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Lipophilic Thioglycosides for the Solution-Phase Synthesis of Oligosaccharides Using Biphasic Liquid-Liquid Separation

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Dedicated to Prof. Josep Font on the occasion of his 70th birthday

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A simple "heavy" lipophilic tag readily prepared from inexpensive gallic acid can greatly simplify the purification steps in oligosaccharide synthesis through liquid-liquid extraction (LLE) using two immiscible organic solvents. By introducing the tag at the anomeric position of the carbohydrate acceptor, this simple LLE purification can be advantageously carried out at each step throughout the synthetic route. We have developed efficient tagging and detagging procedures and have shown that a single tag is sufficient to ensure a high affinity of the tagged molecule for alkane solvents even in the case of highly polar substrates.

Introduction

In spite of recent accomplishments in solid-phase[1] and enzymatic[2] methods, the synthesis of complex oligosaccharides is still today a very challenging undertaking. In recent years, new solution-phase techniques have been developed to ease reaction work-up and product isolation, avoiding the pitfalls of solid-phase approaches. These techniques include the use of soluble polymer-supported methods,[3] lipophilic[4] or fluorophilic[5] protecting groups, tagging methods for post-synthesis purification using scavenging resins,[6] solid-phase capture-release strategies,[3j,3o,7] and polymer-bound reagents and catalysts.[8] These approaches rely on the common theme of phase tagging to assist reaction work-up and product isolation.[9] The specific advantages of solution phase methods as compared to the alternative solid phase approach are well recognized: (a) solution phase approaches have no scale limitations, (b) they allow the implementation of convergent synthetic schemes, which are not feasible in the solid phase approach, (c) monitoring of the reactions can be easily performed using standard techniques, (d) substrates usually show higher reactivity in solution than when attached to a solid support, and (e) intermediate product purification along the synthetic route can be readily accomplished after each reaction step, if required.

Herein, we describe our exploratory studies on the development of a lipophilic tag for the efficient purification of synthetic oligosaccharides using biphasic liquid-liquid extraction (LLE) with two immiscible organic solvents. To date, the use of LLE to facilitate the synthesis of oligosaccharides by simplifying the purification steps has been exclusively limited to organic/fluorous solvent mixtures by prior labelling of the carbohydrate component with a "heavy" fluorous tag.[5] However, fluorous solvents and fluorous tags are still costly today and pose an environmental concern due to their high chemical stability. In addition, "heavy" fluorous tags can drastically limit the solubility of the labelled molecule in common organic solvents requiring the additional use of polyfluorinated cosolvents. Tags based on linear alkyl chains are a more environmentally friendly alternative since they are readily biodegradable, but retain a high chemical stability under most laboratory conditions. These tags confer a lipophilic character to the labelled molecule allowing its selective extraction into the most lipophilic phase in a LLE process using a mixture of immiscible organic solvents. Alternatively, the tagged compound can also be selectively recovered by adsorption onto reverse-phase C18 silica gel.[10] The use of reverse phase C18 SPE purification of lipophilically labelled molecules has many precedents in carbohydrate chemistry,[4] but, surprisingly, this is not the case for LLE,[11] which has the important advantage of being more readily scalable.

Results and Discussion

Many literature reports on synthetic applications of lipophilically tagged carbohydrates rely on the use of multiple tags, usually long-chain carboxylic acids, attached to dif-

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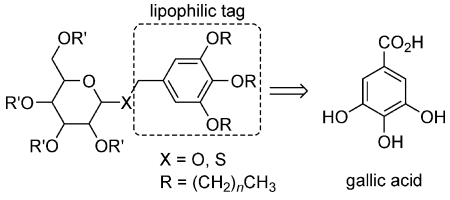
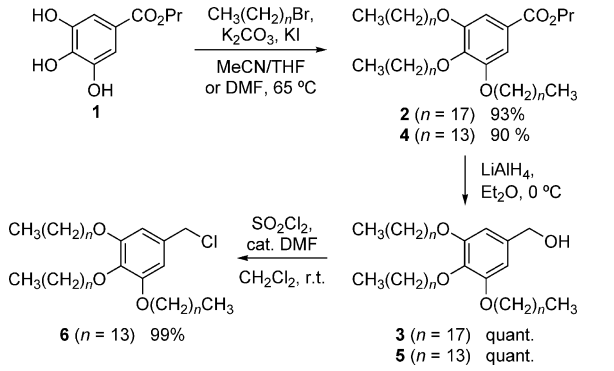
ferent hydroxy groups. We followed the strategy of attaching a single "heavy" lipophilic tag to the anomeric position of a glycosyl acceptor. This allows manipulations of all the other hydroxy groups through protection, deprotection or glycosylation reactions without prior removal the tag, thus taking advantage of its presence to assist purification over a number of different synthetic steps.

Our general strategy for the synthesis of lipophilically tagged carbohydrate substrates relied on the use of gallic acid as a scaffold for the preparation of the tag (Scheme 1). Gallic acid is readily available and inexpensive, it possesses three phenolic hydroxy groups that allow the attachment of 1–3 alkyl chains, and it has a well developed derivatization chemistry using long alkyl or polyfluoroalkyl chains due to the interesting properties of the corresponding derivatives as liquid-crystalline materials.[12] In addition, we have previously shown that a lipophilic gallic acid derivative is a very efficient solubilizing group for unprotected glycopyranosylamines in apolar organic solvents.[13]

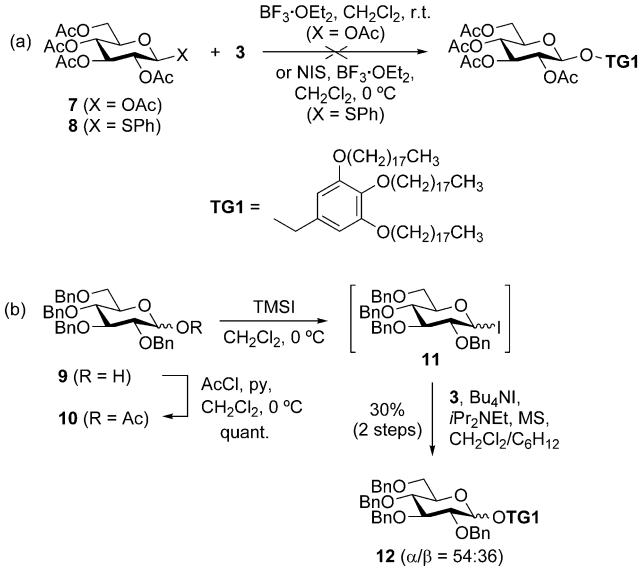


Scheme 1. General strategy for the synthesis of lipophilically tagged monosaccharides.

Ideally, the inherent solubility of the tag in the specific solvent should be only marginally affected by the carbohydrate component attached to it, irrespective of changes in molecular size and functionalization of the tagged molecule throughout the synthetic route. At the outset, we decided to incorporate three linear octadecyl chains onto the tag to boost its relative molecular weight and to maximize its lipophilicity, thus guaranteeing a high partition coefficient in alkane solvents. Accordingly, we selected 3,4,5-tris(octadecyloxy)benzyl alcohol (**3**) as the initial tag, which was readily prepared from commercially available *n*-propyl gallate (**1**) and stearyl bromide (Scheme 2).[14] Preliminary attempts at introducing **3** in a monosaccharide moiety via a glycosylation reaction under Lewis acid catalysis met with failure (Scheme 3a). A complex mixture of products was formed using either peracetylated D-glucose (**7**) or the corresponding thiophenyl D-glucoside **8** as donors, from which we could not isolate the expected glycoside. Milder and neutral glycosylation conditions[15] were assayed using a benzylated D-glucosyl iodide (**11**)[16] as a model glycosyl donor. This reaction did provide the expected glycoside **12**,[17] but in a non practical yield and as a mixture of anomers (Scheme 3b). The instability of the electron-rich benzylic alcohol **3** under acidic conditions and its modest solubility in the usual solvents used for glycosylation at the low temperatures normally required for a clean reaction are likely responsible for this failure.[17]



Scheme 2. Synthesis of the tags starting from propyl gallate (**1**).

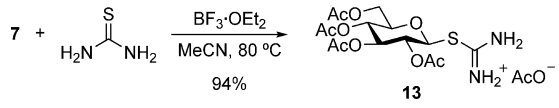


Scheme 3. Attempted tagging of D-glucose by chemical glycosylation of benzylic alcohol **3**.

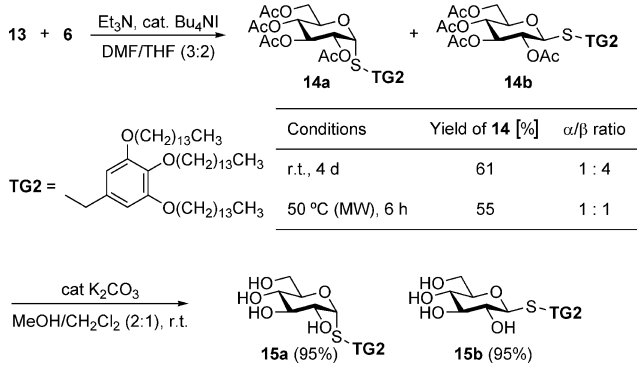
In order to overcome these difficulties, we decided to change our initial approach. Thus, to improve the solubility in common organic solvents, the alkyl chains were truncated from C18 to C14 and to deal with the acid lability we decided to introduce the tag by alkylation of a glycosyl isothiouronium salt under basic conditions, which would afford a predictably more stable tagged thioglycoside.

The required benzyl chloride reagent **6** was readily available by chlorination of benzylic alcohol **5**,[18] which was obtained following a procedure similar to that described for the C18 analog **3** (Scheme 2). As glycosyl partner, we selected 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl isothiouronium acetate **13**, readily prepared by reaction of peracetylated D-glucose with thiourea promoted by $BF_3{\cdot}OEt_2$ (Scheme 4).[19] We tested different conditions for the alkylation of the glycosyl isothiouronium salt **13** with benzyl chloride **6** using either Et_3N or iPr_2NEt as bases and MeCN, THF, or DMF as solvents, with or without added water. The best yield was obtained with Et_3N in a DMF/THF solvent mixture and in the presence of a catalytic amount of *n*-Bu_4NI (Scheme 5). The expected tagged thioglycoside **14** was obtained in 61% yield as a 1:4 α/β mixture

of anomers when the reaction was performed at room temperature. The reaction time could be significantly shortened by heating at 50 °C under microwave irradiation, to give a 55% yield of **14** as a 1:1 α/β mixture of anomers that were readily separated by column chromatography.



Scheme 4. Synthesis of glycosyl isothiouronium salt **13**.



Scheme 5.

With a lipophilically tagged monosaccharide finally in hand, we proceeded to test its performance in LLE separations using a biphasic hexane/MeCN solvent system. To this end, compounds **14a**,**b** were first fully deacetylated to yield tetraols **15a**,**b** (Scheme 5). We used **15b** as a model of highly polar tagged carbohydrate. This model was intended to provide a stringent test of the efficiency and selectivity of the LLE separation process. For comparison, we included in the study two untagged D-glucose derivatives with different protecting group patterns, peracetylated β-D-glucose (**16**) and 2,3,4,6-tetra-*O*-benzyl-D-glucose (**17**), as typical representatives of possible glycosyl donors or side-products found in glycosylation reactions. The results of the LLE for each of these compounds using an equal-volume hexane/MeCN solvent mixture are shown in Table 1.

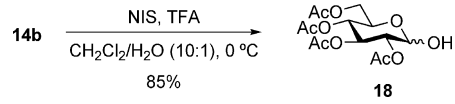
Table 1. Molar percent of extracted **15b**, **16** or **17** in the hexane phase after LLE using a hexane/MeCN biphasic system.

Number of consecutive LLE	mol-% of **15b** in hexane[a]	mol-% of **16** in hexane[b]	mol-% of **17** in hexane[b]
1st extraction	72	0.8	1.6
2nd extraction	24	–	–
3rd extraction	2	–	–
Total	98	<0.8	<1.6

[a] Conditions: 47 mg of **15b**, 7 mL each of hexane and MeCN, 3 min mixing time at 22 °C, phase separation followed by two successive re-extractions of the MeCN phase with additional 7 mL portions of hexane. [b] Conditions: 100 mg of compound **16** or **17**, 9 mL each of hexane and MeCN, 3 min mixing time, 22 °C.

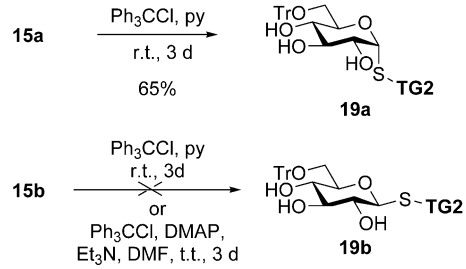
The data in the Table show that even a highly polar tagged carbohydrate such as **15b** could be practically fully recovered in the hexane phase after a typical three-step extractive work-up protocol using a hexane-immiscible polar organic solvent. In contrast, the non-tagged substrates were barely extracted into hexane, remaining almost quantitatively (>98%) in the MeCN phase, even in the case of the more lipophilic **17**.

Easy detagging is a prerequisite for any synthetically useful tag. Oxidative hydrolysis of the thioglycoside promoted by NIS/TFA[20] provided a simple and high yielding detagging method, as shown in Scheme 6 for compound **14b**. LLE of the crude reaction mixture with hexane/MeCN afforded almost pure **18** in the MeCN phase free from tag by-products, and could then be further purified through a short flash column.



Scheme 6. Hydrolytic detagging of compound **14b** under oxidative conditions.

