5$ Hz, 1H, H-3'), 2.13 (s, 3H), 2.10 (s, 3H), 2.06 (s, 3H), 0.15 (s, 9H), 0.13 (s, 9H), 0.11 (s, 9H), 0.103 (s, 9H), 0.102 (s, 9H), 0.10. ^{13}C NMR (200 MHz, CDCl_3) δ 170.6, 170.5, 169.4, 102.8, 91.8, 75.9, 74.9, 72.5, 72.0, 71.8, 71.5, 71.2, 71.1, 62.4, 62.3, 20.94, 20.91, 20.8, 0.7, 0.6, 0.4, 0.3, -0.03. **2 β** : TLC (EA/Hex = 2:8) R_f 0.32. ^1H NMR (800 MHz, CDCl_3) δ 5.42 (d, $J = 7.7$ Hz, 1H, H-1), 4.42 (dd, $J = 2.0, 11.9$ Hz, 1H, H-6a), 4.29 (dd, $J = 5.6, 12.0$ Hz, 1H, H-6b), 4.24 (dd, $J = 6.0, 10.8$ Hz, 1H, H-6'a), 4.07 (dd, $J = 7.4, 10.8$ Hz, 1H, H-6'b), 4.03 (d, $J = 7.5, 1\text{H}$, H-1'), 3.71 (d, $J = 2.3$ Hz, 1H, H-4'), 3.65 (app t, $J = 7.5, 9.1$ Hz, 1H, H-2'), 3.62 – 3.57 (m, 1H, H-5), 3.57 – 3.44 (m, 4H, H-2, H-3, H-4, H-5'), 3.30 (dd, $J = 2.5, 9.2$ Hz, 1H, H-3'), 2.12 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 0.17 – 0.13 (m, 27H), 0.098 (s, 9H), 0.089 (s, 9H). ^{13}C NMR (200 MHz, CDCl_3) δ 170.71, 170.65, 169.4, 103.0, 94.3, 76.16, 76.12, 75.2, 74.23, 74.14, 72.1, 71.51, 71.50, 62.75, 62.68, 21.41, 21.06, 20.94, 1.1, 0.96, 0.94, 0.60, 0.52. ESI-HRMS (m/z) calcd. for $\text{C}_{33}\text{H}_{68}\text{O}_{14}\text{Si}_5$ $[\text{M}+\text{NH}_4]^+$: 846.3799; found: 846.3828.

(6-O-Acetyl-2,3,4-tri-O-trimethylsilyl- β -D-galactopyranosyl)-(1-4)-O-(6-O-acetyl-2,3-di-O-trimethylsilyl)- α -D-glucopyranosyl iodide (2I)

In an oven-dried NMR tube, compound **1**, **2 α** or **2 β** (0.04 mmol) was added and dissolved in dry benzene- d_6 (0.4 mL). After introducing TMSI (7 μL , 0.048 mmol) to the reaction vessel, the reaction was kept at 0 $^\circ\text{C}$ and gradually warmed to 25 $^\circ\text{C}$ over 4–5 h. The reaction was monitored by NMR until its corresponding iodide formed. The iodide is highly reactive and moisture sensitive. Column chromatography or aqueous work-up should be avoided. After azotroped the iodide with anhydrous benzene (5 mL $\times$ 3) and concentrated under reduced pressure, a light yellow amorphous foam of **2I** could be obtained. *In situ* ^1H NMR (800 MHz, C_6D_6) δ 6.69 (d, $J = 4.0$ Hz, 1H, H-1), 4.72 – 4.67 (m, 2H, H-6ab), 4.38 – 4.28 (m, 4H, H-1', H-6'ab, H-5), 4.05 (t, $J = 8.7$ Hz, 1H, H-3), 3.94 (dd, $J = 8.9, 10.1$ Hz, 1H, H-4), 3.89 (ddd, $J = 10.1, 7.6, 2.5$ Hz, 1H, H-5'), 3.75 (d, $J = 2.4$ Hz, 1H, H-4'), 3.53 (dd, $J = 12.1, 5.3$ Hz, 1H, H-2'), 3.36 (dd, $J = 2.6, 9.3$ Hz, 1H, H-3'), 2.56 (dd, $J = 3.9, 8.6$ Hz, 1H, H-2), 1.74 (s, 3H), 1.64 (s, 3H), 0.36 (s, 9H), 0.31 (s, 9H), 0.23 (s, 9H), 0.22 (s, 9H), 0.14 (s, 9H), 0.11 (s, 9H), 0.02 (s, 9H). *In situ* ^{13}C NMR (200 MHz, C_6D_6) δ 169.4, 169.3, 103.0, 83.6, 76.8, 75.2, 75.1, 75.0, 72.8, 72.1, 71.7, 71.6, 62.6, 61.5, 22.0, 19.9, 1.7, 0.7, 0.6, 0.4, 0.4, 0.2.

(6-O-Acetyl-2,3,4-tri-O-trimethylsilyl- β -D-galactopyranosyl)-(1-4)-O-(1,2,6-tri-O-acetyl-3-O-trimethylsilyl)-D-glucopyranoside (3)

Compound **3** (50 mg, 12%) was obtained as a white amorphous foam (Table 1, Entry 1; see compound **1** for reaction and purification condition). TLC (EA/Hex = 3:7) R_f 0.28. ^1H NMR (600 MHz, CDCl_3) δ 5.59 (d, $J = 8.4$ Hz, 1H, H-1), 4.99 – 4.93 (m, 1H, H-2), 4.47 (dd, $J = 2.0, 12.0$ Hz, 1H, H-6a), 4.28 (dd, $J = 5.3, 12.0$ Hz, 1H, H-6b), 4.17 (dd, $J = 6.2, 10.9$ Hz, 1H, H-6'a), 4.11 (dd, $J = 6.9, 10.9$ Hz, 1H, H-6'b), 4.06 (d, $J = 7.5$ Hz, 1H, H-1'), 3.71–3.67 (m, 3H, H-3, H-5, H-4'), 3.63–3.60 (m, 2H, H-2', H-4), 3.49 (t, $J = 6.5$ Hz, 1H, H-5'), 3.31 (dd, $J = 2.5, 9.2$ Hz, 1H, H-3'), 2.09 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 2.06 (m, 3H), 0.15 (s, 9H), 0.11 (s, 9H), 0.10 (s, 18H). ^{13}C NMR (150 MHz, CDCl_3) δ 170.69, 170.62, 169.50,

169.42, 102.8, 92.3, 75.68, 75.12, 74.44, 73.76, 72.96, 72.37, 71.70, 71.62, 62.97, 62.37, 21.14, 21.07, 20.99, 20.98, 0.96, 0.62, 0.59, 0.53. ESI-HRMS (m/z) calcd. for C₃₂H₆₂O₁₅Si₄ [M+NH₄]⁺: 816.3510; found: 816.3488.

