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Solution- and solid-phase oligosaccharide synthesis using glucosyl iodides: a comparative study

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This paper is dedicated to Professor Derek Horton on his 70th birthday in recognition of his lifelong contribution to carbohydrate chemistry

Abstract

Glycosyl iodide donors have been used in both solid- and solution-phase syntheses yielding α-(1→6)-linked glucosyl oligomers in highly efficient protocols. While the solid-phase strategy offers advantages in terms of ease of purification, it requires a total of 7.5 equiv of donor and approximately 12 h to complete the incorporation of one monosaccharide unit. In contrast, solution-phase methods require only 2.5 equiv of donor and 2–3 h reaction time per glycosylation. Moreover, since the reactions are virtually quantitative (>90%) column chromatography of the material is facile. The overall advantages of solution-phase oligosaccharide synthesis were further illustrated in the convergent synthesis of a hexamer (methoxycarbonylmethyl 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl-(1→6)-tetrakis-(2,3,4-tri-*O*-benzyl-α-D-glucopyranosyl-(1→6))-2,3,4-tri-*O*-benzyl-1-thio-α-D-glucopyranoside) that was constructed from dimer donor iodides in a two-plus-two and a two-plus-four fashion.

Keywords: Glycosyl iodides; Oligosaccharide synthesis; Stereoselective; α-Linked gluco-homopolymer

1. Introduction

Of the many glycosylation methods available,[1] those employing glycosyl halides as donors are well established, especially those utilizing glycosyl bromides. Glycosyl chlorides can be very useful for specific applications, but their general use is limited due to their reduced activity. In contrast, glycosyl iodides were once thought to be too reactive for any useful synthetic purposes.[2] Since the last review of glycosyl iodides appeared in 1998, there has been a remarkable increase in the number of papers appearing in the literature that report both the use and formation of glycosyl iodides in organic synthesis.[3] The rebirth of glycosyl iodide chemistry began with a report that utilized glycosyl iodides, which were isolated and spectroscopically characterized,[4] as starting materials in the syntheses of *C*-, *N*-, and *O*-linked glycosylic compounds under anionic conditions.[5] Hadd and Gervay further illustrated the utility of glycosyl iodides through syntheses of *O*-linked glycosylic compounds with high α-stereoselectivity.[6] In related studies, Hashimoto and co-workers[7] and Schmid and Waldmann[8] independently reported methods for the stereoselective formation of α-*O*-glycosides through in situ formation of glycosyl iodides. Uchiyama and Hindsgaul also used in situ generation of fucosyl io-

Abbreviations: DIPEA, diisopropylethylamine (Hünig's base); NMP, *N*-methyl-2-pyrrolidinone; BOP, Benzotriazole-1-yl-oxy-tris(dimethylamino)-phosphonium hexafluorophosphate; TMSI, iodo trimethylsilane; NBS, *N*-bromosuccinimide; DTBP, 2,6-di-*tert*-butylpyridine; CH_2Cl_2, dichloromethane, methylene chloride; DMF, *N*,*N*-dimethylformamide; PhH, benzene; PhMe, toluene; MeOH, methanol; NaOMe, sodium methoxide; $LiOH{\cdot}H_2O$, lithium hydroxide monohydrate; TBAI, tetrabutylammonium iodide; EtOAc, ethyl acetate; Na_2SO_4, sodium sulfate; pet ether, petroleum ether.

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dides to achieve highly α-selective glycosylations.[9] More recently, Bhat and Gervay-Hague extended the utility of glycosyl iodides through the efficient and stereoselective preparation of β-glycosyl cyanides from per-*O*-silylated glycosyl iodide precursors.[10] β-*C*-Glycosylic compounds were also prepared by Beau and co-workers using reductive samariation of glycosyl iodides in the presence of carbonyl electrophiles.[11] Iodide donors have clearly become an important reactive intermediate, which has led to the development of new preparative methods.[12] However, in many cases iodotrimethylsilane remains the reagent of choice, due to its ease of use and volatile byproducts.[13]

With the advantages of using glycosyl iodide donors clearly delineated, their implementation in oligosaccharide assembly seemed a natural progression.[14] Syntheses of α-(1→6)-*O*-linked glucose homooligomers (oligoisomaltosides, **1**, Fig. 1) were chosen as targets in order to make direct comparisons to previously reported methods. As early as 1976, Eby and Schuerch,[15] in a stepwise fashion, constructed oligoisomaltosides through use of glycosyl tosylate intermediates generated from α-glycosyl chlorides by action of excess AgOTs. Excellent results were obtained, as the yields were consistently ~90% per glycosylation with 95% α-selectivity, but the glycosylations required long reaction times (16 h) and showed 5% gentiobioside linkages (β-linkage) per glycosylation step. Kováč and co-workers[16] improving upon the utility of glycosyl chlorides (α and β glycosyl chlorides) through activation with excess $AgClO_4$ were able to form the desired α-linkage in similar yields in greatly reduced time (15 min), but they also found ~5% β-linkages. In both of these examples, glycosylation yields diminished with longer oligomer lengths. Oligo-isomaltosides, as precursors to cyclic oligo-isomaltosides, were also synthesized from glycosyl fluorides with moderate yields and reduced α-stereoselectivity (90%)[17] compared to the aforementioned glycosyl chloride routes. Use of dicyclohexylmethyl thioglycosides, activated with NIS–TMSOTf, as building blocks also showed moderate success with wide-ranging yields and 85% α-selectivity at best.[18] Attempts to apply glycal chemistry, through use of $AgBF_4$ as a promoter with concomitant glycosylation by stannylated acceptors, showed α-selectivity with moderate yields.[19]

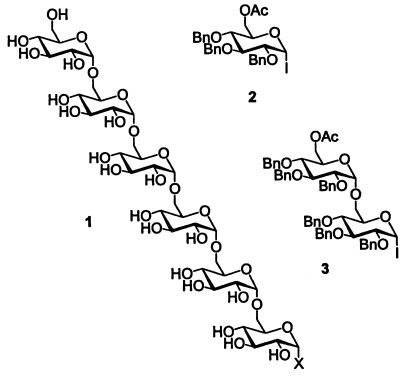


Fig. 1. Target **1** and glycosyl donors **2** and **3**.

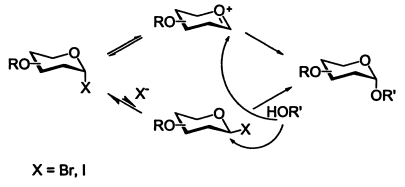


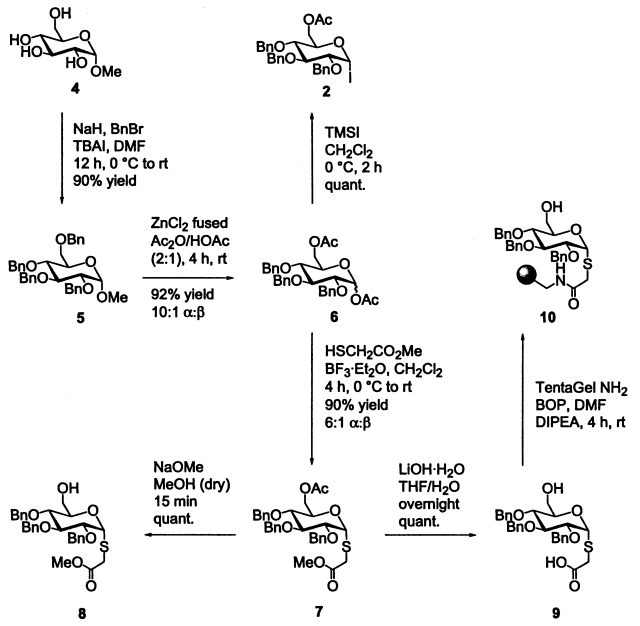
Fig. 2. Halide-catalyzed in-situ anomerization.

The use of glycosyl iodides to afford α-glycosidic linkages was derived from the breakthrough work of Lemieux and co-workers,[20] who showed that glycosylations of glycosyl bromides catalyzed by bromide ions provided α-glycosides with good yields. This in-situ anomerization strategy relied upon an equilibrium (α and β halides) established by treating α-glycosyl halides with quaternary ammonium halides leading to the more reactive β-glycosyl halides, which when attacked by the glycosyl acceptor provided the desired α-linked glycosides (Fig. 2). In fact, Fréchet and co-workers used glycosyl bromides in the assembly of oligosaccharides with great success, but the reaction times were on the order of 2–4 days, and the stereochemical outcome was not clearly defined.[21] Exploring the possible advantages of using glycosyl iodides in oligosaccharide synthesis was an obvious next step. In preliminary studies, glucosyl donor **2** was treated with allyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside to afford the α-linked disaccharide in 78% isolated yield without the formation of undesired gentiobioside linkage, suggesting that the synthesis of oligosaccharides was worthy of pursuit.[3]

Here we report the results of further investigations into the use of glycosyl iodides as building blocks in the stepwise construction of oligosaccharides in the form of **1**. The use of glycosyl iodides as both monosaccharide **2** and disaccharide **3** donors has resolved several of the issues faced by the aforementioned groups. In the reported glycosylations, no β-glycosidic linkages were detected, yields were equal to those reported for the glycosyl chlorides, reaction times typically ranged 2–4 h, and oligomer length did not affect the efficiency of further elongation.

2. Results and discussion

The investigations began with the syntheses of monomeric building blocks. Consistent with the goal of maintaining overall efficiency in the construction of oligosaccharide **1**, the monomer syntheses were designed to be rapid and amenable to large-scale production. The benzyl group was chosen as a robust



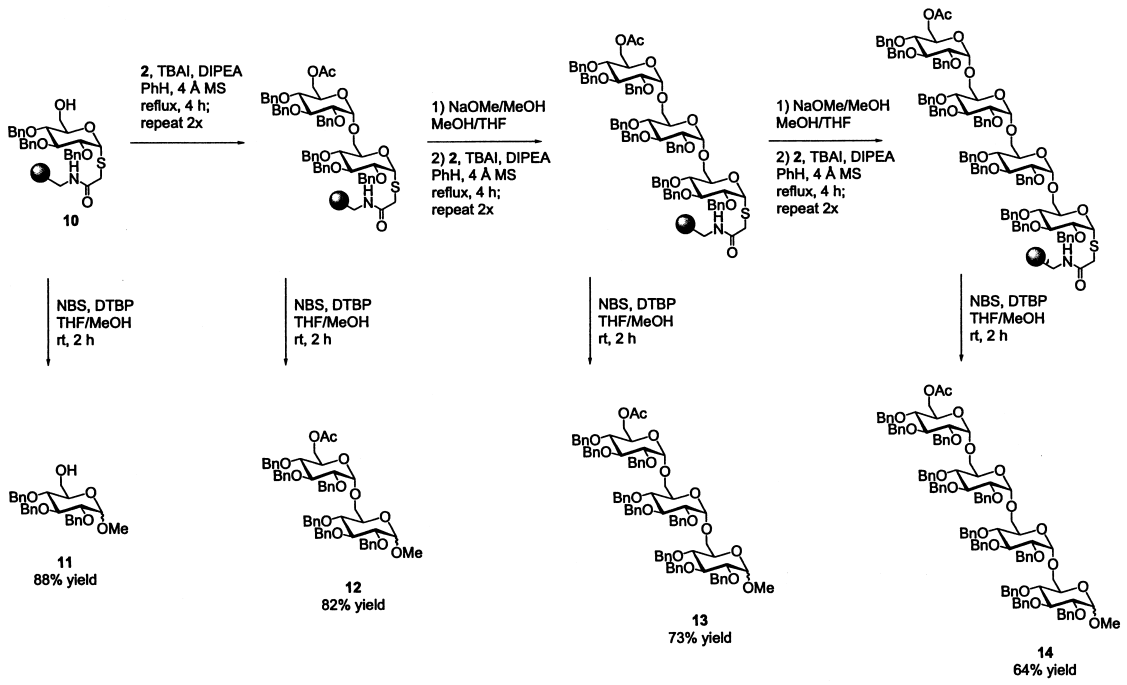
Scheme 1. Synthesis of building blocks.