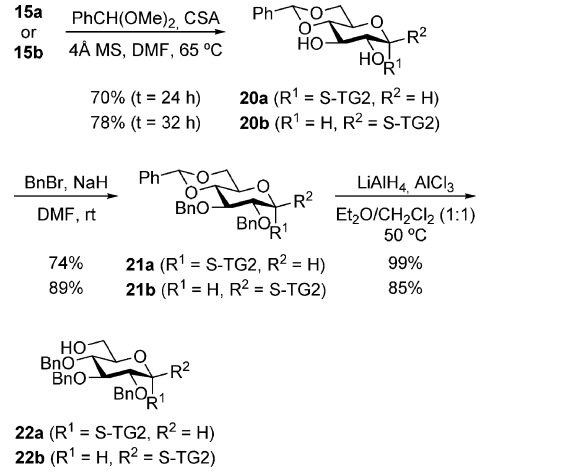
The next task was to unmask one of the hydroxy groups of the tagged monosaccharides in order to evaluate the performance of the tag under standard protecting group manipulations and in the subsequent glycosylation as a glycosyl acceptor. Exposing the primary hydroxy group generally proves most simple and, in addition, it provides a highly reactive glycosyl acceptor. A classical synthetic route to this end consists of three standard steps: regioselective protection of the primary hydroxy group as a triphenylmethyl ether, protection of the other hydroxy groups as benzyl ethers, and detritylation under acidic conditions. However, when we proceeded to apply this simple protocol to tetraols **15a** and **15b** we obtained an unexpected outcome (Scheme 7). Thus, while the α-anomer **15a** could be regioselectively protected with trityl chloride to give **19a** in moderate yield under the usual conditions (although in a slow reaction), the corresponding β-anomer **15b** was completely unreactive to prolonged treatment with trityl chloride under similar or modified conditions. We do not have a clear explanation for this unusual behaviour, although a reasonable possibility would be that the tagged carbohydrate with free hydroxy groups probably forms inverse micellar aggregates in aprotic organic solvents that confine the polar carbohydrate head to the interior of the micelle, thus shielding the hydroxy



Scheme 7. Tritylation of **15a** and **15b**.

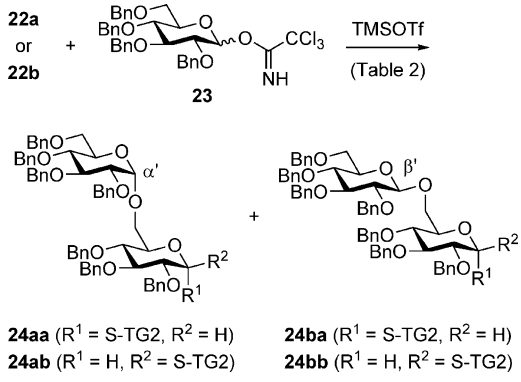
groups from added reagents. In support of this explanation, it is known that related gallic acid derivatives containing lipophilic chains and a hydroxylated amide polar head readily form reverse micelles.[21] To explain our observations one has to additionally hypothesize that the more linear β-isomer **15b** should form more densely packed micelles with less accessible, and consequently less reactive, hydroxy groups than the corresponding α-anomer.[22]

We next tried a different three-step protocol to the same tagged glycosyl acceptors with a primary free hydroxy group. For this, we assayed a more electrophilic and less sterically demanding reagent for the initial selective protection of tetraols **15a** and **15b** (Scheme 8). Thus, treatment of **15a** and **15b** with benzaldehyde dimethyl acetal under acidic conditions gave the corresponding 4,6-di-*O*-benzylidene acetals **20a** and **20b** in good yield. The reaction was slower than with similar untagged analogs and, again, the β-anomer was less reactive than the α-anomer. Protection of the 2- and 3-hydroxy groups as benzyl ethers to give **21a** and **21b** followed by regioselective opening of the benzylidene acetal with $LiAlH_4/AlCl_3$ proceeded uneventfully to give the target glycosyl acceptors **22a** and **22b**. The hexane/MeCN LLE protocol greatly facilitated purification of the intermediate compounds throughout this synthetic route.



Scheme 8. Synthesis of the tagged glycosyl acceptors **22a** and **22b**.

The performance of the tagged glycosyl acceptors **22a** and **22b** in glycosylation reactions was examined using perbenzylated D-glucopyranosyl trichloroacetimidate **23**[23] as a model glycosyl donor and TMSOTf as Lewis acid promoter (Scheme 9 and Table 2). Due to the low solubility of **22a** and **22b** in CH_2Cl_2 at low temperature, solvent mixtures containing either toluene or cyclohexane were used to ensure homogeneous reaction conditions. As previously observed in the preceding protecting group chemistry, the β-anomeric glycosyl acceptor **22b** showed also a reduced reactivity in the glycosylation reaction as compared to the corresponding α-anomer **22a**. Thus, in the case of **22b** higher temperatures and larger amounts of both donor **23** and TMSOTf promoter were needed for the reaction to proceed (Table 2, entries 1 and 2). However, even under these more vigorous conditions only moderate yields of disaccharides **24** were obtained. The relatively large amounts of TMSOTf required to promote the glycosylation of **22b** caused the partial β→α anomerization of the thioglycoside center to give finally a mixture of the four possible α′/β′,α/β-disaccharides **24**. Larger amounts of TMSOTf and longer reaction times did not improve the yield, but resulted in a more extended anomerization of the thioglycoside (Table 2; entry 1, α/β = 27:53; entry 2, α/β = 54:46). Not surprisingly, increased reaction temperatures afforded a higher α′/β′ stereoselectivity in the glycosylation reaction (Table 2; entry 1, α′/β′ = 95:5; entry 2, α′/β′ = 80:20). The facile α/β-anomerization of the thioglycosidic moiety took place also in the absence of glycosyl donor upon treatment of **22b** with TMSOTf (1 mol-equiv., 0 °C, $CDCl_3$, 1 h), as independently confirmed by ^1H NMR (see Supporting Information). The anomerization of thioglycosides promoted by Lewis or protic acids is a well known reaction[24] that has also found a preparative utility.[25] In the case of TMSOTf activation, this anomerization is probably an intramolecular process that proceeds via attack of the hard electrophilic silicon centre on O-5[26] with opening of the pyranose ring to give a sulfonium ion (**A**) stabilized by the electron rich S-TG2 group (Scheme 10). In support of this mechanistic hypothesis is the fact that we have not observed any aglycon transfer[27] under the glycosylation conditions tested.



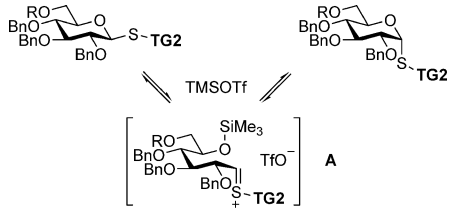
Scheme 9. Glycosylation of **22a** and **22b**.

Table 2. Glycosylation of **22a**,**b** with **23** (see Scheme 9).

Entry	Acc.	Equiv. **23**	Equiv. TMSOTf	*T* [°C]	*t* [h]	Yield of **24** [%] (**aa/ba/ab/bb**)[a]
1	**22b**[b]	2.0	1.0	22	0.8	38 (27:0:68:5)[c]
2	**22b**[d]	2.5	3.0	0	16	37 (42:12:38:8)[e]
3	**22a**[b]	1.2	0.2	–60 to –35	5	74 (25:75:0:0)[f]

[a] Ratio of anomers = α′α/β′α/α′β/β′β was determined from the ^1H NMR of the crude reaction mixture. [b] The reaction was run in CH_2Cl_2/C_6H_{12} (1:1). [c] Considering recovered unreacted **22b**, the calculated yield of **24** was 40%. [d] The reaction was run in CH_2Cl_2/toluene (1:1). [e] Considering recovered unreacted **22b**, the calculated yield of **23** was 54%. [f] Considering recovered unreacted **22b**, the calculated yield of **24** was 98%.

In contrast, the glycosylation of **22a** with a small excess of **23** proceeded uneventfully at low temperature and using substoichiometric amounts of TMSOTf to give the expected disaccharide **24** in 74% yield as a separable 25:75



Scheme 10. Proposed mechanism for the intramolecular anomerization of the tagged thioglycosides promoted by TMSOTf.

α′/β′-mixture of disaccharides, without any observable α/β-anomerization (Table 2, entry 3). Under these non optimized conditions a 24% of unreacted **22a** was recovered, which accounts for an almost quantitative conversion of transformed **22a** into glycoside **24**. After reaction, the tagged products were readily isolated by standard aqueous/organic work-up using hexane as solvent followed by washing of the combined hexane extracts with MeCN to remove non-tagged by-products. The crude mixture of tagged disaccharides **24** was recovered free from untagged compounds by evaporation of the hexane phase and it was further purified by usual flash column chromatography on silica gel to separate the disaccharide anomers.

Conclusions

In conclusion, we have shown that a simple "heavy" lipophilic tag readily prepared from inexpensive gallic acid can greatly simplify the purification steps in oligosaccharide synthesis by means of LLE using two immiscible organic solvents. By introducing the tag at the anomeric position of the carbohydrate acceptor, this simple LLE purification can be advantageously carried out at each step throughout the synthetic route. We have developed simple tagging and detagging procedures and have shown that a single tag is sufficient to ensure a high affinity of the tagged molecule for alkane solvents even in the case of highly polar substrates. However, at this early stage of development there are several things that could also detract from this work and require further improvement. The first is the control of the stereoselectivity of the tagging step, which provides anomeric mixtures of labelled thioglycosides. The second is the problem of possible reverse micelle formation in apolar solvents when free hydroxy groups are present in the substrate, which compromise the reactivity of these groups. Another problem is the acid lability of the tag due to the highly electron rich aromatic ring. And the last point that merits attention is that, while the LLE procedure does work well, the reaction products are not always sufficiently pure due to side reactions and hence further purification by short flash chromatography is sometimes required. We are now addressing all these points and will further report on our progress in future publications.

Experimental Section

General Methods: All melting points were measured with a Reichert Jung Thermovar micro melting apparatus. Optical rotations were obtained using a Perkin–Elmer 241-MC polarimeter. Infrared (FT-IR) spectra were obtained using a Perkin–Elmer Spectrum One spectrophotometer and are reported in cm^{-1}. Proton and carbon-13 nuclear magnetic resonance (^1H NMR or ^{13}C NMR) spectra were recorded on a BRUKER AMX-300 (300 and 75 MHz), a Varian INOVA 300 (300 and 75 MHz), a Varian INOVA 400 (400 and 100 MHz) or a Varian UNITY 500 (500 and 125 MHz) spectrometers. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ = 7.26; CH_2Cl_2: δ = 5.30 ppm). Data are presented as follows: chemical shift, multiplicitiy (s = singlet, d = doublet, t = triplet, m = multiplet and/or multiplet resonances, br. = broad), integration and coupling constants in Hertz [Hz]. Proton and carbon-13 assignments are based on DQ-COSY and HSQC correlation experiments. Thin-layer chromatography (TLC) was performed with Merck Silica Gel 60 F254. Detection was achieved by treatment with a solution of 50 g of ammonium molybdate and 1 g of cerium(IV) sulfate in 1 L of 5% H_2SO_4 solution in H_2O and heating at 150 °C. MALDI-TOF MS were recorded on a Voyaguer-DEPRO (Applied Biosystems) spectrometer. Elemental analyses were performed in a Heraus CHN-O analyser.

Propyl 3,4,5-Tris(octadecyloxy)benzoate (2): To a MeCN/THF solution (120 mL, 2:1) of propyl 3,4,5-trihydroxybenzoate (2.0 g, 9.42 mmol) and 1-bromooctadecane (12.6 g, 37.7 mmol) was added K_2CO_3 (9.2 g, 66.0 mmol) and KI (70 mg, 0.47 mmol) and the reaction mixture was stirred at 85 °C for 6 h. The cooled mixture was dissolved in EtOAc and aq. 1 N HCl was added dropwise to adjust to pH<3. The aqueous layer was successively washed with EtOAc and the organic layers were combined, dried with Na_2SO_4 and the solvents evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc 13:0.1) to afford **2** (8.5 g, 93%) as a white solid; m.p. 60–61 °C; R_f = 0.5 (10:1 hexane/EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.9 Hz, 9 H, CH_3), 1.02 (t, J = 7.4 Hz, 3 H, CH_3), 1.25–13 [m, 92 H, $(CH_2)_{15}$], 1.44–1.51 (m, 6 H, $OCH_2CH_2CH_2$), 1.71–1.85 (m, 8 H, OCH_2CH_2-propyl, OCH_2CH_2), 4.01 (t, J = 6.5 Hz, 6 H, OCH_2), 4.26 (t, J = 6.7 Hz, 2 H, OCH_2-propyl), 7.26 (s, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.5 (CH_3-propyl), 14.1 (CH_3), 22.2 (OCH_2CH_2-propyl), 22.7, 26.1 ($OCH_2CH_2CH_2$), 26.1 ($OCH_2CH_2CH_2$), 29.3, 29.4, 29.4, 29.6, 29.6, 29.7, 29.7, 30.3, 31.9, 66.5 (OCH_2-propyl), 69.1 ($2OCH_2$), 73.5 (OCH_2), 108.0 (ArCH), 125.0, 142.3, 152.8, 166.5 ppm. FT-IR (KBr): $\tilde{\nu}$ = 2917, 2850, 1717, 1589, 1504, 1471, 1431, 1388, 1339, 1219, 1124, 1014, 766, 719 cm^{-1}. MS-APCI: m/z = 969 (M^+), 968 (M-1), 391, 279. MALDI: m/z = $[M]^+$ 968.01, $[M + H]^+$ 969.02, $[M + Na]^+$ 991.01. $C_{64}H_{120}O_5$ (969.63): calcd. C 79.28, H 12.47; found C 79.57, H 12.18.