(2,3,6-Tri-O-acetyl-4-O-trimethylsilyl-β-D-galactopyranosyl)-(1-4)-O-(1,2,3,6-tetra-O-acetyl)-D-glucopyranoside (4)

Following the general procedure described above, per-O-TMS lactose (500 mg, 0.54 mmol) was acetylated using Ac₂O/pyridine and glacial acetic acid (216 μL, 3.78 mmol, 7.0 equiv.) followed by nine microwave irradiation cycles (standard mode, 100 W, 125 °C, ~40 psi, 25 min). The reaction mixture was purified using flash column chromatography (EA/Hex = 20:80 – 50:50) to afford compounds **4** and **5** (Table 1, Entry 7). Mono-silylated compound **4** (69 mg, 18%) was obtained as a white amorphous foam. TLC (EA/Hex = 5:5) R_f 0.34. ¹H NMR (600 MHz, CDCl₃) δ 6.24 (d, *J* = 3.7 Hz, 2H, H-1_α), 5.66 (d, *J* = 8.3 Hz, 1H, H-1_β), 5.45 (app t, *J* = 9.6, 10.2 Hz, 1H, H-3_α), 5.22 (t, *J* = 9.2 Hz, 1H, H-3_β), 5.16–5.12 (m, 2H, H-2'_α, H-2'_β), 5.03 (dd, *J* = 8.4, 9.3 Hz, 1H, H-2_β), 4.99 (dd, *J* = 3.7, 10.3 Hz, 1H, H-2_α), 4.85–4.80 (m, 2H, H-3'_α, H-3'_β), 4.47–4.41 (m, 4H, H-1'_α, H-6_α, H-1'_β, H-6_β), 4.26–4.21 (m, 2H, H-6_α, H-6_β), 4.10–4.07 (m, 2H, H-6'_α, H-6'_β), 4.05–3.97 (m, 5H, H-6'_α, H-4'_α, H-5_α, H-6'_β, H-4'_β), 3.83–3.78 (m, 2H, H-4_α, H-4_β), 3.74 (ddd, *J* = 2.0, 5.0, 9.9 Hz, 1H, H-5_β), 3.66–3.63 (m, 2H, H-5'_α, H-5'_β), 2.16 (s, 3H), 2.11 (s, 3H), 2.10 (s, 3H), 2.09 (s, 3H), 2.09 (s, 3H), 2.06 (s, 3H), 2.05 (s, 3H), 2.04 (s, 3H), 2.03 (s, 3H), 2.02 (s, 3H), 2.015 (s, 3H), 2.00 (s, 3H), 0.12 (s, 9H), 0.117 (s, 9H). ¹³C NMR (150 MHz, CDCl₃) δ 170.50, 170.48, 170.47, 170.46, 170.32, 170.10, 169.85, 169.72, 169.33, 169.24, 169.09, 169.00, 101.3, 101.1, 91.7, 89.2, 75.58, 75.49, 73.67, 73.53, 73.50, 72.81, 72.34, 72.33, 71.0, 70.7, 69.8, 69.7, 69.64, 69.60, 68.1, 62.00, 61.82, 61.77, 61.71, 21.08, 20.98, 20.90, 20.85, 20.7, 0.32, 0.32. ESI-HRMS (m/z) calcd. for C₂₉H₄₄O₁₈Si [M+NH₄]⁺: 726.2641; found: 726.2639.

(2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)-(1-4)-O-(1,2,3,6-tetra-O-acetyl)-D-glucopyranoside (5)

Compound **5** (224 mg, 61%) was obtained as a white amorphous foam (Table 1, Entry 7; see compound **4** for reaction and purification condition). TLC (EA/Hex = 5:5) R_f 0.18. ¹H NMR (600 MHz, CDCl₃) δ 6.25 (d, *J* = 3.7 Hz, 1H), 5.66 (d, *J* = 8.3 Hz, 1H), 5.47 (app t, *J* = 9.6, 10.2 Hz, 1H), 5.38–5.31 (m, 2H), 5.24 (t, *J* = 9.2 Hz, 1H), 5.11 (ddd, *J* = 8.0, 9.1, 10.3 Hz, 2H), 5.04 (dd, *J* = 8.3, 9.4 Hz, 1H), 5.00 (dd, *J* = 3.7, 10.3 Hz, 1H), 4.95 (ddd, *J* = 3.5, 9.1, 10.4 Hz, 2H), 4.51–4.39 (m, 5H), 4.18–4.04 (m, 7H), 4.00 (ddd, *J* = 2.0, 4.1, 10.1 Hz, 1H), 3.87 (app dd, *J* = 6.6, 12.5 Hz, 3H), 3.85–3.78 (m, 2H), 3.75 (ddd, *J* = 2.0, 4.8, 9.9 Hz, 1H), 2.07 (m, 6H). ¹³C NMR (150 MHz, CDCl₃) δ 170.50, 170.47, 170.45, 170.42, 170.27, 170.26, 170.20, 170.19, 170.06, 169.75, 169.73, 169.70, 169.26, 169.14, 169.06, 168.99, 101.4, 101.1, 91.6, 89.1, 75.94, 75.80, 73.6, 72.7, 71.12, 71.08, 70.85, 70.61, 69.71, 69.23, 69.09, 66.70, 66.69, 61.85, 61.56, 60.95, 60.89, 21.00, 20.99, 20.82, 20.80, 20.80, 20.78, 20.76, 20.75, 20.65. ESI-HRMS (m/z) calcd. for C₂₈H₃₈O₁₉ [M+NH₄]⁺: 696.2351; found: 696.2346.

(2,3,6-Tri-O-acetyl-4-ol- β -D-galactopyranosyl)-(1-4)-O-(1,2,3,6-tetra-O-acetyl)-D-glucopyranoside (6)

To a MeOH (2 mL) solution of compound **4** (63 mg, 0.09 mmol) was added Dowex H⁺ resin (~250 mg). The suspension was allowed to stir at rt until TLC showed the starting material was completely consumed (12 h). Next, the resin was removed via filtration and the solution was concentrated to afford a viscous oil. The crude mixture was immediately purified using flash column chromatography (EA/Hex = 70:30) to obtain compounds **6** (50 mg, 90%) as a white amorphous foam. TLC (EA/Hex = 2:1) R_f 0.27. ¹H NMR (800 MHz, CDCl₃) δ 6.25 (d, *J* = 3.7 Hz, 1H, H-1_a), 5.66 (d, *J* = 8.3 Hz, 1H, H-1 _{β}), 5.44 (t, *J* = 9.8 Hz, 1H, H-3_a), 5.23 (t, *J* = 9.2 Hz, 1H, H-3 _{β}), 5.18–5.14 (m, 2H, H-2'_a, H-2' _{β}), 5.05 (app t, *J* = 8.4, 9.0 Hz, 1H, H-2 _{β}), 5.01 (dd, *J* = 3.7, 10.3 Hz, 1H, H-2_a), 4.92–4.84 (m, 2H, H-3'_a, H-3' _{β}), 4.48–4.41 (m, 4H, H-1'_a, H-6_a, H-1' _{β} , H-6 _{β}), 4.33–4.23 (m, 4H, H-6'_{ab}, H-6'_{ab}), 4.13–4.11 (m, 2H, H-6_a, H-6 _{β}), 4.01–3.98 (m, 3H, H-4'_a, H-5_a, H-4' _{β}), 3.83–3.79 (m, 2H, H-4_a, H-4 _{β}), 3.77–3.75 (m, 1H, H-5 _{β}), 3.71–3.69 (m, 2H, H-5'_a, H-5' _{β}), 2.46 (s, 2H), 2.17 (s, 3H), 2.14–1.98 (m, 43H). ¹³C NMR (200 MHz, CDCl₃) δ 170.91, 170.88, 170.49, 170.45, 170.18, 170.07, 169.98, 169.95, 169.68, 169.44, 169.36, 169.08, 169.00, 101.2, 101.0, 91.7, 89.1, 75.9, 75.7, 73.7, 73.42, 73.37, 72.7, 72.23, 72.18, 70.9, 70.6, 69.7, 69.6, 69.5, 66.9, 66.8, 62.03, 62.00, 61.97, 61.7, 21.08, 21.00, 20.98, 20.96, 20.94, 20.90, 20.83, 20.77, 20.74, 20.65. ESI-HRMS (*m/z*) calcd. for C₂₆H₃₆O₁₈ [M+NH₄]⁺: 654.2245; found: 654.2243.

