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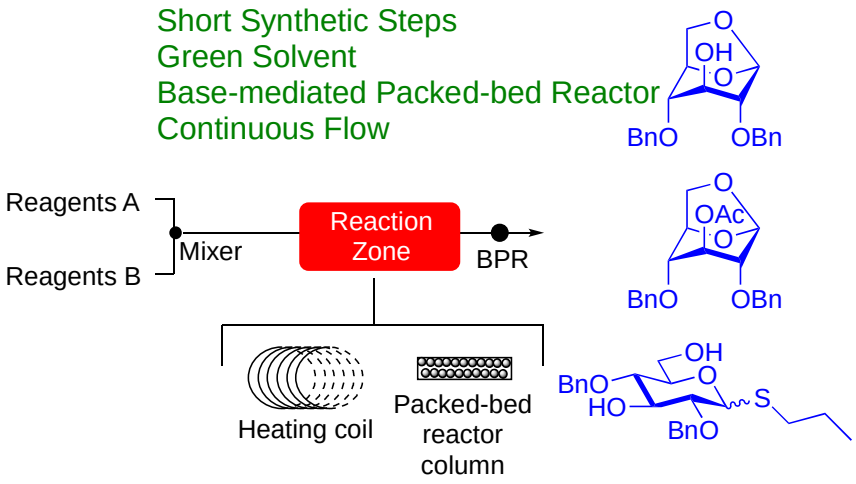

Synthesis of Protected Glucose Derivatives from Levoglucosan by Development of Common Carbohydrate Protecting Group Reactions Under Continuous Flow Conditions

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ABSTRACT: Common carbohydrate protecting group reactions under continuous flow processes are reported in the context of producing partially-protected glucose building blocks from levoglucosan. Benzyl ether protection was demonstrated without the use of NaH using barium oxide, which, however, pointed to the need for forms of this catalyst not as susceptible to close packing under flow. Acylation conditions were developed under continuous flow in acetonitrile and avoiding pyridine. Ring-opening the derivatized levoglucosan with propanethiol was also demonstrated producing *S*-alkyl 2,4-di-*O*-benzyl-glucopyranoside building block in 2 rather than 12 steps in increased overall yield.

KEYWORDS: *Continuous flow process, Glucose building blocks, Levoglucosan, Green solvent*

1. Introduction

Carbohydrates play an important role in biological systems and the ability to synthesize complex oligosaccharides in gram quantities amenable for in vivo studies has been challenging[1]. Given the narrow range of stable glycosyltransferases, chemical synthesis has been one of the predominant ways to synthesize complex oligosaccharides.[2] Although methods have been developed to automate the coupling of monosaccharide and nucleoside building blocks in various fashions including continuous flow,[3-10] new efficient technologies and techniques for the gram to kilogram scale production of these selectively protected monosaccharide building blocks has become a major obstacle to the widespread use of automated oligosaccharide synthesis.

Monosaccharides have been traditionally protected in multistep batch processes. However, more recently, continuous flow processes have found their way into various academic and pharmaceutical labs to synthesize complex natural products.[11-18] Continuous flow processes are highly adaptable; many reaction zones (for example UV irradiation, supercritical fluids, and solid reactor beds) can be used to synthesize compounds under diverse conditions.[19-25] Successful reactions on the milligram scale can also easily be scaled to the gram or kilogram scale by keeping the parameters of the reaction the same but increasing the flow time until the desired quantity is met [26, 27] or performing multiple reactions in parallel. This smart dimensioning and scaling-out is a significant advantage over batch scale processes, but is still relatively unexplored for fine chemical synthesis such as the production of carbohydrate derivatives. Herein we report the development of the first continuous flow process for the production of partially-protected glucose building blocks from levoglucosan—with process evaluations based on green chemistry considerations—and demonstrate the ability to produce a carbohydrate building block in 2 rather than 12 steps in increased overall yield.

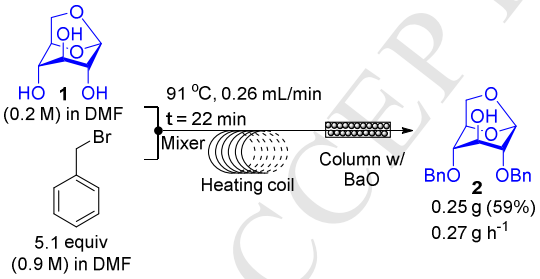
Levoglucosan is a derivative of glucose in which the 6-OH of the sugar closes onto its anomeric center to form a second ring structure. Increased efforts to produce levoglucosan from biomass have led to significant cost decreases,[28-30] thereby making this molecule a more desirable chiral pool material.

Past efforts have shown that levoglucosan can be used to produce functionalized glucose analogs in batch production.[31-33] However, these batch production methods do not readily lend themselves to a continuous synthesis process and have not been carried out with the use of green solvents in mind. With green chemistry becoming increasingly common on the industry scale,[15, 16, 34, 35] processes to modify carbohydrate precursors with protecting groups commonly used in carbohydrate synthesis could be designed without resorting to halogenated solvents, very long reaction times, and significant waste production.