3,4,5-Tris(octadecyloxy)benzyl Alcohol (3): To an ice-chilled anhydrous Et_2O solution (31 mL) of **2** (1 g, 1.03 mmol) was added $LiAlH_4$ (0.05 g, 1.30 mmol) under argon atmosphere and the mixture was refluxed for 2 h. After the mixture was cooled, EtOAc (1.5 mL) was added and the mixture was stirred for 10 min. Then, water (200 μL) and aq. 15% NaOH (200 μL) were added dropwise to give a precipitate. The filtered solid was treated with THF and the undissolved products were removed by filtration. The filtrate was concentrated in vacuo and the residue was recrystallized from 2-propanol to give pure **3** (0.94 g, 99.9%) as a white solid; m.p. (2-propanol) 72 °C; R_f = 0.8 (toluene/Et_2O, 10:0.1), R_f = 0.23 (5:1 hexane/EtOAc). ^1H NMR (300 MHz, $CDCl_3$, 30 °C): δ = 0.88 (t, J = 6.7 Hz, 9 H, CH_3), 1.18–1.46 [br. s, 90 H, $(CH_2)_{15}$], 1.71–1.82 (m, 6 H, OCH_2CH_2), 3.91–3.99 (m, 6 H, OCH_2), 4.59 (d, J = 5.6 Hz, 2 H, 1′-H), 6.56 (s, 2 H, Ar-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7 (CH_2CH_3), 26.1–30.3 ($13CH_2$), 31.9

($CH_2CH_2CH_3$), 65.6 (2 × OCH_2), 69.1 ($C1'$), 73.4 (OCH_2), 105.3, 136.0, 137.5, 153.3 ppm. FT-IR (KBr): $\tilde{\nu}$ = 3473, 2918, 2850, 1595, 1504, 1464, 1439, 1387, 1330, 1224, 1122, 1059, 813, 721 cm^{-1}. MALDI: *m/z* = $[M]^+$ 912.09, $[M + Na]^+$ 935.05. $C_{61}H_{116}O_4$ (913.57): calcd. C 80.20, H 12.80; found C 79.98, H 12.57.

Propyl 3,4,5-Tris(tetradecyloxy)benzoate (4): To a dry DMF solution (71 mL) of propyl 3,4,5-trihydroxybenzoate (3.0 g, 0.014 mol) and 1-bromotetradecane (17 mL, 0.057 mol) was added K_2CO_3 (15.5 g, 0.112 mol) and KI (0.101 g, 0.70 mmol) and the reaction mixture was stirred at reflux for 4 h. The cooled mixture was dissolved in EtOAc and aq. 1 N HCl was added dropwise to adjust to pH<3. The aqueous layer was successively washed with EtOAc and the organic layers were combined, dried with Na_2SO_4 and the solvents evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc, 10:0.1) to afford **4** (10.1 g, 90%) as a white solid; m.p. 42–44 °C; R_f = 0.76 (5:1 hexane/EtOAc). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 6.8 Hz, 9 H, CH_3), 1.00 (t, *J* = 7.4 Hz, 3 H, CH_3-propyl), 1.24 [br. s, 60 H, $(CH_2)_{10}$], 1.42–1.49 (m, 6 H, $OCH_2CH_2CH_2$), 1.70–1.81 (m, 8 H, OCH_2CH_2, OCH_2CH_2-propyl), 3.99 (t, *J* = 6.5 Hz, 6 H, OCH_2), 4.23 (t, *J* = 6.8 Hz, 2 H, OCH_2-propyl), 7.24 (s, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 10.5 (CH_3-propyl), 14.1 (CH_3), 22.1 (OCH_2CH_2-propyl), 22.7, 26.0, 26.1, 29.3, 29.4, 29.4, 29.6, 29.6, 29.7, 29.7, 29.7, 30.3, 31.9, 66.5 (OCH_2-propyl), 69.1 (OCH_2), 73.4 (OCH_2), 108.0 (ArCH), 125.0, 142.3, 152.8, 166.5 ppm. FT-IR (KBr): $\tilde{\nu}$ = 2950, 2917, 2850, 1716, 1588, 1471, 1430, 1388, 1339, 1215, 1112, 765, 719 cm^{-1}. MALDI: *m/z* = $[M]^+$ 800.12, $[M + H]^+$ 801.13, $[M + Na]^+$ 823.12. $C_{52}H_{96}O_5$ (801.32): calcd. C 77.94, H 12.08; found C 78.10, H 12.21.

3,4,5-Tris(tetradecyloxy)benzyl Alcohol (5): To an ice-chilled anhydrous Et_2O solution (114 mL, 0.033 M) of **4** (3 g, 3.75 mmol) was added $LiAlH_4$ (0.195 g, 4.88 mmol) under argon atmosphere and the mixture was refluxed for 3 h. After the mixture was cooled, EtOAc (6 mL) was added and the crude was stirred 10 min. Then, water (8 mL) and aq. 15% NaOH (8 mL) were added dropwise to give a precipitate. The filtered solid was treated with THF and the undissolved products were removed. The filtrate was concentrated in vacuo and the residue was recrystallized from 2-propanol to give pure **5** (2.79 g, 99.9%) as a white solid; m.p. (2-propanol) 56–57 °C; R_f = 0.19 (hexane/EtOAc, 5:1). ^1H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.6 Hz, 9 H, CH_3), 1.27 [br. s, 60 H, $(CH_2)_{10}$], 1.67–1.84 (m, 6 H, OCH_2CH_2), 3.91–3.98 (m, 6 H, OCH_2), 4.57 (s, 2 H, CH_2OH), 6.54 (s, 2 H, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7 (CH_2CH_3), 26.1–30.3 [$(CH_2)_{10}$], 31.9 ($CH_2CH_2CH_3$), 65.6 (CH_2OH), 69.1 ($OCH2 \times 2$), 73.4 ($OCH2$), 105.3 (C2), 136.0 (C1), 137.5 (C4), 153.3 (C3) ppm. FT-IR (KBr): $\tilde{\nu}$ = 3435, 2919, 2851, 1591, 1507, 1470, 1438, 1384, 1337, 1229, 1126, 721 cm^{-1}. MALDI: *m/z* = $[M]^+$ 744.21, $[M + Na]^+$ 767.19. $C_{49}H_{92}O_4$ (745.25): calcd. C 78.97, H 12.44; found C 78.67, H 12.71.

3,4,5-Tris(tetradecyloxy)benzyl Chloride (6): To a solution of **5** (0.40 g, 0.54 mmol) in anhydrous CH_2Cl_2 (3.5 mL, 0.15 M) was added $SOCl_2$ (55 μL, 0.75 mmol) and a catalytic amount of DMF (15 μL) under an argon atmosphere and the mixture was stirred for 2 h at room temperature. The solvent and excess of $SOCl_2$ were removed at reduced pressure, affording the pure product (0.41 g, 99%) as a pale yellow solid; m.p. 56–57 °C; R_f = 0.83 (hexane/EtOAc, 3:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 6.9 Hz, 9 H, CH_3), 1.27 [br. s, 60 H, $(CH_2)_{10}$], 1.34–1.50 (m, 6 H, $OCH_2CH_2CH_2$), 1.70–1.83 (m, 6 H, OCH_2CH_2), 3.93–3.99 (m, 6 H, OCH_2), 4.51 (s, 2 H, CH_2Cl), 6.57 (s, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 26.1 ($OCH_2CH_2CH_2 \times 3$), 29.4, 29.4, 29.6, 29.6, 29.7, 29.7, 29.7, 30.3, 31.9, 47.0 (OCH_2Cl), 69.1 (OCH_2), 73.4 (OCH_2), 107.0 (ArCH), 132.3, 138.3, 153.2 ppm. FT-IR (KBr): $\tilde{\nu}$ = 2920, 2849, 1593, 1506, 1466, 1441, 1393, 1334, 1245, 1232, 1124, 723, 701, 673 cm^{-1}. MALDI: *m/z* = $[M^+]$ 762.64, $[M + Na]^+$ 785.65, $[M + K]^+$ 809.71. $C_{49}H_{91}ClO_3$ (763.70): calcd. C 77.06, H 12.01, Cl 4.64; found C 76.94, H 12.26, Cl 4.76.

1-*O*-Acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (10):[28] Pyridine (0.6 mL, 7.45 mmol) and acetyl chloride (0.4 mL, 5.92 mmol) were added to a stirred solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranoside (**9**) (800 mg, 1.48 mmol) in CH_2Cl_2 (3 mL) at 0 °C. After stirring the mixture at room temp. for 3 h, it was diluted with CH_2Cl_2 (15 mL) and washed with H_2SO_4 2 M (2×) and brine (1×). The crude product was purified by column chromatography (hexane/EtOAc, 7:1) to afford **10** as a colorless oil (860 mg, 100%), mixture of anomers α/β = 9:1. Anomer α: R_f (hexane/EtOAc, 4:1) = 0.3. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.18 (s, 3 H, $COCH_3$), 3.65–4.06 (m, 6 H), 4.50–5.05 (m, 8 H, 4 PhCH_2), 6.42 (d, *J* = 2.5 Hz, 1 H, 1-H), 7.17–7.42 (m, 20 H, Ar-H) ppm. Anomer β: R_f (hexane/EtOAc, 4:1) = 0.3. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.10 (s, 3 H, $COCH_3$), 3.65–4.06 (m, 6 H), 4.50–5.05 (m, 8 H, 4 PhCH_2), 5.67 (d, *J* = 7.9 Hz, 1 H, 1-H), 7.17–7.42 (m, 20 H, Ar-H) ppm.

3,4,5-Tris(octadecyloxy)benzyl 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranoside (12):[17] To a CH_2Cl_2 (1.6 mL, 0.1 M) solution of **10** (90 mg, 0.155 mmol) at 0 °C was added trimethylsilyl iodide (30 μL, 0.217 mmol). The reaction mixture was stirred at room temp. for 45 min and the solvent was evaporated at reduced pressure to afford the glycosyl iodide **11**, which was used in the next step without further purification.

To a solution of nBu_4NI (0.118 g, 0.313 mmol), DIEA (54 μL, 0.313 mmol), 3,4,5-tris(octadecyloxy)benzyl alcohol (**3**) (0.070 g, 0.077 mmol), and 4 Å MS in CH_2Cl_2/cyclohexane (1:1, 2 mL) was added a solution of crude **11** (100 mg, 0.154 mmol) in CH_2Cl_2 (1.2 mL). After stirring the mixture at reflux for 20 h, the volatiles were removed at reduced pressure and the residue was purified by column chromatography (hexane/EtOAc, 9:1) to give **12** (0.066 g, 30%) as a mixture of anomers (α/β = 2:3). Anomer α: R_f (hexane/EtOAc, 8:1) = 0.26, ^1H NMR (300 MHz, $CDCl_3$): δ = 0.86 (m, 9 H, CH_3), 1.23–1.45 (m, 90 H, $15CH_2$), 1.70–1.75 (m, 6 H, OCH_2CH_2), 3.64–4.10 (m, 12 H), 4.45–5.00 (m, 9 H, 4PhCH_2 and 1′-H), 6.07 (d, *J* = 3.8 Hz, 1 H, 1-H), 6.56 (s, 2 H, Ar-H), 7.14–7.36 (m, 20 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7 (CH_2CH_3), 26.1 ($OCH_2CH_2CH_2$), 29.4–30.3 ($13CH_2$), 31.9 ($CH_2CH_2CH_3$), 65.7, 67.7, 69.1, 73.0, 73.3, 73.4, 73.5, 75.2, 75.8, 76.4, 79.8, 81.4, 93.9, 105.8, 127.7–128.6, 136.0, 137.4, 137.6, 138.0, 138.5, 153.7 ppm. Anomer β: R_f (hexane/EtOAc, 8:1) = 0.32, ^1H NMR (400 MHz, $CDCl_3$): δ = 0.86 (m, 9 H, CH_3), 1.23–1.45 (m, 90 H, $15CH_2$), 1.70–1.75 (m, 6 H, OCH_2CH_2), 3.53 (dd, *J* = 3.7, *J* = 9.5 Hz, 1 H, 2-H), 3.59–3.62 (m, 1 H, 4-H), 3.68–3.72 (m, 1 H, 6-H), 3.79–3.82 (m, 1 H, 5-H), 3.83–3.94 (m, 7 H, OCH_2, 6′-H), 4.04 (t, *J* = 9.2 Hz, 1 H, 3-H), 4.52 (d, 2 H, 1′-H), 4.52 (dd, *J* = 12.0 Hz, 2 H, PhCH_2), 4.53 (dd, *J* = 12.1 Hz, 2 H, PhCH_2), 4.63 (dd, *J* = 10.8 Hz, 2 H, PhCH_2), 4.84 (d, *J* = 3.5 Hz, 1 H, 1-H), 4.89 (dd, *J* = 10.8 Hz, 2 H, PhCH_2), 6.57 (s, 2 H, Ar-H), 7.10–7.33 (m, 20 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7 (CH_2CH_3), 26.1 ($OCH_2CH_2CH_2$), 29.4–30.4 ($13CH_2$), 31.9 ($CH_2CH_2CH_3$), 69.1 (OCH_2, C6), 70.3 (C1′), 72.7–75.0 (PhCH_2), 75.8 (C5), 79.6 and 82.2 (C2, C3 and C4), 94.9 (C1), 107.2 (C3′), 127.7–128.4, 132 (C2′), 138.1, 138.8, 153.1 (C4′) ppm.

