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Stereoselective tris-glycosylation to introduce β-(1→3)-branches into gentiotetraose for the concise synthesis of phytoalexin-elicitor heptaglucoside

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Summary

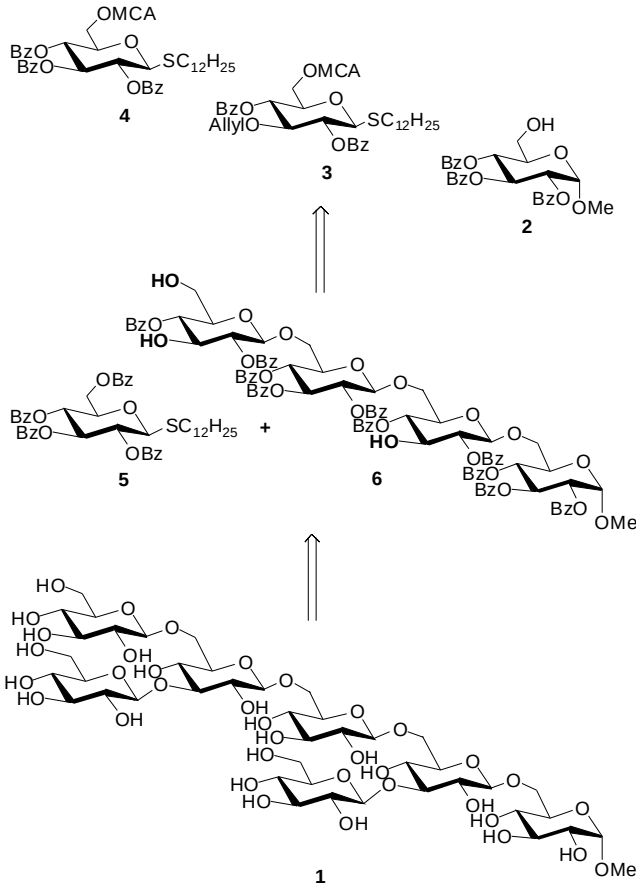
Dodecyl thioglycosides (**3**, **4**, **5**) were prepared by conventional transformation of D-glucose and used as new glycosyl donors for a short-step synthesis of phytoalexin elicitor heptaglucoside. A gentio-tetraoside derivative (**6**) having three hydroxyl groups was synthesized by NIS-TfOH promoted glycosylate in more than 90% yields followed by selective removal of temporary protective groups. Undesired formation of α-glycosides in introduction of β-(1→3)-branches into gentio-oligosaccharides was found to be suppressed by use of a thiophilic reagent system, BSP (1-benzenesulfinyl piperidine)-Tf_2O, giving the heptaglucoside in only four glycosylation steps.

Introduction

Since Albersheim identified a heptaglucoside analogous to **1** that elicits production of phytoalexin in soybeans,[1] its unique structure has often been used as a model compound to demonstrate the feasibility of new methodologies in chemical synthesis of oligosaccharides, *e.g.,* convergent block synthesis, one-pot sequential glycosylation, and chemoselective glycosylation.[2] Compound **1** consists of a β-(1→6)-linked D-glucopyranose backbone (gentiopentaose unit) and two β-(1→3)-linked branches (laminaribiose units). Because of the difficulty of glycosylating the sterically hindered 3-hydroxyl group, the most successful syntheses of **1** reported to date involved construction of the laminaribiose units at an earlier stage of the synthetic scheme. In contrast to this laminaribiose route, van Boom proposed a seemingly straightforward strategy, in which the β-(1→6)-linked backbone of **1** would be first synthesized and subsequently two β-(1→3)-linked branches introduced.[3] However, no one has reported total synthesis of **1** via this gentio-oligosaccharide route. Recently, while investigating the regioselective introduction of a β-(1→3)-linked branch into gentio-oligosaccharides using our newly-developed dodecyl thioglycoside donors,[4] we found that BSP-Tf_2O[5] was a suitable promoter to our purpose. In this paper, we report the first successful results using this approach, which involves tris-glycosylation of a gentiotetraose intermediate.

Results and discussion

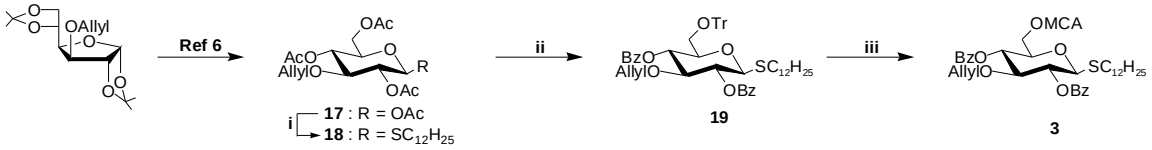
Following the retrosynthetic analysis of the target heptaglucoside **1** proposed by van Boom, elimination of three glucose moieties at the non-reducing end and branches leaves a β-(1→6)-linked gentiotetraoside **6** as shown in Scheme 1.



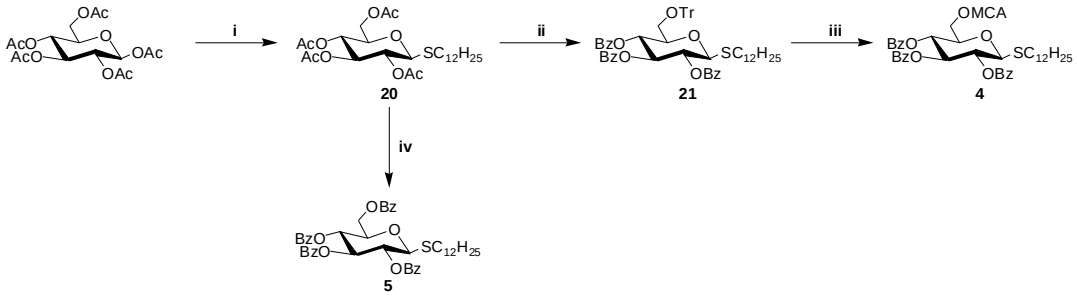
Scheme 1 Retrosynthetic analysis of the heptaglucoside **1** by tris-glycosylation.

Provision for further tris-glycosylation sites in **6** is anticipated through the use of temporary protecting groups, *O*-chloroacetyl (MCA) and *O*-allyl groups, allowing for exposure of the free hydroxylic acceptor sites. Furthermore, participation of the neighboring 2-*O*-benzoyl protection groups in the dodecyl thioglucosyl donors would afford desired all β-glucosidic linkages. As a result, the total synthesis can be initiated from a known acceptor **2** and three dodecyl thioglycosyl donors (**3**, **4**, **5**). Starting from readily available D-glucose derivatives and non-volatile l-dodecanethiol, the glycosyl donors (**3**, **4**, **5**) were prepared by means of conventional transformations as shown in schema 2 and 3. Using the thioglycosides **3** and **4** as glycosyl donors, and

N-iodosuccinimide (NIS)-triflic acid (TfOH),[7] as the promoter, we proceeded sequential glycosylation to synthesize the gentio-tetraoside **6**, as outlined Scheme 4.

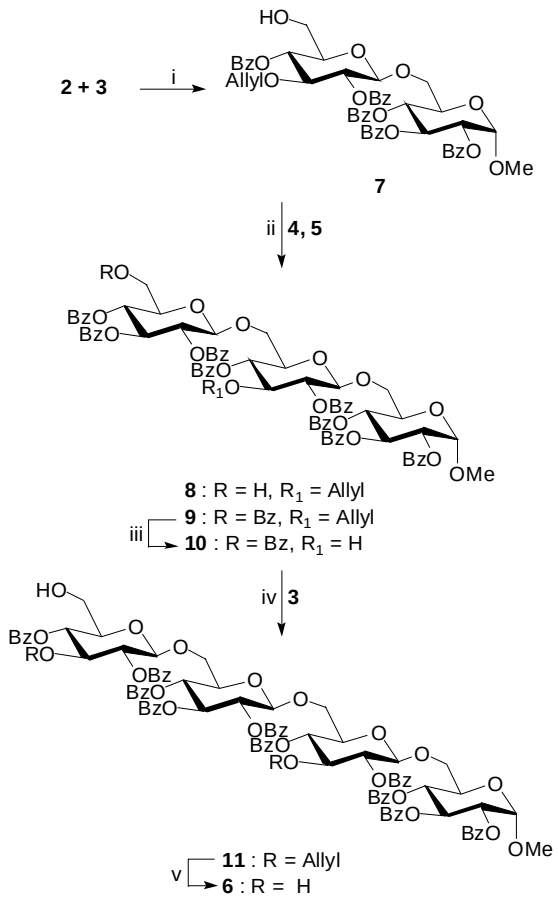


Scheme 2 Synthesis of glycosyl donor **3**. *Reagents and conditions*: (i) $C_{12}H_{25}SH$, $BF_3{\cdot}Et_2O$, $(CH_2)_2Cl_2$, 0 °C, 87%; (ii) a) NaOMe, MeOH, 3 h; b) TrCl, pyridine, DMAP, 60 °C, 5 h; c) BzCl, pyridine, 60 °C, overnight, 91% over 3 steps; (iii) a) $AcOH/H_2O$ = 5/1, 70 °C, 1 h; b) $(MCA)_2O$, pyridine/CH_2Cl_2 = 1/10, 3 h, 92%, over 2 steps. DMAP = *N*, *N*-dimethylaminopyridine, MCA = chloroacetyl.