(2,3,4-Tri-O-trimethylsilyl-6-O-acetyl- α -D-galactopyranosyl)-(1-6)-O-(1,2,3,4-tetra-O-trimethylsilyl)- α -D-glucopyranoside (7)

Following the general procedure described above, per-*O*-TMS melibiose (500 mg, 0.54 mmol) was acetylated using Ac₂O/pyridine and glacial acetic acid (62 μ L, 1.08 mmol, 2 equiv.) followed by six irradiation cycles (standard mode, 100 W, 125 °C, ~40 psi, 25 min). The reaction mixture was purified using flash column chromatography (EA/Hex = 5:95 – 12:88) to afford compounds **7** and **8** (Table 2, Entry 1). Mono-acetylated analogue **10** (190 mg, 39%) was obtained as a white foam. TLC (EA/Hex = 15:85) R_f 0.59. ¹H NMR (800 MHz, CDCl₃) δ 5.07 (d, *J* = 3.4 Hz, 1H, H-1'), 4.92 (d, *J* = 3.0, 1H, H-1), 4.17–4.10 (m, 2H, H-6'ab), 3.88–3.64 (m, 9H, H-3, H-4, H-5, H-6ab, H-2', H-3', H-4', H-5'), 3.33 (dd, *J* = 3.1, 9.1 Hz, 1H, H-2), 2.06 (s, 3H), 0.20 (s, 9H), 0.14 (s, 9H), 0.13 (s, 9H), 0.127 (s, 9H), 0.122 (s, 9H), 0.121 (s, 9H), 0.11 (s, 9H). ¹³C NMR (200 MHz, CDCl₃) δ 170.8, 99.6, 93.8, 74.3, 74.2, 72.9, 72.82, 71.82, 70.6, 69.2, 68.6, 63.7, 21.0, 1.4, 1.1, 0.69, 0.63, 0.53, 0.33, 0.30. ESI-HRMS (*m/z*) calcd. for C₃₅H₈₀O₁₂Si₇ [M+NH₄]⁺: 906.4378; found: 906.4390.

(2,3,4-Tri-O-trimethylsilyl-6-O-acetyl- α -D-galactopyranosyl)-(1-6)-O-(2,3,4-tri-O-trimethylsilyl-1-O-acetyl)-D-glucopyranoside (8)

Compound **8** (90 mg, 20%) was obtained as a white foam (Table 2, Entry 1; see compound **7** for reaction and purification condition). TLC (EA/Hex = 15:85) R_f 0.40. ¹H NMR (800 MHz, CDCl₃) δ 6.02 (d, *J* = 3.5 Hz, 4H, H-1_a), 5.33 (d, *J* = 8.0 Hz, 1H, H-1 _{β}), 5.06 (d, *J* = 3.4 Hz, 1H, H-1' _{β}), 5.00 (d, *J* = 3.4 Hz, 4H, H-1'_a), 4.15–4.07 (m, 12H, H-6ab), 3.90–3.63 (m, 50H, H-5, H-2', H-6', H-3', H-5', H-4', H-4, H-3, H-6'), 3.53 (dd, *J* = 3.6, 9.0 Hz, 4H, H-3_a), 3.45 (t, *J* = 8.8 Hz, 1H), 3.42–3.39 (m, 1H), 3.36 (d, *J* = 9.2 Hz, 1H), 2.08 (s, 12H),

2.07 (s, 4H), 2.07 (s, 13H), 2.05 (s, 3H), 0.21 – 0.11 (m, 313H). ^{13}C NMR (200 MHz, CDCl_3) δ 170.9, 170.8, 169.7, 169.4, 99.7, 99.6, 94.5, 92.1, 78.1, 77.9, 75.4, 74.9, 74.2, 73.0, 72.9, 72.5, 70.9, 70.6, 70.5, 69.1, 69.1, 68.8, 68.7, 63.8, 63.7, 62.7, 62.1, 21.3, 21.2, 21.08, 21.06, 1.5, 1.4, 1.10, 1.05, 1.01, 0.7, 0.63, 0.60, 0.4, 0.31, 0.25, 0.2. ESI-HRMS (m/z) calcd. for $\text{C}_{34}\text{H}_{74}\text{O}_{13}\text{Si}_6$ $[\text{M}+\text{NH}_4]^+$: 876.4089; found: 876.4105.

(2,3,4-Tri-*O*-trimethylsilyl-6-*O*-acetyl- α -D-galactopyranosyl)-(1-6)-*O*-(1,2,3,4-tetra-*O*-acetyl)-D-glucopyranoside (9)

Following the general procedure described above, per-*O*-TMS melibiose (500 mg, 0.54 mmol) was acetylated using Ac_2O /pyridine and glacial acetic acid (216 μL , 3.78 mmol, 7.0 equiv.) followed by six cycles of microwave irradiation (standard mode, 100 W, 125 $^\circ\text{C}$, ~40 psi, 25 min). The reaction mixture was purified using flash column chromatography (EA/Hex = 40:60 – 60:40) to afford compounds **9**, **10**, **11** and **12** (Table 2, Entry 2). Penta-acetylated analogue **9** (21 mg, 7%) was obtained as a white foam. TLC (EA/Hex = 1/1) R_f 0.81. ^1H NMR (800 MHz, CDCl_3) δ 6.27 (d, J = 3.7 Hz, 1H, H-1 $_{\alpha}$), 5.64 (d, J = 8.4 Hz, 1H, H-1 $_{\beta}$), 5.46 (t, J = 9.8 Hz, 1H, H-3 $_{\alpha}$), 5.23 (t, J = 9.4 Hz, 1H, H-3 $_{\beta}$), 5.16 (td, J = 6.2, 9.8, 2H, H-4 $_{\alpha}$, H-4 $_{\beta}$), 5.09 (app t, J = 8.0, 9.6 Hz, 1H, H-2 $_{\beta}$), 5.03 (dd, J = 3.7, 10.3 Hz, 1H, H-2 $_{\alpha}$), 4.75 (d, J = 3.2 Hz, 1H, H-1' $_{\beta}$), 4.73 (d, J = 4.0 Hz, 1H, H-1' $_{\alpha}$), 4.13 (dd, J = 5.6, 11.2 Hz, 1H, H-6' $_{\beta}$), 4.15 – 4.08 (m, 3H, H-6' $_{\alpha}$, H-6' $_{\alpha}$, H-5 $_{\beta}$), 4.05 (dd, J = 7.3, 11.2 Hz, 1H, H-6' $_{\beta}$), 3.91 (app t, J = 6.4 Hz, 1H, H-5' $_{\beta}$), 3.90 – 3.85 (m, 3H, H-2' $_{\alpha}$, H-5' $_{\alpha}$, H-2' $_{\beta}$), 3.83 (m, 3H, H-5 $_{\alpha}$, H-3' $_{\alpha}$, H-3' $_{\beta}$), 3.79 (d, J = 1.2 Hz, 2H, H-4' $_{\alpha}$, H-4' $_{\beta}$), 3.70 (dd, J = 5.3, 11.6 Hz, 2H, H-6 $_{\alpha}$, H-6 $_{\beta}$), 3.59 (dd, J = 1.7, 11.6 Hz, 1H, H-6 $_{\beta}$), 3.52 (dd, J = 1.8, 11.5 Hz, 1H, H-6 $_{\alpha}$), 2.16 (s, 3H), 2.07 (app d, J = 3.0 Hz, 9H), 2.04 (s, 3H), 2.03 (app dd, J = 3.3, 7.7 Hz, 12H), 2.01 (s, 3H), 0.17 (s, 9H), 0.16 (s, 9H), 0.14 (s, 9H), 0.13 (app d, J = 1.1 Hz, 27H). ^{13}C NMR (200 MHz, CDCl_3) δ 170.8, 170.5, 170.4, 169.9, 169.5, 169.4, 169.3, 169.1, 169.0, 99.9, 91.9, 89.1, 74.2, 73.3, 73.1, 72.9, 71.1, 70.5, 70.4, 70.3, 69.5, 69.3, 69.2, 69.0, 68.7, 68.5, 65.8, 65.5, 63.9, 63.7, 21.0, 20.9, 20.8, 20.8, 20.7, 0.72, 0.72, 0.60, 0.58, 0.43, 0.37. ESI-HRMS (m/z) calcd. for $\text{C}_{31}\text{H}_{56}\text{O}_{16}\text{Si}_3$ $[\text{M}+\text{NH}_4]^+$: 786.3220; found: 786.3183.