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl Isothiourea Derivative (13): Compound **13** was prepared according to the described procedure[18] (94% yield); m.p. (2-propanol) 180–184 °C. ^1H NMR

(300 MHz, [D$_6$]DMSO): δ = 1.97, 1.99, 2.02, 2.05 (4s, 12 H, OAc), 4.08 (dd, J = 11.6, J = 1.7 Hz, 1 H, 6-H), 4.10–4.18 (m, 1 H, 5-H), 4.20 (dd, J = 12.1, J = 4.9 Hz, 1 H, 6-H), 5.10 (t, J = 9.5 Hz, 1 H, 4-H), 5.11 (t, J = 9.7 Hz, 1 H, 2-H), 5.32 (t, J = 9.4 Hz, 1 H, 3-H), 5.60 (d, J = 10.0 Hz, 1 H, 1-H), 9.11 (br. s, 4 H, NH_2) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 20.3, 20.4, 20.5, 20.6, 61.8, 67.5, 68.8, 72.5, 75.5, 80.0 (C1), 166.4 [S*C*(NH$_2$)$_2$], 169.4, 169.5, 169.7, 170.2 ppm. FT-IR (KBr): $\tilde{\nu}$ = 3309, 3268, 3056, 1755, 1657, 1428, 1373, 1253, 1224, 1123, 1084, 1057, 1035, 960, 908, 807, 702, 600, 533 cm^{-1}. MS-API-ES: m/z = 407 [M], 331 [M – 76].

3,4,5-Tris(tretradecyloxy)benzyl 2,3,4,6-Tetra-*O*-acetyl-1-thio-α-D-glucopyranoside (14a). Microwave Procedure: To a suspension of **13** (0.32 g, 0.68 mmol), 3,4,5-tris(tetradecyloxy)benzyl chloride (0.40 g, 0.52 mmol) and *n*Bu$_4$NI (10 mmol-%, 0.025 g) in DMF/THF (12 mL, 7:5) was added Et$_3$N (0.7 mL, 1 M) and the mixture was heated at 50 °C for 6 h in a CEM microwave reactor. The volatiles were removed at reduced pressure to afford a crude residue that was partitioned in hexane/MeCN (50 mL each), the hexane phase was separated and the MeCN layer was extracted with hexane (2 × 20 mL). The combined hexane phases were concentrated and the resultant residue was purified by column chromatography (hexane/EtOAc, 6:1) to give **14** (0.32 g, 55%, 1:1 α/β-mixture). The mixture of anomers could be separated by carefull flash chromatography under the same conditions.

Room Temperature Procedure: To a suspension of **13** (0.8 g, 1.7 mmol), 3,4,5-tris(tetradecyloxy)benzyl chloride (1 g, 1.3 mmol) and *n*Bu$_4$NI (cat, 0.13 g) in DMF/THF (50 mL, 1:2) was added Et$_3$N (2 mL, 1 M) and the mixture was stirred at room temperatura for 4 d. The volatiles were removed at reduced pressure to afford a crude residue that was partitioned in hexane/MeCN (70 mL each), the hexane phase was separated and the MeCN layer was extracted with hexane (2 × 30 mL). The combined hexane phases were concentrated and the resultant residue was purified by column chromatography (hexane/EtOAc, 6:1) to give **14** (0.86 g, 61%, 1:4, α/β). The mixture of anomers could be separated by carefull flash chromatography under the same conditions.

14a: White solid; m.p. 43–45 °C; R_f = 0.50 (hexane/EtOAc, 3:1). $[\alpha]_D^{20}$ = +106.6 (c = 0.49, CHCl$_3$). ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.88 (t, J = 6.7 Hz, 9 H, CH_3), 1.26 [br. s, 60 H, (CH_2)$_{10}$], 1.40–1.52 (m, 6 H, OCH$_2$CH$_2$CH_2), 1.68–1.83 (m, 6 H, OCH$_2$CH_2), 2.00, 2.00, 2.03, 2.09 (4s, 12 H, OAc), 3.62 (s, 2 H, SCH_2), 3.89–3.96 (m, 6 H, OCH_2), 4.00 (dd, J = 12.3, J = 2.0 Hz, 1 H, 6-H), 4.28 (dd, J = 12.3, J = 4.3 Hz, 1 H, 6-H), 4.41 (ddd, J = 10.3, J = 4.3, J = 2.0 Hz, 1 H, 5-H), 5.01–5.07 (m, 2 H, 2-H, 4-H), 5.38 (t, J = 9.8 Hz, 1 H, 3-H), 5.56 (d, J = 5.7 Hz, 1 H, 1-H), 6.46 (s, 2 H, Ar-H) ppm. ^{13}C NMR (75 MHz, CDCl$_3$): δ = 14.1 (*C*H$_3$), 20.6, 20.6, 20.6, 20.6, 20.7, 22.7, 26.1, 26.2, 29.4, 29.4, 29.5, 29.6, 29.7, 29.7, 29.7, 29.8, 29.8, 30.3, 31.9, 34.3 (S*C*H$_2$), 61.9 (C6), 67.8 (C5), 68.6, 69.2 (OCH$_2$ × 2), 70.4, 70.7 (C3), 73.5 (OCH$_2$), 81.3 (C1), 107.3 (Ar*C*H), 131.9, 137.5, 153.1, 169.6 (*C*O), 169.6 (CO), 169.9 (*C*O), 170.5 (*C*O) ppm. FT-IR (KBr): $\tilde{\nu}$ = 2956, 2919, 2851, 1747, 1591, 1468, 1430, 1377, 1336, 1232, 1115, 1041, 917, 803, 721 cm^{-1}. MALDI: m/z = [M$^+$] 1090.75, [M + Na]$^+$ 1113.77, [M + K]$^+$ 1129.74. C$_{63}$H$_{110}$O$_{12}$S (1091.61): calcd. C 69.32, H 10.16, S 2.94; found C 69.11, H 10.35, S 2.94.

14b: As a pale white solid; m.p. 52–53 °C; R_f = 0.47 (3:1 hexane/EtOAc). $[\alpha]_D^{20}$ = –56.5 (c = 0.31, CHCl$_3$). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.88 (t, J = 6.9 Hz, 9 H, CH_3), 1.26 [br. s, 60 H, (CH_2)$_{10}$], 1.42–1.47 (m, 6 H, OCH$_2$CH$_2$CH_2), 1.67–1.82 (m, 6 H, OCH$_2$CH_2), 2.00, 2.02, 2.03, 2.10 (4s, 12 H, OAc), 3.61–3.66 (m, 1 H, 5-H), 3.78–3.83 (m, 2 H, SCH_2), 3.91–3.96 (m, 6 H, OCH_2), 4.14 (dd, J = 12.4, J = 2.4 Hz, 1 H, 6-H), 4.27 (dd, J = 12.4, J = 5.0 Hz, 1 H, 6-H), 4.37 (d, J = 9.8 Hz, 1 H, 1-H), 5.09 (t, J = 9.6 Hz, 1 H, 4-H), 5.09 (t, J = 9.7 Hz, 1 H, 2-H), 5.18 (t, J = 9.3 Hz, 1 H, 3-H), 6.48 (s, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, CDCl$_3$): δ = 14.1 (*C*H$_3$), 20.6, 20.6, 20.7, 20.8, 22.7, 26.1, 29.4, 29.4, 29.5, 29.6, 29.7, 29.7, 29.7, 29.8, 29.8, 30.4, 31.9, 34.1 (S*C*H$_2$), 62.1 (C6), 68.3, 69.2 (OCH$_2$), 69.7, 73.4 (OCH$_2$ × 2), 73.8 (C3), 75.8 (C5), 82.1 (C1), 107.6 (Ar*C*H), 131.5, 137.5, 153.1, 169.4 (*C*O), 169.4 (CO), 170.2 (*C*O), 170.6 (*C*O) ppm. FT-IR (KBr): $\tilde{\nu}$ = 2956, 2919, 2851, 1747, 1591, 1468, 1430, 1377, 1336, 1232, 1115, 1041, 917, 803, 721 cm^{-1}. MALDI: m/z = [M$^+$] 1090.75, [M + Na]$^+$ 1113.77, [M + K]$^+$ 1129.74. C$_{63}$H$_{110}$O$_{12}$S (1091.61): calcd. C 69.32, H 10.16, S 2.94; found C 69.11, H 10.35, S 2.94.

3,4,5-Tris(tretradecyloxy)benzyl 1-Thio-α-D-glucopyranoside (15a): To a solution of **14a** or **14b** (0.07 g, 0.0625 mmol) in MeOH (1.5 mL) and CH$_2$Cl$_2$ (0.8 mL), was added K$_2$CO$_3$ (0.004 g) and the reaction mixture was stirred at room temp. for 3 h. The reaction mixture was neutralized with Amberlite IR-120 H$^+$, the resin was filtered and rinsed with CH$_2$Cl$_2$, and the solvent was evaporated to afford **15a** or **15b** (0.04 g, 95%) as white solids; **15a**: ^{1}H NMR (500 MHz, CDCl$_3$): δ = 0.88 (t, J = 6.7 Hz, 9 H, CH_3), 1.26 [br. s, 60 H, (CH_2)$_{10}$], 1.42–1.46 (m, 6 H, OCH$_2$CH$_2$CH_2), 1.70–1.77 (m, 6 H, OCH$_2$CH_2), 3.30–3.50 (br. s, 1 H, OH), 3.45–3.55 (m, 2 H, 5-H, 3-H), 3.65 (m, 2 H, SCH_2), 3.69 (d, J = 11.5 Hz, 1 H, 6-H), 3.74 (dd, J = 8.6, J = 5.3 Hz, 1 H, 2-H), 3.70 (d, J = 10.8 Hz, 1 H, 6-H), 3.88–3.93 (m, 7 H, OCH_2 × 3, 4-H), 5.25 (d, J = 4.9 Hz, 1 H, 1-H), 6.49 (s, 2 H, Ar-H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 14.1 (*C*H$_3$), 22.7, 26.2, 26.2, 29.4, 29.5, 29.6, 29.7, 29.7, 29.8, 29.8, 30.4, 31.9, 35.2 (S*C*H$_2$), 61.6 (C6), 69.2 (OCH$_2$ × 2), 69.7, 71.5 (C2), 72.1, 73.5 (OCH$_2$), 75.0 (C3), 85.5 (C1), 107.5 (Ar*C*H), 132.5, 137.3, 153.0 ppm. **15b**: ^{1}H NMR (500 MHz, CDCl$_3$): δ = 0.88 (t, J = 6.9 Hz, 9 H, CH_3), 1.26 [br. s, 60 H, (CH_2)$_{10}$], 1.41–1.44 (m, 6 H, OCH$_2$CH$_2$CH_2), 1.70–1.76 (m, 6 H, OCH$_2$CH_2), 3.25 (m, 1 H, 5-H), 3.42 (m, 1 H, 2-H), 3.48 (dd, J = 8.6, J = 8.1 Hz, 1 H, 3-H), 3.60 (dd, J = 9.3, J = 8.6 Hz, 1 H, 4-H), 3.78–3.85 (m, 4 H, SCH_2, 6s-H), 3.89–3.95 (m, 6 H, OCH_2 × 3), 4.31 (d, J = 9.3 Hz, 1 H, 1-H), 6.50 (s, 2 H, Ar-H) ppm. ^{13}C NMR (125 MHz, CDCl$_3$): δ = 14.1 (*C*H$_3$), 22.7, 22.9, 26.2, 26.2, 29.4, 29.5, 29.5, 29.7, 29.7, 29.8, 30.4, 31.9, 34.9 (S*C*H$_2$), 61.8 (C6), 69.2 (OCH$_2$), 69.2 (C4), 72.5 (C2), 73.5 (OCH$_2$ ×2), 77.9 (C3), 79.4 (C5), 84.8 (C1), 107.4 (Ar*C*H), 132.1, 137.3, 153.1 ppm.

Oxidative Hydrolysis of Compound 14b: To a vigorously stirred solution of thioglycoside **14b** (15.5 mg, 0.014 mmol) in CH$_2$Cl$_2$ (0.5 mL) and H$_2$O (50 μL) was added at 0 °C NIS (16 mg, 0.071 mmol) and TFA (6 μL, 0.078 mmol). After stirring for 3 h at 0 °C, the reaction was quenched with satd aq. Na$_2$S$_2$O$_3$ and washed with satd aq. NaHCO$_3$. The organic layer was dried with Na$_2$SO$_4$ and concentrated in vacuo. The crude residue was dissolved in a 1:1 v/v mixture of MeCN and hexane (10 mL). The phases were separated and the MeCN layer was extracted with hexane (5 mL). The MeCN layer was evaporated at reduced pressure and the crude residue was further purified through a short (2 mL) silica cartridge (EtOAc/hexane, 1:1) to afford **18**[19] (4.2 mg, 84%).