Scheme 3 Synthesis of glycosyl donor **4** and **5**. *Reagents and conditions*: (i) $C_{12}H_{25}SH$, $BF_3{\cdot}Et_2O$, $(CH_2)_2Cl_2$, 94%; (ii) a) NaOMe, MeOH, 3 h; b) TrCl, pyridine, 60 °C, overnight; c) BzCl, pyridine, 0 °C to rt, overnight, 86% over 3 steps; (iii) a) $AcOH/H_2O$ = 5/1, 70 °C, 1 h; b) MCA, pyridine/CH_2Cl_2 = 1/10, 87% over 2 steps; (iv) a) NaOMe, MeOH, 5 h; b) BzCl, pyridine, rt, overnight, 86% over 2 steps.

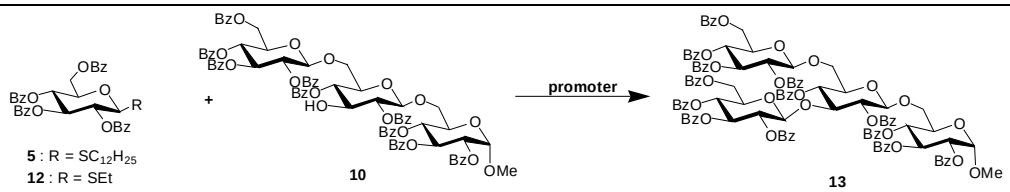
Coupling **2** and the dodecylthio donor **3**, which has a MCA and an *O*-allyl protecting group, was first performed in dry CH_2Cl_2 using NIS-TfOH as a promoter, and the temporary *O*-MCA protecting group was subsequently removed by treatment with aqueous pyridine, giving the desired disaccharide acceptor **7** in 92% overall yield. Moreover, two gentiotrioses **8** and **9** were synthesized under similar conditions with the *O*-MCA protected **4**, and the per-benzoylated donors **5** in high yields, respectively. The acceptor **8** was further glycosylated with **3** to give the tetraose **11** which has two *O*-allyl groups. Finally, selective removal of the *O*-allyl groups in **9** and **11** was successfully performed by ultrasonication with $PdCl_2$,[8] giving the acceptors **10**[3] and **6** in 90% yields. The triol **6**, obtained in an excellent overall yield, was a potential intermediate in our synthetic route to **1**. Compound **10** was used as a model acceptor for the examination to introduce β-(1→3)-linked branch.



Scheme 4 Synthesis of gentio-oligosaccharide intermediate. *Reagents and conditions*: (i) NIS-TfOH, CH_2Cl_2, -20 °C to rt; then H_2O/Pyridine, 50 °C, overnight, **7**: 92%; (ii) NIS-TfOH, CH_2Cl_2, -20 °C to rt; then H_2O/Pyridine, 50 °C, overnight, **4**→**8**: 92% and **5**→**9**: 88%; (iii) $PdCl_2$, NaOAc/95% AcOHaq., ultrasonication, rt, **10**: 90%; (iv) NIS-TfOH, CH_2Cl_2, -20 °C to rt; then H_2O/Pyridine, 50 °C, overnight, **11**: 92%; (v) $PdCl_2$, NaOAc/95% AcOHaq., ultrasonication, rt, **6**: 90%.

Our attention next focused on tris-glycosylation to introduce β-D-glucose residues into **6** concurrently. As a preliminary experiment, the triol **6** was treated with the donor **5** (3.6 equiv.) in the presence of NIS-TfOH for 2 days. As predicted by van Boom,[3] this was less successful and led to a complex mixture of products, from which crude fully benzoylated heptaglucoside, hexaoside, and gentiopentaoside were obtained 25%, 39%, and 18% yields, respectively. However, ^{1}H NMR spectra of the crude oligosaccharide thus obtained revealed contamination of several undesired α-glucosidic linkages.

Table 1 Evaluation of promoter system of thioglycosides in β-(1→3)-branch formation[a]



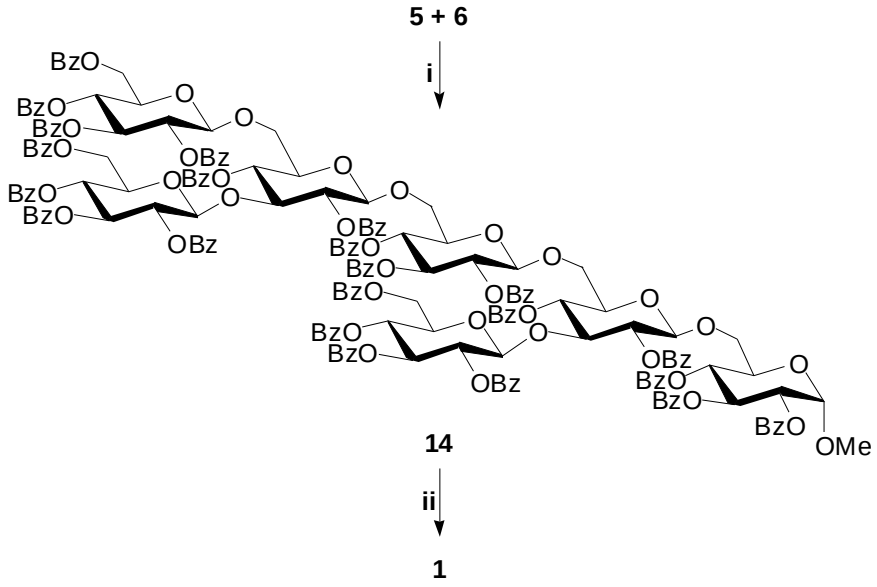
Entry	Promoter	Temp.	Yield (α:β)
1	NIS-TfOH	-40 ºC to rt	41% (1:1.4)
2[b]	NIS-TfOH	-40 ºC to rt	39% (1:1.2)
3[c]	NIS-TfOH	-40 ºC to rt	33% (1:1.3)
4	NIS-TfOH-AgOTf	-40 ºC to rt	28% (1:1.4)
5	ICl-AgOTf	-40 ºC to rt	no trace
6	BSP-Tf_2O	-78 ºC to rt	44% (β only)
7[c]	BSP-Tf_2O	-78 ºC to rt	60% (β only)

[a] All reactions were performed with 1.2 eq. of donor in CH_2Cl_2. Anomeric ratio determined by integration of the ^{1}H NMR spectrum of the crude reaction mixture. [b] glycosyl donor **12** was used. [c] donor **5** (1.5 eq.) was used.