(3,4-Di-*O*-trimethylsilyl-2,6-di-*O*-acetyl- α -D-galactopyranosyl)-(1-6)-*O*-(1,2,3,4-tetra-*O*-acetyl)-D-glucopyranoside (10)

Compound **10** (52 mg, 26%) was obtained as a white foam (Table 2, Entry 2; see compound **9** for reaction and purification condition). TLC (EA/Hex = 1/1) R_f 0.70. ^1H NMR (800 MHz, CDCl_3) δ 6.26 (d, J = 3.7 Hz, 3H, H-1 $_{\alpha}$), 5.64 (d, J = 8.3 Hz, 1H, H-1 $_{\beta}$), 5.45 (t, J = 9.9 Hz, 3H, H-3 $_{\alpha}$), 5.22 (t, J = 9.4 Hz, 1H, H-3 $_{\beta}$), 5.17 (td, J = 5.0, 9.8 Hz, 4H, H-4 $_{\alpha}$, H-4 $_{\beta}$), 5.11 (d, J = 3.5, 4H, H-1' $_{\alpha}$, H-1' $_{\beta}$), 5.05 (app t, J = 8.8, 9.6 Hz, 1H, H-2 $_{\beta}$), 5.01 (dd, J = 3.7, 10.3 Hz, 3H, H-2 $_{\alpha}$), 4.90 – 4.85 (m, 4H, H-2' $_{\alpha}$, H-2' $_{\beta}$), 4.14 – 4.05 (m, 9H, H-6' $_{\alpha}$, H-6' $_{\beta}$, H-6' $_{\alpha}$, H-6' $_{\beta}$), 4.03 (m, 7H, H-3' $_{\alpha}$, H-5 $_{\alpha}$, H-3' $_{\beta}$), 3.85 (d, J = 2.6 Hz, 3H, H-4' $_{\alpha}$), 3.84 – 3.79 (m, 6H, H-5' $_{\alpha}$, H-5' $_{\beta}$, H-4' $_{\beta}$), 3.73 (dd, J = 2.6, 9.8 Hz, 1H, H-5 $_{\beta}$), 3.66 (dt, J = 5.4, 10.8 Hz, 4H, H-6 $_{\alpha}$, H-6 $_{\beta}$), 3.54 (dd, J = 1.7, 11.8 Hz, 1H, H-6' $_{\beta}$), 3.49 (dd, J = 1.7, 11.7 Hz, 3H, H-6' $_{\alpha}$), 2.17 (s, 8H), 2.14 (s, 3H), 2.10 (s, 9H), 2.09 (s, 4H), 2.06 (s, 12H), 2.04 (s, 9H), 2.03 (app d, J = 3.1 Hz, 7H), 2.02 (app d, J = 3.3 Hz, 18H), 2.00 (s, 4H), 0.18 (s, 10H), 0.17 – 0.16 (m, 25H), 0.11 (app d, J = 3.4 Hz, 37H). ^{13}C NMR (200 MHz, CDCl_3) δ 170.8, 170.74,

170.72, 170.69, 170.4, 170.3, 169.9, 169.5, 169.4, 169.3, 169.1, 168.96, 96.6, 96.2, 91.7, 89.1, 77.3, 77.2, 77.0, 73.8, 73.2, 72.5, 72.4, 71.42, 71.35, 70.5, 70.3, 70.2, 69.4, 69.0, 68.8, 68.5, 68.4, 68.2, 67.9, 64.9, 63.7, 63.5, 21.23, 21.22, 21.00, 20.90, 20.83, 20.75, 20.7, 20.6, 0.6, 0.50, 0.49. ESI-HRMS (m/z) calcd. for $C_{30}H_{50}O_{17}Si_2$ $[M+NH_4]^+$: 756.2930; found: 756.2903.

(2,3,6-Tri-O-acetyl-4-O-trimethylsilyl- α -D-galactopyranosyl)-(1-6)-O-(1,2,3,4-tetra-O-acetyl)-D-glucopyranoside (11)

Compound **11** (43 mg, 22%) was obtained as a white foam (Table 2, Entry 2; see compound **9** for reaction and purification condition). TLC (EA/Hex = 1/1) R_f 0.55. 1H NMR (800 MHz, $CDCl_3$) δ 6.27 (d, J = 3.6 Hz, 1H, H-1 $_{\alpha}$), 5.66 (d, J = 8.3 Hz, 1H, H-1 $_{\beta}$), 5.46 (t, J = 9.9 Hz, 1H, H-3 $_{\alpha}$), 5.25 – 5.20 (m, 3H, H-3' $_{\alpha}$, H-3' $_{\beta}$, H-3 $_{\beta}$), 5.18 – 5.09 (m, 6H, H-4 $_{\alpha}$, H-2' $_{\alpha}$, H-1' $_{\alpha}$, H-4 $_{\beta}$, H-2' $_{\beta}$, H-1' $_{\beta}$), 5.06 (app t, J = 8.8, 9.6 Hz, 1H, H-2 $_{\beta}$), 5.03 (dd, J = 4.0, 10.4 Hz, 1H, H-2 $_{\alpha}$), 4.17 – 4.10 (m, 4H, H-4' $_{\alpha}$, H-6' $_{\alpha}$, H-4' $_{\beta}$, H-6' $_{\beta}$), 4.04 – 4.06 (m, 1H, H-5 $_{\alpha}$), 4.03 – 3.96 (m, 3H, H-6' $_{\alpha}$, H-5' $_{\alpha}$, H-6' $_{\beta}$), 3.94 (app t, J = 6.5 Hz, 1H, H-5' $_{\beta}$), 3.78 – 3.74 (m, 1H, H-5 $_{\beta}$), 3.70 (dd, J = 4.5, 11.7 Hz, 2H, H-6 $_{\alpha}$, H-6 $_{\beta}$), 3.59 (dd, J = 2.4, 11.7 Hz, 1H, H-6 $_{\beta}$), 3.54 (dd, J = 2.5, 11.5 Hz, 1H, H-6 $_{\alpha}$), 2.18 (s, 3H), 2.11 (s, 3H), 2.09 – 2.08 (m, 12H), 2.06 (app d, 6H), 2.04 – 2.03 (m, 6H), 2.02 (app d, 6H), 2.00 (app d, 6H), 0.11 (app d, 18H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 170.76, 170.67, 170.6, 170.5, 170.4, 170.3, 170.2, 169.8, 169.5, 169.4, 169.09, 169.05, 96.5, 96.1, 91.7, 89.0, 73.5, 73.0, 70.5, 70.3, 70.0, 69.91, 69.4, 69.3, 69.2, 68.6, 68.4, 68.34, 68.26, 68.1, 65.7, 65.6, 64.5, 62.8, 62.6, 21.29, 21.27, 21.03, 20.95, 20.94, 20.90, 20.83, 20.75, 20.74, 20.73, 20.71, 20.6, 0.4. ESI-HRMS (m/z) calcd. for $C_{29}H_{44}O_{18}Si$ $[M+NH_4]^+$: 726.2641; found: 726.2616.