3,4,5-Tris(tretradecyloxy)benzyl 6-*O*-Trityl-1-thio-α-D-glucopyranoside (19a): A solution of **15a** (0.036 g, 0.038 mmol) and trityl chloride (0.021 g, 0.076 mmol) in pyridine (0.4 mL, 0.1 M) under argon atmosphere was stirred for 3 d at room temperature. Pyridine was removed at reduced pressure to afford a residue that was purified by column chromatography (CH$_2$Cl$_2$/Et$_3$N, 9:0.1) to give **19a** (0.028 g, 65%) as a colorless oil. R_f = 0.8 (CH$_2$Cl$_2$/MeOH/Et$_3$N, 9:0.1:0.1). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.88 (t, J = 6.9 Hz, 9 H, CH_3), 1.26 (br. s, 60 H, 10CH_2), 1.36–1.49 (m, 6 H, OCH$_2$CH$_2$CH_2), 1.69–1.76 (m, 6 H, OCH$_2$CH_2), 2.25 (br. s, 1 H,

OH), 2.50 (br. s, 1 H, OH), 2.84 (br. s, 1 H, OH), 3.38 (dd, J = 10.1, J = 5.5 Hz, 1 H, 6-H), 3.45 (dd, J = 10.0, J = 3.8 Hz, 1 H, 6-H), 3.49 (t, J = 9.2 Hz, 1 H), 3.62 (t, J = 9.2 Hz, 1 H), 3.76 (m, 2 H, SCH_2), 3.71–3.96 (m, 1 H), 3.86 (t, J = 6.5 Hz, 6 H, OC$H_2\times$2), 3.91 (t, J = 6.6 Hz, 3 H, OCH_2), 4.16 (ddd, J = 9.5, J = 5.3, J = 4.1 Hz, 1 H, 5-H), 5.30 (d, J = 5.5 Hz, 1 H, 1-H), 6.51 (s, 2 H, Ar-H), 7.22–7.32 (m, 9 H, Ar-H), 7.45–7.48 (m, 6 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (*C*H$_3$), 22.7, 26.1, 26.1, 29.4, 29.4, 29.5, 29.7, 29.7, 29.7, 29.7, 29.7, 29.8, 29.8, 30.4, 31.9, 34.5 (S*C*H$_2$), 63.9 (C6), 69.1 (OCH$_2$), 70.8, 71.6, 71.9, 73.4 (OCH$_2$), 75.3, 84.2, 87.1, 107.5 (Ar*C*H), 127.2, 127.3, 127.7, 128.0, 128.6, 132.0, 137.4, 143.6, 153.1 ppm.

3,4,5-Tris(tretradecyloxy)benzyl 4,6-*O*-Benzylidene-1-thio-α-D-glucopyranoside (20a): PhCH(OMe)$_2$ (43 μL, 0.303 mmol) was added to a solution of **15a** (0.093 g, 0.101 mmol) in dry DMF (0.6 mL) containing Å MS at room temperature under argon atmosphere. After stirring the mixture for 30 min, was added CSA (0.005 g, 0.020 mmol) and the reaction mixture was stirred at 65 °C for 24 h. The solvent was evaporated under reduced pressure to give a crude residue that was partitioned in hexane/MeCN (10 mL each), the hexane phase was separated and the MeCN layer was extracted with hexane (2 × 5 mL). The combined hexane phases were concentrated and the resultant residue was purified by silica gel column chromatography (hexane/EtOAc, 20:1 to 4:1) to give **20a** (0.071 g, 70%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.0 Hz, 9 H, CH_3), 1.26 [br. s, 60 H, (CH_2)$_{10}$], 1.43–1.49 (m, 6 H, OCH$_2$CH$_2$CH_2), 1.70–1.81 (m, 6 H, OCH$_2$CH_2), 3.48 (dd, J = 9.5, J = 9.0 Hz, 1 H, 4-H), 3.70–3.77 (m, 3 H, SCH_2, 6-H), 3.80 (t, J = 9.2 Hz, 1 H, 3-H), 3.86 (dd, J = 9.3, J = 5.4 Hz, 1 H, 2-H), 3.91–3.97 (m, 6 H, OC$H_2\times$3), 4.18–4.22 (m, 2 H, 5-H, 6-H), 5.31 (d, J = 5.6 Hz, 1 H, 1-H), 5.51 [s, 1 H, PhC*H*(OC)$_2$], 6.51 (s, 2 H, Ar-H), 7.35–7.38 (m, 3 H, Ar-H), 7.47–7.50 (m, 2 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (*C*H$_3$), 22.7, 26.1, 26.1, 29.4, 29.4, 29.4, 29.5, 29.6, 29.7, 29.7, 29.7, 29.7, 29.7, 29.8, 30.3, 31.9, 35.4 (S*C*H$_2$), 63.5 (C5), 68.8 (C6), 69.2 (OCH$_2\times$2), 72.2, 72.2, 73.4 (OCH$_2$), 81.1 (C4), 85.9 (C1), 102.0 [Ph*C*H(OC)$_2$], 107.4 (Ar*C*H), 126.3, 128.3, 129.3, 132.1, 136.9, 137.5, 153.1 ppm.

3,4,5-Tris(tretradecyloxy)benzyl 4,6-*O*-Benzylidene-1-thio-β-D-glucopyranoside (20b): PhCH(OMe)$_2$ (100 μL, 0.366 mmol) was added to a solution of **15b** (0.225 g, 0.244 mmol) in dry DMF (0.8 mL) containing 4 Å MS at room temperature under argon atmosphere. After stirring the mixture for 30 min, CSA (0.011 g, 0.049 mmol) was added and the reaction mixture was stirred at 65 °C for 32 h. The solvent was evaporated under reduced pressure to give a crude residue that was partitioned in hexane/MeCN (30 mL each), the hexane phase was separated and the MeCN layer was extracted with hexane (2 × 20 mL). The combined hexane phases were concentrated and the resultant residue was purified by silica gel column chromatography (hexane/EtOAc, 4:1) to give **20b** (0.191 g, 78%) as a white solid; m.p. 69–80 °C; R_f = 0.40 (hexane/EtOAc, 2:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.8 Hz, 9 H, CH_3), 1.26 [br. s, 60 H, (CH_2)$_{10}$], 1.43–1.49 (m, 6 H, OCH$_2$CH$_2$CH_2), 1.71–1.82 (m, 6 H, OCH$_2$CH_2), 3.43 (dt, J = 9.7, J = 4.9 Hz, 1 H, 5-H), 3.50–3.58 (m, 2 H, 2-H), 3.73–3.81 (m, 2 H, 6-H), 3.86 (s, 2 H, SCH_2), 3.90–3.97 (m, 6 H, OC$H_2\times$3), 4.33 (dd, J = 10.4, J = 4.9 Hz, 1 H, 6-H), 4.39 (d, J = 9.8 Hz, 1 H, 1-H), 5.53 [s, 1 H, PhC*H*(OC)$_2$], 6.51 (s, 2 H, Ar-H), 7.35–7.39 (m, 3 H, Ar-H), 7.46–7.50 (m, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (*C*H$_3$), 22.7, 26.1, 29.3, 29.4, 29.4, 29.6, 29.7, 29.7, 30.3, 31.9, 34.9 (S*C*H$_2$), 68.5 (C6), 69.1 (O*C*H$_2\times$2), 70.5 (C5), 73.2, 73.4 (OCH$_2$), 74.6, 80.3, 85.4 (C1), 101.9 [Ph*C*H(OC)$_2$], 107.3 (Ar*C*H), 126.2, 128.3, 129.3, 131.8, 136.8, 137.4, 153.2 ppm. MALDI: m/z = [M$^+$] 1010.75, [M + Na]$^+$ 1033.77, [M + K]$^+$ 1049.74. $C_{62}H_{106}O_8S$ (1011.57): calcd. C 73.61, H 10.56, S 3.17; found C 73.37, H 10.81, S 2.99.

3,4,5-Tris(tretradecyloxy)benzyl 4,6-*O*-Benzylidene-2,3-di-*O*-benzyl-1-thio-α-D-glucopyranoside (21a): To a stirred solution of **20a** (0.070 g, 0.069 mmol) in DMF (0.9 mL, 0.08 M) under argon atmosphere was added NaH (60%, 0.028 g, 0.694 mmol). After 15 min, benzyl bromide (84 μL, 0.694 mmol) was added and the reaction mixture was stirred at room temp. for 24 h. The reaction was quenched with MeOH and stirred for 30 min. The crude was diluted with CH_2Cl_2 and washed with water. The organic layer was dried with Na_2SO_4, filtered and evaporated at reduced pressure. Column chromatographic purification of the residue (hexane/EtOAc, 35:1) afforded **21a** (0.061 g, 74%) as a white solid; m.p. 48–52 °C; R_f = 0.40 (hexane/EtOAc, 6:1). $[a]_D^{20}$ = +81.5 (c = 0.52, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.81 (t, J = 6.9 Hz, 9 H, CH_3), 1.25 [br. s, 60 H, (CH_2)$_{10}$], 1.34–1.42 (m, 6 H, OCH$_2$CH$_2$CH_2), 1.70–1.73 (m, 6 H, OCH$_2$CH_2), 3.53 (t, J = 9.3 Hz, 1 H, 4-H), 3.57 (s, 2 H, SCH_2), 3.66 (t, J = 10.2 Hz, 1 H, 6-H), 3.69 (dd, J = 9.2, J = 5.7 Hz, 1 H, 2-H), 3.82 (t, J = 9.3 Hz, 1 H, 3-H) 3.84–3.88 (m, 6 H, OC$H_2\times$3), 4.15 (dd, J = 10.1, J = 4.9 Hz, 1 H, 6-H), 4.26–4.31 (m, 1 H, 5-H), 4.41 (d, J = 11.8 Hz, 1 H, PhCH$_2$), 4.48 (d, J = 11.8 Hz, 1 H, PhCH$_2$), 4.74 (d, J = 11.4 Hz, 1 H, PhCH$_2$), 4.78 (d, J = 11.4 Hz, 1 H, PhCH$_2$), 5.16 (d, J = 5.7 Hz, 1 H, 1-H), 5.48 [s, 1 H, PhC*H*(OC)$_2$], 6.47 (s, 2 H, Ar-H), 7.16–7.23 (m, 8 H, Ar-H), 7.26–7.33 (m, 5 H, Ar-H), 7.41–7.43 (m, 2 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (*C*H$_3$), 22.7, 26.1, 26.1, 29.4, 29.4, 29.4, 29.5, 29.6, 29.7, 29.7, 29.7, 29.7, 29.7, 29.8, 30.3, 31.9, 33.9 (S*C*H$_2$), 63.2 (C5), 68.9 (C6), 69.0 (O*C*H$_2\times$2), 72.0 (Ph*C*H$_2$), 73.4 (O*C*H$_2\times$1), 75.3 (Ph*C*H$_2$), 78.4 (C2), 78.9 (C3), 81.7 (C4), 83.1 (C1), 101.2 [Ph*C*H(OC)$_2$], 107.3 (Ar*C*H), 126.0, 127.5, 127.7, 127.9, 128.2, 128.2, 128.3, 128.9, 132.7, 137.3, 137.5, 138.6, 153.0 ppm. MALDI: m/z = [M + Na]$^+$ 1213.94, [M + K]$^+$ 1229.91. $C_{76}H_{118}O_8S$ (1191.81): calcd. C 76.59, H 9.98, S 2.69; found C 76.74, H 10.21, S 2.49.

3,4,5-Tris(tretradecyloxy)benzyl 4,6-*O*-Benzylidene-2,3-di-*O*-benzyl-1-thio-β-D-glucopyranoside (21b): To a stirred solution of **20b** (0.189 g, 0.187 mmol) in DMF (1.5 mL, 0.1 M) under argon atmosphere was added NaH (60%, 0.077 g, 1.868 mmol). After 15 min, benzyl bromide (0.3 mL, 1.868 mmol) was added and the reaction mixture was stirred at room temp. for 24 h. The reaction was quenched with MeOH and stirred for 30 min. The crude was diluted with CH_2Cl_2 and washed with water. The organic layer was dried with Na_2SO_4, filtered and evaporated at reduced pressure. Column chromatographic purification of the residue (hexane/EtOAc, 35:1) afforded **21b** (0.198 g, 89%).as a white solid; m.p. 72–81 °C; R_f = 0.74 (hexane/EtOAc, 4:1). $[a]_D^{20}$ = –34.6 (c = 0.77, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, J = 6.9 Hz, 9 H, CH_3), 1.26 [br. s, 60 H, (CH_2)$_{10}$], 1.40–1.51 (m, 6 H, OCH$_2$CH$_2$CH_2), 1.70–1.80 (m, 6 H, OCH$_2$CH_2), 3.39 (ddd, J = 9.9, J = 9.1, J = 5.0 Hz, 1 H, 5-H), 3.50 (dd, J = 9.8, J = 8.0 Hz, 1 H, 2-H), 3.72 (t, J = 9.3 Hz, 1 H, 4-H), 3.77 (dd, J = 9.3, J = 7.9 Hz, 1 H, 3-H), 3.80 (t, J = 10.4 Hz, 1 H, 6-H), 3.87 (m, 2 H, SCH_2), 3.89–3.95 (m, 6 H, OC$H_2\times$3), 4.48 (d, J = 9.9 Hz, 1 H, 1-H), 4.78 (d, J = 11.3 Hz, 1 H, PhCH$_2$), 4.78 (d, J = 10.3 Hz, 1 H, PhCH$_2$), 4.83 (d, J = 10.3 Hz, 1 H, PhCH$_2$), 4.93 (d, J = 11.3 Hz, 1 H, PhCH$_2$), 5.58 [s, 1 H, PhC*H*(OC)$_2$], 6.52 (s, 2 H, Ar-H), 7.26–7.40 (m, 15 H, Ar-H), 7.47–7.50 (m, 2 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (*C*H$_3$), 22.7, 26.1, 26.1, 29.4, 29.4, 29.5, 29.7, 29.7, 29.7, 29.7, 29.8, 30.3, 31.9, 35.3 (S*C*H$_2$), 68.7 (C6), 69.0 (OCH$_2\times$2), 70.2 (C5), 73.4 (OCH$_2$), 75.2 (Ph*C*H$_2$), 75.8 (Ph*C*H$_2$), 81.1 (C2), 81.6 (C4), 82.7 (C3), 84.7 (C1), 101.1 [Ph*C*H(OC)$_2$], 107.3 (Ar*C*H), 126.0, 127.7, 127.8, 128.0, 128.1, 128.2, 128.3, 128.3, 129.0, 132.1, 137.2, 137.3, 137.9, 138.3, 153.1

ppm. MALDI: *m*/*z* = [M + Na]$^+$ 1213.94, [M + K]$^+$ 1229.91. $C_{76}H_{118}O_8S$ (1191.81): calcd. C 76.59, H 9.98, S 2.69; found C 76.74, H 10.21, S 2.49.