These disappointing results forced us to seek better reaction conditions for the introduction of the β-(1→3)-linked branches. Using the model acceptor **10** and the

disarmed donor **5**, we evaluated the recently developed promoters of thioglycosides; the results are summarized in Table 1. To our surprise, the reaction using NIS-TfOH at -40 °C to room temperature in dry CH_2Cl_2 (entry 1) afforded **13** which was isolated as an anomeric mixture (α/β = 1:1.4) in 41% yield, even though a participating benzoyl ester is present at C-2 position in **5**. Similarly, the well-known thioethyl counterpart **12** was also able to provide **13** with slightly poorer α/β ratio (entry 3). Furthermore, we also examined milder thiophilic reagents, NIS-TfOH-AgOTf [9] and ICl-AgOTf,[10] for which a substoichomeric amount of promoter has been reported to activate the thioglycoside, producing a sulfonium bypoduct that can further promote glycosylations. However, **13** was obtained in 28% yield and with disappointing stereoselectivity (α/β = 1:1.4); representative reactions are highlighted in entry 4. Although the unusual formation of 1,2-*cis*-glycosides has been explained by unfavorable and mismatched structure between a glycosyl donor and an acceptor,[11] little has been reported on β-(1→3)-linked system. We hypothesized that severe steric hindrance between acceptor **10** and orthoester intermediate derived from the donor **5** occurred in oxocarbenium ion leading to the β-glycosidic bond, but not in the transition state leading to the α-bond. We next focused on BSP-Tf_2O promoter system developed by Crich, which is known to facilitate formation of a highly reactive glycosyl triflate intermediate. As shown in entries 6 and 7, BSP-Tf_2O mediated condensation between **10** and **5** proceeded with complete stereoselectivity to yield the β-linked tetraglucoside **13** in 44% yield. Use of slightly excess donor was more effective to yield **13** (60%). This β-selectivity can be explained by the rapid S_N2-like displacement of the intermediate α-triflate, which has also been observed by the groups of Crich,[5, 12a] van der Marel,[12b, c] and Yoshida, J. I.[12d] The satisfactory stereoselectivity and product yield

of the BSP-Tf_2O mediate glycosylation made it applicable to our purpose.



Scheme 6 Synthesis of the heptaglucoside **1**. *Reagents and conditions*: (i) BSP-Tf_2O, CH_2Cl_2, -78 °C to -40 °C, overnight, **14**: 47%; (ii) NaOMe, MeOH/H_2O = 1/1, 24 h, rt, **1**: 74%.

Based on these fruitful results, we finally undertook the culminating step of our synthetic scheme, the tris-glycosylation of **6** to construct the heptaglucoside. The dodecylthio donor **5** was pre-activated with BSP-Tf_2O at -78 ºC for 15 min, and the tetraose acceptor **6**, which has three hydroxyl groups, was subsequently added and the reaction was completed while gradually increasing the reaction temperature from -78 ºC to -40 ºC overnight. As we expected, the activation and condensation proceeded smoothly, as monitored by two-dimensional TLC analysis (hexane/EtOAc, 1/1 and toluene/EtOAc 5/1, v/v). Repeated chromatography on silica gel column with these solvent systems furnished the fully protected heptaglucoside **14** in 47% yield together with a mixture of hexaglucoside in 42% yield. In a 600 MHz ^{1}H NMR spectrum of **14**,

six anomeric protons, except for one at the reducing end, appeared as doublets with large coupling constants, suggesting all glucosidic linkages were β in configuration. Final removal of all benzoyl groups was performed with NaOMe in MeOH/H_2O to give known target compound **1**, of which the ^{1}H NMR spectrum was consistent with the reported data.[2c, 3]

Conclusions

It has been shown for the first time that a concise synthesis of the branched structure of the phytoalexin elicitor heptaglucoside **1** is enabled by employing sulfonyl triflate mediated tris-glucosylation of the gentiotetraose intermediate **6**. Since this approach allowed the introduction of two β-(1→3)-glucosyl branches at the final stage of the synthesis, this strategy would be applicable to synthesis of various analogues of **1** that have different mono- and/or oligo-saccharide branches.

Experimental

General methods

All chemicals were purchased as reagent grade and used without further purification whereas NIS was recrystallized by 1,4-dioxane and diethyl ether (1/1, v/v) before use. Dichloromethane (CH_2Cl_2) and 1,2-dichloroethane were distilled over calcium hydride. Molecular sieves used for glycosylation were MS4Å, which was activated at 200 ˚C under reduced pressure prior to use. Reaction monitoring with analytical thin-layer chromatography (TLC) on the silica gel 60F_{254} plates (layer-thickness, 0.25 mm; E. Merck, Darmstadt, Germany) and visualized under UV (254 nm) and/or by spraying with *p*-methoxybenzaldehyde/H_2SO_4/MeOH (1/2/17, v/v). Medium pressure column

chromatography was performed on silica gel (LiChroprep Si 60; 40-63 μm, Merck, Darmstadt, Germany). Column chromatography was performed on silica gel (Silica gel 60; 70-230 mesh ASTM, Merck, Darmstadt, Germany).

^{1}H and ^{13}C NMR spectra were recorded with a Bruker ASX 300 (300 and 75.1 MHz, respectively), JEOL A 500 (500 and 125 MHz) or JEOL ECA 600 (600 and 150 MHz). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; brs, broad singlet for ^{1}H NMR data. Signals were assigned on basis of ^{1}H-^{1}H COSY and ^{1}H-^{1}H TOCSY NMR experiments. ESI-HR mass spectra were recorded on a JEOL JMS-100TJ spectrometer and ESI-TOF HR mass spectra were measured on a Bruker micro TOF focus spectrometer. MALDI-TOF mass spectrometry was carried out using a Bruker-Daltonik Ultraflex TOF mass spectrometer equipped with a pulsed ion extraction system.

Dodecyl 2,4,6-tri-*O*-acetyl-3-allyl-*O*-1-thio-β-D-glucopyranoside (18)

Compound **17** (500 mg, 1.3 mmol) and 1-dodecanethiol (0.5 mL, 2.0 mmol) was dissolved in 1,2-dichloroethane (10 mL) and the solution was cooled to 0 ˚C. To the solution was added slowly $BF_3{\cdot}Et_2O$ (0.45 mL, 1.9 mmol), then the mixture was stirred for 30 min at 0 ˚C, TLC (toluene/EtOAc, 5/1, v/v) confirmed complete disappearance of the stating material. Reaction mixtures was poured into ice-water, and extracted with $CHCl_3$. The resulting mixture was successively washed with saturated aqueous (sat. aq.) $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated. The residue was recrystallized in EtOH to yield **18** (600 mg, 87%). $[\alpha]_D^{27}$ = -30.8 (*c* 1.24, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.81 (ddd, 1H, *J* = 5.5 Hz, *J* = 10.6 Hz, *J* = 22.6 Hz, CH_2-C*H*=CH_2), 5.30 (d, 1H, *J* = 17.0 Hz, CH_2-CH=C*H*$_2$), 5.18 (d, 1H, *J* = 7.7 Hz, CH_2-CH=C*H*$_2$), 5.10 (t, 1H, J_4,

$_5$ = 10.2 Hz, H-4), 5.04 (t, 1H, $J_{2,3}$ = 9.8 Hz, H-2), 4.40 (d, 1H, $J_{1,2}$ = 10.0 Hz, H-1), 4.26 (dd, 1H, $J_{5,6b}$ = 4.1 Hz, H-6b), 4.13 (dd, 1H, $J_{5,6a}$ = 2.2 Hz, $J_{6a,6b}$ = 14.7 Hz, H-6a), 4.30-4.00 (m 2H, C*H*$_2$-CH=CH$_2$), 3.61 (t, 1H, $J_{3,4}$ = 9.2 Hz, H-3), 3.70-3.50 (m 1H, H-5), 2.90-2.60 (m, 2H, SC*H*$_2$), 2.10, 2.10, 2.09 (3s, each 3H, CH$_3$Ac), 1.87-1.65 (m, 20H, SCH$_2$(C*H*$_2$)$_{10}$CH$_3$), 0.92 (t, 3H, *J* = 4.1 Hz, CH$_2$C*H*$_3$); ^{13}C NMR(75 MHz, CDCl$_3$): δ 171.0, 169.5, 169.4 (C=O Ac), 134.4, 131.1, 117.2, 84.0, 81.5, 76.8, 76.4, 73.3, 71.4, 69.8, 62.8, 32.2, 30.6, 30.1, 29.9, 29.8, 29.6, 29.4, 29.1, 22.9, 21.2, 21.1, 14.4, 11.2; Anal. Calcd for $C_{27}H_{46}O_8S$: C, 61.10; H, 8.74; s, 6.04%; Found: C, 60.96; H, 8.75; S, 6.07%.