(2,3,4,6-Tetra-O-acetyl- α -D-galactopyranosyl)-(1-6)-O-(1,2,3,4-tetra-O-acetyl)-D-glucopyranoside (12)

Compound **12** (81 mg, 44%) was obtained as a white foam (Table 2, Entry 2; see compound **9** for reaction and purification condition). TLC (EA/Hex = 1/1) R_f 0.33. 1H NMR (800 MHz, $CDCl_3$) δ 6.25 (d, J = 3.4 Hz, 1H), 5.64 (d, J = 8.3 Hz, 1H), 5.46 – 5.39 (m, 4H), 5.30 (ddd, J = 3.3, 6.7, 10.2 Hz, 3H), 5.21 (t, J = 9.5 Hz, 1H), 5.14 – 5.09 (m, 5H), 5.08 – 4.97 (m, 5H), 4.16 (dt, J = 6.5, 21.6 Hz, 3H), 4.06 – 4.00 (m, 7H), 3.75 (d, J = 10.0 Hz, 1H), 3.68 (dd, J = 4.2, 11.8 Hz, 3H), 3.59 (d, J = 11.7 Hz, 1H), 3.55 (d, J = 11.5 Hz, 1H), 2.16 (s, 3H), 2.10 (dd, J = 3.5, 5.7 Hz, 13H), 2.08 (d, J = 6.5 Hz, 8H), 2.01 (dd, J = 3.3, 7.5 Hz, 17H), 2.00 (d, J = 2.3 Hz, 7H), 1.98 (d, J = 4.9 Hz, 8H), 1.95 (s, 7H). ^{13}C NMR (200 MHz, $CDCl_3$) δ 170.8, 170.7, 170.6, 170.5, 170.42, 170.36, 170.3, 170.03, 169.99, 169.9, 169.8, 169.5, 169.4, 169.1, 169.0, 96.5, 96.2, 91.7, 89.0, 77.5, 77.4, 77.3, 77.1, 73.6, 73.1, 73.0, 70.6, 70.3, 70.0, 69.4, 69.1, 68.6, 68.4, 68.20, 68.17, 68.13, 68.08, 67.6, 67.5, 66.6, 66.5, 66.4, 65.9, 65.7, 61.9, 61.8, 21.2, 21.04, 20.92, 20.91, 20.87, 20.84, 20.82, 20.81, 20.80, 20.79, 20.78, 20.74, 20.72, 20.6. ESI-HRMS (m/z) calcd. for $C_{28}H_{38}O_{19}$ $[M+NH_4]^+$: 696.2351; found: 696.2315.

(6-O-Acetyl-2,3,4-tri-O-trimethylsilyl-β-D-glucopyranosyl)-(1-4)-O-(6-O-acetyl-1,2,3-tri-O-trimethylsilyl)-D-glucopyranoside (13)

Following the general procedure described above, per-*O*-TMS cellobiose (107 mg, 0.12 mmol) was acetylated using Ac₂O/pyridine and glacial acetic acid (50 μL, 0.84 mmol, 7.0 equiv.) followed by one cycle of microwave irradiation (standard mode, 100 W, 125 °C, ~40 psi, 25 min). The reaction mixture was purified using flash column chromatography (EA/Hex = 10:90 – 30:70) to afford compounds **13**, **14a** and **14b** (Table 3, Entry 2).

Compound **13** (17 mg, 17%) was obtained as a colorless oily solid. TLC (EA/Hex = 1/4) R_f 0.6. ¹H NMR (800 MHz, CDCl₃) δ 4.50 (d, *J* = 10.6 Hz, 1H, H-6'a), 4.45 (d, *J* = 7.5 Hz, 1H, H-1), 4.30 (dd, *J* = 11.8, 2.5 Hz, 1H, H-6a), 4.28–4.26 (m, 1H, H-6'b), 4.09–4.06 (m, 2H, H-1', H-6b), 3.47–3.42 (m, 4H, H-3, H-4, H-3', H-4'), 3.33–3.30 (m, 2H, H-5, H-3'), 3.25 (t, *J* = 7.7 Hz, 1H, H-2), 3.22 (dd, *J* = 8.6, 7.6 Hz, 1H, H-2'), 2.06 (s, 3H), 2.05 (s, 3H), 0.154 (s, 9H), 0.152 (s, 9H), 0.14 (s, 9H), 0.13 (s, 9H), 0.12 (s, 9H), 0.11 (s, 9H). ¹³C NMR (200 MHz, CDCl₃): δ 170.8, 170.5, 102.8, 97.9, 77.7, 77.6, 77.5, 75.8, 74.4, 73.9, 73.2, 71.7, 63.6, 62.8, 29.7, 20.9, 20.8, 1.3, 1.06, 1.04, 1.00, 0.9, 0.2. ESI-HRMS (*m/z*) calcd. for C₃₆H₈₆O₁₁Si₈ [M+NH₄]⁺: 936.4668; found 936.4689.

(6-O-Acetyl-2,3,4-tri-O-trimethylsilyl-β-D-glucopyranosyl)-(1-4)-O-(1,6-di-O-acetyl-2,3-di-O-trimethylsilyl)-D-glucopyranoside (14)

Compound **14a** and **14b** (44 mg, 45%) were obtained as a colorless waxy solid (Table 3, Entry 2; see compound **13** for reaction and purification condition). **14a**: TLC (EA/Hex = 1/4) R_f 0.5. ¹H NMR (800 MHz, CDCl₃): δ 6.07 (d, *J* = 3.6 Hz, 1H, H-1), 4.42–4.37 (m, 2H, H-6ab), 4.33 (dd, *J* = 12.0, 2.4 Hz, 1H, H-6'a), 4.10 (d, *J* = 7.7 Hz, 1H, H-1'), 4.06 (dd, *J* = 12.0, 4.0 Hz, 1H, H-6'b), 3.88–3.86 (m, 1H, H-5), 3.72 (t, *J* = 9.2 Hz, 1H, H-3), 3.60 (dd, *J* = 9.1, 3.6 Hz, 1H, H-2), 3.57 (dd, *J* 10.0, 9.3= Hz, 1H, H-4), 3.48 (t, *J* = 9.0 Hz, H-4'), 3.32–3.29 (m, 2H, H-3', H-5'), 3.20 (dd, *J* = 8.8, 7.8 Hz, 1H, H-2'), 2.13 (s, 3H), 2.09 (s, 3H), 2.07 (s, 3H), 0.16 (s, 9H), 0.15 (s, 9H), 0.14 (s, 9H), 0.11 (s, 18H). ¹³C NMR (200 MHz, CDCl₃): δ 170.8, 170.4, 169.4, 102.7, 91.7, 77.4, 74.4, 73.9, 72.4, 72.1, 71.5, 71.1, 63.5, 62.1, 21.0, 20.9, 1.3, 1.0, 0.9, 0.7, 0.04. **14b**: TLC (EA/Hex = 1/4) R_f 0.45. ¹H NMR (800 MHz, CDCl₃): δ 5.41 (d, *J* = 7.9 Hz, 1H, H-1), 4.42–4.36 (m, 2H, H-6ab), 4.43–4.31 (m, 1H, H-6'a), 4.11–4.06 (m, 2H, H-1', H-6'b), 3.61–3.59 (m, 1H, H-5), 3.57–3.51 (m, 2H, H-4, H-4'), 3.49–3.44 (m, 2H, H-2, H-3), 3.32–3.28 (m, 2H, H-3', H-5'), 3.21 (t, *J* = 8.2 Hz, 1H, H-2'), 2.13 (s, 3H), 2.08 (s, 3H), 2.07 (s, 3H), 0.15 (s, 9H), 0.14 (s, 18H), 0.13 (s, 9H), 0.12 (s, 9H). ¹³C NMR (200 MHz, CDCl₃): δ 170.8, 170.4, 169.3, 102.7, 94.0, 77.5, 76.6, 75.9, 74.3, 73.9, 71.5, 63.5, 62.2, 21.3, 20.9, 1.3, 1.1, 0.9, 0.86, 0.81. ESI-HRMS (*m/z*) calcd. for C₃₆H₉₀NO₁₁Si₈ [M+NH₄]⁺: 936.4668; found 936.4687.