2. Results and discussion

One of the widely used protecting groups in carbohydrate chemistry is the benzyl ether protecting group.[36] The benzyl ether serves as a so-called "permanent" protecting group due to its ability to withstand a wide range of chemical conditions used in protecting group manipulations and oligosaccharide construction.[36] The ability to benzylate regioselectively in the early stages of a monosaccharide building block synthesis is important because it can drastically reduce the number of synthetic steps.[37, 38] However, common benzylation methods are not readily amenable to flow chemistry as they require a variety of heterogeneous reagents such as sodium hydride in DMF and can result in pressure buildup from the release of hydrogen gas resulting in runaway reactions.[39-41] A benzylation reagent that is safe on large scale and amenable to a continuous flow process is needed. A batch process to regioselectively benzylate the 2- and 4-positions of levoglucosan has been reported using the uncommon base barium oxide.[42] Unfortunately, barium oxide has very poor solubility in standard organic solvents used for alkylation reactions. Due to this solubility problem, a column packed with solid barium oxide was tested for its ability to sustain a benzylation reaction when benzyl bromide and the levoglucosan were flowed across the bed (Scheme 1). To that end, a syringe pump containing two 8-mL stainless steel syringes connected to perfluoroalkoxy (PFA) tubing (I.D. 0.04 in, 1/16 in) using flangeless fittings (1/16 in) containing a ferrule (1/16 in) was constructed. The PFA tubing was joined together via a Y connector (0.02 in I.D.) and connected to a PFA tubing reactor coil (12.5 ft, 3 mL, I.D. 0.04) which was placed in a hot bath connected to a stainless steel column (25 cm x 4.6 mm I.D.). The preparation of **2** was achieved by using 0.2 M of levoglucosan **1** and 0.9 M of BnBr which were brought together at a flowrate of 0.26 mL/min at 91°C into the barium oxide packed-bed reactor for 22 min.

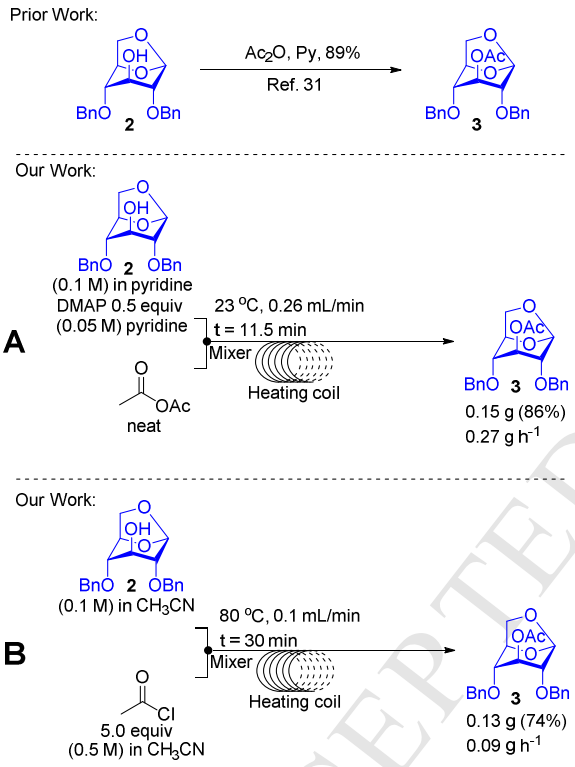
Scheme 1. Continuous Synthesis of 1,6-Anhydro-2,4-di-O-benzyl-β-D-glucopyranose (2) Using a Barium Oxide Packed-bed Reactor.



This process did produce the desired product after flash chromatography in a 59% isolated yield. However, this process also made clear current limitations in available reagents for column packing. The moderate yield could be due to material retained in the column, which has been an issue previously reported[43] with packed-bed approaches. Pressure build up during the continuous flow process was also problematic despite various attempts to pack columns with this reagent (see Supporting Information). The morphology of the BaO powder does not have a known porous matrix to allow liquids to easily flow through. Consistent reaction performance and thereby wide-scale adoption of this method will require the production of BaO catalysts with a consistent size, shape, and porosity.

With flow conditions established for the production of 2,4-di-*O*-benzylated levoglucosan **2**, we turned our attention to functionalizing the 3-OH of the resulting compound by incorporating a temporary acyl protecting group (Scheme 2). Acetyl groups are often used in carbohydrate synthesis as temporary protecting groups that allow further modification at the site by simple removal of the acyl group under basic conditions. Unlike benzylation reactions, acylation reactions have been performed as continuous processes before.[16, 44, 45] To this end, common methods to acylate sugars in batch were explored in flow. Fortunately, the preparation of known[31] compound **3** proved to be straightforward using 0.1 M of 2,4-di-*O*-benzyl levoglucosan with 0.05 M 4-(dimethylamino)pyridine (DMAP) in pyridine and neat acetic anhydride which was flowed together at a flow rate of 0.26 mL/min for 11.5 min at 23 °C. The reaction mixture at steady state was worked up with ethyl acetate and water; the resulting organic layer was then purified to provide 86% of product **3** (Scheme 2A).

Scheme 2. Standard Batch Acylation Conditions Converted to a Continuous Flow Process (A) and (B).



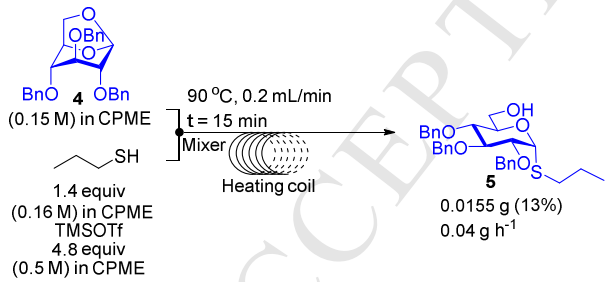
Although this set of conditions did produce the desired compound, ideally pyridine and DMAP could be replaced with more environmentally-benign reagents and acetic anhydride could be replaced with a more atom economical alternative. To this end, acetyl chloride was tested as the acyl source along with acetonitrile as solvent, which is favored under green standards as compared to pyridine[35] (Scheme 2B). When this acylation was carried out at 80 °C and 0.5 mL/min for 6 min, full conversion of starting material was not observed at steady state; therefore, higher temperatures were explored. Fortunately, product **3** was produced in 58% yield utilizing a flow rate of 0.5 mL/min for 6 min at 100 °C with a 250 psi backpressure regulator (BPR) (see Supporting Information). Acylation of compound **2** could also be performed at higher concentration without a 250 psi BPR (see Supporting Information). The low isolated yield could be the result of side products from competing reactions formed at the higher temperature (100 °C). As a result of low yields at higher temperatures, the acylation of compound **2** was explored with a longer residence time and lower temperature. The acylation was conducted with a

flowrate of 0.1 mL/min for 30 min at 80 °C producing 74% of the desired product **3** (Scheme 2). When the original and the modified acylation reactions are compared side by side, condition B avoids the use of DMAP and pyridine, reagent and solvent that is not environmentally benign. As a result, condition B holds promise for use in the larger-scale flow-based production of acetylated carbohydrates when a green process perspective is in mind.