Dodecyl 3-*O*-allyl-2,4-di-*O*-benzoyl-6-*O*-trityl-1-thio-β-D-glucopyranoside (19)

To a solution of **18** (500 mg, 0.9 mmol) in MeOH (10 mL) was added 25% solution of NaOMe in MeOH to adjust pH>12, and the mixture was stirred at room temperature for 3 h, when TLC (CHCl$_3$/MeOH, 10/1, v/v) indicated that the reaction of complete. The reaction mixture was neutralized with Amberlite IR-120 (H^+ form), filtered, and concentrated to give the 2,4,6-triol. To a dry pyridine (10 mL) solution of the resulting triol, DMAP (165 mg, 1.35 mmol), and chlorotriphenylmethane (362 mg, 1.3 mmol) were added, and the solution was stirred at 60 ˚C for 5 h, when TLC (toluene/EtOAc, 20/1, v/v) indicated that the reaction was completed. After addition of benzoyl chloride (0.6 mL, 5.6 mmol) the reaction mixture was stirred at 60 ˚C, overnight. The mixture was partitioned between CHCl$_3$ and ice-water. The organic phase was washed with 1M HCl, sat. aq. NaHCO$_3$, brine, dried (MgSO$_4$), and concentrated. Purification on silica gel column chromatography with hexane/EtOAc, 20/1→5/1, v/v as the eluant afforded compound **19** (700 mg, 91%). $[\alpha]_D^{26}$ = -19.8 (*c* 1.22, CHCl$_3$); ^{1}H NMR (300

MHz, $CDCl_3$): δ 8.20-7.10 (m, 25H, CH_{arom}), 5.62 (ddd, 1H, *J* = 5.8 Hz, *J* = 8.0 Hz, *J* = 16.9 Hz, CH_2-C*H*=CH_2), 5.51 (t, 1H, $J_{4,5}$ = 9.6 Hz, H-4), 5.52 (t, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 5.05 (dd, 1H, *J* = 1.4 Hz, *J* = 17.2 Hz, CH_2-CH=CH_2), 4.93 (d, 1H, *J* = 10.4 Hz, CH_2-CH=CH_2), 4.77 (d, 1H, $J_{1,2}$ = 10.0 Hz, H-1), 4.09 (d, 2H, CH_2-CH=CH_2), 4.00 (t, 1H, $J_{3,4}$ = 9.2 Hz, H-3), 3.84-3.81 (m, 1H, H-5), 3.50-3.30 (m, 2H, H-6a, 6b), 3.04-2.80 (m, 2H, SCH_2), 1.85-1.68, 1.47-1.28 (m, 20H, $SCH_2(CH_2)_{10}CH_3$), 0.98 (t, 3H, *J* = 6.9 Hz, CH_2CH_3); ^{13}C NMR(75 MHz, $CDCl_3$): δ 171.3, 165.2, 164.9, 147.1, 143.9, 143.5, 134.5, 133.4, 133.3, 130.0, 129.9, 129.2, 128.8, 128.7, 128.5, 128.2, 128.1, 127.9, 127.4, 127.3, 127.1, 117.6, 86.8, 83.9, 81.6, 78.5, 73.5, 72.6, 71.0, 63.0, 60.6, 32.1, 30.2, 30.1, 29.9, 29.8, 29.6, 29.3, 29.3, 22.9, 14.4; ESI-HRMS (*m/z*) calcd for $C_{54}H_{62}O_7SNa^+$: 877.4108; Found: 877.4113.

Dodecyl 3-*O*-allyl-2,4-di-*O*-benzoyl-6-*O*-chroloacetyl-1-thio-β-D-glucopyranoside (3)

A solution of the tritylated compound **19** (500 mg, 0.58 mmol) in acetic acid (40 mL) was added H_2O (8 mL) at 70 ^oC. The mixture kept stirring at this temperature for 1 h, after which time the reaction was completed as indication by TLC (hexane/EtOAc, 3/1, v/v). The reaction mixture was evaporated then subjected to co-evaporation with toluene three times. Purification on silica gel column chromatography (hexane/EtOAc, 7/1→5/1, v/v) gave colorless oil (330 mg, 93%).

To a solution of the resulting de-*O*-tritylated thioglycoside (330 mg, 0.54 mmol) in pyridine/CH_2Cl_2 (1/10, v/v, 10 mL) was treated with chloroacetic anhydride (103 mg, 0.6 mmol), the reaction was allowed to process for 3 h. The mixture was successively washed ice-water, sat. aq. $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated.

Purification on silica gel column chromatography (hexane/EtOAc, 7/1→5/1, v/v) gave compound **5** (380 mg, 92% in two steps). $[\alpha]_D^{25}$ = -13.7 (*c* 0.96, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18 -7.27 (m, 10H, CH_{arom}), 5.54 (ddd, 1H, *J* = 5.8 Hz, *J* = 10.4 Hz, *J* = 22.6 Hz, CH_2-C*H*=CH_2), 5.39 (t, 1H, $J_{4,5}$ = 9.7 Hz, H-4), 5.35 (t, 1H, $J_{2,3}$ = 9.7 Hz, H-2), 5.03 (dd, 1H, *J* = 1.4 Hz, *J* = 17.2 Hz, CH_2-CH=C*H*$_2$), 4.90 (d, 1H, *J* = 10.3 Hz, CH_2-CH=C*H*$_2$), 4.66 (d, 1H, $J_{1,2}$ = 10.0 Hz, H-1), 4.38-4.31(m, 2H, H-6a, 6b), 4.10-4.00 (m, 4H, COC*H*$_2$Cl, C*H*$_2$-CH=CH_2), 3.98 (t, 1H, $J_{3,4}$ = 9.1 Hz, H-3), 3.95-3.78 (m, 1H, 5H), 2.78-2.63 (m, 2H, SC*H*$_2$), 1.30-1.08 (m, 20H, $SCH_2(CH_2)_{10}CH_3$), 0.88 (t, 3H, *J* = 7.0 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.4, 165.4, 165.3, 140.0, 133.7, 134.4, 130.2, 130.1, 130.0, 129.4, 129.0, 128.8, 117.9, 84.3, 81.1, 73.8, 72.3, 70.8, 64.7, 63.3, 41.1, 30.3, 30.5, 30.0, 29.9, 29.8, 29.7, 29.5, 29.1, 23.0, 14.5; ESI-HRMS (*m/z*) calcd for $C_{37}H_{49}O_8ClSNa^+$: 711.2729; Found: 711.2748.

Dodecyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (20)

To a solution of 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (780 mg, 2.0 mmol) and 1-dodecanethiol (0.53 mL, 2.2 mmol) in 1,2-dichloroethane (10 mL) was added $BF_3{\cdot}Et_2O$ (0.3 mL, 2.4 mmol) and was stirred for 40 min at room temperature. The reaction was quenched with Et_3N and evaporated. The residue was recrystallized in EtOH to yield **20** (1.0 g, 94%). $[\alpha]_D^{25}$ = -29.2 (*c* 0.12, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.24 (t, 1H, $J_{3,4}$ = 9.3 Hz, H-3), 5.10 (t, 1H, $J_{4,5}$ = 9.5 Hz, H-4), 5.05 (t, 1H, $J_{2,3}$ = 9.4 Hz, H-2), 4.49 (d, 1H, $J_{1,2}$ = 10.0 Hz, H-1), 4.26 (dd, 1H, $J_{5,6b}$ = 4.9 Hz, H-6b), 4.05 (dd, 1H, $J_{5,6a}$ = 2.2 Hz, $J_{6a,6b}$ = 12.3 Hz, H-6a), 3.75-3.65 (m, 1H, H-5), 2.76-2.60 (m, 2H, SC*H*$_2$), 2.10, 2.08, 2.04, 2.03 (4s, each 3H, CH_3Ac), 1.66-1.26 (m, 20H, $SCH_2(CH_2)_{10}CH_3$), 0.88 (t, 3H, *J* = 4.1 Hz, CH_2CH_3); ^{13}C NMR (75 MHz,

$CDCl_3$): δ 171.1, 170.7, 169.9, 169.9 (C=O), 84.2, 76.4, 74.5, 70.5, 68.9, 62.8, 32.4, 30.6, 30.2, 30.1, 30.1, 29.9, 29.7, 29.3, 23.2, 21.2, 21.1, 14.6; Anal. Calcd for $C_{26}H_{44}O_9S$: C, 58.62; H, 8.33; S, 6.02%; Found: C, 58.55; H, 8.46; S, 6.17%.