6-O-Acetyl-2,3,4,2',3',4',6'-hepta-O-trimethylsilyl-α,α-trehalose (15)

Following the general procedure described above, per-*O*-TMS trehalose (230 mg, 0.25 mmol) was acetylated using Ac₂O/pyridine and glacial acetic acid (57 μL, 1.00 mmol, 4.0 equiv.) followed by two microwave irradiation cycles (standard mode, 100 W, 110 °C, ~40 psi, 15 min). The reaction mixture was purified using flash column chromatography (EA/Hex/NEt₃ = 5:95:5 – EA/Hex = 10:90) to afford compounds **15** and **16** (Table 4, Entry 2). Mono-acetylated analogue **15** (49 mg, 22%) was obtained as a white solid. TLC (EA/Hex

= 10:90) R_f 0.53. $[\alpha]_D^{25} +80$ (c 1.04, CHCl_3). ^1H NMR (800 MHz, CDCl_3) δ 4.95 (d, J = 3.1 Hz, 1H, H-1), 4.89 (d, J = 3.1 Hz, 1H, H-1'), 4.24 (dd, J = 11.9, 2.2 Hz, 1H, H-6a), 4.09 (dd, J = 11.9, 4.5 Hz, 1H, H-6b), 4.01 (ddd, J = 9.5, 4.4, 2.2 Hz, 1H, H-5), 3.91–3.88 (m, 2H, H-3, H-3'), 3.77 (dt, J = 9.4, 3.1 Hz, H5'), 3.66 (d, J = 3.1 Hz, 2H, H-6'ab), 3.48 (t, J = 9.1 Hz, 1H, H-4), 3.46–3.41 (m, 2H, H-4', H-2), 3.39 (dd, J = 9.3, 3.1 Hz, 1H, H-2'), 2.10 (s, 3H), 0.14 (s, 9H), 0.138 (s, 9H), 0.137 (s, 9H), 0.13 (s, 9H), 0.12 (s, 18H), 0.08 (s, 9H). ^{13}C NMR (200 MHz, CDCl_3) δ 171.0, 94.4, 94.1, 73.5, 73.4, 73.3, 72.7, 72.6, 71.9, 71.5, 70.5, 21.0, 1.044, 1.040, 0.9, 0.8, 0.2, 0.1, –0.3. ESI-HRMS (m/z) calcd. for $\text{C}_{35}\text{H}_{80}\text{O}_{12}\text{Si}_7$ $[\text{M}+\text{NH}_4]^+$: 906.4373; found: 906.4385.

6,6'-Di-O-acetyl-2,3,4,2',3',4'-hexa-O-trimethylsilyl- α,α -trehalose (16)

di-acetylated analogue **16** (121 mg, 56%) was obtained as a white solid (Table 4, Entry 2; see compound **15** for reaction and purification condition). TLC (EA/Hex = 1:9) R_f 0.22. $[\alpha]_D^{25} +97$ (c 0.77, CHCl_3). ^1H NMR (800 MHz, CDCl_3) δ 4.93 (d, J = 3.0 Hz, 2H, H-1, H-1'), 4.22 (dd, J = 11.9, 2.2 Hz, 2H, H-6a, H-6'a), 4.08 (dd, J = 11.9, 4.7 Hz, 2H, H-6b, H-6'b), 4.03–3.98 (m, 2H, H-5, H-5'), 3.90 (t, J = 9.0 Hz, 2H, H-3, H-3'), 3.50–3.44 (m, 4H, H-2, H-2', H-4, H-4'), 2.09 (s, 6H), 0.14 (s, 18H), 0.14 (s, 18H), 0.12 (s, 18H). ^{13}C NMR (200 MHz, CDCl_3) δ 170.9, 94.3, 73.4, 72.6, 71.9, 70.6, 63.7, 21.0, 1.0, 0.8, 1.2. ESI-HRMS (m/z) calcd. for $\text{C}_{34}\text{H}_{74}\text{O}_{13}\text{Si}_6$ $[\text{M}+\text{NH}_4]^+$: 876.4083; found: 876.4107.

6,2',3',4',5',6'-Penta-O-Acetyl-2,3,4-tri-O-trimethylsilyl- α,α -trehalose (17)

Following the general procedure described above, per-*O*-TMS trehalose (230 mg, 0.25 mmol) was acetylated using Ac_2O /pyridine and glacial acetic acid (115 μL , 2.00 mmol, 8.0 equiv.) followed by three irradiation cycles (standard mode, 100 W, 110 $^\circ\text{C}$, ~40 psi, 30 min). The reaction mixture was purified using flash column chromatography (EA/Hex/ NEt_3 = 30:70:5 – EA/Hex = 60:40) to afford compounds **17**, **18** and **19** (Table 4, Entry 3). Penta-acetylated analogue **17** (26 mg, 14%) was obtained as a white amorphous foam. TLC (EA/Hex = 7:3) R_f 0.42. $[\alpha]_D^{25} +83$ (c 1.80, CHCl_3). ^1H NMR (800 MHz, CDCl_3) δ 5.54 (t, J = 9.8 Hz, 1H, H-3), 5.23 (d, J = 3.5 Hz, 1H, H-1), 5.14 (t, J = 9.7 Hz, 1H, H-4), 4.99 (dd, J = 10.3, 3.5 Hz, 1H, H-2), 4.92 (d, J = 3.3 Hz, 1H, H-1'), 4.38–4.34 (m, 1H, H-5), 4.29 (dd, J = 12.4, 3.6 Hz, 1H, H-6a), 4.19 (dd, J = 11.7, 2.3 Hz, 1H, H-6'a), 4.10 (dd, J = 11.8, 6.5 Hz, 1H, H-6'b), 4.01 (dd, J = 12.4, 2.2 Hz, 1H, H-6b), 3.87 (t, J = 9.0 Hz, 1H, H-3'), 3.83–3.78 (m, 1H, H-5'), 3.48 (dd, J = 9.4, 3.3 Hz, 1H, H-2'), 3.41 (t, J = 9.1 Hz, 1H, H-4'), 2.09 (s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 2.022 (s, 3H), 2.017 (s, 3H), 0.19 (s, 9H), 0.15 (s, 9H), 0.14 (s, 9H). ^{13}C NMR (200 MHz, CDCl_3) δ 170.8, 170.7, 170.1, 169.8, 169.6, 95.8, 92.1, 73.4, 72.5, 72.1, 71.3, 70.2, 69.9, 68.2, 67.6, 63.4, 61.7, 20.8, 20.7, 20.6, 20.5, 1.1, 0.8, 0.2. ESI-HRMS (m/z) calcd. for $\text{C}_{31}\text{H}_{56}\text{O}_{16}\text{Si}_3$ $[\text{M}+\text{NH}_4]^+$: 786.3214; found: 786.3229.

4,6,2',3',4',5',6'-Hexa-O-Acetyl-2,3,4-di-O-trimethylsilyl- α,α -trehalose (18)

hexa-acetylated analogue **18** (17 mg, 9%) was obtained as a white solid (Table 4, Entry 3; see compound **17** for reaction and purification condition). TLC (EA/Hex = 3:7) R_f 0.20. $[\alpha]_D^{25} +94$ (c 1.27, CHCl_3). ^1H NMR (600 MHz, CDCl_3) δ 5.56 (t, J = 9.8 Hz, 1H, H-3'), 5.25 (d, J = 3.5 Hz, 1H, H-1'), 5.16 (t, J = 9.8 Hz, 1H, H-4'), 5.02 (dd, J = 10.3, 3.6 Hz, 1H, H-2'), 4.98 (d, J = 3.3 Hz, 1H, H-1), 4.89 (t, J = 9.6 Hz, 1H, H-4), 4.37–4.29 (m, 2H, H-5',

H-6'a), 4.21 (dd, $J = 12.7, 6.3$ Hz, 1H, H-6a), 4.06 – 4.00 (m, 2H, H-3, H-6'b), 3.96 – 3.87 (m, 2H, H-5, H-6b), 3.62 (dd, $J = 9.2, 3.4$ Hz, 1H, H-2), 2.10 (s, 3H), 2.10 (s, 3H), 2.07 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 0.15 (s, 9H), 0.14 (s, 9H). ESI-HRMS (m/z) calcd. for $C_{30}H_{50}O_{17}Si_2 [M+NH_4]^+$: 756.2925; found: 756.2938.