protecting group for positions 2, 3, and 4 that is capable of withstanding glycosylation conditions, yet is easily removable by catalytic hydrogenation. The acetyl group was chosen as a temporary blocking group because it can be efficiently and mildly removed under Zemplén conditions. Commercially available methyl α-D-glucopyranoside (**4**) was converted to perbenzylated sugar **5** through the action of excess NaH, BnBr, and catalytic TBAI in DMF (Scheme 1). Using methodology developed by Kong and co-workers,[22] methyl per-*O*-benzylated-α-D-glucopyranoside (**5**) dissolved in a mixture of 2:1 Ac_2O–AcOH was treated with freshly fused $ZnCl_2$ (20 equiv) in 2:1 Ac_2O–AcOH affording the 1,6-di-*O*-acetyl monosaccharide (**6**). Decreasing the amounts of toxic fused $ZnCl_2$ (10 equiv) and decreasing the concentration (0.18 M), achieved the same transformation with identical reaction times. This transformation affording the glycosyl donor precursor **6** has been performed on a scale as high as 70 g of **5**. By the method of Thiem and Meyer,[13] compound **6** was quickly and efficiently transformed into the α-glycosyl iodide **2**.[†] The versatile 1,6-di-*O*-acetyl monosaccharide was also transformed into thioglycoside **7**, whereby the thioglycoside moiety was used at the reducing end as a robust and orthogonal protecting group, which also dictated the direction of oligomer elongation. Treatment of compound **6** with excess $BF_3{\cdot}Et_2O$ in the presence of methyl thioglycolate provided **7** in 90% yield. Subsequent removal of the acetate quickly afforded the glycosyl acceptor **8**, which was used in the construction of the target oligosaccharides in the solution phase. Alternatively, saponification of the acetyl moieties in **7** using $LiOH{\cdot}H_2O$ in a THF–H_2O mixture provided acid **9**.

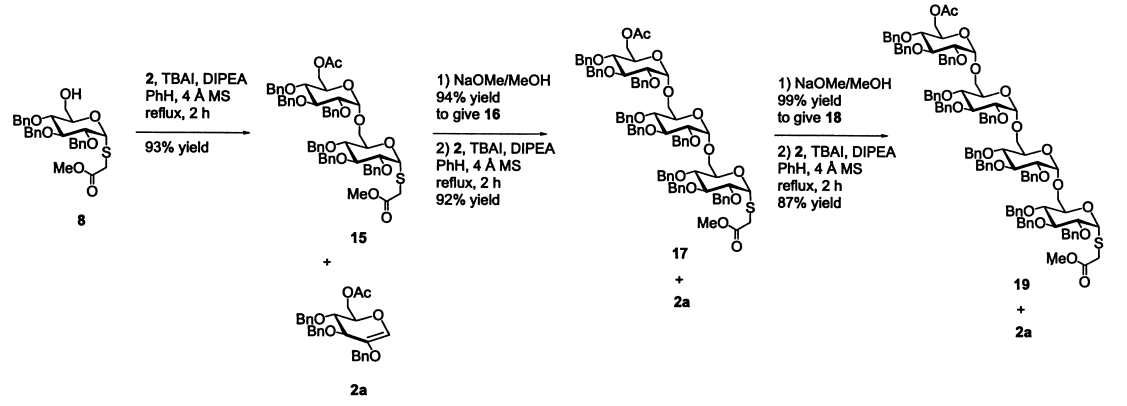
TentaGel amine resin (0.3 mmol/g loading) was treated with acid **9** under typical peptide coupling conditions (BOP, Hünig's base, DMF) to afford resin-linked monosaccharide **10**. To ensure that **9** was coupled onto the resin, a Kaiser test was performed, which indicated the absence of a 1° amine. Next, the thioglycolate linkage was cleaved to give resin-released monosaccharide **11**[24] (Scheme 2). Over the two steps, **11** was isolated in 88% yield after chromatography, based upon the theoretical loading capacity of the resin as provided by the manufacturer. With roughly 94% transformation per step (loading and releasing), solid-phase oligosaccharide synthesis was primed for further elaboration. As is common with solid-phase oligosaccharide synthesis,[25] numerous glycosylations were performed for each coupling step. Resin-linked monosaccharide **10** (1.0 equiv) was treated with **2** ($\sim$2.5 equiv) under in-situ anomerization conditions at 60 °C for 4 h then washed with copious amounts of CH_2Cl_2, MeOH, CH_2Cl_2, and distilled PhH; the glycosylation and washing processes were performed a total of three times. Following the glycosylations, the disaccharide was cleaved from the solid support and chromatographed to provide **12** in 82% yield. Successive solid-phase elongation experiments to afford trisaccharide **13** and tetrasaccharide **14** were accomplished though in moderate yields, 73 and 64%, respectively. These results compared favorably to earlier reports. The yields were similar, and fewer equivalents of donor were required (7.5 equiv of iodide compared to 12 equiv of bromide).[21,26a,26b] The reaction times were greatly reduced, $\sim$12 h to complete three iterations of each glycosylation, when compared with glycosyl bromides (2–5 days).[26] Moreover, only α-glycosidic linkages were detected by NMR spectroscopy. The formation of α/β mixtures plagued earlier studies making oligomer purification difficult. While these studies clearly demonstrated the advantages of glycosyl iodides in solid-phase synthesis, including ease of purification, enthusiasm for this protocol was tempered by the need to run each glycosylation three times. This requirement increased the reaction time to 12 h per sugar unit and required 7.5 equiv of donor. Previous experience with solution-phase glycosylations suggested that they should be pursued as an alternative strategy.

In order to directly compare with the solid-phase studies, a one-plus-one strategy of monomer incorporation was first investigated.[14] Treatment of a stirring solution of **8**, tetrabutylammonium iodide, Hünig's base, and 4 Å molecular sieves in anhyd benzene (in-

[†] In preparing the glycosyl donor, it was important to use flame-dried glassware and an inert atmosphere (argon). Chilling the mixture on an ice bath throughout the course of the reaction also prevented formation of side products, as TMSI is also known to cleave benzyl ethers.[23]



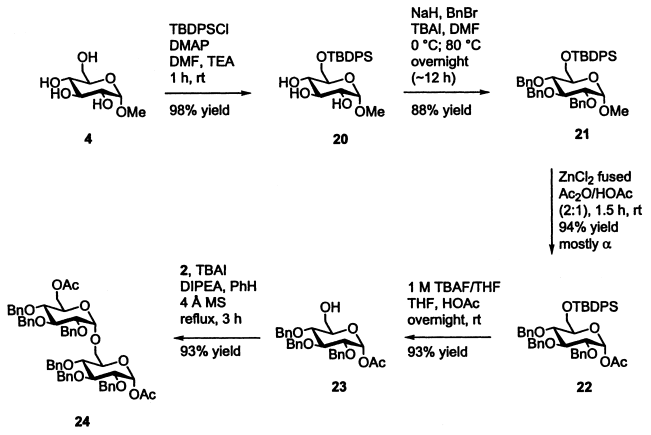
Scheme 2. Linear solid-phase glycosylation approach.



Scheme 3. Linear solution-phase glycosylation approach.

situ anomerization conditions) with glycosyl donor **2**‡ under reflux conditions for 2 h provided disaccharide **15** in 93% yield after chromatography (Scheme 3). The glycal **2a** was a major side product of the glycosylation ($\sim$50% of donor). Therefore, reactions were typically carried out using an excess of glycosyl donor to acceptor ($\sim$2.5:1). As demonstrated in previous reports, glucosyl iodides are particularly susceptible to elimination, in contrast to galactosyl and mannosyl iodides.[5,6] It is possible that other donors will not require as many equivalents of donor. Nonetheless, oligomer synthesis continued with deacetylation of **15** and repeated glycosylation to provide trisaccharide **17** in high yield. The tetrasaccharide **19** was prepared in a similar fashion. Overall, these glycosylations were more efficient than the solid-phase protocol, and since the reactions were high yielding, purification was facile. Generally, an oligomer could be prepared and purified in less time than it took to do three iterations on solid-phase. The only drawback that arose in this protocol was the occasional hydrolysis of the thioglycolate ester under Zemplén conditions. Trace amounts of water led to partial hydrolysis of the ester yielding the carboxylic acid ($<10\%$). This was a relatively minor problem that could be alleviated by using a *tert*-butyl ester or simply by treating the mixture with diazomethane prior to column chromatography.

‡ Glycosyl donor **2** was used immediately after preparation; however, **2** stored in the freezer under argon in anhydrous PhH remained stable with only a small degree of degradation even after 1 month as monitored by ^{1}H NMR spectroscopy.



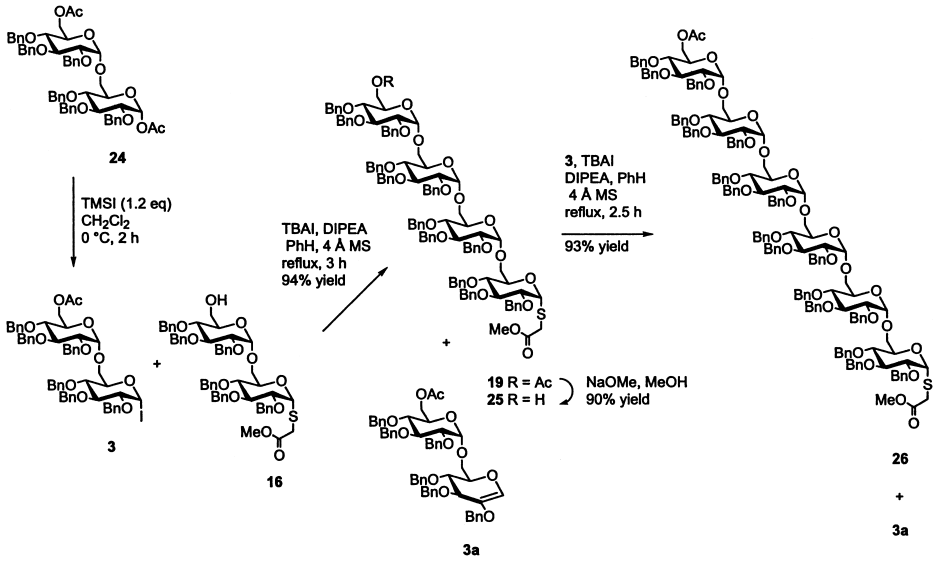
Scheme 4. Synthesis of di-*O*-acetyl-isomaltose.