To produce glucose derivatives destined for oligosaccharide synthesis, we turned our attention next to the formation of a thiol-linked glycoside. Thioglycosides are important anomeric constituents that can be activated for glycosylation.[46, 47] Their range of stabilities under basic and acidic conditions,[48] ability to be activated with various promoters such as *N*-iodosuccinimide (NIS), hypervalent iodine and pentavalent bismuth (V),[49-53] their orthogonal activation over common glycosyl donors,[54] and their ability to be preactivated and coupled selectively in the presence of other thioglycosides[55] makes them ideal for building block production and oligosaccharide synthesis. The stereoselective ring opening of functionalized levoglucosan with bis(trimethylsilyl) sulfide, trimethylsilyl azide, and aryl(halo)-alanes under batch conditions has been reported,[31-33] although the production of thiol substrates requires 4 to 6 hours in CH_2Cl_2.[31] With the use of trimethylsilyl azide, alpha glycosyl azides can be produced in roughly 24 minutes for click chemistry applications, but this method is not ideal for carbohydrate building block production. The synthesis of beta *C*-arylglucosides using aryl(halo)-alanes requires anywhere from 2 to 24 hours. Ideally, a flow process could be developed that avoids such long reaction times and incorporates alkyl thiols.

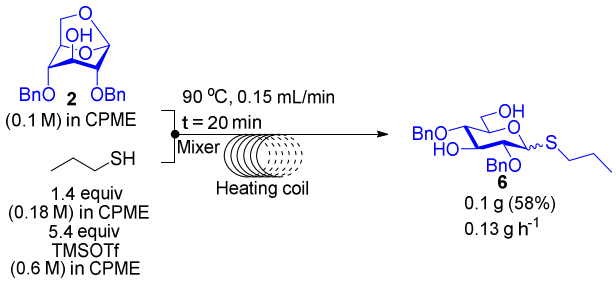
Acids can promote the nucleophilic ring-opening of the levoglucosan ring. Therefore, a first attempt at the stereoselective ring-opening of known compound **4**[31] employed a DOWEX H^+ packed-bed reactor column produced in lab; this approach resulted in irreproducible performance under multiple attempts (Supporting Information). As a result, the Lewis acids TMSOTf and BF_3•OEt_2 were explored next (Scheme 3). Under these conditions trace amounts of product were obtained with a residence time of 9 minutes and 15 minutes with a flow rate of 0.2 mL/min at 90 °C. Multiple attempts were performed utilizing the greener solvents acetonitrile and cyclopentyl methyl ether (CPME) solvent. Acylation was performed to confirm the regioisomer of the alcohol produced by ^{1}H NMR analysis of the neighboring proton shift (Supporting Information). The poor reaction performance could be due to the sterically-hindered environment created by the benzyl group at C-3.

Scheme 3. Ring Opening of 1,6-Anhydro-2,3,4-tri-*O*-benzyl-β-D-glucopyranose (4).



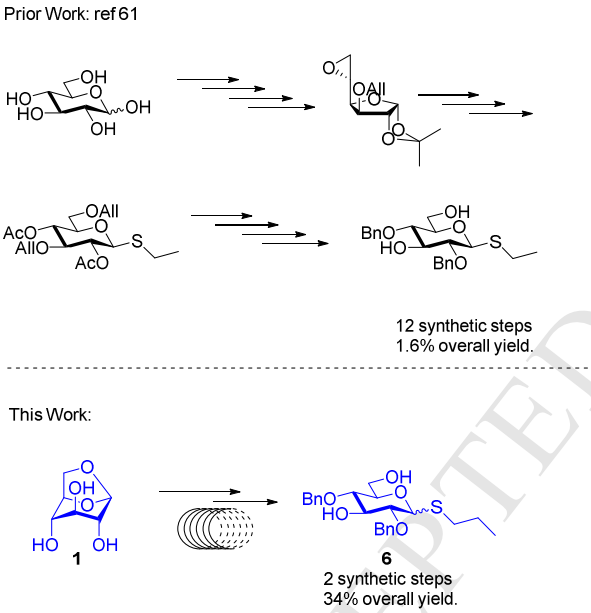
Given the slow reaction of **4**, compound **2**—which lacks the C-3 benzyl protection—was probed. Our attention was turned to substrate **2** and with a flow rate of 0.15 mL/min and a residence time of 20 minutes at 90 °C; compound **6** was produced with full conversion of starting material with an alpha/beta ratio of 1.7:1 for the product (Scheme 4). Removal of the benzyl group clearly has a dramatic effect on the reaction outcome. Cyclopentyl methyl ether (CPME) showed good solubility of reactants and its high boiling point (106 °C) makes it ideal for this high temperature reaction. The importance of using solvents such as CPME that reduce the negative impact on the environment is increasing in both industrial and academic settings;[56-58] therefore, the development of chemical synthesis/processes that are green in nature are key for a sustainable chemical industry.[59, 60]

Scheme 4. Ring Opening of 1,6-Anhydro-2,4-di-O-benzyl-β-D-glucopyranose (2).