2,3,4,6,2',3',4',5',6'-Octa-O-Acetyl- α,α -trehalose (19)

per-*O*-acetylated analogue **19** (74 mg, 44%) was obtained as a white solid (Table 4, Entry 3; see compound **17** for reaction and purification condition). TLC (EA/Hex = 1:1) R_f 0.24. $[\alpha]_D^{25} +132$ (c 1.11, $CHCl_3$). 1H NMR (800 MHz, $CDCl_3$) δ 5.48 (t, $J = 9.8$ Hz, 2H, H-3, H-3'), 5.28 (d, $J = 3.7$ Hz, 2H, H-1, H-1'), 5.05–5.01 (m, 4H, H-2, H-2', H-4, H-4'), 4.24 (dd, $J = 12.2, 5.7$ Hz, 2H, H-6a, H-6'a), 4.04 (dt, $J = 19.8, 10.0$ Hz, 2H, H-5, H-5'), 4.00 (dd, $J = 12.2, 2.0$ Hz, 2H, H-6b, H-6'b), 2.08 (s, 6H), 2.07 (s, 6H), 2.04 (s, 6H), 2.03 (s, 6H). ^{13}C NMR (200 MHz, $CDCl_3$) 170.6, 170.0, 169.6, 169.5, 92.2, 69.9, 69.9, 68.5, 68.1, 61.7, 20.7, 20.6, 20.5. ESI-HRMS (m/z) calcd. for $C_{28}H_{38}O_{19} [M+Na]^+$: 701.1900; found: 701.1898.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This work is supported by NIH R01GM090262, NSF CHE-0196482, NSF CRIF Program (CHE-9808183), and NSF OSTI 97-24412. 600 and 800 MHz NMR instruments in the UC Davis NMR Facility are supported by NSF DBIO 722538 and NIH PR1973. We also want to thank Dr. William Jewell for assisting in the analysis of HRMS samples, Dr. Jerry Dallas for assistance with NMR experiments, and Dr. Ryan Davis for insightful discussion and technical support.

References

- Moremen KW, Tiemeyer M, Nairn AV. Nat Rev Mol Cell Biol. 2012; 13(7):448–62. [PubMed: 22722607]
- Kiessling LL, Splain RA. Annu Rev Biochem. 2010; 79(1):619–653. [PubMed: 20380561]
- Ghazarian H, Idoni B, Oppenheimer SB. Acta Histochem. 2011; 113(3):236–247. [PubMed: 20199800]
- Wender PA, Verma VA, Paxton TJ, Pillow TH. Acc Chem Res. 2008; 41(1):40–9. [PubMed: 18159936]
- Wang CC, Lee JC, Luo SY, Kulkarni SS, Huang YW, Lee CC, Chang KL, Hung SC. Nature. 2007; 446(7138):896–899. [PubMed: 17443183]
- Johnsson R, Ellervik U. Synlett. 2005; 19:2939–2940.
- Khan R, Konowicz PA, Gardossi L, Matulov M, Paoletti S. Tetrahedron Lett. 1994; 35(24):4247–4250.
- Khan R, Konowicz PA, Gardossi L, Matulova M, Degennaro S. Aust J Chem. 1996; 49(3):293–298.
- Mikamo M. Carbohydr Res. 1989; 191(1):150–153.
- Evtushenko EV. Carbohydr Res. 2012; 359(0):111–119. [PubMed: 22925773]
- Faber K, Riva S. Synthesis. 1992; 10:895–910.
- Theil F, Schick H. Synthesis. 1991; 7:533–535.
- Therisod M, Klibanov AM. J Am Chem Soc. 1986; 108(18):5638–5640.
- Therisod M, Klibanov AM. J Am Chem Soc. 1987; 109(13):3977–3981.
- Wang YF, Lalonde JJ, Momongan M, Bergbreiter DE, Wong CH. J Am Chem Soc. 1988; 110(21):7200–7205.

16. Hennen WJ, Sweers HM, Wang YF, Wong CH. *J Org Chem*. 1988; 53(21):4939–4945.
17. Kim MJ, Hennen WJ, Sweers HM, Wong CH. *J Am Chem Soc*. 1988; 110(19):6481–6486.
18. Kennedy JF, Kumar H, Panesar PS, Marwaha SS, Goyal R, Parmar A, Kaur S. *J Chem Technol Biotechnol*. 2006; 81(6):866–876.
19. La Ferla B, Lay L, Russo G, Panza L. *Tetrahedron: Asymmetry*. 2000; 11(18):3647–3651.
20. Woudenberg-van Oosterom M, van Rantwijk F, Sheldon RA. *Biotechnol Bioeng*. 1996; 49(3):328–333. [PubMed: 18623584]
21. Danieli B, Luisetti M, Sampognaro G, Carrea G, Riva S. *J Mol Catal B: Enzym*. 1997; 3(1–4):193–201.
22. Riva S, Chopineau J, Kieboom APG, Klibanov AM. *J Am Chem Soc*. 1988; 110(2):584–589.
23. Hudlicky T, Reed JW. *Chem Soc Rev*. 2009; 38(11):3117–3132. [PubMed: 19847346]
24. Gonzalez-Sabin J, Moran-Ramallal R, Rebolledo F. *Chem Soc Rev*. 2011; 40(11):5321–5335. [PubMed: 21691665]
25. Zhou Y, Ramstrom O, Dong H. *Chem Commun*. 2012; 48(43):5370–5372.
26. Kurahashi T, Mizutani T, Yoshida J. *J Chem Soc, Perkin Trans I*. 1999:465–473.
27. Ishihara K, Kurihara H, Yamamoto H. *J Org Chem*. 1993; 58(15):3791–3793.
28. Kattinig E, Albert M. *Org Lett*. 2004; 6(6):945–948. [PubMed: 15012071]
29. Liang PH, Lu YJ, Tang TH. *Tetrahedron Lett*. 2010; 51(52):6928–6931.
30. McDonnell C, Lopez O, Murphy P, Fernandez Bolanos JG, Hazell R, Bols M. *J Am Chem Soc*. 2004; 126(39):12374–12385. [PubMed: 15453771]
31. Marzo M, Gervasini A, Carniti P. *Carbohydr Res*. 2012; 347(1):23–31. [PubMed: 22127325]
32. Brito-Arias, M. *Synthesis and Characterization of Glycosides*. Springer; US: 2007. *Hydrolysis of Glycosides*; p. 304–313.
33. Witschi MA, Gervay-Hague J. *Org Lett*. 2010; 12(19):4312–4315. [PubMed: 20799705]
34. Bhat A, Gervay-Hague J. *Org Lett*. 2001; 3(13):2081–2084. [PubMed: 11418054]
35. Hu T, Li C, Zhao X, Li G, Yu G, Guan H. *Carbohydr Res*. 2013; 373(0):53–58. [PubMed: 23584235]
36. Xing R, Liu S, Yu H, Guo Z, Wang P, Li C, Li Z, Li P. *Carbohydr Res*. 2005; 340(13):2150–3. [PubMed: 16040021]
37. Palm M, Zacchi G. *Biomacromolecules*. 2003; 4(3):617–23. [PubMed: 12741777]
38. Warrand J, Janssen HG. *Carbohydr Polym*. 2007; 69(2):353–362.
39. Moody W, Richards GN. *Carbohydr Res*. 1982; 111(1):23–29.
40. Lam SN, Gervay-Hague J. *Org Lett*. 2002; 4(12):2039–2042. [PubMed: 12049512]
41. Douglas NL, Ley SV, Lucking U, Warriner SL. *J Chem Soc Perkin Trans I*. 1998; (1):51–65.
42. Chen W, Xia C, Wang J, Thapa P, Li Y, Nadas J, Zhang W, Zhou D, Wang PG. *J Org Chem*. 2007; 72(26):9914–9923. [PubMed: 18020363]
43. Xia C, Yao Q, Schumann J, Rossy E, Chen W, Zhu L, Zhang W, De Liberoc G, Wang PG. *Bioorg Med Chem Lett*. 2006; 16:2195–2199. [PubMed: 16458002]
44. Danishefsky SJ, Allen JR. *Angew Chem, Int Ed*. 2000; 39(5):836–863.
45. Hakomori S. *Acta Anat (Basel)*. 1998; 161(1–4):79–90. [PubMed: 9780352]
46. Galoni DP, Gin DY. *Nature*. 2007; 446(7139):1000–1007. [PubMed: 17460660]
47. Astronomo RD, Burton DR. *Nat Rev Drug Discovery*. 2010; 9(4):308–24.
48. Jimenez Blanco JL, Ortiz Mellet C, Garcia Fernandez JM. *Chem Soc Rev*. 2013; 42(11):4518–4531. [PubMed: 22911174]
49. Zhu J, Wan Q, Ragupathi G, George CM, Livingston PO, Danishefsky SJ. *J Am Chem Soc*. 2009; 131(11):4151–4158. [PubMed: 19253940]
50. Minko, T. *Advances in Delivery Science and Technology*. In: Siepmann, J.; Siegel, RA.; Rathbone, MJ., editors. *Fundamentals and Applications of Controlled Release Drug Delivery*. Springer; New York: 2012. p. 329–355.
51. Bertozzi CR, Fukuda S, Rosen SD. *Biochemistry*. 1995; 34(44):14271–8. [PubMed: 7578028]
52. Bruehl RE, Bertozzi CR, Rosen SD. *J Biol Chem*. 2000; 275(42):32642–8. [PubMed: 10938267]