Dodecyl 2,3,4-tri-*O*-benzoyl-6-*O*-trityl-1-thio-β-D-glucopyranoside (21)

To a solution of **20** (1.0 g, 1.9 mmol) in MeOH (50 mL) was added 25% solution of NaOMe in MeOH to adjust the pH>12 at room temperature. After 3 h, TLC ($CHCl_3$/MeOH, 5/1, v/v) showed that the reaction was completed. The reaction mixture was neutralized with Amberlite IR-120 (H^+ form), filtered, concentrated *in vacuo*. The product and chlorotriphenylmethane (1.2 g, 4.0 mmol) was dissolved in dry pyridine (10 mL) and the solution was heated to 60 ˚C, overnight. TLC (toluene/EtOAc, 20/1, v/v) indicated that the reaction was completed, and that a one product was formed. To the reaction mixture was added benzoyl chloride (1.3 mL, 11.1 mmol) at 0 ˚C, the reaction mixture was stirred at the same temperature for 30 min and at room temperature for overnight. TLC (hexane/EtOAc, 5/1, v/v) then showed that the reaction was completed. The mixture was diluted with $CHCl_3$, then poured to ice-water. The organic phase was washed with 1 M HCl, sat. aq. $NaHCO_3$, brine, dried ($MgSO_4$), and concentrated. Purification on silica gel column chromatography (hexane/EtOAc, 15/1→5/1, v/v) as the eluant afforded compound **21** (1.5 g, 86%) as colorless oil. $[\alpha]_D^{26}$ = +0.26 (*c* 0.99, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.29-7.07 (m, 30H, CH_{arom}), 5.86 (t, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 5.68 (t, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 5.64 (t, 1H, $J_{2,3}$ = 9.5 Hz, H-2), 4.85 (d, 1H, $J_{1,2}$ = 9.8 Hz, H-1), 3.95-3.89 (m, 1H, H-5), 3.40 (dd, 1H, $J_{5,6a}$ = 2.2 Hz, $J_{6a,6b}$ = 10.6 Hz, H-6a), 3.30 (dd, 1H, $J_{5,6b}$ = 4.9 Hz, H-6b), 2.97-2.82 (m, 2H, SCH_2), 1.87-1.25 (m, 20H, $SCH_2(CH_2)_{10}CH_3$), 0.92 (t, 3H, *J* = 7.0 Hz,

CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.2, 165.6, 165.1, 143.9, 133.5, 133.4, 133.4, 130.5, 130.2, 130.1, 130.0, 129.6, 129.3, 128.9, 128.8, 128.7, 128.6, 128.5, 128.0, 127.2, 87.0, 84.0, 74.8, 71.2, 69.7, 62.9, 60.7, 32.2, 30.3, 30.2, 30.0, 29.8, 29.7, 29.5, 29.3, 23.0, 14.5; ESI-HRMS (*m/z*) calcd for $C_{58}H_{62}O_8S\ Na^+$: 941.4058; Found: 941.4061.

Dodecyl 2,3,4-tri-*O*-benzoyl-6-*O*-chloroacetyl-1-thio-β-D-glucopyranoside (4)

A solution of the tritylated compound **21** (500 mg, 0.5 mmol) in acetic acid (40 mL) was added H_2O (8 mL) at 70 °C. The mixture kept stirring at the same temperature for 1 h, when the reaction was complete as indication by TLC (hexane/EtOAc, 3/1, v/v). The reaction mixture was evaporated then subjected to co-evaporation with toluene three times and purification by silica gel column chromatography (hexane/EtOAc, 7/1→5/1, v/v) gave colorless oil (318 mg, 94%).

To a solution of the resulting de-*O*-tritylated thioglycoside (318 mg, 0.47 mmol) in pyridine/CH_2Cl_2 (1/10, v/v, 10 mL) was treated with chloroacetic anhydride (100 mg, 0.6 mmol), the reaction was stirred for 2 h. The mixture was successively washed ice water, sat. aq. $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated. Purification by silica gel column chromatography (hexane/EtOAc, 7/1→5/1, v/v) gave compound **4** (312 mg, 87% in two steps). $[\alpha]_D^{25}$ = -6.2 (*c* 1.24, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.09-7.10 (m, 15H, CH_{arom}), 5.93 (t, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 5.59 (t, 1H, $J_{4,5}$ = 10.0 Hz, H-4), 5.64 (t, 1H, $J_{2,3}$ = 9.8 Hz, H-2), 4.83 (d, 1H, $J_{1,2}$ = 10.0 Hz, H-1), 4.50-4.30 (m, 2H, H-6a, 6b), 4.20-4.00 (m, 3H, H-5, $COCH_2Cl$), 2.81-2.70 (m, 2H, SCH_2), 1.34-1.24 (m, 20H, $SCH_2(CH_2)_{10}CH_3$), 0.92 (t, 3H, *J* = 6.9 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 167.3, 165.5, 165.1, 165.3, 133.9, 133.6, 130.1, 130.1, 129.9, 129.3,

128.9, 128.8, 128.7, 128.6, 128.6, 84.3, 74.2, 70.7, 69.4, 64.3, 40.9, 32.2, 30.4, 29.9, 29.8, 29.8, 29.6, 29.4, 29.0, 22.9, 14.4; ESI-HRMS (*m/z*) calcd for $C_{41}H_{50}O_9S\ Na^+$: 741.3068; Found: 741.3071.

Dodecyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-glucopyranoside (5)

To a solution of the acetate **20** (600 mg, 1.13 mmol) in MeOH (20 mL) was added NaOMe (20 mg), and the solution was stirred at room temperature for 5 h. After neutralization with Amberlite IR-120 (H^+ form), solvent was evaporated and the residue was dissolved in pyridine (8 mL). Benzoyl chloride (0.8 mL, 6.8 mmol) was added to the solution. The mixture was stirred at room temperature for overnight, poured into crashed ice-water and extracted with $CHCl_3$. The extract was washed successively with 1 M HCl, sat. aq. $NaHCO_3$ and brine, died with $MgSO_4$, and evaporated. The residue was chromatographed on silica gel (toluene/EtOAc 20/1→10/1, v/v) to give the benzoate **5** (757 mg, 86%) as colorless oil. $[\alpha]_D^{25}$ = +12.4 (*c* 1.70, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03-7.17 (m, 20H, CH_{arom}), 5.95 (t, 1H, $J_{3,4}$ = 9.5 Hz, H-3), 5.69 (t, 1H, $J_{4,5}$ = 9.7 Hz, H-4), 5.56 (t, 1H, $J_{2,3}$ = 9.6 Hz, H-2), 4.87 (d, 1H, $J_{1,2}$ = 10.0 Hz, H-1), 4.65 (dd, 1H, $J_{5,6b}$ = 3.1 Hz, H-6b), 4.51 (dd, 1H, $J_{5,6a}$ = 5.4 Hz, $J_{6a,6b}$ = 12.2 Hz, H-6a), 4.26-4.16 (m, 1H, H-5), 2.76-2.60 (m, 2H, SCH_2), 1.66-1.26 (m, 20H, $SCH_2(CH_2)_{10}CH_3$), 0.88 (t, 3H, *J* = 4.1 Hz, CH_2CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.4, 166.2, 165.6, 165.5, 133.8, 133.6, 133.6, 133.4, 130.2, 130.2, 130.1, 129.6, 129.2, 129.2, 128.7, 128.7, 128.6, 84.4, 76.7, 74.6, 71.1, 70.1, 63.7, 32.3, 30.5, 30.1, 30.0, 30.0, 29.9, 29.8, 29.7, 29.4, 29.1, 23.0, 14.4; Anal. Calcd for $C_{46}H_{52}O_9S$: C, 70.74; H, 6.71; S, 4.11%; Found: C, 70.92; H, 6.65; S, 3.97%.

General procedure for the preparation of gentio-oligosaccharides using NIS/TfOH:

A solution of the glycosyl donor (1.2 equiv to acceptor), glycosyl acceptor (1.0 equiv) and freshly recrystallized NIS (1.2 equiv to donor) in CH_2Cl_2 was stirred, for 30 min over activated molecular sieves under nitrogen atmosphere. TfOH (5 μL) was added at -20 ºC with micro syringe. The reaction mixture was stirred and the temperature was warmed slowly to room temperature. After TLC (toluene/EtOAc, 5/1, v/v) analysis to check the glycosyl donor was consumed, the reaction was quenched with Et_3N (about 2 mL) and the diluted with $CHCl_3$. The mixture was filtered thought a Celite pad, and the filtrate was washed successively with sat. aq. $Na_2S_2O_3$, sat. aq. $NaHCO_3$, and brine, dried ($MgSO_4$), and concentrated to gave a crude oil, which was mainly consisted of a chloroacetated product.