The new continuous flow processes developed for the di-*O*-benzylation and alkythiol installation represents a significant improvement to the previously reported[61] batch synthesis of ethyl 2,4-di-*O*-benzyl-1-thio-β-D-glucopyranoside, an advanced monosaccharide intermediate used in the total synthesis of Kaempferol 3-O-(3'',6''-di-O-*E*-*p*-coumaroyl)-*β*-D-glucopyranoside. That synthesis required 12 synthetic steps for an overall yield of 1.6% (Scheme 5).[61] With the use of levoglucosan and the described continuous flow processes, functionally equivalent compound **6** could be produced in 2 synthetic steps with an overall yield of 34% (Scheme 5) even without further optimization.

Scheme 5. Comparison of Synthetic Routes to the *n*-Alkyl-2,4-di-*O*-benzyl-1-thio-*β*-D-glucopyranoside Building Block.



3. Conclusions

Several continuous flow processes that define key steps in the protection of carbohydrate building blocks—namely *O*-benzylation and *O*-acetylation—have been investigated. Through these experiments, we have demonstrated the first continuous flow process for *O*-benzylation by the use of BaO in a packed-bed reactor column and highlighted the problems with using this reagent in its current availability under flow conditions. The chemistries have also been adapted to eliminate the use of very common toxic reagents and solvents traditionally used in carbohydrate acylation processes. Incorporation of *n*-propanethiol with the use of the green solvent CPME at high temperature results in the production of an advanced carbohydrate building block in a much shorter synthetic sequence than previously published and avoids the use of hazardous CH_2Cl_2. This work sets the foundation for future work in developing catalysts and reagents for continuous flow processes for the efficient production of the many different carbohydrate building blocks needed to feed automated oligosaccharide synthesizers. The very recent report of a high-throughput experimentation (HTE) and high-throughput analytics[62]

platform to accelerate reaction optimization in flow should further aid efforts to screen reaction conditions to optimize carbohydrate building block production.

4. Experimental

4.1. General Experimental Information

All solvents used for air- and moisture-sensitive reactions were high purity reagent grade. Solvent was collected from a solvent tower followed by the addition of oven-dried room temperature (~23 °C) 4 Å molecular sieves and placed under argon gas via a syringe, balloon and septum contained in an Erlenmeyer flask or glass bottle and stored for 12 hours before use. Compounds were dissolved in anhydrous solvent prior to loading into stainless steel 8-mL VWR syringes. Thin layer chromatography (TLC) was performed using Sorbent Technologies silica gel TLC plates, glass-backed and pre-coated with a thickness of 0.25 mm. After TLC development, TLC plates were visualized using UV light followed by *p*-anisaldehyde solution containing absolute ethanol and sulfuric acid (1:18:1, *p*-anisaldehyde:ethanol:sulfuric acid). Flash silica gel chromatography was carried out using the Teledyne ISCO CombiFlash® purification system (Combi flash R_f 200 and 200i) with preloaded silica columns and operated under the conditions stated for the column used.

Proton nuclear magnetic resonance (^{1}H NMR) and carbon nuclear magnetic resonance (^{13}C NMR) were performed on either 1) a Varian 500 MHz NMR containing a dual pulsed field gradient (PFG) probe with proton (^{1}H) signal to noise ratio 390 to 1, carbon (^{13}C) signal to noise ratio 290 to 1, and temperature range from -80 to 120 °C or 2) a Varian 400 MHz NMR containing a pulsed field gradient (PFG) probe with proton (^{1}H) signal to noise ratio 175 to 1, carbon (^{13}C) signal to noise ratio 160 to 1, and temperature range from -80 to 130 °C. Proton, carbon, and 2D analyses (dqCOSY, HMBC, HSQC) were performed and recorded in parts per million (ppm) and the residual signal of chloroform ($CDCl_3$) (δ 7.26 ppm ^{1}H NMR; δ 77.0 ppm ^{13}C NMR) was used as reference. ESI-MS Agilent 1200 HPLC-6130 MSD was used for mass analysis of synthesized compounds.

BaO Packed-bed Reactor Column Construction

The stainless steel column (25 cm x 4.6 mm I.D.) was end-capped and position end up. BaO was added to the column and packed by tapping on the bench as well as inserting a boiling stick to remove any BaO that might stick on the side of the column. The column was capped and further packed by flowing the solvent used for the reaction through the column to remove any air bubbles. The column was then capped closed at both ends and weighed. The difference between the dry and wet column divided by the density of the solvent was used to determine the void volume.

BaO/Al_2CO_3, DOWEX and Amberlite Packed-bed Reactor Column Construction

The same packing procedure as above was used but with Amberlite, Dowex or BaO and Al_2CO_3 in a 3:2 ratio. BaO and Al_2CO_3 were premixed by placing the two in a vial and agitating until both powders were observed to be well mixed.

4.2. Design and Construction of Flow Apparatus

See supporting information for figures.

<u>Continuous flow equipment:</u>

Perfluoroalkoxy (PFA) tubing (I.D. 0.04 in, 1/16 in)

Flangeless fittings (1/16 in)

Ferrule (1/16 in)

Y connector (0.02 in I.D.)