53. Bernardi A, Jimenez-Barbero J, Casnati A, De Castro C, Darbre T, Fieschi F, Finne J, Funken H, Jaeger KE, Lahmann M, Lindhorst TK, Marradi M, Messner P, Molinaro A, Murphy PV, Nativi C, Oscarson S, Penades S, Peri F, Pieters RJ, Renaudet O, Reymond JL, Richichi B, Rojo J, Sansone F, Schaffer C, Turnbull WB, Velasco-Torrijos T, Vidal S, Vincent S, Wennekes T, Zuilhof H, Imberty A. *Chem Soc Rev.* 2013; 42(11):4709–4727. [PubMed: 23254759]
54. Schombs, MW. Dissertation. University of California; Davis: 2010. I. Stereoselective Synthesis of α -linked Glycolipids. II. Regioselective Protection of per-*O*-TMS protected Disaccharides and their Application to Oligosaccharide Synthesis. III. Design, Synthesis and Evaluation of a Potential HCV-NS3 Protease Inhibitor.
55. Joseph AA, Verma VP, Liu XY, Wu CH, Dhurandhare VM, Wang CC. *Eur J Chem.* 2012; 2012(4):744–753.
56. Shiao TC, Roy R. *New J Chem.* 2012; 36(2):324–339.
57. Buskas T, Thompson P, Boons GJ. *Chem Commun.* 2009; (36):5335–5349.
58. Nicolaou KC, Caulfield T, Kataoka H, Kumazawa T. *J Am Chem Soc.* 1988; 110(23):7910–7912.
59. Schombs M, Park FE, Du W, Kulkarni SS, Gervay-Hague J. *J Org Chem (Featured Article).* 2010; 75(15):4891–4898.
60. Pedersen CM, Nordstrom LU, Bols M. *J Am Chem Soc.* 2007; 129(29):9222–9235. [PubMed: 17602482]
61. Bisht KS, Bhatt S, Muppalla K. *Tetrahedron Lett.* 2006; 47(49):8645–8649.
62. Furstner A, Radkowski K, Grabowski J, Wirtz C, Mynott R. *J Org Chem.* 2000; 65(25):8758–8762. [PubMed: 11112600]
63. Ichikawa Y, Manaka A, Kuzuhara H. *Carbohydr Res.* 1985; 138(1):55–64.
64. Ferrand Y, Crump MP, Davis AP. *Science.* 2007; 318(5850):619–22. [PubMed: 17962557]
65. Fujita Y, Abdel-Aal AB, Wimmer N, Batzloff MR, Good MF, Toth I. *Bioorg Med Chem.* 2008; 16(19):8907–13. [PubMed: 18789866]
66. Yang TC, Chou CC, Li CF. *Int J Food Microbiol.* 2005; 97(3):237–245. [PubMed: 15582734]
67. Patel MK, Davis BG. *Org Biomol Chem.* 2010; 8(19):4232–5. [PubMed: 20668770]
68. Paul MJ, Primavesi LF, Jhurrea D, Zhang Y. *Annu Rev Plant Biol.* 2008; 59:417–41. [PubMed: 18257709]
69. Echigo R, Shimohata N, Karatsu K, Yano F, Kayasuga-Kariya Y, Fujisawa A, Ohto T, Kita Y, Nakamura M, Suzuki S, Mochizuki M, Shimizu T, Chung U-i, Sasaki N. *J Transl Med.* 2012; 10(1):80. [PubMed: 22546323]
70. Chiara JL, Storch de Gracia I, Garcia A, Bastida A, Bobo S, Martin-Ortega MD. *Chembiochem.* 2005; 6(1):186–91. [PubMed: 15532066]
71. Du TJ, Wu QP, Liu HX, Chen X, Shu YN, Xi XD, Zhang QS, Li YZ. *Tetrahedron.* 2011; 67(6): 1096–1101.
72. Crouch RD. *Tetrahedron.* 2013; 69(11):2383–2417.
73. Cui Y, Cheng Z, Mao J, Yu Y. *Tetrahedron Lett.* 2013; 54(29):3831–3833.
74. Hsu Y, Lu XA, Zulueta MML, Tsai CM, Lin KI, Hung SC, Wong CH. *J Am Chem Soc.* 2012; 134(10):4549–4552. [PubMed: 22390569]

Figure 1.
Plausible mechanism of regioselective silyl/acetate exchange

Electron withdrawing acetates decrease basicity of ether and acetal oxygen lone pairs

Figure 2.

Protodesilylation of TMS protecting group by acidic resin

Scheme 1. Selective acetylation of per-*O*-trimethylsilyl galactose

Scheme 2.

Concept of a selectively acetylated bifunctional intermediate

Scheme 3.

Compounds **1** and **2** converge to the same glycosyl iodide (**2I**)

Scheme 4.

Unmasking of acceptor **6** upon acidic hydrolysis of the TMS ether

Scheme 5.
Substrate recycling

Table 1

Selective acetylation of per-*O*-TMS lactose

Entry	AcOH (equiv.)	Temp.	Time	Product Distribution (Yield)
1	3	rt	5 d	1 (19%) 2 (55%) 3 (12%)
2	3	40 °C	2.5 d	1 (6%) 2 (63%)
3	3	60 °C	1.5 d	1 (14%) 2 (60%) 4 (5%)
4	3	80 °C	1 d	4 (23%) 5 (42%)
5	3	μwave, 125 °C	1.25 h	1 (20%) 2 (53%)
6	5	μwave, 125 °C	7 h	4 (21%) 5 (67%)
7	7	μwave, 125 °C	3.75 h	4 (18%) 5 (61%)

Table 2

Selective acetylation of per-*O*-TMS melibiose

Entry	AcOH (equiv.)	Temp.	Time	Product Distribution (Yield)
1	2	μ wave, 125 °C	2.5 h	7 (39%) 8 (20%)
2	7	μ wave, 125 °C	2.5 h	9 (7%) 10 (26%) 11 (22%) 12 (44%)

Selective acetylation of per-*O*-TMS cellobiose

Table 3

per-*O*-TMS cellobiose

Ac₂O, pyridine, AcOH, temp., time

13: R¹ = Ac, R² = R³ = TMS
14: R¹ = R² = Ac, R³ = TMS

Entry	AcOH (equiv.)	Temp.	Time	Product Distribution (Yield)
1	3	μwave, 110 °C	150 min	13 (20%) 14 (36%)
2	7	μwave, 110 °C	25 min	13 (17%) 14 (45%)

Selective acetylation of per-*O*-TMS trehalose

Table 4

Entry	AcOH (equiv.)	Temp.	Time	Product Distribution (Yield)	
1	2	μwave, 110 °C	1.5 h	15 (18%)	16 (49%)
2	4	μwave, 110 °C	0.5 h	15 (22%)	16 (56%)
3	8	μwave, 110 °C	1.5 h	17 (14%)	18 (9%) 19 (44%)