Since the solution-phase experiments were more efficient than the solid-phase route, a more convergent process that employed isomaltosyl donor **3** was explored. The synthesis of **3** began with the silylation of **4** using TBDPSCl and DMAP in DMF to afford **20** in 98% yield. Tri-benzylation of **20** with NaH, BnBr, and TBAI in DMF provided **21** in 88% yield. In Kong and co-workers' work on the zinc acetolysis of benzyl and methyl ethers of mono- and disaccharides, they reported that acetolysis occurred at the 1° C-6 benzyl ether prior to that of the 2° anomeric methyl ether.[22] We were hoping to get a reversal in reactivity by incorporating a *tert*-butyldiphenylsilyl protecting group at C-6, and indeed this was the case. When **21** was subjected to acetolysis conditions, **22** was obtained in 94% yield as primarily the α anomer. Combining the sequence leading to **22** into a one-pot, large-scale process also proved successful. Desilylation of **22** under standard conditions furnished glucosyl acceptor **23**, using a direct, efficient, and improved protocol as compared to previously reported methods.[27] Glucosylation of **23** with **2** under in-situ anomerization conditions afforded **24** with yields typically in the low 90s (Scheme 4).

Taking care to rigorously exclude water, **24** was converted into disaccharide glycosyl donor **3** upon treatment with TMSI at 0 °C (Scheme 5). After rotoevaporation of byproducts, isomaltosyl iodide **3** was treated with disaccharide acceptor **16** under in-situ anomerization conditions. Tetrasaccharide **19** was isolated in 94% after chromatography in addition to glycal **3a**. Deacetylation of **19** gave the acceptor **25** in 90% yield and subsequent glycosylation using donor **3** provided hexasaccharide **26** in 93% purified yield. In all cases the only anomer isolated was the desired α-glycosidic linkage as determined by conventional NMR techniques.

3. Conclusions

The utility of glycosyl iodides in both solid- and solution-phase oligosaccharide synthesis has been demonstrated. Problems that prevented earlier strategies from becoming general routes to α-linked oligosaccharides including long reaction times, complex α/β-mixtures, and diminished yields when applied to higher order oligomers were not encountered when employing glycosyl iodides under in-situ anomerization conditions. While the solid-phase synthesis offers advantages in terms of ease of purification, it is still plagued by the need to repeat the glycosylation three times with 2.5 equiv of donor. This leads to a total reaction time of 12 h. In contrast, solution-phase glyco-



Scheme 5. Convergent solution-phase oligosaccharide assembly.

sylations are complete within 2–3 h and only 2.5 equiv of donor are required. The reactions are virtually quantitative, making purification easy. In many cases, solution-phase glycosylation and purification can be carried out faster than solid-phase reactions. The solution-phase methodology was further improved upon by utilizing a disaccharide donor as demonstrated by the synthesis of hexasaccharide **26**. A particularly attractive feature of this methodology is that oligomers can be constructed from diacetate precursors, which are readily available on large scale. Extension of this chemistry to more complex systems is currently underway.

4. Experimental

General experimental protocol.—Solvents (PhH 99.8%, CH_2Cl_2 99.8%, PhMe 99.8%) were purchased in anhyd Sure/Seal™ bottles from Aldrich, used without further purification, and stored under argon. CH_2Cl_2 and PhH were distilled from powdered CaH_2 and potassium with benzophenone, respectively. Hünig's base (99.5%) was also purchased from Aldrich in Sure/Seal™ bottles, used without purification, and stored under argon. TMSI was purchased from Fluka ($\geq$ 98%) and used without purification unless the color had changed to a dark brown shade, in which case it was discarded or distilled under an argon atmosphere from quinoline. TMSI was stored at -15 °C in a desiccated atmosphere. Dowex 50W × 8 (H^+) (200 mesh) resin was purchased from Aldrich, washed copiously with MeOH, and used without further purification. NaOMe–MeOH (25% wt/vol and 0.5 M solution) was purchased from Aldrich. Glass-backed EM Science TLC plates (Silica Gel 60 with a 254 nm fluorescent indicator) were purchased from VWR International, cut into 2 cm × 5 cm portions, used without further manipulation, and stored over desiccant. Developed TLC plates were visualized under a short-wave UV lamp, stained with an I_2–SiO_2 mixture, and/or treated with a cerium–molybdate solution and charred. Column chromatography was conducted using flash silica gel (32–63 μm) available from Scientific Adsorbents, and solvents were purchased from EM Science. NMR experiments (1D and 2D) were conducted on Bruker DRX500 MHz and/or DRX600 MHz spectrometers using C_6D_6 and/or $CDCl_3$ (Aldrich) at 298 K. To distinguish between the different subunits of the oligosaccharides, ^1H and ^{13}C NMR assignments were made with the designations 'I, II, III, and IV' with sugar 'I' as the subunit containing the thioglycosidic link. Optical data were taken at 25 °C on a JASCO DIP-1000 Digital Polarimeter.

General synthesis of glycosyl iodides: synthesis of 6-O-acetyl-2,3,4-tri-O-benzyl-α-D-glucopyranosyl iodide (**2**).—A solution of 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**6**) (1.26 g, 2.35 mmol) in CH_2Cl_2 (10 mL) was cooled in an ice bath under a flow of dry argon for 20 min. Afterwards, TMSI (370 μL, 2.6 mmol) was syringed into the stirring mixture. The reaction was allowed to proceed for 2 h at 0 °C, at which point, anhyd PhMe was syringed into the reaction vessel, and the solvents and volatile side products were removed in vacuo. Azeotroping with anhyd toluene was continued until a colorless distillate persisted. The resulting pale yellow oil was redissolved in anhyd PhH and stored at 0 °C for later use in glycosylations without further purification.

Methoxycarbonylmethyl 6-O-acetyl-2,3,4-tri-O-benzyl-1-thio-α-D-glucopyranoside (**7**).—A solution containing 1,6-di-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**6**) (610 mg, 1.1 mmol) and methyl thioglycolate (120 μL, 1.4 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C under an argon atmosphere, and freshly distilled $BF_3{\cdot}Et_2O$ (505 μL, 3.99 mmol) was added to the stirring mixture. The solution was stirred for 4 h during which time the color changed from yellow to orangish–red. The reaction was then diluted with CH_2Cl_2 (20 mL), extracted with 3 × 10 mL 5% aq sodium hydroxide, washed with water (3 × 10 mL), and dried over anhyd Na_2SO_4. Concentration of the organic layer in vacuo provided a yellow oil. TLC in 2:1 pet ether–EtOAc revealed that a major product had R_f 0.77. Following silica gel column chromatography with 4:1 pet ether–EtOAc as the eluent, 490 mg of compound **7** was isolated in 76% yield: $[\alpha]_D$ +122° (*c* 1.06, $CDCl_3$). ^1H NMR (DRX500, C_6D_6): δ 7.39–7.24 (6H, Ph-H), 7.16–7.05 (9H, Ph-H), 5.73 (d, 1H, *J* 5.5 Hz, H-1), 4.91 (d, 1H, *J* 11.0 Hz, PhC*H*), 4.84 (d, 1H, *J* 11.0 Hz, PhC*H*), 4.65 (d, 2H, *J* 11.5 Hz, 2PhC*H*), 4.54 (d, 1H, *J* 11.0 Hz, PhC*H*), 4.42 (m, 1H, H-6), 4.33 (m, 3H, H-5, H-6', PhC*H*), 4.02 (t, 1H, *J* 9.5 Hz, H-3), 3.79 (dd, 1H, *J* 5.5 Hz, 9.5 Hz, H-2), 3.49 (t, 1H, *J* 9.5 Hz, H-4), 3.28 (s, 3H, OCH_3), 3.18 (d, 1H, *J* 15.5 Hz, SCH), 2.89 (d, 1H, *J* 15.5 Hz, SCH), 1.66 (s, 3H, $COCH_3$). ^{13}C NMR (DRX500, C_6D_6): δ 170.35 (CO), 169.81 (CO), 139.46 (Ph-C), 138.69 (Ph-C), 138.18 (Ph-C), 128.55–127.59 (15C, Ph), 82.98 (C-1), 82.71 (C-3), 79.68 (C-2), 77.36 (H-4), 75.58 ($PhCH_2$), 74.99 ($PhCH_2$), 71.87 ($PhCH_2$), 70.06 (C-5), 63.17 (C-6), 51.84 (OCH_3), 29.91 (SCH_2), 20.35 ($COCH_3$). HRFABMS *m/z* $[M+H]^+$ Calcd for $C_{32}H_{37}O_8S$: 581.2209. Found: 581.2224.

General protocol for solution phase deacetylation: methoxycarbonylmethyl 2,3,4-tri-O-benzyl-1-thio-α-D-glucopyranoside (**8**).—To a solution of **7** (96 mg, 0.17 mmol) in anhyd MeOH was added three drops of 25% wt/vol NaOMe–MeOH, and the mixture was stirred at rt. After 15 min, TLC (2:1 pet ether–EtOAc) revealed the reaction was complete. Dowex 50W × 8 (H^+) resin ($\sim$50 mg) was added to the flask to neutralize the reaction. After filtration of the resin and concentration in vacuo of the filtrate, compound **8** was isolated in

quantitative yield as determined by ^{1}H NMR: $[\alpha]_D$ + 139° (*c* 0.65, $CDCl_3$). ^{1}H NMR (DRX500, C_6D_6): δ 7.35–7.05 (15H, Ph-H), 5.69 (d, 1H, *J* 5.5 Hz, H-1), 4.89 (d, 1H, *J* 11.0 Hz, PhC*H*), 4.86 (d, 1H, *J* 11.0 Hz, PhC*H*), 4.66 (d, 1H, *J* 11.0 Hz, PhC*H*), 4.66 (d, 1H, *J* 11.0 Hz, PhC*H*), 4.59 (d, 1H, *J* 11.0 Hz, PhC*H*), 4.39 (d, 1H, *J* 11.0 Hz, PhC*H*), 4.12 (m, 1H, H-5), 4.01 (t, 1H, *J* 9.5 Hz, H-3), 3.75–3.67 (m, 3H, H-2, H-6, H-6'), 3.52 (t, 1H, *J* 9.5 Hz, H-4), 3.29 (s, 3H, OCH_3), 3.13 (d, 1H, *J* 15.0 Hz, SCH), 2.86 (d, 1H, *J* 15.0 Hz, SCH), 1.57 (t, 1H, *J* 6.0 Hz, OH). ^{13}C NMR (DRX500, C_6D_6): δ 170.69 (CO), 139.55 (Ph-C), 138.99 (Ph-C), 138.31 (Ph-C), 128.59–127.52 (15C, Ph), 83.38 (C-1), 82.58 (C-3), 79.75 (C-2), 77.67 (C-4), 75.57 ($PhCH_2$), 75.08 ($PhCH_2$), 72.53 (C-5), 71.98 ($PhCH_2$), 62.13 (C-6), 51.86 (OCH_3), 30.19 (SCH_2). HRFABMS *m*/*z* $[M + H]^+$ Calcd $C_{30}H_{33}O_7S$: 537.1947. Found: 537.1954.