The crude mixture of above mentioned glycosylation was dissolved in pyridine (20 mL) and H_2O (4 mL). After stirring for overnight at 50 ˚C, the reaction was completed as indication by TLC (toluene/EtOAc, 2.5/1, v/v). The reaction mixture was evaporated then subjected to co-evaporation with toluene three times. Purification on silica gel column chromatography (toluene/ EtOAc).

Methyl 6-*O*-(3-*O*-allyl-2,4-di-*O*-benzoyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (7)

The glycosyl donor **3** (689 mg, 1.0 mmol) was condensed with glycosyl acceptor **2** (761 mg, 1.2 mmol) using NIS (270 mg, 1.2 mmol), and TfOH (0.02 mmol, 5 μL) in dry CH_2Cl_2 (20 mL) according to the general procedure described above. To provide the compound **7** as a colorless oil (845 mg, 92% in two steps). $[\alpha]_D^{26}$ = +2.4 (*c* 1.25, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.13-7.22 (m, 25H, CH_{arom}), 6.07 (t, 1H, $J_{3,4}$ =

9.9 Hz, H-3), 5.60-5.50 (ddd, 1H, J = 6.0 Hz, J = 11.0 Hz, J = 22.5 Hz, CH_2-C*H*=CH_2), 5.42 (t, 1H, $J_{4,5}$ = 9.3 Hz, H-4), 5.30 (t, 1H, $J_{2',3'}$ = 8.2 Hz, H-2'), 5.19 (t, 1H, $J_{4',5'}$ = 9.3 Hz, H-4'), 5.11 (dd, 1H, J = 3.8 Hz, $J_{2,3}$ = 10.2 Hz, H-2), 5.01 (d, 1H, J = 10.4 Hz, CH_2-CH=C*H*$_2$), 4.95 (d, 1H, $J_{1,2}$ = 3.8 Hz, H-1), 4.90 (d, 1H, J = 10.4 Hz, CH_2-CH=C*H*$_2$), 4.79 (d, 1H, $J_{1',2'}$ = 8.2 Hz, H-1'), 4.23- 4.17 (m, 1H, H-5), 4.09 (dd, 1H, $J_{5,6b}$ = 2.2 Hz, H-6b), 4.03 (d, 2H, J = 5.5 Hz, C*H*$_2$-CH=CH_2), 3.98 (t, 1H, $J_{3',4'}$ = 9.3 Hz, H-3'), 3.75 (dd, 1H, $J_{5,6a}$ = 6.6 Hz, $J_{6a,6b}$ = 11.0 Hz, H-6a), 3.73-3.67 (m, 1H, H-6'b), 3.65-3.60 (1m, 1H, H-5'), 3.58-3.52 (m, 1H, H-6'b), 3.15 (s, 3H, OMe), 2.80-2.72 (m, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.7, 166.1, 166.0, 134.6, 134.0, 133.7, 133.4, 130.3, 130.2, 130.1, 130.0, 129.6, 129.4, 129.2, 128.9, 128.8, 128.6, 117.5, 101.0, 97.2, 80.0, 75.3, 73.4, 72.4, 70.9, 69.9, 68.7, 67.2, 61.8, 55.9; ESI-HRMS (*m/z*) calcd for $C_{51}H_{48}O_{16}Na^+$: 939.2835; Found: 939.2833.

Methyl 6-*O*-(6-*O* -2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl)-3-*O*-allyl-2,4-di-*O* -benzoyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (8)

The glycosyl donor **4** (459 mg, 0.5 mmol) was condensed with glycosyl acceptor **7** (452 mg, 0.42 mmol) using NIS (270 mg, 1.2 mmol), and TfOH (0.02 mmol, 5 μL) in dry CH_2Cl_2 (10 mL) according to the general procedure described above. To provide the compound **8** (643 mg, 92% in two steps) as colorless oil. $[\alpha]_D^{26}$ = +0.18 (*c* 0.95, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.10-7.10 (m, 40H, CH_{arom}), 6.06 (t, 1H, $J_{3,4}$ = 9.7 Hz, H-3), 5.93 (t, 1H, $J_{3'',4''}$ = 9.7 Hz, H-3''), 5.57-5.49 (ddd, 1H, J = 4.4 Hz, J = 5.5 Hz, J = 16.4 Hz, CH_2-C*H*=CH_2), 5.41 (t, 1H, $J_{4,5}$ = 9.7 Hz, H-4), 5.27 (t, 1H, $J_{2',3'}$ = 9.8 Hz, H-2'), 5.26 (t, 1H, $J_{4',5'}$ = 9.1 Hz, H-4'), 5.23 (t, 1H, $J_{4'',5''}$ = 9.8 Hz, H-4''), 5.19 (t, 1H, $J_{2'',3''}$ = 9.3 Hz, H-2''), 5.11 (dd, 1H, J = 3.8 Hz, $J_{2,3}$ = 10.2 Hz, H-2), 5.02 (d, 1H, $J_{1,}$

$_{2}$ = 3.8 Hz, H-1), 4.98 (dd, 1H, *J* = 1.6 Hz, *J* = 17.3 Hz, CH_2-CH=C*H*$_2$), 4.93 (d, 1H, $J_{1', 2'}$ = 7.7 Hz, H-1'), 4.87 (dd, 1H, *J* = 1.6 Hz, *J* = 13.2 Hz, CH_2-CH=C*H*$_2$), 4.59 (d, 1H, $J_{1'', 2''}$ = 8.2 Hz, H-1''), 4.07-4.02 (m, 1H, H-5), 4.15-3.93 (m, 4H, H-6b, 6'b, C*H*$_2$-CH=CH_2), 3.85 (t, 1H, $J_{3', 4'}$ = 9.3 Hz, H-3'), 3.84-3.72 (m, 4H, H-5', 5'', 6'a, 6''b), 3.63-3.57 (m, 1H, H-6''a), 3.52 (dd, 1H, $J_{5, 6a}$ = 6.0 Hz, $J_{6a, 6b}$ = 11.5 Hz, H-6a), 3.13 (s, 3H, OMe), 2.93-2.87 (m, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.1, 166.0, 165.7, 165.4, 165.2, 134.5, 133.8, 133.7, 133.6, 133.6, 133.6, 133.5, 133.4, 133.3, 130.2, 130.0, 130.0, 130.0, 130.0, 130.0, 129.4, 129.4, 129.3, 129.2, 129.0, 125.6, 117.7, 101.7, 100.9, 96.8, 79.6, 74.8, 74.0, 73.5, 73.3, 73.1, 72.4, 72.2, 72.0, 70.6, 70.1, 69.5, 68.9, 68.4, 61.5, 55.5, 21.8; ESI-HRMS (*m/z*) calcd for $C_{78}H_{70}O_{24}Na^+$: 1413.4149; Found: 1413.4143.

Methyl 6-*O*-(6-*O*-(6-*O*-(3-*O*-allyl-2,4-di-*O*-benzoyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl)-3-*O*-allyl-2,4-di-*O*-benzoyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (11)

The glycosyl donor **3** (83 mg, 0.12 mmol) was condensed with glycosyl acceptor **8** (143 mg, 0.1 mmol) using NIS (32.4 mg, 0.144 mmol), and TfOH (0.02 mmol, 5 μL) in dry CH_2Cl_2 (10 mL) according to the general procedure described above. To provide the compound **11** (198 mg, 92%) as a colorless oil. $[\alpha]_D^{23}$ = -7.6 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.20-7.13 (m, 50H), 6.07 (t, 1H, $J_{3, 4}$ = 9.9 Hz, H-3), 5.73 (t, 1H, $J_{3'', 4''}$ = 9.9 Hz, H-3''), 5.61-5.51 (m, 2H, CH_2-C*H*=CH_2), 5.38 (t, 1H, $J_{4, 5}$ = 9.9 Hz, H-4), 5.29 (t, 1H, $J_{2', 3'}$ = 8.8 Hz, H-2'), 5.21 (t, 1H, $J_{4', 5'}$ = 9.9 Hz, H-4'), 5.17 (t, 1H, $J_{2''', 3'''}$ = 8.9 Hz, H-2'''), 5.11 (dd, 1H, *J* = 7.8 Hz, $J_{2'', 3''}$ = 9.8 Hz, H-2''), 5.10 (dd, 1H, *J* = 3.8 Hz, $J_{2, 3}$ = 10.2 Hz, H-2), 5.03 (d, 2H, *J* = 17.0 Hz, CH_2-CH=C*H*$_2$), 5.00 (t, 1H, $J_{4'', 5''}$ = 9.9 Hz, H-4''), 5.00 (t, 1H, $J_{4''', 5'''}$ = 9.9 Hz, H-4'''), 4.99 (d, 1H, $J_{1, 2}$ = 3.8 Hz, H-1), 4.91 (d,