3,4,5-Tris(tretradecyloxy)benzyl 2,3,4-Tri-*O*-benzyl-1-thio-α-D-glucopyranoside (22a): To a solution of **21a** (0.061 g, 0.051 mmol) in Et_2O/CH_2Cl_2 (1 mL, 1:1 v/v) under argon atmosphere was added $LiAlH_4$ (0.009 g, 0.241 mmol). After stirring the reaction mixture at 50 °C (bath temperature), was added a solution of $AlCl_3$ (0.027 g, 0.205 mmol) in Et_2O (0.5 mL). The suspension was stirred at 50 °C for 3 h. When the reaction was judged complete by TLC analysis, EtOAc and H_2O were sequentially added dropwise, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4, and evaporated at reduced pressure. The residue was purified by silica gel column chromatography (hexane/EtOAc, 15:1) to afford **22a** (0.60 g, 99%) as a white solid; m.p. 42–44 °C; R_f = 0.24 (hexane/EtOAc, 5:1). $[\alpha]_D^{20}$ = +95.7 (*c* = 1.15, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.0 Hz, 9 H, C*H*$_3$), 1.26 [br. s, 60 H, (C*H*$_2$)$_{10}$], 1.41–1.46 (m, 6 H, OCH$_2$CH$_2$C*H*$_2$), 1.71–1.80 (m, 6 H, OCH$_2$C*H*$_2$), 3.53 (dd, *J* = 9.8, *J* = 9.0 Hz, 1 H, 4-H), 3.61 (m, 2 H, SC*H*$_2$), 3.72 (dd, *J* = 9.5, *J* = 5.4 Hz, 1 H, 2-H), 3.74–3.76 (m, 2 H, 6s-H), 3.86 (t, *J* = 9.3 Hz, 1 H, 3-H), 3.90–3.95 (m, 6 H, OC*H*$_2$ ×3), 4.09 (dt, *J* = 9.8, *J* = 3.2 Hz, 1 H, 5-H), 4.43 (d, *J* = 11.7 Hz, 1 H, PhC*H*$_2$), 4.51 (d, *J* = 11.7 Hz, 1 H, PhC*H*$_2$), 4.64 (d, *J* = 11.0 Hz, 1 H, PhC*H*$_2$), 4.78 (d, *J* = 10.8 Hz, 1 H, PhC*H*$_2$), 4.88 (d, *J* = 11.2 Hz, 1 H, PhC*H*$_2$), 4.96 (d, *J* = 11.0 Hz, 1 H, PhC*H*$_2$), 5.21 (d, *J* = 5.6 Hz, 1 H, 1-H), 6.54 (s, 2 H, Ar-H), 7.22–7.36 (m, 15 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (*C*H$_3$), 22.7, 26.1, 26.1, 29.4, 29.4, 29.4, 29.5, 29.6, 29.7, 29.7, 29.7, 29.7, 29.7, 29.8, 30.3, 31.9, 33.9 (S*C*H$_2$), 61.9 (C6), 69.1 (O*C*H$_2$ × 2), 71.4 (C5), 71.7 (Ph*C*H$_2$), 73.4 (O*C*H$_2$), 75.1 (Ph*C*H$_2$), 75.7 (Ph*C*H$_2$), 76.9 (C4), 79.0 (C2), 82.1 (C1), 82.5 (C3), 107.3 (Ar*C*H), 127.6, 127.8, 127.8, 127.9, 128.0, 128.1, 128.3, 128.4, 128.5, 132.8, 137.1, 137.5, 138.0, 138.6, 153.0 ppm. FT-IR (KBr): $\tilde{\nu}$ = 3436, 2919, 2850, 1593, 1506, 1468, 1442, 1381, 1337, 1238, 1133, 1117, 1085, 1027, 735, 695 cm^{-1}. MALDI: *m*/*z* = [M + Na]$^+$ 1215.94, [M + K]$^+$ 1231.93. $C_{76}H_{120}O_8S$ (1193.83): calcd. C 76.46, H 10.13, S 2.69; found C 76.18, H 10.16, S 2.57.

3,4,5-Tris(tretradecyloxy)benzyl 2,3,4-Tri-*O*-benzyl-1-thio-β-D-glucopyranoside (22b): To a solution of **21b** (0.061 g, 0.051 mmol) in Et_2O/CH_2Cl_2 (1 mL, 1:1 v/v) under argon atmosphere was added $LiAlH_4$ (0.009 g, 0.246 mmol). After stirring the reaction mixture at 50 °C (bath temperature), was added a solution of $AlCl_3$ (0.027 g, 0.205 mmol) in Et_2O (0.5 mL). The suspension was stirred at 50 °C for 1.5 h. When the reaction was judged complete by TLC analysis, EtOAc and H_2O were sequentially added dropwise, and the mixture was extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4, and the solvents evaporated. The residue was purified by silica gel column chromatography (hexane/EtOAc, 15:1) to afford **22b** (0.52 g, 85%) as a white solid; m.p. 61–63 °C; R_f = 0.32 (hexane/EtOAc, 4:1). $[\alpha]_D^{20}$ = –10.1 (*c* = 0.41, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 6.8 Hz, 9 H, C*H*$_3$), 1.26 [br. s, 60 H, (C*H*$_2$)$_{10}$], 1.41–1.50 (m, 6 H, OCH$_2$CH$_2$C*H*$_2$), 1.70–1.80 (m, 6 H, OCH$_2$C*H*$_2$), 3.29 (ddd, *J* = 9.6, *J* = 4.8, *J* = 2.7 Hz, 1 H, 5-H), 3.44 (dd, *J* = 9.7, *J* = 8.8 Hz, 1 H, 2-H), 3.56 (t, *J* = 9.3 Hz, 1 H, 4-H), 3.66 (t, *J* = 8.9 Hz, 1 H, 3-H), 3.66–3.69 (m, 1 H, 6-H), 3.79–3.94 (m, 9 H, OC*H*$_2$ × 3, 6-H, SC*H*$_2$), 4.39 (d, *J* = 9.8 Hz, 1 H, 1-H), 4.64 (d, *J* = 11.0 Hz, 1 H, PhC*H*$_2$), 4.72 (d, *J* = 10.3 Hz, 1 H, PhC*H*$_2$), 4.84 (d, *J* = 10.8 Hz, 1 H, PhC*H*$_2$), 4.85 (d, *J* = 10.9 Hz, 1 H, PhC*H*$_2$), 4.86 (d, *J* = 10.1 Hz, 1 H, PhC*H*$_2$), 4.90 (d, *J* = 11.0 Hz, 1 H, PhC*H*$_2$), 6.49 (s, 2 H, Ar-H), 7.24–7.33 (m, 15 H, Ar-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (*C*H$_3$), 22.7, 26.1, 29.4, 29.4, 29.4, 29.7, 29.7, 29.7, 30.3, 30.9 (acetone), 31.9, 35.4 (S*C*H$_2$), 62.1 (C6), 69.0 (O*C*H$_2$ × 2), 73.4 (O*C*H$_2$), 75.1 (Ph*C*H$_2$), 75.4 (Ph*C*H$_2$), 75.8 (Ph*C*H$_2$), 77.6 (C4), 79.2 (C5), 81.6 (C2), 84.0 (C1), 85.4 (C3), 107.2 (Ar*C*H), 127.7, 127.8, 127.8, 128.0, 128.0, 128.1, 128.4, 128.4, 128.5, 132.3, 137.3, 137.9, 138.3, 153.1 ppm. FT-IR (KBr): $\tilde{\nu}$ = 3436, 2919, 2850, 1593, 1506, 1468, 1442, 1381, 1337, 1238, 1133, 1117, 1085, 1027, 735, 695 cm^{-1}. MALDI: *m*/*z* = [M + Na]$^+$ 1215.94, [M + K]$^+$ 1231.93. $C_{76}H_{120}O_8S$ (1193.83): calcd. C 76.46, H 10.13, S 2.69; found C 76.18, H 10.16, S 2.57.

General Procedure for Glycosylation: To a solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranosyl trichloroacetimidate **23** and compound **22** (0.03–0.04 M in **22**) under the reaction conditions showed in Table 2 was added TMSOTf. After stirring the indicated time, the reaction mixture was quenched with Et_3N (1 drop). The crude was diluted with hexane and washed with aq. sat. $NaHCO_3$. The organic layer was washed with MeCN and the MeCN layer was back-extracted with hexane (2×). The combined hexane phases were dried (Na_2SO_4) and concentrated at reduced pressure. The crude product was purified by a silica gel chromatography (hexane/EtOAc, 10:1), to afford the disaccharide products **24** with the yields and stereoselectivities shown in Table 2. Compounds **24aa**, **24ab**, and **24ba** could be obtained pure, while **24bb** was obtained partially contaminated with **24ab**.

6-*O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-3,4,5-tris(tretradecyloxy)benzyl 2,3,4-Tri-*O*-benzyl-1-thio-α-D-glucopyranoside (24aa): Colorless solid; m.p. 49–51 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.0 Hz, 9 H, C*H*$_3$), 1.25 [br. s, 60 H, (C*H*$_2$)$_{10}$], 1.33–1.48 (m, 6 H, OCH$_2$CH$_2$C*H*$_2$), 1.67–1.74 (m, 6 H, OCH$_2$C*H*$_2$), 3.52 (dd, *J* = 9.6, *J* = 3.4 Hz, 1 H, 2′-H), 3.56 (dd, *J* = 10.4, *J* = 1.8 Hz, 1 H, 6′-H), 3.59–3.65 (m, 5 H, 4-H, 4′-H, 6′-H, SC*H*$_2$), 3.65 (dd, *J* = 9.5, *J* = 5.7 Hz, 1 H, 2-H), 3.72 (bd, *J* = 10.6 Hz, 1 H, 6-H), 3.77 (ddd, *J* = 9.8, *J* = 5.2, *J* = 2.4 Hz, 1 H, 5′-H), 3.84–3.91 (m, 8 H, OC*H*$_2$ × 3, 6-H, 3-H), 3.95 (t, *J* = 9.3 Hz, 1 H, 3′-H), 4.29 (dd, *J* = 10.1, *J* = 3.7 Hz, 1 H, 5-H), 4.32 (d, *J* = 11.6 Hz, 1 H, PhC*H*$_2$), 4.41 (d, *J* = 12.0 Hz, 1 H, PhC*H*$_2$), 4.43 (d, *J* = 10.6 Hz, 1 H, PhC*H*$_2$), 4.43 (d, *J* = 11.5 Hz, 1 H, PhC*H*$_2$), 4.56 (d, *J* = 12.1 Hz, 1 H, PhC*H*$_2$), 4.63 (s, 1 H, PhC*H*$_2$), 4.63 (d, *J* = 9.8 Hz, 1 H, PhC*H*$_2$), 4.65 (d, *J* = 10.9 Hz, 1 H, PhC*H*$_2$), 4.67 (d, *J* = 10.8 Hz, 1 H, PhC*H*$_2$), 4.74 (d, *J* = 10.7 Hz, 1 H, PhC*H*$_2$), 4.80 (d, *J* = 11.0 Hz, 1 H, PhC*H*$_2$), 4.87 (d, *J* = 10.9 Hz, 1 H, PhC*H*$_2$), 4.91 (d, *J* = 11.1 Hz, 1 H, PhC*H*$_2$), 4.92 (d, *J* = 10.8 Hz, 1 H, PhC*H*$_2$), 4.96 (d, *J* = 3.4 Hz, 1 H, 1′-H), 5.20 (d, *J* = 5.6 Hz, 1 H, 1-H), 6.55 (s, 2 H, Ar-H), 7.08–7.33 (m, 35 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (*C*H$_3$), 22.7, 26.1, 29.4, 29.4, 29.5, 29.7, 29.7, 30.3, 31.9, 33.4 (S*C*H$_2$), 68.4 (C6), 69.0 (C6′, O*C*H$_2$ × 2), 70.2 (C5′), 71.2 (C5), 71.7 (Ph*C*H$_2$), 72.4 (Ph*C*H$_2$), 73.4 (OCH$_2$, Ph*C*H$_2$), 74.9 (Ph*C*H$_2$), 75.0 (Ph*C*H$_2$), 75.5 (Ph*C*H$_2$), 75.7 (Ph*C*H$_2$), 77.4 (C4, C4′), 79.2 (C2), 79.9 (C2′), 81.6 (C1), 81.8 (C3′), 82.7 (C3), 97.4 (C1′), 107.3 (Ar*C*H), 127.5, 127.5, 127.6, 127.7, 127.7, 127.8, 127.8, 127.9, 128.0, 128.0, 128.2, 128.3, 128.3, 128.3, 128.4, 132.8, 137.0, 137.6, 137.9, 138.4, 138.7, 153.0 ppm. $C_{110}H_{154}O_{13}S$ (1716.46): calcd. C 76.97, H 9.04, S 1.87; found C 76.86, H 8.95, S 1.73.