*Carbonyloxymethyl 2,3,4-tri-*O*-benzyl-1-thio-α-*D*-glucopyranoside* (**9**).—To a solution containing **7** (0.50 g, 0.87 mmol) in THF (10 mL) was added a solution of $LiOH{\cdot}H_2O$ (180 mg, 4.3 mmol) in water (1 mL). After stirring for 20 h at rt, the mixture was neutralized with Dowex® 50W × 8 (H^+) resin. The resin was then filtered, and the solvent was removed in vacuo to afford a faint yellow amorphous solid in 93% yield. $[\alpha]_D$ + 114° (*c* 0.76, $CDCl_3$). ^{1}H NMR (DRX600, $CDCl_3$): δ 7.44 (d, 2H, *J* 7.2 Hz, 2PhH), 7.38 (d, 2H, *J* 7.2 Hz, 2PhH), 7.33 (d, 2H, *J* 6.0 Hz, 2PhH), 7.27–7.20 (m, 6H, PhH), 7.17 (apparent q, 3H, PhH), 5.71 (d, 1H, *J* 6.0 Hz, H-1), 4.98 (d, 1H, *J* 11.4 Hz, PhC*H*), 4.95 (d, 1H, *J* 11.4 Hz, PhC*H*), 4.77 (d, 1H, *J* 11.4 Hz, PhC*H*), 4.71 (d, 1H, *J* 11.4 Hz, PhC*H*), 4.69 (d, 1H, *J* 11.4 Hz, PhC*H*), 4.50 (d, 1H, *J* 11.4 Hz, PhC*H*), 4.34 (m, 1H, H-5), 4.09 (t, 1H, *J* 9.6 Hz, H-4), 3.94 (apparent d, 1H, *J* 10.8 Hz, H-6), 3.89 (dd, 1H, *J* 3.6 Hz, 9.6 Hz, H-2), 3.83 (apparent dd, 1H, *J* 4.8 Hz, 11.4 Hz, H-6′), 3.59 (t, 1H, *J* 9.6 Hz, H-3), 3.25 (d, 1H, *J* 15.6 Hz, SC*H*), 3.04 (d, 1H, *J* 15.6 Hz, SC*H*), 3.34–3.31 (m, 2H, H-3, SCH), 3.29 (d, 1H, SCH). ^{13}C NMR (DRX600, $CDCl_3$): δ 175.12 (CO), 139.43 (Ph-C), 138.85 (Ph-C), 138.28 (Ph-C), 128.63 (Ph), 128.57 (Ph), 128.53 (Ph), 128.44 (Ph), 128.35 (Ph), 128.31 (Ph), 128.29 (Ph), 128.16 (Ph), 128.07 (Ph), 127.99 (Ph), 127.92 (Ph), 127.84 (Ph), 127.74 (Ph), 127.58 (Ph), 84.21 (C-1), 82.57 (C-3), 79.89 (C-2), 77.85 (C-4), 75.63 (C-OBn), 75.12 (C-OBn), 72.51 (C-5), 72.22 (C-OBn), 62.20 (C-6), 31.42 (SCH_2). HRFABMS *m*/*z* $[M + Na]^+$ Calcd $C_{29}H_{37}O_7S$: 547.1766. Found: 547.1770.

*Resin-linked-*N*-carbonylmethyl-2,3,4-tri-*O*-benzyl-6-O-acetyl-1-thio-α-*D*-glucopyranoside* (**10**).—TentaGel S NH_2 resin (0.081 g, 0.024 mmol) was swelled in DMF, agitated by a gentle flow of argon for 20 min, and the solvent was drained. To the solid-phase apparatus was added **9** (0.019 g, 0.036 mmol), BOP (0.016 g, 0.036 mmol), DIPEA (8.5 μL, 0.048 mmol), and DMF (2 mL). The mixture was agitated for 4 h by a flow of argon. A negative Kaiser test[28] of a small sample (~ 15 beads) indicated reaction completion. The reaction mixture was drained, and the resin was washed sequentially with copious amounts of CH_2Cl_2, MeOH, and CH_2Cl_2.

General solid-phase oligosaccharide assembly: syntheses of resin-linked disaccharide, trisaccharide, and tetrasaccharide.—Glycosyl iodide **2** was prepared according to the aforementioned protocol. Best results were found when the glycosyl donor was used within 24 h of synthesis and stored in anhyd PhH under argon in the freezer. Monosaccharide-loaded resin **10** was swelled in dry CH_2Cl_2 and agitated by a flow of argon for 20 min. After filtration to remove the solvent, **10** was washed with copious amounts of distilled PhH. To the reaction vessel, containing **10** (0.028 mmol), was added TBAI (0.032 g, 0.086 mmol), DIPEA (10 μL, 0.057 mmol), distilled PhH (2 mL), and 4 Å ms. The reaction was gently agitated for 4 h by a flow of argon and heated to 60 °C with a condenser attached to the vessel. The reaction mixture was then drained, and the resin was washed with CH_2Cl_2 until the filtrate was colorless, followed by washes with distilled PhH (3 × 5 mL). The resin was resubjected twice more to glycosylation conditions and washings to ensure complete glycosylation of all available sites to provide the resin-linked disaccharide. To further elongate the oligomer, the resin-linked disaccharide was swelled in 1:1 MeOH–THF (5 mL) for 20 min, drained, and treated with 25% w/v NaOMe–MeOH (5 drops) in 1:1 MeOH–THF (5 mL) with argon agitation for 2 h to provide deacetylated disaccharide-linked resin. This deprotection was repeated twice. Following copious washings sequentially with MeOH, H_2O, MeOH, CH_2Cl_2, and distilled PhH. The resin was resubjected to the aforementioned glycosylation conditions to provide trisaccharide-linked resin. Resin-linked tetrasaccharide was arrived at after treating trisaccharide-linked resin with deacetylation and glycosylation conditions.

General release[24] of oligosaccharides from the solid support: synthesis of monosaccharide (**11**),[29] *disaccharide* (**12**),[16,30,31] *trisaccharide* (**13**),[16,29,30] *and tetrasaccharide* (**14**)[30,32].—Disaccharide-linked resin (0.028 mmol) was swelled in 1:10 MeOH–THF (5 mL) for 20 min, and the solvent was drained. To the reaction vessel were added NBS (20 mg, 0.11 mmol), DTBP (26 μL, 0.11 mmol), and 1:10 MeOH–THF (3 mL) and agitated by a flow of argon. The color became increasingly dark yellow over the course of the reaction, 2 h. The reaction mixture was filtered and the resin was washed with 1:10 MeOH–THF (5 mL), MeOH, and EtOAc. The filtrate was extracted with satd aq $Na_2S_2O_3$ (3 × 15 mL), brine (2 × 15 mL), dried over anhyd Na_2SO_4, and concentrated in vacuo. The yellow oil was flash chromatographed using 1:4 EtOAc–hexanes as the eluent to provide 12 mg of methyl glycoside **12** (~ 2:1 β:α) in 82% isolated yield. These cleavage conditions were also

applied to afford monosaccharide **11**, trisaccharide **13**, and tetrasaccharide **14** in 88, 73, and 64% yields, respectively, after silica gel column chromatography using EtOAc–hexanes as the eluent. The NMR spectra of products **11**–**14** matched those reported in the references cited.

*Methoxycarbonylmethyl (6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-*D*-glucopyranosyl)-α-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-α-*D*-glucopyranoside* (**15**).—TBAI (431 mg, 1.17 mmol), DIPEA (102 μL, 0.58 mmol) and activated 4 Å MS were added to a solution of **8** (118 mg, 0.23 mmol) in anhyd PhH (2 mL). The mixture was stirred at rt under an argon atmosphere for 30 min. A solution of glycosyl donor **2** (0.68 mmol) in anhyd PhH (2 mL) was cannulated into the stirring glycosyl acceptor mixture, and the reaction was refluxed for 4 h. The reaction was diluted with EtOAc and cooled to 0 °C. The white precipitate and 4 Å MS were removed by filtration through a pad of Celite, and the filtrate was washed with satd aq $Na_2S_2O_4$ (1 × 20 mL) and with brine (1 × 20 mL). The organic layer was dried over anhyd Na_2SO_4 and concentrated in vacuo. A new dominant spot with R_f 0.14 appeared on TLC using 1:3 EtOAc–hexanes as the eluent. Silica gel column chromatography with 1:4 EtOAc–hexanes as the eluent provided 207 mg of **15** in 88% yield: $[\alpha]_D$ +104° (*c* 0.80, $CDCl_3$). ^{1}H NMR (DRX500, C_6D_6): δ 7.37–7.05 (30H, Ph-H), 5.80 (d, 1H, *J* 5.5 Hz, H-1^I), 5.08 (d, 1H, *J* 11.0 Hz, PhC*H*), 5.00 (d, 1H, *J* 11.5 Hz, PhC*H*), 4.98 (d, 1H, *J* 3.5 Hz, H-1^{II}), 4.91 (d, 1H, *J* 11.0 Hz, PhC*H*), 4.90 (d, 1H, *J* 11.0 Hz, PhC*H*), 4.89 (d, 1H, *J* 11.5 Hz, PhC*H*), 4.72 (d, 1H, *J* 11.5 Hz, PhC*H*), 4.68 (d, 1H, *J* 11.5 Hz, PhC*H*), 4.63 (d, 1H, *J* 11.5 Hz, PhC*H*), 4.59 (d, 1H, *J* 11.0 Hz, PhC*H*), 4.47 (m, 3H, H-6^{II}, 2PhC*H*), 4.38 (m, 1H, H-5^I), 4.34 (d, 1H, *J* 11.5 Hz, PhC*H*), 4.32 (dd, 1H, *J* 4.5 Hz & 12.0 Hz, H-6^{II}), 4.23 (t, 1H, *J* 9.5 Hz, H-3^{II}), 4.07 (t, 1H, *J* 9.0 Hz, H-3^I), 4.02 (m, 1H, H-5^{II}), 3.95 (dd, 1H, *J* 5.0 Hz, 11.5 Hz, H-6^I), 3.78 (dd, 1H, *J* 5.5 Hz, 9.0 Hz, H-2^I), 3.77 (t, 1H, *J* 9.0 Hz, H-4^I), 3.73 (d, 1H, *J* 11.5 Hz, H-6^I), 3.56 (t, 1H, *J* 9.5 Hz, H-4^{II}), 3.53 (dd, 1H, *J* 3.5 Hz, 9.5 Hz, H-2^{II}), 3.36 (d, 1H, *J* 15.5 Hz, SCH), 3.31 (s, 3H, OCH_3), 2.98 (d, 1H, *J* 15.5 Hz, SCH), 1.70 (s, 3H, CH_3). ^{13}C NMR (DRX500, C_6D_6): δ 170.53 (CO), 169.88 (CO), 139.61 (Ph-C), 139.50 (Ph-C), 139.14 (Ph-C), 139.00 (Ph-C), 138.82 (Ph-C), 138.29 (Ph-C), 128.67–127.53 (30C, Ph), 97.42 (C-1^{II}), 83.01 (C-1^I), 82.85 (C-3^I), 82.16 (C-3^{II}), 81.00 (C-2^{II}), 79.92 (C-2 ^{I}), 77.90 (C-4^{II}), 77.79 (C-4^I), 75.63 (C-OBn), 75.57 (C-OBn), 75.14 (C-OBn), 75.08 (C-OBn), 72.66 (C-5^I), 72.01 (C-OBn), 71.95 (C-OBn), 69.46 (C-5^{II}), 66.51 (C-6^I), 63.26 (C-6^{II}), 51.86 (OCH_3), 29.96 (SCH_2), 20.43 (CH_3). HRFABMS *m*/*z* $[M+Na]^+$ Calcd $C_{59}H_{64}NaO_{13}S$: 1035.3963. Found: 1035.4100.