250 psi back pressure regulator

PFA tubing reactor coil (0.04 I.D., 381 cm (12.5 ft), 3 mL)
PFA tubing reactor coil (0.03 I.D., 670.56 cm (22 ft), 3 mL)
PFA tubing reactor coil (0.02 I.D., 1524 cm (50 ft), 3 mL)
Stainless steel column (25 cm x 4.6 mm I.D.)
Stainless steel column (50 mm x 4.6 mm I.D.)
Genie Touch Dual Syringe Pump
Hitachi (Model L-7100) HPLC Pump

4.3. Synthetic Procedures

4.4. 1,6-Anhydro-2,4-di-*O*-benzyl-*β*-D-glucopyranose **(2)**

Levoglucosan **1** (200 mg, 1.2 mmol) was dissolved in anhydrous *N*,*N*-dimethylformamide (7 mL) and loaded into an 8-mL stainless steel syringe. Benzyl bromide (0.75 mL, 6.3 mmol) was dissolved in *N*,*N*-dimethylformamide (6.25 mL) and loaded into a separate 8-mL stainless steel syringe. A reactor coil high purity PFA tubing (0.04 I.D., 381 cm (12.5 ft), 3 mL) was placed in a hot bath at 91 °C to warm the reaction solution. The levoglucosan and benzyl bromide solutions were flowed together at a flowrate of 0.26 mL/min through the PFA tubing into the packed barium oxide column (3.0 g, 2.7 mL void volume, 25 cm x 4.6 mm I.D.) with a residence time of 22 min. The reaction solution was collected at steady state in a flask containing methanol (0.5 mL) to quench the reaction. The reaction mixture was diluted with dichloromethane (10 mL) and washed with water (10 mL), brine (10 mL), and lithium chloride solution (10 mL). The organic layer was collected, dried over anhydrous sodium sulfate and concentrated under vacuum via rotary evaporation. The residue was subjected to column purification via Teledyne ISCO CombiFlash® Rf 200i in hexane/ethyl acetate in a stepwise gradient with elution of compound in 15% ethyl acetate to provide **2** as a white solid (0.25 g, 0.73 mmol, 59%). See **Figure S4 in supporting information.** R_f 0.46 (1:1 hexane: ethyl acetate); **^{1}H NMR** (500 MHz, chloroform-*d*) δ = 7.44 - 7.29 (m, 10 H, Ph), 5.47 (s, 1 H, H-1), 4.77 - 4.67 (m, 5 H, $\underline{CH_2}$ Ph), 4.59 (d, *J* = 4.9 Hz, 1 H, H-5), 3.89 (t, *J* = 4.1 Hz, 1 H, H-3), 3.83 (d, *J* = 7.3 Hz, 1 H, H-6), 3.68 (dd, *J* = 5.4, 7.3 Hz, 1 H, H-6), 3.36 (d, *J* = 3.4 Hz, 1 H, H-2), 3.28 (d, *J* = 3.9 Hz, 1 H, H-4), 2.20 (bs, 1 H, OH).

^{1}H NMR matches a previously reported spectrum: Iversen, T; Bundle, D. R. *Can. J. Chem.* **1982**, *60*, 299.

Void volume = 2.7 mL BaO column

4.5. 1,6-Anhydro-2,4-di-O-benzyl-3-*O*-acyl-*β*-D-glucopyranose **(3)**

With acetic anhydride

Compound **2** (155.8 mg, 0.45 mmol) and 4-(dimethylamino)pyridine (27.8 mg, 0.23 mmol) were dissolved in anhydrous pyridine (4.25 mL) and uploaded into an 8-mL stainless steel syringe. Acetic anhydride (4.25 mL) was uploaded into an 8-mL stainless steel syringe and the solutions were flowed together via syringe pump at a flowrate of 0.26 mL/min through high purity PFA tubing [0.02 I.D., 1524 cm (50 ft), 3 mL] with a residence time of 11.5 min at 23 °C. The reaction solution was collected in test tubes containing ethyl acetate and water (0.2 mL each) to quench the reaction and TLC monitoring was performed on small aliquots of the reaction. Reaction at steady state was collected with ethyl acetate (2 mL, 1.8 g) and water (2 mL, 2 g) total quenching solution. The reaction solution was diluted with ethyl acetate (12 mL, 10.8 g) and extraction was performed on the reaction mixture with water (10 mL, 10 g). The organic solution was collected and dried over anhydrous sodium sulfate (10 g). The organic solution was decanted and ethyl acetate (18 mL, 16.2 g) was used to rinse the sodium sulfate. The

organic solution was concentrated via rotary evaporation with 2.9 g of silica and the residue was subjected to column purification via Teledyne ISCO CombiFlash® Rf 200i using 12 g ISCO column in hexane ethyl acetate in a stepwise gradient with elution of compound in 15% ethyl acetate. A total of 1042.5 mL (687 g) of hexane was used for purification along with 157.5 mL (142 g) ethyl acetate to give a total volume of 1200 mL for purification and 89.9 mL (81.2 g) of ethyl acetate used to rinse test tubes to provide **3** as an oil (0.15 g, 0.39 mmol, 86%). See **Figure S5 in supporting information** for details of the setup. $\boldsymbol{R_f}$ 0.6 (1:1 hexane: ethyl acetate).