6-*O*-(2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl)-3,4,5-tris(tretradecyloxy)benzyl 2,3,4-Tri-*O*-benzyl-1-thio-β-D-glucopyranoside (24ab): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.0 Hz, 9 H, C*H*$_3$), 1.25 [br. s, 60 H, (C*H*$_2$)$_{10}$], 1.38–1.45 (m, 6 H, OCH$_2$CH$_2$C*H*$_2$), 1.69–1.75 (m, 6 H, OCH$_2$C*H*$_2$), 3.21 (t, *J* = 9.3 Hz, 1 H, 2-H), 3.40 (ddd, *J* = 9.6, *J* = 2.9, *J* = 2.9 Hz, 1 H, 5-H), 3.58 (t, *J* = 9.1 Hz, 1 H, 3-H), 3.59 (dd, *J* = 9.5, *J* = 3.3 Hz, 1 H, 2′-H), 3.64 (dd, *J* = 10.3, *J* = 1.3 Hz, 1 H, 6′-H), 3.64–3.68 (m, 1 H, 4′-H), 3.72 (d, *J* = 9.9 Hz, 1 H, 6′-H), 3.72–3.75 (m, 2 H, 4-H, SC*H*$_2$), 3.84 (d, *J* =

2.8 Hz, 2 H, 6s-H), 3.86–3.91 (m, 8 H, OCH_2×3, 5′-H, SCH_2), 4.02 (t, J = 9.3 Hz, 1 H, 3′-H), 4.32 (d, J = 9.9 Hz, 1 H, 1-H), 4.44 (d, J = 11.0 Hz, 1 H, PhCH_2), 4.45 (d, J = 12.3 Hz, 1 H, PhCH_2), 4.51 (d, J = 10.3 Hz, 1 H, PhCH_2), 4.62 (d, J = 12.0 Hz, 1 H, PhCH_2), 4.66 (d, J = 10.3 Hz, 1 H, PhCH_2), 4.67 (d, J = 11.1 Hz, 1 H, PhCH_2), 4.71 (d, J = 10.8 Hz, 1 H, PhCH_2), 4.74 (d, J = 12.0 Hz, 1 H, PhCH_2), 4.78 (d, J = 11.0 Hz, 1 H, PhCH_2), 4.85 (d, J = 11.7 Hz, 1 H, PhCH_2), 4.82 (d, J = 10.6 Hz, 1 H, PhCH_2), 4.84 (d, J = 10.7 Hz, 1 H, PhCH_2), 4.87 (d, J = 10.7 Hz, 1 H, PhCH_2), 4.93 (d, J = 10.8 Hz, 1 H, PhCH_2), 5.14 (d, J = 3.3 Hz, 1 H, 1′-H), 6.50 (s, 2 H, Ar-H), 7.09–7.41 (m, 35 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2 (CH_3), 22.7, 26.2, 29.4, 29.5, 29.5, 29.7, 29.7, 31.9, 34.7 (SCH_2), 65.4 (C6), 68.4 (C6′), 69.0 (OCH_2×2), 70.0 (C5′), 72.2 (PhCH_2), 73.3 (PhCH_2), 73.4 (OCH_2), 74.8 (PhCH_2), 75.0 (PhCH_2), 75.3 (PhCH_2), 75.5 (PhCH_2), 75.6 (PhCH_2), 77.4 (C4′), 77.6 (C4), 78.9 (C5), 80.0 (C2′), 81.6 (C2), 81.7 (C3′), 83.2 (C1), 86.4 (C3), 97.0 (C1′), 107.2 (ArCH), 127.4, 127.6, 127.9, 128.0, 128.1, 128.2, 128.3, 128.3, 128.3, 128.4, 128.4, 132.3, 137.1, 137.9, 137.9, 138.1, 138.4, 138.5, 138.5, 138.7, 153.0 ppm. $C_{110}H_{154}O_{13}S$ (1716.46): calcd. C 76.97, H 9.04, S 1.87; found C 76.86, H 8.95, S 1.73.

6-*O*-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-3,4,5-tris(tretradecyloxy)benzyl 2,3,4-Tri-*O*-benzyl-1-thio-α-D-glucopyranoside (24ba): Colorless solid; m.p. 57–58 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.0 Hz, 9 H, CH_3), 1.26 [br. s, 60 H, $(CH_2)_{10}$], 1.38–1.49 (m, 6 H, $OCH_2CH_2CH_2$), 1.69–1.77 (m, 6 H, OCH_2CH_2), 3.43 (ddd, J = 9.4, J = 4.8, J = 1.8 Hz, 1 H, 5′-H), 3.50 (dd, J = 9.0, J = 7.8 Hz, 1 H, 2′-H), 3.56–3.65 (m, 5 H, 4-H, 4′-H, 3′-H, SCH_2), 3.68 (dd, J = 10.9, J = 4.8 Hz, 1 H, 6′-H), 3.73 (dd, J = 9.6, J = 5.5 Hz, 1 H, 2-H), 3.74 (dd, J = 10.8, J = 1.6 Hz, 1 H, 6′-H), 3.78 (dd, J = 11.2, J = 4.6 Hz, 1 H, 6-H), 3.84 (t, J = 9.4 Hz, 1 H, 3-H), 3.83–3.93 (m, 6 H, OCH_2×3), 4.21 (dd, J = 11.1, J = 1.7 Hz, 1 H, 6-H), 4.34 (ddd, J = 10.1, J = 4.4, J = 1.7 Hz, 1 H, 5-H), 4.39 (d, J = 7.8 Hz, 1 H, 1′-H), 4.39 (d, J = 11.7 Hz, 1 H, PhCH_2), 4.48 (d, J = 11.7 Hz, 1 H, PhCH_2), 4.50 (d, J = 11.1 Hz, 1 H, PhCH_2), 4.53 (d, J = 10.9 Hz, 1 H, PhCH_2), 4.54 (d, J = 12.2 Hz, 1 H, PhCH_2), 4.61 (d, J = 12.2 Hz, 1 H, PhCH_2), 4.69 (d, J = 11.0 Hz, 1 H, PhCH_2), 4.72 (d, J = 11.1 Hz, 1 H, PhCH_2), 4.77 (d, J = 11.0 Hz, 1 H, PhCH_2), 4.78 (d, J = 11.0 Hz, 1 H, PhCH_2), 4.81 (d, J = 11.3 Hz, 1 H, PhCH_2), 4.90 (d, J = 10.9 Hz, 1 H, PhCH_2), 4.93 (d, J = 10.9 Hz, 1 H, PhCH_2), 4.97 (d, J = 11.0 Hz, 1 H, PhCH_2), 5.26 (d, J = 5.5 Hz, 1 H, 1-H), 6.51 (s, 2 H, Ar-H), 7.15–7.34 (m, 35 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.1 (CH_3), 22.7, 26.1, 29.4, 29.4, 29.4, 29.5, 29.6, 29.7, 29.7, 29.8, 29.8, 30.3, 31.9, 33.6 (SCH_2), 68.5 (C6), 68.9 (C6′), 69.0 (OCH_2×2), 70.9 (C5), 71.6 (PhCH_2), 73.4 (PhCH_2), 73.4 (OCH_2), 74.9 (PhCH_2), 75.0 (C5′), 75.6 (PhCH_2), 75.7 (PhCH_2), 77.6 (C4), 77.8 (C4′), 78.8 (C2), 82.0 (C2′), 82.1 (C1), 82.5 (C3), 84.8 (C3′), 103.8 (C1′), 107.2 (ArCH), 127.5, 127.6, 127.6, 127.6, 127.7, 127.7, 127.7, 127.7, 127.8, 127.9, 127.9, 128.0, 128.3, 128.3, 128.3, 128.4, 128.4, 133.0, 137.0, 137.5, 138.0, 138.1, 138.2, 138.3, 138.4, 138.7, 153.0 ppm. $C_{110}H_{154}O_{13}S$ (1716.46): calcd. C 76.97, H 9.04, S 1.87; found C 76.86, H 8.95, S 1.73.

6-*O*-(2,3,4,6-Tetra-*O*-benzyl-β-D-glucopyranosyl)-3,4,5-tris(tretradecyloxy)benzyl 2,3,4-Tri-*O*-benzyl-1-thio-β-D-glucopyranoside (24bb): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.88 (t, J = 7.0 Hz, 9 H, CH_3), 1.25 [br. s, 60 H, $(CH_2)_{10}$], 1.38–1.45 (m, 6 H, $OCH_2CH_2CH_2$), 1.69–1.75 (m, 6 H, OCH_2CH_2), 3.41–3.96 (m, 20 H), 4.20 (d, J = 9.5 Hz, 1 H), 4.38 (d, J = 9.8 Hz, 1 H, 1-H), 4.41 (d, J = 7.8 Hz, 1 H, 1′-H), 4.50–5.03 (m, 14 H, PhCH_2), 6.43 (s, 2 H, Ar-H), 7.13–7.47 (m, 35 H, Ar-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 83.9 (C1), 104.2 (C1′), 107.2 ppm.

Supporting Information (see also the footnote on the first page of this article): ^{1}H NMR of the anomerization reaction of **22b** promoted by TMSOTf.

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[1] a) J. M. Frechet, C. Schuerch, *J. Am. Chem. Soc.* **1971**, *93*, 492–496; b) H. M. I. Osborn, T. H. Khan, *Tetrahedron* **1999**, *55*, 1807–1850; c) P. H. Seeberger, W. C. Haase, *Chem. Rev.* **2000**, *100*, 4349–4393; d) P. H. Seeberger, *Chem. Soc. Rev.* **2008**, *37*, 19–28.

[2] a) G. Perugino, B. Cobucci-Ponzano, M. Rossi, M. Moracci, *Adv. Synth. Catal.* **2005**, *347*, 941–950; b) A. Trincone, A. Giordano, *Curr. Org. Chem.* **2006**, *10*, 1163–1193; c) D. A. Thayer, C. H. Wong, *Top. Curr. Chem.* **2007**, *267*, 37–63.

[3] a) S. P. Douglas, D. M. Whitfield, J. J. Krepinsky, *J. Am. Chem. Soc.* **1991**, *113*, 5095–5097; b) S. P. Douglas, D. M. Whitfield, J. J. Krepinsky, *J. Am. Chem. Soc.* **1995**, *117*, 2116–2117; c) Y. Ito, O. Kanie, T. Ogawa, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2510–2512; d) Y. Ito, T. Ogawa, *J. Am. Chem. Soc.* **1997**, *119*, 5562–5566; e) S. Mehta, D. Whitfield, *Tetrahedron Lett.* **1998**, *39*, 5907–5910; f) F. Y. Yan, W. W. Wakarchuk, M. Gilbert, J. C. Richards, D. M. Whitfield, *Carbohydr. Res.* **2000**, *328*, 3–16; g) S. Manabe, Y. Ito, T. Ogawa, *Synlett* **1998**, 628–630; M. Jesberger, J. Jaunzems, A. Jung, G. Jas, A. Schonberger, A. Kirschning, *Synlett* **2000**, 1289–1293; h) A. J. Ross, I. A. Ivanova, A. P. Higson, A. V. Nikolaev, *Tetrahedron Lett.* **2000**, *41*, 2449–2452; i) S. Mehta, D. M. Whitfield, *Tetrahedron* **2000**, *56*, 6415–6425; j) H. Ando, S. Manabe, Y. Nakahara, Y. Ito, *Angew. Chem. Int. Ed.* **2001**, *40*, 4725–4728; k) H. Ando, S. Manabe, Y. Nakahara, Y. Ito, *J. Am. Chem. Soc.* **2001**, *123*, 3848–3849; l) X. F. Huang, K. L. Witte, D. E. Bergbreiter, C. H. Wong, *Adv. Synth. Catal.* **2001**, *343*, 675–681; m) F. Y. Yan, M. Gilbert, W. W. Wakarchuk, J. R. Brisson, D. M. Whitfield, *Org. Lett.* **2001**, *3*, 3265–3268; n) R. Geurtsen, G. J. Boons, *Eur. J. Org. Chem.* **2002**, 1473–1477; o) Y. Ito, S. Manabe, *Chem. Eur. J.* **2002**, *8*, 3077–3084; p) S. Hanashima, S. Manabe, Y. Ito, *Synlett* **2003**, 979–982; q) S. Hanashima, S. Manabe, K. Inamori, N. Taniguchi, Y. Ito, *Angew. Chem. Int. Ed.* **2004**, *43*, 5674–5677; r) S. Hanashima, S. Manabe, Y. Ito, *Angew. Chem. Int. Ed.* **2005**, *44*, 4218–4224; s) R. Blattner, R. H. Furneaux, M. Ludewig, *Carbohydr. Res.* **2006**, *341*, 299–321; t) S. Hanashima, K. I. Inamori, S. Manabe, N. Taniguchi, Y. Ito, *Chem. Eur. J.* **2006**, *12*, 3449–3462.