*2,3,4-Tri-*O*-benzyl-6-*O*-acetyl-α-*D*-glucal* (**2a**).—$[\alpha]_D$ +1.18° (*c* 1.01, $CDCl_3$): ^{1}H NMR (DRX500, $CDCl_3$): δ 7.36–7.25 (m, 15H, PhH), 6.27 (s, 1H, H-1), 4.79 (d, 1H, *J* 11.5 Hz, PhC*H*), 4.72 (d, 1H, *J* 12.0 Hz, PhC*H*), 4.71 (apparent s, 2H, 2PhC*H*), 4.65 (d, 1H, *J* 11.5 Hz, PhC*H*), 4.61 (d, 1H, *J* 11.5 Hz, PhC*H*), 4.36 (dd, 1H, *J* 6.5 Hz, 12.0 Hz, H-6), 4.30 (dd, 1H, *J* 2.0 Hz, 12.0 Hz, H-6), 4.25 (d, 1H, *J* 4.7 Hz, H-3), 4.11 (m, 1H, H-5), 3.82 (t, 1H, *J* 4.7 Hz, H-4), 2.06 (s, 3H, OAc). ^{13}C NMR (DRX500, $CDCl_3$): δ 170.70 (CO), 139.29 (C-2), 138.19 (Ph-C), 137.56 (Ph-C), 137.00 (Ph-C), 128.47 (Ph), 128.42 (Ph), 128.35 (Ph), 127.94 (Ph), 127.92 (Ph), 127.87 (Ph), 127.67 (Ph), 127.53 (Ph), 126.88 (C-1), 75.18 (C-3), 74.64 (C-5), 73.99 (C-4), 72.70 (C-OBn), 72.54 (C-OBn), 70.95 (C-OBn), 62.52 (C-6), 20.83 (CH_3). HRFABMS *m*/*z* $[M]^+$ Calcd $C_{29}H_{30}O_6$: 474.2056. Found: 474.2056.

*Methoxycarbonylmethyl 6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-*D*-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-α-*D*-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-1-thio-α-*D*-glucopyranoside* (**17**).—Deacetylation of **15** was carried out according to the aforementioned procedure. The desired material **16** had R_f 0.30 on TLC with 1:1 EtOAc–hexanes was isolated in 98% yield following silica gel column chromatography using 1:2 EtOAc–hexanes as the eluent: $[\alpha]_D$ +124° (*c* 0.80, $CDCl_3$): δ 7.39–7.04 (30H, Ph-H), 5.83 (d, 1H, *J* 5.5 Hz, H-1^I), 5.06 (d, 1H, *J* 11.5 Hz, PhCH), 5.01 (d, 1H, *J* 11.5 Hz, PhCH), 4.97 (d, 1H, *J* 3.4 Hz, H-1^{II}), 4.93 (t, 2H, *J* 11.8 Hz, 2PhCH), 4.92 (d, 1H, *J* 11.3 Hz, PhCH), 4.72 (d, 1H, *J* 11.5 Hz, PhCH), 4.69 (d, 1H, *J* 11.2 Hz, PhCH), 4.66 (t, 2H, *J* 11.3 Hz, 2PhCH), 4.55 (d, 1H, *J* 12.0 Hz, PhCH), 4.54 (d, 1H, *J* 12.0 Hz, PhCH), 4.38 (m, 1H, H-5^I), 4.34 (d, 1H, *J* 11.5 Hz, PhCH), 4.23 (t, 1H, *J* 9.5 Hz, H-3^{II}), 4.08 (t, 1H, *J* 9.2 Hz, H-3^I), 3.93 (dd, 1H, *J* 6.6 Hz & 11.6 Hz, H-6^I), 3.84 (m, 1H, H-5^{II}), 3.81–3.69 (m, 5H, H-2^I, H-4^I, H-6^I, H-6^{II}, H-6^{II}), 3.66 (t, 1H, *J* 9.5 Hz, H-4^{II}), 3.50 (dd, 1H, *J* 3.4 Hz, 9.5 Hz, H-2^{II}), 3.40 (d, 1H, *J* 15.5 Hz, SCH), 3.29 (s, 3H, OCH_3), 2.99 (d, 1H, *J* 15.5 Hz, SCH), 1.74 (s, 1H, OH). ^{13}C NMR (DRX500, C_6D_6): δ 170.58 (CO), 139.69 (Ph-C), 139.50 (Ph-C), 139.15 (3C, Ph-C), 128.69–127.53 (30C, Ph), 97.66 (C-1^{II}), 82.91 (C-1^I), 82.84 (C-3^I), 82.02 (C-3^{II}), 80.98 (C-2^{II}), 79.93 (C-2^I), 78.07 (C-4^{II}), 77.80 (C-4^I), 75.61 (C-OBn), 75.53 (C-OBn), 75.14 (2C, C-OBn), 72.76 (C-OBn), 72.02 (C-OBn), 71.95 (C-5^I), 71.74 (C-5^{II}), 66.50 (C-6^I), 62.03 (C-6^{II}), 51.85 (OCH_3), 29.86 (SCH_2). HRFABMS *m*/*z* $[M+Na]^+$ Calcd $C_{57}H_{62}NaO_{12}S$: 993.3858. Found: 993.3812.

The disaccharide glycosyl acceptor **16** (100 mg, 0.10 mmol) was allowed to react with **2** (0.29 mmol) in PhH (4 mL) under the aforementioned conditions for 2.5 h. TLC in 1:2 EtOAc–hexanes indicated a major spot R_f 0.21. Silica gel column chromatography using 1:4 EtOAc–hexanes as the eluent provided 138 mg of compound **17** in a 92% yield: $[\alpha]_D$ +133° (*c* 0.95, $CDCl_3$). ^{1}H NMR (DRX500, C_6D_6): ^{1}H NMR (DRX500, C_6D_6) δ 7.49–7.15 (45H, Ph-H), 5.97 (d, 1H, *J* 5.5 Hz, H-1^I), 5.27 (d, 1H, *J* 3.1 Hz, H-1^{II}), 5.22 (d,

1H, *J* 11.5 Hz, PhC*H*), 5.18 (d, 1H, *J* 11.2 Hz, PhC*H*), 5.17 (t, 2H, *J* 11.0 Hz, PhC*H*), 5.12 (d, 1H, *J* 3.3 Hz, H-1^{III}), 5.05–5.01 (3H, 3PhC*H*), 4.97 (d, 1H, *J* 11.6 Hz, PhC*H*), 4.86 (d, 1H, *J* 11.3 Hz, PhC*H*), 4.81 (d, 1H, *J* 11.3 Hz, PhC*H*), 4.75 (d, 1H, *J* 11.5 Hz, PhC*H*), 4.71 (d, 1H, *J* 11.2 Hz, PhC*H*), 4.68 (d, 1H, *J* 11.8 Hz, PhC*H*), 4.61–4.52 (5H, H-6^{III}, 3PhC*H*, H-5^{I}), 4.46 (d, 1H, *J* 11.5 Hz, PhC*H*), 4.42–4.34 (3H, H-6^{III}, H-3^{III}, H-3^{II}), 4.21 (t, 1H, *J* 9.2 Hz, H-3^{I}), 4.14–4.05 (5H, H-5^{II}, H-5^{III}, H-6^{II}, H-4^{III}, H-6^{I}), 3.95–3.87 (4H, H-2^{I}, H-4^{I}, H-6^{I}, H-6^{II}), 3.69 (t, 1H, *J* 9.6 Hz, H-4^{II}), 3.66 (dd, 1H, *J* 3.1 Hz, 9.6 Hz, H-2^{II}), 3.62 (dd, 1H, *J* 3.3 Hz, 9.5 Hz, H-2^{III}), 3.55 (d, 1H, *J* 15.5 Hz, SCH), 3.43 (s, 3H, OCH_3), 3.11 (d, 1H, *J* 15.5 Hz, SCH), 1.78 (s, 3H, CH_3). ^{13}C NMR (DRX500, C_6D_6): δ 170.58 (CO), 169.91 (CO), 139.66 (Ph-C), 139.51 (2C, Ph-C), 139.34 (Ph-C), 139.20 (Ph-C), 139.16 (Ph-C), 139.03 (Ph-C), 138.81 (Ph-C), 138.30 (Ph-C), 128.67–127.56 (45C, Ph), 97.71 (C-1^{III}), 97.20 (C-1^{II}), 82.92 (C-1^{I}), 82.86 (C-3 ^{I}), 82.27 (C-3^{III}), 82.06 (C-3^{II}), 81.15 (C-2^{III}), 80.95 (C-2^{II}), 79.97 (C-2^{I}), 78.08 (C-4^{III}), 77.94 (C-4^{I}), 77.89 (C-4^{II}), 75.63 (C-OBn), 75.59 (C-OBn), 75.51 (C-OBn), 75.24 (C-OBn), 75.20 (C-OBn), 75.04 (C-OBn), 72.84 (C-OBn), 72.37 (C-OBn), 72.01 (C-OBn, C-5^{I}), 71.51 (C-5^{III}), 69.43 (C-5^{II}), 66.55 (C-6^{II}), 66.92 (C-6^{I}), 63.32 (C-6^{III}), 51.87 (OCH_3), 29.85 (SCH_2), 14.81 (CH_3). HRFABMS *m*/*z* $[M + Na]^+$ Calcd $C_{86}H_{92}NaO_{18}S$: 1467.5901. Found: 1467.5801.