With acetyl chloride and back pressure regulator

Compound **2** (250.1 mg, 0.73 mmol) was dissolved in anhydrous acetonitrile (7 mL). Acetyl chloride (0.25 mL, 3.7 mmol) was diluted with acetonitrile (7 mL) and the two solutions were streamed together via HPLC pump at a flowrate of 0.5 mL/min through high purity PFA tubing [0.03 I.D., 670.56 cm (22 ft), 3 mL] with a residence time of 6 min at 100 °C with an inline 250 psi back pressure regulator. Additional acetonitrile was passed through the flow system to collect the remaining reaction solution (8 mL, 6.3 g). The reaction solution was collected in test tubes containing ethyl acetate (0.2 mL) and water (0.2 mL) to quench the reaction and TLC performed. Reaction at steady state was collected with ethyl acetate (2 mL, 1.8 g) and water (2 mL, 2 g) total quenching solution. The reaction solution was diluted with ethyl acetate (15 mL, 11.8 g) extraction was performed on the reaction mixture with water (10 mL, 10 g), and brine (10 mL, 11.8 g). The organic solution was collected, dried with anhydrous sodium sulfate (10 g) and concentrated via rotary evaporation with 3 g silica. The residue was subjected to column purification via Teledyne ISCO CombiFlash® Rf 200i using 12 g Isco column in hexane ethyl acetate in a stepwise gradient with elution of compound in 15% ethyl acetate. A total of 1202.2 mL (792.24 g) of hexane was used for purification along with 213.8 mL (192.8 g) ethyl acetate to give a total volume of 1416 mL for purification and 55.4 mL (49.9 g) of ethyl acetate used to rinse test tubes to provide **3** as an oil (0.162 g, 0.42 mmol, 58%). See **Figure S3 in supporting information** for details of the setup. $\boldsymbol{R_f}$ 0.6 (1:1 hexane: ethyl acetate).

With acetyl chloride without back pressure regulator

Compound **2** (395 mg, 1.2 mmol) was dissolved in anhydrous acetonitrile (2.7 mL). Acetyl chloride (0.4 mL, 5.8 mmol) diluted with acetonitrile (2.7 mL) and each of the two solutions were streamed together via HPLC pump at a flowrate of 0.7 mL/min through high purity PFA tubing [0.02 I.D., 1524 cm (50 ft), 3 mL] with a residence time of 4 min at 100 °C. Additional acetonitrile was passed through the flow system to collect the remaining reaction solution (8 mL). The reaction solution was collected in test tubes containing ethyl acetate (0.5 mL) and water (0.5 mL) to quench the reaction and TLC performed. Samples at steady state were collected. The reaction solution was diluted with ethyl acetate (15 mL) extraction was performed on the reaction mixture with water (10 mL), and brine (10 mL). The organic solution for both steady state and non-steady state were collected, dried with anhydrous sodium sulfate (10 g) and concentrated via rotary evaporation. The steady state and non-steady state were evaluated by HPLC and a standard curve was produce to determine yield of product, how much starting material reacted at steady state and how much starting material was in non-steady state. At steady state, the flow system provided **3** as an oil (0.248 g, 0.65 mmol, 56%). See **Figure S2 in supporting information** for details of the setup. $\boldsymbol{R_f}$ 0.6 (1:1 hexane: ethyl acetate)

With increased residence time and lower temperature

Compound **2** (155.8 mg, 0.45 mmol) was dissolved in anhydrous acetonitrile (4.25 mL) and uploaded into an 8 mL stainless steel syringe. Acetyl chloride (0.16 mL, 2.3 mmol) diluted with acetonitrile (4.09 mL) and placed in a separate 8 mL stainless steel syringe and the two solutions were streamed together via syringe pump at a flowrate of 0.1 mL/min through high purity PFA tubing [0.02 I.D., 1524 cm (50 ft), 3 mL] with a residence time of 30 min at 80 °C. The reaction solution was collected in test tubes containing ethyl acetate (0.2 mL) and water (0.2 mL) to quench the reaction and TLC performed. Samples at steady state were collected with ethyl acetate (2 mL, 1.8 g) and water (2 mL, 2 g) total quenching solution. The reaction solution was diluted with ethyl acetate (12 mL, 11 g) extraction was

performed on the reaction mixture with water (10 mL, 10 g). The organic solution was dried with anhydrous sodium sulfate (6.6 g). The organic solution was decanted and ethyl acetate (18 mL, 16.2 g) was used to rinse the sodium sulfate. The organic solution was concentrated via rotary evaporation with 3.0 g of silica and the residue was subjected to column purification via Teledyne ISCO CombiFlash® Rf 200i using 12 g ISCO column in hexane ethyl acetate in a stepwise gradient with elution of compound in 15% ethyl acetate. A total of 1042.5 mL (687 g) of hexane was used for purification along with 157.5 mL (142 g) ethyl acetate to give a total volume of 1200 mL for purification and 89.9 mL (81.2 g) of ethyl acetate used to rinse test tubes to provided **3** as an oil (0.13 g, 0.33 mmol, 74%). See **Figure S5 in supporting information** for details of the setup.

R_f 0.6 (1:1 hexane: ethyl acetate); **^{1}H NMR** (500 MHz, chloroform-*d*) δ = 7.43 - 7.29 (m, 10 H, Ph), 5.43 (s, 1 H, H-3), 5.08 (t, *J* = 1.5 Hz, 1 H, H-1), 4.82 (d, *J* = 12.7 Hz, 2 H, $\underline{CH_2}$Ph), 4.70 (dd, *J* = 12.7, 15.1 Hz, 2 H, $\underline{CH_2}$Ph), 4.62 (d, *J* = 4.9 Hz, 1 H, H-5), 3.90 (d, *J* = 7.3 Hz, 1 H, H-6), 3.77 - 3.70 (m, 1 H, H-6), 3.27 (d, *J* = 12.9 Hz, 2 H, H-2,H-4), 2.08 (s, 3 H, CH_3); **^{13}C NMR** (126 MHz, chloroform-*d*) δ = 169.7, 137.8, 137.7, 128.5, 128.4, 128.0, 127.9, 127.8, 127.8, 100.4, 74.8, 74.3, 74.1, 71.7, 71.1, 68.7, 65.0, 21.2; **HRMS (ESI)**: $[M + Na]^+$ *m/z* calc. for $C_{22}H_{24}O_6Na^+$ 407.1465; found 407.1469.