[4] a) M. M. Palcic, L. D. Heerze, M. Pierce, O. Hindsgaul, *Glycoconjugate J.* **1988**, *5*, 49–63; b) P. Stangier, M. M. Palcic, D. R. Bundle, *Carbohydr. Res.* **1995**, *267*, 153–159; c) O. Kanie, F. Barresi, Y. L. Ding, J. Labbe, A. Otter, L. S. Forsberg, B. Ernst, O. Hindsgaul, *Angew. Chem. Int. Ed. Engl.* **1996**, *34*, 2720–2722; d) Y. Ding, J. Labbe, O. Kanie, O. Hindsgaul, *Bioorg. Med. Chem.* **1996**, *4*, 683–692; e) U. J. Nilsson, *J. Chromatogr. A* **2000**, *885*, 305–319; V. Pozsgay, *Org. Lett.* **1999**, *1*, 477–479; f) U. J. Nilsson, E. J. L. Fournier, O. Hindsgaul, *Bioorg. Med. Chem.* **1998**, *6*, 1563–1575; g) V. Pozsgay, *Tetrahedron: Asymmetry* **2000**, *11*, 151–172; h) R. Sato, K. Toma, K. Nomura, M. Takagi, T. Yoshida, Y. Azefu, H. Tamiaki, *J. Carbohydr. Chem.* **2004**, *23*, 375–388; i) J. Bauer, J. Rademann, *J. Am. Chem. Soc.* **2005**, *127*, 7296–7297; j) O. Kanie, I. Ohtsuka, T. Ako, S. Daikoku, Y. Kame, R. Kato, *Angew. Chem. Int. Ed.* **2006**, *45*, 3851–3854.

[5] a) D. P. Curran, R. Ferritto, Y. Hua, *Tetrahedron Lett.* **1998**, *39*, 4937–4940; b) T. Miura, Y. Hirose, M. Ohmae, T. Inazu, *Org. Lett.* **2001**, *3*, 3947–3950; c) L. Manzoni, *Chem. Commun.* **2003**, 2930–2931; d) T. Miura, *Trends Glycoscience Glycotechnol.* **2003**, *15*, 351–358; e) T. Miura, T. Inazu, *Tetrahedron Lett.* **2003**, *44*, 1819–1821; f) K. Goto, T. Miura, D. Hosaka, H.

Matsumoto, M. Mizuno, H. K. Ishida, T. Inazu, *Tetrahedron* **2004**, *60*, 8845–8854; g) K. Goto, T. Miura, M. Mizuno, H. Takaki, N. Imai, Y. Murakami, T. Inazu, *Synlett* **2004**, 2221–2223; h) Y. Q. Jing, X. F. Huang, *Tetrahedron Lett.* **2004**, *45*, 4615–4618; i) L. Manzoni, R. Castelli, *Org. Lett.* **2004**, *6*, 4195–4198; j) T. Miura, K. Goto, H. Waragai, H. Matsumoto, Y. Hirose, M. Ohmae, H. Ishida, A. Satoh, T. Inazu, *J. Org. Chem.* **2004**, *69*, 5348–5353; k) K. Goto, T. Miura, M. Mizuno, *Tetrahedron Lett.* **2005**, *46*, 8293–8297; l) T. Miura, A. Satoh, K. Goto, Y. Murakami, N. Imai, T. Inazu, *Tetrahedron: Asymmetry* **2005**, *16*, 3–6; m) T. Miura, S. Tsujino, A. Satoh, K. Goto, M. Mizuno, M. Noguchi, T. Kajimoto, M. Node, Y. Murakami, N. Imai, T. Inazu, *Tetrahedron* **2005**, *61*, 6518–6526; n) K. S. Ko, F. A. Jaipuri, N. L. Pohl, *J. Am. Chem. Soc.* **2005**, *127*, 13162–13163; o) K. Ikeda, H. Mori, M. Sato, *Chem. Commun.* **2006**, 3093–3094; p) M. Kojima, Y. Nakamura, T. Ishikawa, S. Takeuchi, *Tetrahedron Lett.* **2006**, *47*, 6309–6314; q) S. K. Mamidyala, K. S. Ko, F. A. Jaipuri, G. Park, N. L. Pohl, *J. Fluorine Chem.* **2006**, *127*, 571–579; r) L. Manzoni, R. Castelli, *Org. Lett.* **2006**, *8*, 955–957; s) M. Mizuno, K. Goto, T. Miura, T. Inazu, *QSAR Comb. Sci.* **2006**, *25*, 742–752; t) M. Mizuno, H. Matsumoto, K. Goto, K. Hamasaki, *Tetrahedron Lett.* **2006**, *47*, 8831–8835; u) F. R. Carrel, K. Geyer, J. D. C. Codee, P. H. Seeberger, *Org. Lett.* **2007**, *9*, 2285–2288; v) K. Goto, M. Mizuno, *Tetrahedron Lett.* **2007**, *48*, 5605–5608; w) M. Kojima, Y. Nakamura, S. Takeuchi, *Tetrahedron Lett.* **2007**, *48*, 4431–4436; x) F. R. Carrel, P. H. Seeberger, *J. Org. Chem.* **2008**, *73*, 2058–2065; y) F. A. Jaipuri, N. L. Pohl, *Org. Biomol. Chem.* **2008**, *6*, 2686–2691; z) M. Mizuno, S. Kitazawa, K. Goto, *J. Fluorine Chem.* **2008**, *129*, 955–960; G. Park, K.-S. Ko, A. Zakharova, N. L. Pohl, *J. Fluorine Chem.* **2008**, *129*, 978–982.

[6] a) E. R. Palmacci, M. C. Hewitt, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2001**, *40*, 4433–4437; b) A. Dondoni, A. Marra, A. Massi, *Angew. Chem. Int. Ed.* **2005**, *44*, 1672–1676; c) J. Wu, Z. W. Guo, *J. Org. Chem.* **2006**, *71*, 7067–7070.

[7] a) K. Egusa, S. Kusumoto, K. Fukase, *Synlett* **2001**, 777–780; b) K. Egusa, S. Kusumoto, K. Fukase, *Eur. J. Org. Chem.* **2003**, 3435–3445.

[8] For the first example of glycoside synthesis using a solid-phase supported reagent, see: a) H. Paulsen, O. Lockhoff, *Chem. Ber.* **1981**, *114*, 3102–3114. For recent reports, see: b) K. Toshima, K. Kasumi, S. Matsumura, *Synlett* **1999**, 813–815; c) A. Kirschning, M. Jesberger, H. Monenschein, *Tetrahedron Lett.* **1999**, *40*, 8999–9002; d) K. Toshima, H. Nagai, S. Matsumura, *Synlett* **1999**, 1420–1422; e) H. Yoshizaki, N. Fukuda, K. Sato, M. Oikawa, K. Fukase, Y. Suda, S. Kusumoto, *Angew. Chem. Int. Ed.* **2001**, *40*, 1475–1480; f) A. Kirschning, M. Jesberger, A. Schonberger, *Org. Lett.* **2001**, *3*, 3623–3626; g) H. Nagai, K. Kawahara, S. Matsumura, K. Toshima, *Tetrahedron Lett.* **2001**, *42*, 4159–4162; h) H. Nagai, S. Matsumura, K. Toshima, *Tetrahedron Lett.* **2002**, *43*, 847–850; i) J. Jaunzems, G. Sourkouni-Argirusi, M. Jesberger, A. Kirschning, *Tetrahedron Lett.* **2003**, *44*, 637–639; j) J. Jaunzems, E. Hofer, M. Jesberger, G. Sourkouni-Argirusi, A. Kirschning, *Angew. Chem. Int. Ed.* **2003**, *42*, 1166–1170; k) J. Jaunzems, D. Kashin, A. Schonberger, A. Kirschning, *Eur. J. Org. Chem.* **2004**, 3435–3446; l) I. Ohashi, M. J. Lear, F. Yoshimura, M. Hirama, *Org. Lett.* **2004**, *6*, 719–722; m) M. Oikawa, T. Tanaka, N. Fukuda, S. Kusumoto, *Tetrahedron Lett.* **2004**, *45*, 4039–4042; n) B. Mukhopadhyay, B. Collet, R. A. Field, *Tetrahedron Lett.* **2005**, *46*, 5923–5925; o) J. L. Chiara, L. Encinas, B. Diaz, *Tetrahedron Lett.* **2005**, *46*, 2445–2448; p) Y. G. Du, G. H. Wei, S. H. Cheng, Y. X. Hua, R. J. Linhardt, *Tetrahedron Lett.* **2006**, *47*, 307–310; q) E. Kunst, F. Gallier, G. Dujardin, M. S. Yusubov, A. Kirschning, *Org. Lett.* **2007**, *9*, 5199–5202; r) Q. Tian, S. Zhang, Q. Yu, M. B. He, J. S. Yang, *Tetrahedron* **2007**, *63*, 2142–2147; s) B. Roy, B. Mukhopadhyay, *Tetrahedron Lett.* **2007**, *48*, 3783–3787; t) E. Kunst, F. Gallier, G. Dujardin, A. Kirschning, *Org. Biomol. Chem.* **2008**, *6*, 893–898; u) L. Encinas, J. L. Chiara, *J. Comb. Chem.* **2008**, *10*, 361–363.

[9] For recent reviews, see: a) D. P. Curran, *Angew. Chem. Int. Ed.* **1998**, *37*, 1175–1196; b) J. i. Yoshida, K. Itami, *Chem. Rev.* **2002**, *102*, 3693–3716; c) C. C. Tzschucke, C. Markert, W. Bannwarth, S. Roller, A. Hebel, R. Haag, *Angew. Chem. Int. Ed.* **2002**, *41*, 3964–4000.

[10] For a review, see: U. J. Nilsson, *J. Chromatogr. A* **2000**, *885*, 305–319.

[11] During the preparation of this work, Chiba reported the first example of the use of LLE with two immiscible organic solvents as a separation method for the purification of synthetic oligosaccharides: S. Kim, A. Tsuruyama, A. Ohmori, K. Chiba, *Chem. Commun.* **2008**, 1816–1818.

[12] For some recent examples, see: a) V. S. K. Balagurusamy, G. Ungar, V. Percec, G. Johansson, *J. Am. Chem. Soc.* **1997**, *119*, 1539–1555; b) T. Hatano, T. Kato, *Chem. Commun.* **2006**, 1277–1279; c) T. Ichikawa, M. Yoshio, A. Hamasaki, T. Mukai, H. Ohno, T. Kato, *J. Am. Chem. Soc.* **2007**, *129*, 10662–10663.

[13] V. Vicente, J. Martin, J. Jiménez-Barbero, J. L. Chiara, C. Vicent, *Chem. Eur. J.* **2004**, *10*, 4240–4251.

[14] Benzyl alcohol **3** has been used before as a carboxyl-protecting group for the solution-phase synthesis of peptides with simple purification by gel-filtration: H. Tamiaki, T. Obata, Y. Azefu, K. Toma, *Bull. Chem. Soc. Jpn.* **2001**, *74*, 733–738.

[15] M. R. Pratt, D. L. Clifton, C. R. Bertozzi, *Org. Lett.* **2003**, *5*, 3185–3188.

[16] M. J. Hadd, J. Gervay, *Carbohydr. Res.* **1999**, *320*, 61–69.

[17] The difficulties found in the glycosylation of **3** have a precedent: R. Sato, K. Toma, K. Nomura, M. Takagi, T. Yoshida, Y. Azefu, H. Tamiaki, *J. Carbohydr. Chem.* **2004**, *23*, 375–388.

[18] V. S. K. Balagurusamy, G. Ungar, V. Percec, G. Johansson, *J. Am. Chem. Soc.* **1997**, *119*, 1539–1555.

[19] F. M. Ibatullin, K. A. Shabalin, J. V. Jänis, A. G. Shavva, *Tetrahedron Lett.* **2003**, *44*, 7961–7964.

[20] J. Dinkelaar, M. D. Witte, L. J. van den Bos, H. S. Overkleeft, G. A. van der Marel, *Carbohydr. Res.* **2006**, *341*, 1723–1729.

[21] K. Borisch, S. Diele, P. Goring, H. Kresse, C. Tschierske, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2087–2089.

[22] It is well known that the structure of the miscellar agregates formed by 1-alkyl glycosides depend on their anomeric configuration: a) B. Focher, G. Savelli, G. Torri, G. Vecchio, D. C. McKenzie, D. F. Nicoli, C. A. Bunton, *Chem. Phys. Lett.* **1989**, *158*, 491–494; b) C. Dupuy, X. Auvray, C. Petipas, I. Rico-Lattes, A. Lattes, *Langmuir* **1997**, *13*, 3965–3967.

[23] Trichloroacetimidate **23** was readily prepared without purification using PS-DBU as a catalytic and recyclable solid supported base following our recently reported procedure (see ref. 8o).

[24] a) V. S. Rao, A. S. Perlin, *Carbohydr. Res.* **1981**, *92*, 141–148; b) M.-O. Contour, J. Defaye, M. Little, E. Wong, *Carbohydr. Res.* **1989**, *193*, 283–287; c) K. Takeo, K. Maki, Y. Wada, S. Kitamura, *Carbohydr. Res.* **1993**, *245*, 81–96; d) G. J. Boons, T. Stauch, *Synlett* **1996**, 906–908; e) K. P. R. Kartha, P. Cura, M. Aloui, S. K. Readman, T. J. Rutherford, R. A. Field, *Tetrahedron: Asymmetry* **2000**, *11*, 581–593; f) Q. Tian, S. Zhang, Q. Yu, M.-B. He, J.-S. Yang, *Tetrahedron* **2007**, *63*, 2142–2147.

[25] D. T. Connolly, S. Roseman, Y. C. Lee, *Carbohydr. Res.* **1980**, *87*, 227–239.

[26] Silicon Lewis acids have a much higher affinity for oxygen than for sulfur, which correlates with the dissociation energies of the corresponding bonds: O–Si 530 kJ/mol; S–Si 410 kJ/mol.

[27] a) Z. Li, J. C. Gildersleeve, *J. Am. Chem. Soc.* **2006**, *128*, 11612–11619; b) Z. Li, J. C. Gildersleeve, *Tetrahedron Lett.* **2007**, *48*, 559–562.

[28] J. Gervay, M. J. Hadd, *J. Org. Chem.* **1997**, *62*, 6961–6967.

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