*Methoxycarbonylmethyl (6-*O*-acetyl-2,3,4-tri-*O*-benzyl-α-*D*-glucopyranosyl)-α-(1→6)-bis-((2,3,4-tri-*O*-benzyl-α-*D*-glucopyranosyl)-α-(1→6))-2,3,4-tri-*O*-benzyl-1-thio-α-*D*-glucopyranoside* (**19**).—Trisaccharide **17** (421 mg, 0.29 mmol) was treated with NaOMe in MeOH as previously indicated. The reaction was monitored through TLC in 1:2 EtOAc–hexanes; a product with R_f 0.16 correlated to the deacetylated trisaccharide. Purification through silica gel column chromatography was carried out using 1:2 EtOAc–hexanes as the eluent to remove baseline impurities, which yielded 406 mg of material **18** in 99% yield: $[\alpha]_D$ +157° (*c* 1.04, $CDCl_3$). ^{1}H NMR (DRX500, C_6D_6): δ 7.52–7.15 (45H, Ph-H), 5.98 (d, 1H, *J* 5.6 Hz, H-1^{I}), 5.26 (d, 1H, *J* 3.4 Hz, H-1^{II}), 5.22 (d, 1H, *J* 11.6 Hz, PhCH), 5.19 (d, 1H, *J* 11.4 Hz, PhCH), 5.17 (d, 1H, *J* 2.4 Hz, H-1^{III}), 5.15 (m, 2H, 2PhCH), 5.04 (d, 1H, *J* 10.0 Hz, PhCH), 5.03 (d, 1H, *J* 11.2 Hz, PhCH), 5.02 (d, 1H, *J* 10.7 Hz, PhCH), 4.99 (d, 1H, *J* 11.3 Hz, PhCH), 4.98 (d, 1H, *J* 11.5 Hz, PhCH), 4.86 (d, 1H, *J* 11.5 Hz, PhCH), 4.81 (d, 1H, *J* 11.3 Hz, PhCH), 4.76 (t, 3H, *J* 11.2 Hz, 3PhCH), 4.66 (d, 1H, *J* 12.0 Hz, PhCH), 4.60 (d, 1H, *J* 12.0 Hz, PhCH), 4.57 (d, 1H, *J* 12.0 Hz, PhCH), 4.55 (dd, 1H, *J* 4.4 H, 9.7 Hz, H-5^{I}), 4.46 (d, 1H, *J* 11.5 Hz, PhCH), 4.39 (t, 1H, *J* 9.0 Hz, H-3^{III}), 4.36 (t, 1H, *J* 9.2 Hz, H-3^{II}), 4.22 (t, 1H, *J* 9.1 Hz, H-3^{I}), 4.14 (m, 2H, H-6^{II}, H-5^{II}), 4.10 (t, 1H, *J* 9.0 Hz, H-4^{III}), 4.03 (dd, 1H, *J* 3.4 Hz, 12.2 Hz, H-6^{I}), 3.96–3.81 (6H, H-5^{III}, H-2^{I}, H-6^{II}, H-4^{I}, H-6^{I}, H-6^{III}), 3.76 (t, 1H, *J* 9.2 Hz, H-4^{II}), 3.65 (dd, 1H, *J* 3.4 Hz, 9.2 Hz, H-2^{II}), 3.62 (dd, 1H, *J* 2.4 Hz, 9.0 Hz, H-2^{III}), 3.52 (d, 1H, *J* 15.5 Hz, SCH), 3.42 (s, 3H, OCH_3), 3.11 (d, 1H, *J* 15.5 Hz, SCH), 1.72 (s, 1H, OH). ^{13}C NMR (DRX500, C_6D_6): δ 170.59 (CO), 139.69 (Ph-C), 139.65 (Ph-C), 139.51 (Ph-C), 139.39 (Ph-C), 139.19 (3C, Ph-C), 139.14 (Ph-C), 138.30 (Ph-C), 128.69–127.54 (45C, Ph), 97.81 (C-1^{III}), 97.40 (C-1^{II}), 82.94 (C-1^{I}), 82.87 (C-3^{I}), 82.29 (C-3^{III}), 81.95 (C-3^{II}), 81.19 (C-2^{III}), 80.97 (C-2^{II}), 79.98 (C-2^{I}), 78.13 (C-4^{III}, C-4^{II}), 77.98 (C-4^{I}), 75.66 (C-OBn), 75.60 (C-OBn), 75.48 (C-OBn), 75.26 (C-OBn), 75.20 (C-OBn), 75.13 (C-OBn), 72.90 (C-OBn), 72.50 (C-OBn), 72.03 (C-OBn, C-5^{I}), 71.69 (C-5^{III}), 71.53 (C-5^{II}), 66.68 (C-6^{II}), 65.89 (C-6^{I}), 62.13 (C-6^{III}), 51.87 (OCH_3), 29.83 (SCH_2). HRFABMS *m*/*z* $[M + Na]^+$ Calcd $C_{84}H_{90}NaO_{17}S$: 1425.5795. Found: 1425.5895.

The trisaccharide glycosyl acceptor (**18**, 137 mg, 0.10 mmol) was allowed to react with **2** (0.30 mmol) in anhyd PhH (4 mL) under the aforementioned conditions for 5 h. TLC in 1:2 EtOAc–hexanes indicated a major product with R_f 0.36. Silica gel column chromatography using 1:3 EtOAc–hexanes as the eluent provided 159 mg of compound **19** in an 87% yield: $[\alpha]_D$ +116° (*c* 0.76, $CDCl_3$). ^{1}H NMR (DRX500, C_6D_6): δ 7.52–7.15 (60H, Ph-H), 5.97 (d, 1H, *J* 5.6 Hz, H-1^{I}), 5.32 (d, 1H, *J* 3.4 Hz, H-1^{II}), 5.30 (d, 1H, *J* 3.4 Hz, H-1^{III}), 5.25 (apparent t, 2H, *J* 11.0 Hz, 2PhC*H*), 5.19 (apparent t, 2H, *J* 11.0 Hz, 2PhC*H*), 5.17 (apparent t, 2H, *J* 11.0 Hz, 2PhC*H*), 5.14 (d, 1H, *J* 3.6 Hz, H-1^{IV}), 5.03 (d, 3H, *J* 11.3 Hz, 3PhC*H*), 4.99 (apparent t, 3H, *J* 11.6 Hz, 3PhC*H*), 4.96 (d, 1H, *J* 11.3 Hz, PhC*H*), 4.87 (d, 1H, *J* 11.5 Hz, PhC*H*), 4.81 (d, 1H, *J* 11.3 Hz, PhC*H*), 4.75 (d, 1H, *J* 11.4 Hz, PhC*H*), 4.72 (d, 2H, *J* 11.6 Hz), 4.64 (d, 1H, *J* 12.0 Hz, PhC*H*), 4.59 (d, 2H, *J* 12.0 Hz, 2 PhC*H*), 4.57 (apparent t, 3H, *J* 12.0 Hz, 2PhC*H*, H-6^{IV}), 4.53 (d, 1H, *J* 4.4 Hz, H-5^{I}), 4.45–4.35 (m, 5H, H-3^{III}, H-6^{IV}, H-3^{IV}, PhC*H*, H-3^{II}), 4.21 (t, 1H, *J* 9.1 Hz, H-3^{I}), 4.16–4.05 (m, 8H, H-5^{III}, H-4^{IV}, H-6^{II}, H-5^{II}, H-4^{III}, H-6^{I}, H-5^{IV}), 3.96–3.88 (m, 4H, H-6^{IV}, H-4^{I}, H-6^{I}, H-2^{I}), 3.70 (t, 1H, *J* 9.4 Hz, H-4^{II}), 3.68–3.61 (m, 3H, H-2^{II}, H-2^{IV}, H-2^{III}), 3.51 (d, 1H, *J* 15.5 Hz, SCH), 3.43 (s, 3H, OCH_3), 3.10 (d, 1H, *J* 15.5 Hz, SCH), 1.78 (s, 3H, CH_3). ^{13}C NMR (DRX500, C_6D_6): δ 170.57 (CO), 169.91 (CO), 139.69 (Ph-C), 139.60 (Ph-C), 139.53 (Ph-C), 139.52 (Ph-C), 139.45 (Ph-C), 139.39 (Ph-C), 139.24 (Ph-C), 139.22 (Ph-C), 139.19 (Ph-C), 139.05 (Ph-C), 138.84 (Ph-C), 138.31 (Ph-C), 130.34–127.46 (60C, Ph), 97.78 (C-1^{IV}), 97.56 (C-1^{III}), 97.28 (C-1^{II}), 82.93 (C-1^{I}), 82.88 (C-3^{I}), 82.33 (C-3^{III}), 82.18 (C-3^{IV}), 82.05 (C-3^{II}), 81.22 (C-2^{III}), 81.13 (C-2^{IV}), 80.98 (C-2^{II}), 79.99 (C-2^{I}), 78.13 (C-4^{IV}), 78.01 (C-4^{III}), 77.93 (C-4^{I}), 77.89 (C-4^{II}), 75.66 (C-OBn), 75.63 (C-OBn), 75.55 (C-OBn), 75.51 (C-OBn), 75.31 (C-OBn), 75.27 (C-OBn), 75.20 (C-OBn), 75.05 (C-OBn), 72.90 (C-OBn), 72.62 (C-OBn), 72.35 (C-OBn), 72.03 (C-OBn,

C-OBn, C-5^{I}), 71.63 (C-5^{III}), 71.58 (C-5^{II}), 69.45 (C-5^{II}), 66.51 (C-6^{II}), 65.82 (C-6^{III}, C-6^{I}), 63.34 (C-6^{IV}), 51.88 (OCH_3), 29.83 (SCH_2), 20.44 (CH_3). HRFABMS m/z $[M+Na]^+$ Calcd $C_{113}H_{120}NaO_{23}S$: 1899.7838. Found: 1899.7857.

Preparation of tetrasaccharide **19** *using convergent strategy*.—In a typical experiment, **24** (560 mg, 0.58 mmol) was dissolved in anhyd CH_2Cl_2 (10 mL) and cooled in an ice bath under a flow of dry argon for 20 min. TMSI (99 μL, 0.69 mmol) was then syringed into the stirring mixture. The reaction was proceeded for 2 h at 0 °C, at which point, anhyd PhMe was syringed into the reaction vessel, and the solvents and volatile side products were removed in vacuo. Azeotroping with anhyd toluene was continued until a colorless distillate persisted. The resulting pale-yellow oil **3** was redissolved in anhyd PhH (2.0 mL) and cannulated into a stirring mixture of disaccharide glycosyl acceptor **17** (204 mg, 0.21 mmol), TBAI (428 mg, 1.16 mmol), DIPEA (55 μL, 0.32 mmol), and 4 Å MS in anhyd PhH (2.0 mL). The reaction was immediately set to reflux for 3 h and worked up as previously described. After silica gel column chromatography using 1:3 EtOAc–hexanes as the eluent, 369 mg of desired tetrasaccharide **19** was isolated in 94% yield.

6-O-*Acetyl-2,3,4-tri*-O-*benzyl-α*-D-*glucopyranosyl-(1→6)-2,3,4-tri*-O-*benzyl*-D-*glucal* (**3a**).—$[\alpha]_D$ +33.2° (*c* 0.32, $CDCl_3$). ^{1}H NMR (DRX500, $CDCl_3$): ^{1}H NMR (DRX500, $CDCl_3$) δ 7.45–7.19 (m, 30H, PhH), 6.32 (s, 1H, H-1), 5.16 (d, 1H, *J* 11.5 Hz, PhC*H*), 5.13 (d, 1H, *J* 3.0 Hz, H-1^{II}), 5.03 (d, 1H, *J* 11.5 Hz, PhC*H*), 4.90 (d, 2H, *J* 11.5 Hz, 2PhC*H*), 4.76 (d, 2H, *J* 12.0 Hz, 2PhC*H*), 4.69 (apparent t, 3H, *J* 10.8 Hz, 3PhC*H*), 4.62 (apparent t, 1H, *J* 11.4 Hz, PhC*H*), 4.59 (apparent t, 2H, *J* 11.4 Hz, H-6^{I}, PhC*H*), 4.53–4.47 (m, 4H, 2PhC*H*, H-6^{I}, H-4^{I}), 4.40 (t, 1H, *J* 9.6 Hz, 8.4 Hz, H-3^{II}), 4.35 (br, 1H, H-3^{I}), 4.26–4.21 (m, 3H, H-5^{II}, H-6^{II}, H-5^{I}), 3.91 (m, 1H, C-6^{II}), 3.68 (t, 1H, *J* 9.6 Hz, H-4^{II}), 3.67 (dd, 1H, *J* 3.0 Hz, 9.6 Hz, H-2^{II}), 1.82 (s, 3H, OAc). ^{13}C NMR (DRX500, $CDCl_3$): δ 170.06 (CO), 139.86 (Ph-C), 139.59 (Ph-C), 139.09 (Ph-C), 138.95 (Ph-C), 138.83 (Ph-C), 138.81 (Ph-C), 137.72 (C-2^{I}), 128.56 (Ph), 128.49 (Ph), 128.46 (Ph), 128.32 (Ph-C), 128.19 (Ph-C), 128.11 (Ph-C), 127.99 (Ph), 127.92 (Ph), 127.81 (Ph), 127.69 (Ph), 127.55 (Ph), 127.44 (C-1^{I}), 97.17 (C-1^{II}), 82.20 (C-3^{II}), 80.99 (C-2^{II}), 77.99 (C-4^{II}), 76.39 (C-3^{I}), 75.95 (C-4^{I}), 75.50 (C-OBn), 75.06 (C-OBn), 75.03 (C-5^{I}), 72.79 (C-OBn), 72.74 (C-OBn), 72.70 (C-OBn), 70.87 (C-OBn), 69.42 (C-5^{II}), 65.97 (C-6^{II}), 63.40 (C-6^{I}), 20.46 (CH_3). HRFABMS m/z $[M+Na]^+$ Calcd $C_{56}H_{58}NaO_{11}$: 929.3877. Found: 929.3921.