2H, J = 15.9 Hz, CH_2-CH=CH_2), 4.90 (d, 1H, $J_{1''', 2'''}$ = 8.2 Hz, H-1'''), 4.60 (d, 1H, $J_{1'', 2''}$ = 8.2 Hz, H-1''), 4.57 (d, 1H, $J_{1', 2'}$ = 8.2 Hz, H-1'), 4.12-3.95 (m, 6H, H-5, 6b, CH_2-CH=CH_2), 3.89 (t, 1H, $J_{3''', 4'''}$ = 9.9 Hz, H-3'''), 3.88 (t, 1H, $J_{3', 4'}$ = 9.9 Hz, H-3'), 3.86- 3.81 (m 3H, H-6'b, 5'', 6'''a), 3.79-3.69 (m, 3H, H-6''a, 5''', 6'''b), 3.66-3.61 (m, 1H, H-5'), 3.59 (dd, $J_{5'',6''b}$ = 4.9 Hz, H-6''b), 3.53 (dd, 1H, $J_{5', 6'a}$ = 1.6 Hz, $J_{6'a, 6'b}$ = 7.2 Hz, H-6'a), 3.51 (dd, 1H, $J_{5, 6a}$ = 6.1 Hz, $J_{6a, 6b}$ = 11.3 Hz, H-6a), 3.09 (s, 3H, OMe), 2.79-2.89 (brs, 1H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.5, 166.3, 166.3, 166.1, 166.0, 165.9, 165.8, 165.6, 165.4, 134.9, 134.8, 134.1, 134.0, 134.0, 133.9, 133.8, 133.7, 133.6, 133.5, 133.4, 131.5, 130.6, 130.5, 130.3, 130.2, 130.2, 130.1, 130.0, 129.8, 129.7, 129.5, 129.4, 129.3, 129.2, 129.1, 129.0, 129.0, 128.8, 128.7, 118.0, 117.9, 102.1, 101.3, 100.9, 97.0, 80.1, 79.9, 75.0, 74.5, 74.2, 74.0, 73.8, 73.1, 73.0, 72.8, 72.6, 71.6, 70.8, 70.2, 69.3, 68.7, 68.0, 62.1, 55.6, 39.3, 30.9, 30.3, 29.5, 24.6, 23.6, 14.6, 11.5; ESI-HRMS (*m/z*) calcd for $C_{101}H_{92}O_{31}Na^+$: 1823.5515; Found: 1823.5517.

Methyl 6-*O*-(6-*O*-(6-*O*-(2,4-di-*O*-benzoyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl)-2,4-di-*O*-benzoyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (6)

To a solution of compound **11** (158 mg, 0.09 mmol) in acetic acid (3.8 mL) and H_2O (0.2 mL) were added sodium acetate (74 mg, 0.9 mmol) and palladium (II) chloride (64 mg, 0.36 mmol), and the reaction mixture was sonicated at room temperature for 2 h. The solution was then filtered through a celite bed the filtrate was extracted with $CHCl_3$. The organic layer was washed with H_2O, sat. aq. $NaHCO_3$, and brine, dried ($MgSO_4$), and then purification by silica gel column chromatography (toluene/ EtOAc, 5/1→2/1, v/v) gave compound **6** (139 mg, 90%) as a syrup foam. $[\alpha]_D^{25}$ = -8.7 (*c* 1.04, $CHCl_3$); ^{1}H

NMR (500 MHz, $CDCl_3$): δ 8.20-7.13 (m, 50H), 6.08 (t, 1H, $J_{3,4}$ = 9.8 Hz, H-3), 5.79 (t, 1H, $J_{3'',4''}$ = 9.8 Hz, H-3''), 5.45 (t, 1H, $J_{4,5}$ = 9.8 Hz, H-4), 5.23 (dd, 1H, J = 7.9 Hz, $J_{2'',3''}$ = 9.8 Hz, H-2''), 5.18 (t, 1H, $J_{4'',5''}$ = 9.6 Hz, H-4''), 5.14 (t, 1H, $J_{4',5'}$ = 10.4 Hz, H-4'), 5.14 (t, 1H, $J_{2',3'}$ = 9.2 Hz, H-2'), 5.12 (t, 1H, $J_{2,3}$ = 9.2 Hz, H-2), 5.06 (t, 1H, $J_{2''',3'''}$ = 8.5 Hz, H-2'''), 5.06 (t, 1H, $J_{4''',5'''}$ = 8.5 Hz, H-4'''), 5.02 (d, 1H, $J_{1,2}$ = 3.7 Hz, H-1), 4.88 (d, 1H, $J_{1''',2'''}$ = 7.9 Hz, H-1'''), 4.76 (d, 1H, $J_{1'',2''}$ = 7.9 Hz, H-1''), 4.62 (d, 1H, $J_{1',2'}$ = 7.9 Hz, H-1'), 4.17 (t, 1H, $J_{3''',4'''}$ = 9.2 Hz, H-3''') , 4.15-4.90 (m, 1H, H-5), 4.01 (dd, 1H, $J_{5,6b}$ = 1.8 Hz, H-6b), 3.96 (t, 1H, $J_{3',4'}$ = 9.2 Hz, H-3'), 3.92-3.98 (m, 1H, H-5''), 3.93 (dd, 1H, $J_{5'',6''b}$ = 3.7 Hz, H-6''b), 3.89 (dd, 1H, $J_{5',6'b}$ = 6.1 Hz, H-6'b), 3.81 (dd, 1H, $J_{5'',6''a}$ = 6.1 Hz, $J_{6''a,6''b}$ = 11.0 Hz, H-6''a), 3.78 (dd, 1H, $J_{5''',6'''b}$ = 3.0 Hz, H-6'''b), 3.75 (dd, 1H, $J_{5',6'a}$ = 1.6 Hz, $J_{6'a,6'b}$ = 7.2 Hz, H-6'a), 3.72-3.60 (m, 3H, H-5', 5''', 6'''a), 3.59 (dd, 1H, $J_{5,6a}$ = 6.1 Hz, $J_{6a,6b}$ = 11.3 Hz, H-6a), 3.16 (s, 3H, OMe), 3.00-2.88 (brs, 3H, OH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.9, 166.7, 166.5, 166.4, 166.1, 166.0, 165.9, 165.8, 165.4, 133.9, 133.8, 130.7, 130.6, 130.5, 130.4, 130.3, 130.2, 130.1, 129.9, 129.7, 129.4, 129.2, 128.9, 128.8, 128.7, 128.6, 128.5, 101.4, 101.1, 101.0, 97.0, 75.1, 74.8, 73.9, 73.4, 73.0, 72.3, 70.7, 70.3, 70.1, 69.2, 68.7, 68.4, 68.3, 61.9, 55.6; ESI-HRMS (*m/z*) calcd for $C_{95}H_{84}O_{31}Na^+$: 1743.5889; Found: 1743.5891.

Methyl 6-*O*-(3,6-di-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,4-di-*O*-benzoyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (13)

a) NIS/TfOH promoted glycosylation.

A solution of the glycosyl donor **5** (14l mg, 0.18 mmol), glycosyl acceptor **10** (170 mg, 0.12 mmol), freshly recrystallized NIS (49 mg, 0.22 mmol), and MS4Å (300 mg) in dry

CH_2Cl_2 (5 mL) was stirred at room temperature for 30 min under nitrogen atmosphere. To the mixture was added TfOH (5 μL, 0.02 mmol) at -40 ºC. The reaction mixture was allowed to slowly warm to room temperature for overnight (two dimensional TLC, hexane/EtOAc, (1/1, v/v) and toluene/EtOAc (5/1, v/v)), then quenched Et_3N and diluted $CHCl_3$, filtered, successively washed with sat. aq. $Na_2S_2O_3$, sat. aq. $NaHCO_3$, and brine. After drying ($MgSO_4$) and concentration the residue was purified twice by column chromatography (hexane/EtOAc 1/1, followed by toluene/EtOAc 10/1) to provide **13** as a colorless oil (100.1 mg, 41%, α/β; 1/1.4);

b) BSP/Tf_2O promoted glycosylation.