4.6. *n*-Propyl-2,3,4-tri-*O*-benzyl-1-thio-*α*-D-glucopyranoside **(5)**

Compound **4** (100 mg, 0.29 mmol) was dissolved in cyclopentyl methyl ether (2 mL). 1-Propanethiol (0.03 mL, 0.32 mmol) and trimethylsilyl trifluoromethanesulfonate (0.2 mL, 1.1 mmol) was diluted with cyclopentyl methyl ether (2 mL) and each of the two solutions were streamed together via HPLC pump at a flowrate of 0.2 mL/min through high purity PFA tubing [0.02 I.D., 1524 cm (50 ft), 3 mL] with a residence time of 15 min at 90 °C. Additional cyclopentyl methyl ether was passed through the flow system to collect the remaining reaction solution (8 mL). The reaction solution was collected in test tubes containing triethylamine (0.2 mL) to quench the reaction. Samples at steady state were collected and the reaction solution was concentrated under reduced pressure via rotary evaporation. The residue was subjected to column purification via Teledyne ISCO CombiFlash® Rf 200i in hexane/ethyl acetate in a linear gradient with elution of compound in 10% ethyl acetate to provide **5** as an oil (0.0155 g, 0.03 mmol, 13%). See **Figure S2** for details of the setup. R_f 0.6 (1:1 hexane: ethyl acetate); **^{1}H NMR** (500 MHz, chloroform-*d*) δ = 7.43 - 7.29 (m, 15 H, Ph), 5.33 (d, *J* = 5.4 Hz, 1 H, H-1), 4.99 (d, *J* = 10.7 Hz, 1 H, $\underline{CH_2}$Ph), 4.91 (d, *J* = 11.2 Hz, 1 H, $\underline{CH_2}$Ph), 4.83 - 4.73 (m, 2 H, $\underline{CH_2}$Ph), 4.71 - 4.65 (m, 2 H, $\underline{CH_2}$Ph), 4.10 (td, *J* = 3.1, 10.0 Hz, 1 H, H-5), 3.94 - 3.88 (t, *J* = 9.3 Hz, 1 H, H-3), 3.82 - 3.75 (m, 3 H, H-2, H-6), 3.55 (t, *J* = 9.3 Hz, 1 H, H-4), 2.59 - 2.43 (m, 2 H, $S\underline{CH_2}CH_2CH_3$), 1.65 (ddd, *J* = 4.1, 7.3, 14.4 Hz, 2 H, $SCH_2\underline{CH_2}CH_3$), 1.03 (t, *J* = 7.3 Hz, 3 H, $SCH_2CH_2\underline{CH_3}$); **^{13}C NMR** (126 MHz, chloroform-*d*) δ = 138.7, 138.2, 137.6, 128.5, 128.4, 128.4, 128.1, 128.1, 128.0, 127.9, 127.9, 127.6, 83.5, 82.4, 79.7, 75.7, 75.0, 72.4, 71.1, 62.0, 31.9, 22.8, 13.5; **HRMS (ESI)**: $[M + Na]^+$ *m/z* calc. for $C_{30}H_{36}O_5SNa^+$ 531.2176 ; found 531.2176

4.7. *n*-Propyl-2,3,4-tri-*O*-benzyl-6-acyl-1-thio-*α*-D-glucopyranoside

*Note: Compound **5** was acylated to confirm the position of its free hydroxyl via NMR.*

Compound **5** (48 mg, 0.09 mmol) was dissolved in acetic anhydride (0.4 mL, 4.6 mmol) and supplemented with 1,4-diazabicyclo[2.2.2]octane (DABCO) (10.5 mg, 0.09 mmol) in a round-bottomed flask. The reaction solution was stirred for 2 h at 23 °C. Upon completion, the reaction was quenched with water and diluted with dichloromethane. The organic layer was extracted with brine, dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The residue was subjected to column purification via Teledyne ISCO CombiFlash® Rf 200i in hexane/ethyl acetate in a

linear gradient with elution of compound in 5 to 10% ethyl acetate to provide product in quantitative yield as an oil. R_f 0.8 (1:1 hexane: ethyl acetate); **^{1}H NMR** (400 MHz, chloroform-*d*) δ = 7.43 - 7.21 (m, 15 H, Ph), 5.32 (d, *J* = 5.5 Hz, 1 H, H-1), 4.96 (d, *J* = 10.5 Hz, 1 H, $\underline{CH_2}$Ph), 4.86 (d, *J* = 10.9 Hz, 1 H, $\underline{CH_2}$Ph), 4.78 - 4.60 (m, 3 H, $\underline{CH_2}$Ph), 4.54 (d, *J* = 10.9 Hz, 1 H, $\underline{CH_2}$Ph), 4.33 - 4.17 (m, 3 H, H-5, H-6), 3.92 - 3.76 (m, 2 H, H-2, H-3), 3.45 (t, *J* = 9.2 Hz, 1 H, H-4), 2.59 - 2.39 (m, 2 H, S$\underline{CH_2}CH_2CH_3$), 2.00 (s, 3 H, CH_3), 1.68 - 1.56 (m, 2 H, $SCH_2\underline{CH_2}CH_3$), 1.03 - 0.95 (m, 3 H, $SCH_2CH_2\underline{CH_3}$); **^{13}C NMR** (101 MHz, chloroform-*d*) δ = 170.7, 138.5, 137.8, 137.7, 128.4, 128.4, 128.4, 128.1, 128.0, 128.0, 127.9, 127.9, 127.7, 83.4, 82.4, 79.5, 77.1, 75.7, 75.0, 72.3, 68.9, 63.2, 31.9, 22.9, 20.8, 13.5; **HRMS (APCI)**: $[M + NH_4]^+$ *m/z* calc. for $C_{32}H_{38}O_6SNH_4^+$ 568.2727 ; found 568.2726