Methoxycarbonylmethyl 2,3,4-tri-O-*benzyl-α*-D-*glucopyranosyl-(1→6)-bis-(2,3,4-tri*-O-*benzyl-α*-D-*glucopyranosyl-(1→6))-2,3,4-tri*-O-*benzyl-1-thio-α*-D-*glucopyranoside* (**25**).—Tetrasaccharide **19** (350 mg, 0.18 mmol) in MeOH was treated with 0.5 M NaOMe–MeOH as previously indicated. The reaction was monitored by TLC in 1:2 EtOAc–hexanes. A product with R_f 0.16 correlated to the deacetylated tetrasaccharide **25**. Purification using silica gel column chromatography was carried out using 1:2 EtOAc–hexanes as the eluent to remove baseline impurities, which yielded 308 mg of **25** in 90% yield: $[\alpha]_D$ +98.7° (*c* 0.82, $CDCl_3$). ^{1}H NMR (DRX500, C_6D_6): ^{1}H NMR (DRX500, C_6D_6): δ 7.52–7.14 (60H, Ph-H), 5.97 (d, 1H, *J* 5.6 Hz, H-1^{I}), 5.34 (d, 1H, *J* 3.4 Hz, H-1^{II}), 5.30 (d, 1H, *J* 3.4 Hz, H-1^{III}), 5.27 (apparent t, 2H, 2PhCH), 5.25–5.15 (m, 5H, 4PhCH, H-1^{IV}), 5.05 (apparent t, 3H, 3PhCH), 5.00 (apparent t, 3H, 3PhCH), 4.98 (d, 1H, *J* 11.3 Hz, PhCH), 4.87 (d, 1H, *J* 11.5 Hz, PhCH), 4.82 (d, 1H, *J* 11.3 Hz, PhCH), 4.76 (d, 2H, *J* 11.4 Hz, 2PhCH), 4.66 (apparent dd, 2H, *J* 12.0 Hz, 2PhCH), 4.62–4.56 (m, 5H, 4PhCH, H-6^{IV}), 4.53 (m, 1H, *J* 4.4 Hz, H-5^{I}), 4.46–4.35 (m, 5H, H-3^{III}, H-6^{IV}, H-3^{IV}, PhCH, H-3^{II}), 4.21 (t, 1H, *J* 9.1 Hz, H-3^{I}), 4.16–4.05 (m, 8H, H-5^{III}, H-4^{IV}, H-6^{II}, H-5^{II}, H-4^{III}, H-6^{I}, H-5^{IV}), 3.96–3.88 (m, 4H, H-6^{IV}, H-4^{I}, H-6^{I}, H-2^{I}), 3.70 (t, 1H, *J* 9.4 Hz, H-4^{II}), 3.68–3.61 (m, 3H, H-2^{II}, H-2^{IV}, H-2^{III}), 3.51 (d, 1H, *J* 15.5 Hz, SCH), 3.43 (s, 3H, OCH_3), 3.10 (d, 1H, *J* 15.5 Hz, SCH), 1.79 (t, 1H, OH). ^{13}C NMR (DRX500, C_6D_6): δ 170.62 (CO), 139.68 (Ph-C), 139.61 (Ph-C), 139.51 (Ph-C), 139.45 (Ph-C), 139.22 (Ph-C), 139.18 (Ph-C), 139.14 (Ph-C), 138.31 (Ph-C), 128.66–127.54 (60C, Ph), 97.82 (C-1^{IV}), 97.63 (C-1^{III}), 97.42 (C-1^{II}), 82.92 (C-1^{I}), 82.87 (C-3^{I}), 82.31 (C-3^{III}), 82.19 (C-3^{IV}), 81.91 (C-3^{II}), 81.20 (C-2^{III}), 81.15 (C-2^{IV}), 80.96 (C-2^{II}), 79.99 (C-2^{I}), 78.16 (C-4^{IV}), 78.04 (C-4^{III}), 77.93 (C-4^{I}), 77.89 (C-4^{II}), 75.67 (C-OBn), 75.55 (C-OBn), 75.47 (C-OBn), 75.30 (C-OBn), 75.22 (C-OBn), 75.13 (C-OBn), 72.89 (C-OBn), 72.71 (C-OBn), 72.49 (C-OBn), 72.03 (2C-OBn, C-5^{I}), 71.71 (C-5^{III}), 71.58 (C-5^{II}), 69.45 (C-5^{II}), 66.51 (C-6^{II}), 65.82 (C-6^{III}, C-6^{I}), 62.14 (C-6^{IV}), 51.90 (OCH_3), 29.83 (SCH_2). MALDI-HRMS m/z $[M+Na]^+$ Calcd $C_{111}H_{118}NaO_{22}S$: 1857.7733. Found: 1857.7664.

Methoxycarbonylmethyl 6-O-*acetyl-2,3,4-tri*-O-*benzyl-α*-D-*glucopyranosyl-(1→6)-tetrakis-(2,3,4-tri*-O-*benzyl-α*-D-*glucopyranosyl-(1→6))-2,3,4-tri*-O-*benzyl-1-thio-α*-D-*glucopyranoside* (**26**).—Glycosyl acceptor **25** (300 mg, 0.16 mmol) was allowed to react with **3** (0.38 mmol) in anhyd PhH (4 mL) under the aforementioned conditions for 3 h. TLC in 1:2 EtOAc–hexanes indicated a major product at R_f 0.26. Silica gel column chromatography using 1:3 EtOAc–hexane as the eluent provided 416 mg of compound **26** in 93% yield: $[\alpha]_D$ +88.1° (*c* 1.01, $CDCl_3$). ^{1}H NMR (DRX500, C_6D_6): δ 7.49–7.15 (90H, Ph-H), 5.97 (d, 1H, *J* 5.6 Hz, H-1^{I}), 5.39 (d, 1H, *J* 3.3 Hz, H-1^{II}), 5.37 (apparent t, 2H, *J* 4.6, 3.9 Hz, H-1^{III}, H-1^{IV}), 5.35 (d, 1H, *J* 3.5 Hz, H-1^{V}), 5.33–5.17 (m, 11H, 10 PhCH, H-1^{VI}) [estimated from DQF-COSY data 5.15 (d, 1H, *J* 1.8 Hz, H-1^{VI})], 5.09–4.97 (m, 11H, 11PhCH), 4.92 (d, 1H, *J* 11.5 Hz,

PhCH), 4.85 (d, 1H, *J* 11.3 Hz, PhCH), 4.79 (d, 1H, *J* 11.5 Hz, PhCH), 4.77–4.56 (m, 13H, 11PhCH, H-6^{VI}, H-5^{I}), 4.49–4.39 (m, 7H, H-$6^{VI\prime}$, PhCH, H-3^{III}, H-3^{IV}, H-3^{VI}, H-3^{V}, H-3^{II}), 4.27–4.10 (m, 15H, H-3^{I}, H-4^{IV}, H-4^{VI}, H-4^{III}, H-5^{V}, H-4^{V}, H-6^{II}, H-5^{II}, H-6^{IV}, H-6^{V}, H-6^{III}, H-5^{III}, H-5^{IV}, H-6^{I}, H-5^{VI}), 4.00–3.90 (m, 7H, H-4^{I}, H-2^{II}, H-$6^{IV\prime}$, H-$6^{V\prime}$, H-$6^{III\prime}$, H-$6^{I\prime}$, H-$6^{II\prime}$), 3.76–3.67 (m, 6H, H-4^{II}, H-2^{II}, H-2^{IV}, H-1^{VI}, H-2^{V}, H-2^{III}), 3.55 (d, 1H, *J* 15.5 Hz, SCH), 3.48 (s, 3H, OCH_3), 3.15 (d, 1H, *J* 15.5 Hz, SCH), 1.83 (s, 3H, CH_3). ^{13}C NMR (DRX500, C_6D_6): δ 170.58 (CO), 169.95 (CO), 139.68 (Ph-C), 139.60 (Ph-C), 139.50 (Ph-C), 139.39 (Ph-C), 139.23 (Ph-C), 139.19 (Ph-C), 139.05 (Ph-C), 138.83 (Ph-C), 138.31 (Ph-C), 130.34–127.46 (90C, Ph), 97.79 (C-1^{VI}), 97.66 (C-1^{V}), 97.63 (C-1^{IV}), 97.61 (C-1^{III}), 97.27 (C-1^{II}), 82.95 (C-1^{I}), 82.87 (C-3^{I}), 82.30 (C-3^{III}), 82.19 (C-3^{IV}, C-3^{V}), 82.14 (C-3^{VI}), 82.03 (C-3^{II}), 81.17 (C-2^{III}, C-2^{IV}, C-2E, C-2F), 80.99 (C-2^{II}), 79.99 (C-2^{I}), 78.02 (C-4^{IV}, C-4^{V}, C-4^{VI}), 77.89 (C-4^{III}), 77.62 (C-4^{I}, C-4^{II}), 75.66 (C-OBn), 75.63 (C-OBn), 75.52 (C-OBn), 75.28 (C-OBn), 75.20 (C-OBn), 75.05 (C-OBn), 72.90 (C-OBn), 72.64 (C-OBn), 72.59 (C-OBn), 72.37 (C-OBn), 72.04 (C-OBn, C-5^{I}), 71.66 (C-5^{III}, 5D, 5E, 5F), 69.45 (C-5^{II}), 66.51 (C-6^{II}), 65.71 (C-6^{I}, C-6^{III}, C-6^{IV}, C-6E), 63.34 (C-6F), 51.91 (OCH_3), 29.86 (SCH_2), 20.47 (CH_3). MALDI-HRMS *m*/*z* $[M + Na]^+$ Calcd $C_{167}H_{176}NaO_{33}S$: 2764.1712. Found: 2764.1980.

*Methyl 6-*O*-tert-Butyldiphenylsilyl-α-*D*-glucopyranoside* (**20**).—A flask containing methyl α-D-glucopyranoside, (**4**, 9.2 g, 47 mmol) was charged with dry DMF (100 mL) and cooled to 0°C under argon. To the stirring mixture was added DMAP (cat.), Et_3N (5.5 mL, 39 mmol) by syringe, followed by *tert*-butylchlorodiphenylsilane (8.2 mL, 31 mmol). The reaction was warmed to rt and stirred for an additional 1 h. TLC in EtOAc revealed a new spot (R_f 0.45) corresponding to the desired material **20**. The reaction mixture was diluted with EtOAc (300 mL), washed with water (2 × 200 mL) and brine (2 × 100 mL). The organic layer was dried with anhyd Na_2SO_4 and concentrated in vacuo. The product **20** was recovered as a white solid (19.9 g, 98% yield) after passage through a pad of silica gel using EtOAc as the eluent: $[\alpha]_D$ + 57.4° (*c* 1.08, $CDCl_3$). ^{1}H NMR (DRX500, $CDCl_3$): δ 7.69–7.67 (m, 4H, PhH), 7.39–7.24 (m, 6H, PhH), 5.03 (br, 1H, OH), 4.68 (d, 1H, *J* 3.5 Hz, H-1) 4.06 (br, 2H, 2OH), 3.89 (m, 1H, H-6), 3.81 (dd, 1H, *J* 5.5 Hz, 10.5 Hz, H-6′), 3.74 (apparent t, 1H, *J* 9.3 Hz, H-3), 3.61 (m, 1H, H-5), 3.57 (apparent dd, 1H, *J* 3.5 Hz, 9.3 Hz, H-2), 3.43 (apparent t, 1H, *J* 9.3 Hz, H-4), 3.32 (s, 3H, OMe), 1.03 (s, 9 H, *t*-Bu). ^{13}C NMR (DRX500, $CDCl_3$): δ 135.61 (2Ph-C), 133.34 (Ph-C), 129.61 (Ph), 127.60 (Ph), 99.20 (C-1), 74.33 (C-3), 71.99 (C-2), 71.62 (C-5), 70.99 (C-4), 64.00 (C-6), 54.85 (OCH_3), 26.76 (*t*-Bu), 19.20 (*t*-Bu-C). HRFABMS *m*/*z* $[M + Na]^+$ Calcd $C_{23}H_{32}NaO_6Si$: 455.1866. Found: 455.1874.

*Methyl 2,3,4-tri-*O*-benzyl-6-*O*-tert-butyldiphenylsilyl-α-*D*-glucopyranoside* (**21**).—To a vigorously stirring solution of compound **20** (7.6 g, 17 mmol) in DMF (100 mL), cooled in an ice bath, was slowly added NaH (2.5 g, 105 mmol) in parts over a period of 45 min to prevent caking. TBAI (cat.) was added, and benzyl bromide (12.5 mL, 105 mmol) was syringed into the cooled heterogeneous mixture over a period of 30 min. The reaction was stirred and warmed to rt for 5 h after which time the solution was stirred overnight (~ 10 h) at 80°C. TLC in 1:5 EtOAc–hexanes revealed a major spot at R_f 0.39. The reaction was quenched with MeOH, the mixture was concentrated in vacuo, and the residue was redissolved in CH_2Cl_2. The salts filtered off over a pad of Celite. After silica gel column chromatography using 10% EtOAc–hexanes as the eluent, the titled product **21** was isolated in 88% yield: $[\alpha]_D$ + 8.23° (*c* 0.99, $CDCl_3$). ^{1}H NMR (DRX500, $CDCl_3$): δ 7.70–7.66 (m, 4H, PhH), 7.42–7.24 (m, 19H, PhH), 7.15–7.13 (m, 2H, PhH), 4.96 (d, 1H, *J* 10.7 Hz, PhC*H*), 4.86 (d, 1H, *J* 10.7 Hz, PhC*H*), 4.84 (d, 1H, *J* 10.7 Hz, PhC*H*), 4.80 (d, 1H, *J* 12.0 Hz, PhC*H*), 4.72 (d, 1H, *J* 10.7 Hz, PhC*H*), 4.65 (d, 1H, *J* 3.5 Hz, H-1) 4.61 (d, 1H, *J* 10.7 Hz, PhC*H*), 4.01 (t, 1H, *J* 9.2 Hz, H-3), 3.86 (m, 2H, H-6, H-6′), 3.68 (m, 1H, H-5), 3.61 (t, 1H, *J* 9.2 Hz, H-4), 3.57 (dd, 1H, *J* 3.5 Hz, 9.2 Hz, H-2), 3.37 (s, 3H, OMe), 1.04 (s, 9 H, *t*-Bu). ^{13}C NMR (DRX500, $CDCl_3$): δ 138.75 (Ph-C), 138.29 (Ph-C), 138.27 (Ph), 135.79 (Ph), 135.61 (Ph-C), 133.61 (Ph-C), 133.31 (Ph), 129.56 (Ph), 129.53 (Ph), 128.42 (Ph), 128.40 (Ph), 128.33 (Ph), 128.11 (Ph), 128.02 (Ph), 127.82 (Ph), 127.62 (Ph), 127.51 (Ph), 97.85 (C-1), 82.24 (C-3), 80.28 (C-2), 77.84 (C-4), 75.88 (C-OBn), 75.05 (C-OBn), 73.33 (C-OBn), 71.47 (C-5), 62.96 (C-6), 54.83 (OCH_3), 26.78 (*t*-Bu), 19.27 (*t*-Bu-C). HRFABMS *m*/*z* $[M + Na]^+$ Calcd $C_{44}H_{50}NaO_6Si$: 725.3274. Found: 725.3278.

*1-*O*-Acetyl-2,3,4-tri-*O*-benzyl-6-*O*-tert-butyldiphenylsilyl-α-*D*-glucopyranose* (**22**).—To a stirring solution of compound **21** (1.21 g, 1.72 mmol) in 2:1 acetic anhydride–acetic acid (9.5 mL) was added a mixture of freshly fused zinc chloride (1.99 g, 14.6 mmol) in 2:1 acetic anhydride–acetic acid (19 mL). The reaction was vigorously stirred at rt for 1.5 h. TLC in 1:5 EtOAc–hexanes showed complete disappearance of starting material **21** and the appearance of a major spot, R_f 0.32. The reaction was diluted with EtOAc (200 mL), extracted water (3 × 75 mL), and the organic layer concentrated in vacuo to remove ~95% of the volume. The mixture was diluted in EtOAc (200 mL) and washed with satd aq $NaHCO_3$ until no more gas was evolved. The organic layer was dried with anhyd Na_2SO_4 and concentrated in vacuo. The crude product was purified by silica gel column chromatography using 1:9 EtOAc–hexanes as the eluent and yielded a pale yellow solid in 94%, which was the desired product **22**:

$[\alpha]_D$ +19.6° (*c* 1.03, $CDCl_3$). ^1H NMR (DRX500, $CDCl_3$): δ 7.72–7.66 (m, 6H, PhH), 7.39–7.18 (m, 19H, PhH), 6.43 (d, 1H, *J* 3.5 Hz, H-1), 4.95 (d, 1H, *J* 10.7 Hz, PhC*H*), 4.94 (d, 1H, *J* 10.7 Hz, PhC*H*), 4.84 (d, 1H, *J* 10.7 Hz, PhC*H*), 4.80 (d, 1H, *J* 12.0 Hz, PhC*H*), 4.72 (apparent t, 2H, *J* 12.0 Hz, 2PhC*H*), 4.01–3.88 (m, 4H, H-5, H-6, H-3, H-6′), 3.86 (t, *J* 9.3 Hz, H-4), 3.71 (dd, 1H, *J* 3.5 Hz, 9.5 Hz, H-2), 2.07 (s, 3H, $COCH_3$), 1.07 (s, 9 H, *t*-Bu). ^{13}C NMR (DRX500, $CDCl_3$): δ 169.31 (CO), 138.50 (Ph-C), 138.08 (Ph-C), 137.64 (Ph-C), 132.93 (Ph), 129.57 (Ph), 128.35 (Ph), 127.98 (Ph), 127.94 (Ph), 127.83 (Ph), 127.76 (Ph), 127.66 (Ph), 127.63 (Ph), 127.58 (Ph), 127.54 (Ph), 127.40 (Ph), 89.88 (C-1), 81.68 (C-3), 79.35 (C-2), 76.79 (C-5), 75.76 (C-OBn), 75.26 (C-OBn), 73.85 (C-4), 73.16 (C-OBn), 62.22 (C-6), 26.76 (*t*-Bu), 20.99 ($COCH_3$), 19.23 (*t*-Bu-C). HRFABMS *m*/*z* $[M+Na]^+$ Calcd $C_{45}H_{50}NaO_7Si$: 753.3223. Found: 753.3207.

Large-scale synthesis of **22** *from* **4**.—A solution of **4** (9.9 g, 51 mmol) in dry DMF (30 mL) was cooled to −40 °C and placed under an argon atmosphere. Hünig's base (9.8 mL, 56 mmol) was added via syringe to the stirring mixture, followed the addition of TBDPSCl (13 mL, 51 mmol) in parts over 30 min. The cooled solution was removed from the bath and allowed to warm to rt while stirring during a period of 1 h. The reaction mixture was then concentrated in vacuo, redissolved in EtOAc (300 mL), washed with brine (2 × 100 mL) and water (2 × 100 mL), dried with anhyd Na_2SO_4, and again concentrated in vacuo to dryness to yield **20** as a white solid. Crude **20** in anhyd DMF (20 mL) was cooled in an ice bath under argon. To the vigorously stirring mixture was added NaH (4.89 g, 204 mmol) in portions over 1 h to prevent caking. The reaction was allowed to warm to rt during 5 h after the syringe addition of benzyl bromide (24.3 mL, 204 mmol). The reaction was then stirred overnight (∼12 h) at 80 °C. After cooling to rt, the reaction was poured into a separatory funnel containing ice-cold water (500 mL). Following the addition of EtOAc (200 mL), the layers were separated. The organic layer was further washed with brine (2 × 200 mL), dried with anhyd Na_2SO_4, and concentrated to dryness in vacuo to provide **21** as a pale-yellow solid. Fully protected monosaccharide **21** was dissolved in 2:1 Ac_2O–HOAc (282 mL) and treated with a solution of freshly fused $ZnCl_2$ (29.0 g, 213 mmol) in 2:1 Ac_2O–HOAc (564 mL). The mixture was allowed to stir at rt over 24 h, diluted with EtOAc (500 mL) and washed with brine (4 × 200 mL). The organic layer was concentrated to ∼50 mL, diluted with EtOAc and washed with satd aq $NaHCO_3$ until no more gas evolved. The organic layer was dried with anhyd Na_2SO_4 and concentrated in vacuo to afford a reddish–brown crude oily solid. From a crude mixture of 2.20 g, 1.92 g was isolated as target **22**, in 89% yield from the crude material.

1-O-Acetyl-2,3,4-tri-O-benzyl-α-D-glucopyranose (**23**)[28].—A stirring solution of **22** (1.97 g, 2.69 mmol) was treated with 1 M TBAF–THF (8 mL) and glacial acetic acid (0.5 mL). The mixture was allowed to react overnight (∼10 h) under an inert atmosphere; TLC using 1:2 EtOAc–hexanes indicated a new major spot at R_f 0.17. The mixture was concentrated in vacuo and chromatographed using 1:2 EtOAc–hexanes as the eluent. The desired material **23** was isolated in 92% yield (1.22 g).

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