4.8. *n*-Propyl-2,4-di-*O*-benzyl-1-thio-*α*-D-glucopyranoside **(6)**

Compound **2** (140 mg, 0.41 mmol) was dissolved in cyclopentyl methyl ether (3.5 mL) and loaded into an 8 mL stainless steel syringe. 1-Propanethiol (0.053 mL, 0.57 mmol) and trimethylsilyl trifluoromethanesulfonate (0.4 mL, 2.2 mmol) was diluted with cyclopentyl methyl ether (3.1 mL) and loaded into an 8 mL stainless steel syringe and the two solutions were streamed together via syringe pump at a flowrate of 0.15 mL/min through high purity PFA tubing (0.02 I.D., 1524 cm (50 ft), 3 mL) with a residence time of 20 min at 90 °C. The reaction solution was monitored by TLC until steady state and reaction was collected in a vial containing saturated sodium bicarbonate solution (1.0 mL) to quench the reaction. The reaction solution was extracted with sodium bicarbonate (8 mL) followed by water (8 mL, 8 g). The organic solution was dried with sodium sulfate (2.0 g). The organic solution was decanted and 8 mL (6.9 g) of cyclopentyl methyl ether was used to rinse the sodium sulfate. The organic solution was concentrated via rotary evaporation with 2.8 g of silica and the residue was subjected to column purification via Teledyne ISCO CombiFlash® Rf 200i using 4 g ISCO column in hexane ethyl acetate in a stepwise gradient with elution of compound in 20% ethyl acetate. A total of 450 mL (297 g) of hexane was used for purification a long with 90 mL (81 g) ethyl acetate and 40.2 mL (36.3 g) of ethyl acetate used to rinse test tubes to give a total volume of 540 mL for purification to provide **6** as a white solid (0.100 g, 0.24 mmol, 58%). See **Figure S5** for details of the setup. R_f 0.6 and 0.7 (1:1 hexane: ethyl acetate), 1.7:1 α/β

Alpha anomer:

^{1}H NMR (500 MHz, chloroform-*d*) δ = 7.46 - 7.29 (m, 10 H, Ph), 5.37 (d, *J* = 5.4 Hz, 1 H, H-1), 4.94 (d, *J* = 11.2 Hz, 1 H, $\underline{CH_2}$Ph), 4.80 - 4.69 (m, 2 H, $\underline{CH_2}$Ph), 4.58 (d, *J* = 11.2 Hz, 1 H, $\underline{CH_2}$Ph), 4.12 - 3.98 (m, 2 H, H-3, H-5), 3.80 (br. s., 2 H, H-6), 3.63 (dd, *J* = 5.4, 9.8 Hz, 1 H, H-2), 3.50 (t, *J* = 9.3 Hz, 1 H, H-4), 2.59 - 2.42 (m, 2 H, S$\underline{CH_2}CH_2CH_3$), 1.72 - 1.60 (m, 2 H, $SCH_2\underline{CH_2}CH_3$), 1.01 (t, *J* = 7.3 Hz, 3 H, $SCH_2CH_2\underline{CH_3}$); **^{13}C NMR** (126 MHz, chloroform-*d*) δ = 138.3, 137.4, 128.6, 128.5, 128.5, 128.5, 128.2, 128.2, 128.1, 127.9, 127.9, 82.9, 79.0, 74.5, 74.2, 72.1, 70.6, 62.0, 32.1, 22.9, 13.5; **HRMS (ESI)**: $[M + Na]^+$ *m/z* calc. for $C_{18}H_{22}Cl_3NO_5SNa^+$ 441.1706; found 441.1707.

Beta anomer:

^{1}H NMR (500 MHz, chloroform-*d*) δ = 7.47 - 7.29 (m, 10 H, Ph), 5.01 (d, *J* = 10.7 Hz, 1 H, $\underline{CH_2}$Ph), 4.87 (d, *J* = 11.2 Hz, 1 H, $\underline{CH_2}$Ph), 4.71 (dd, *J* = 7.8, 11.2 Hz, 2 H, $\underline{CH_2}$Ph), 4.48 (d, *J* = 9.8 Hz, 1 H, H-1), 3.91 (dd, *J* = 2.7, 12.0 Hz, 1 H, H-6), 3.82 - 3.70 (m, 2 H, H-3, H-6), 3.49 (t, *J* = 9.5 Hz, 1 H, H-4), 3.42 - 3.35 (m, 1 H, H-5), 3.27 (t, *J* = 9.8 Hz, 1 H, H-2), 2.80 - 2.67 (m, 2 H, S$\underline{CH_2}CH_2CH_3$), 1.78 - 1.64 (m, 3 H, $SCH_2\underline{CH_2}CH_3$), 1.08 - 1.01 (m, 3 H, $SCH_2CH_2\underline{CH_3}$); **^{13}C NMR** (126 MHz, chloroform-*d*) δ = 128.6, 128.6, 128.3, 128.1, 128.1, 85.2, 81.6, 78.9, 78.5, 75.3, 74.7, 62.3, 33.3, 23.3, 13.5; **HRMS (ESI)**: $[M + Na]^+$ *m/z* calc. for $C_{18}H_{22}Cl_3NO_5SNa^+$ 441.1706; found 441.1707.

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Highlights

- A greener approach to carbohydrate acylation under flow conditions was developed with acetyl chloride and acetonitrile, thereby avoiding the use of a DMAP catalyst and pyridine.
- Benzylation without the use of NaH was achieved in a continuous flow process with the use of a barium oxide packed-bed reactor; however, other forms of this catalyst amenable to packing under sustained flow conditions are needed.
- The *n*-propyl-2,4-di-O-benzyl-1-thio-*α*-D-glucopyranoside building block was synthesized from levoglucosan in only 2 steps using continuous flow processes.