A solution of the glycosyl donor **5** (14l mg, 0.18 mmol), BSP (56 mg, 0.27 mmol) and MS4Å (300 mg) was stirred in dry CH_2Cl_2 (3 mL) at room temperature for 30 min under nitrogen atmosphere. The reaction mixture was cooled to -78 ºC, followed by addition of Tf_2O (45 μL, 0.27 mmol) and stirred at this temperature for 15 min. Then a solution of glycosyl acceptor **10** (179 mg, 0.12 mmol) in dry CH_2Cl_2 (2 mL) was added and the reaction mixture was allowed to slowly warm to room temperature for overnight (two dimensional TLC, hexane/EtOAc, (1/1, v/v) and toluene/EtOAc (5/1, v/v)). Purification as described above gave **13** (107.8 mg, 44%, β only)

c) NIS/TfOH/AgOTf promoted glycosylation.

A solution of the glycosyl donor **5** (3l mg, 40 μmol), glycosyl acceptor **10** (116 mg, 80 μmol), freshly recrystallized NIS (6.3 mg, 20 μmol), and MS4Å (300 mg) in dry CH_2Cl_2 (4 mL) was stirred at room temperature for 30 min under nitrogen atmosphere. To the mixture was added TfOH (2 μL, 20 μmol) at -40 ºC and stirred at this temperature for

30 min. Then a solution of AgOTf (7.2 mg, 28 μmol) in Et_2O (1 mL) was added and the reaction mixture was allowed to slowly warm to room temperature for overnight (two dimensional TLC, hexane/EtOAc, (1/1,v/v) and toluene/EtOAc (5/1, v/v)). Purification as described above gave **13** (22.4 mg, 28%, α/β; 1/1.4).

d) ICl/AgOTf promoted glycosylation.

A solution of the glycosyl donor **5** (3l mg, 40 μmol), glycosyl acceptor **10** (116 mg, 80 μmol), AgOTf (15 mg, 60 μmol), and MS4Å (300 mg) in dry CH_2Cl_2 (4 mL) was stirred at room temperature for 30 min under nitrogen atmosphere. The reaction mixture was cooled to -40 ºC, followed by the addition ICl (10 μL, 0.28 mmol) in CH_2Cl_2 (1 mL), and the temperature was increased gradually from –40 ºC to room temperature for overnight (two dimensional TLC, hexane/EtOAc, (1/1, v/v) and toluene/EtOAc (5/1, v/v)) to give no trace condensation products.

Repeated column chromatography of the anomeric mixture of the tetraglucoside with toluene-EtOAc gave pure α- and β-anomers. Spectroscopic data for the β-anomer was identical with that previously prepared by van Boom group.[3]

α-anomer: $[\alpha]_D^{25}$ = -0.54 (*c* 1.00, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.14-7.03 (m, 65H, CH_{arom}), 6.08 (t, 1H, $J_{3,4}$ = 9.9 Hz, H-3), 6.03 (t, 1H, $J_{3'',4''}$ = 9.9 Hz, H-3''), 5.87 (t, 1H, $J_{3''',4'''}$ = 9.9 Hz, H-3'''), 5.56 (t, 1H, $J_{4'',5''}$ = 9.9 Hz, H-4''), 5.51 (t, 1H, $J_{4,5}$ = 9.9 Hz, H-4), 5.48 (t, 1H, $J_{4''',5'''}$ = 9.8 Hz, H-4'''), 5.46 (d, 1H, $J_{1''',2'''}$ = 3.8 Hz, H-1'''), 5.35 (t, 1H, $J_{2',3'}$ = 8.8 Hz, H-2'), 5.35 (t, 1H, $J_{2'',3''}$ = 8.8 Hz, H-2''), 5.13 (dd, 1H, *J* = 3.9 Hz, $J_{2,3}$ = 10.1 Hz, H-2), 5.11 (dd, 1H, *J* = 2.8 Hz, $J_{2''',3'''}$ = 10.4 Hz, H-2'''), 5.08 (t, 1H, $J_{4',5'}$ = 9.9 Hz, H-4'), 5.04 (d, 1H, $J_{1,2}$ = 3.3 Hz, H-1), 5.01 (d, 1H, $J_{1'',2''}$ = 7.7 Hz, H-1''), 4.53 (dd,

1H, $J_{5'', 6''b}$ = 3.3 Hz, H-6''b), 4.49 (d, 1H, $J_{1', 2'}$ = 7.7 Hz, H-1'), 3.37 (dd, 1H, $J_{5'', 6''a}$ = 5.5 Hz, $J_{6''a, 6''b}$ = 12.1Hz, H-6''a), 4.29 (t, 1H, $J_{3', 4'}$ = 9.4 Hz, H-3'), 4.25-4.19 (m, 2H, H-6b, 5''), 4.20-4.13 (m, 1H, H-5), 4.02 (dd, 1H, $J_{5''', 6'''b}$ = 2.8 Hz, H-6'''b), 4.01 (m, 1H, H-5'''), 3.77 (dd, 1H, $J_{5', 6'b}$ = 8.2 Hz, H-6'b), 3.72 (dd, 1H, $J_{5', 6'a}$ = 2.4 Hz, $J_{6'a, 6'b}$ = 9.9 Hz, H-6'a), 3.67-3.61 (m, 1H, H-5'), 3.53 (dd, 1H, $J_{5, 6a}$ = 2.8 Hz, $J_{6a, 6b}$ = 12.4Hz, H-6a), 3.47 (dd, 1H, $J_{5''', 6'''a}$ = 4.9 Hz, $J_{6'''a, 6'''b}$ = 11.3 Hz, H-6'''a), 2.15 (s, 3H, OMe); ^{13}C NMR (150.9 MHz, $CDCl_3$): δ 207.0, 166.2, 166.1, 165.8, 165.8, 165.7, 165.6, 165.4, 165.3, 165.2, 165.2, 164.9, 164.8, 133.6, 133.6, 133.5, 133.2, 133.2, 133.2, 133.1, 133.1, 133.1, 133.0, 133.0, 133.0, 133.0, 133.0, 133.0, 129.4, 129.4, 129.3, 129.2, 129.1, 129.1, 129.0, 128.9, 128.7, 128.6, 128.6, 128.6, 128.5, 128.3, 128.2, 128.1, 101.4, 101.1, 96.7, 74.8, 72.8, 72.5, 72.2, 72.2, 72.1, 70.8, 70.3, 70.2, 69.3, 68.7, 68.6, 68.5, 68.1, 63.3, 61.7, 55.3, 31.0, 29.8; ESI-TOF HRMS (*m/z*) calcd for $C_{116}H_{96}O_{34}Na^+$: 2055.5675; Found: 2055.5669.

β-anomer: $[\alpha]_D^{25}$ = +0.78 (*c* 1.02, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.04-7.09 (m, 65H, CH_{arom}), 6.05 (t, 1H, $J_{3, 4}$ = 9.9 Hz, H-3), 6.01 (t, 1H, $J_{3'', 4''}$ = 9.9 Hz, H-3''), 5.60 (t, 1H, $J_{4, 5}$ = 9.9 Hz, H-4), 5.55 (t, 1H, $J_{3''', 4'''}$ = 9.3 Hz, H-3'''), 5.43 (t, 1H, $J_{2'', 3''}$ = 9.8 Hz, H-2''), 5.40 (t, 1H, $J_{4'', 5''}$ = 9.9 Hz, H-4''), 5.31 (t, 1H, $J_{2''', 3'''}$ = 8.2 Hz, H-2'''), 5.28 (t, 1H, $J_{4''', 5'''}$ = 9.9 Hz, H-4'''), 5.08 (dd, 1H, *J* = 3.3 Hz, $J_{2, 3}$ = 10.4 Hz, H-2), 5.05 (d, 1H, $J_{1'', 2''}$ = 6.6 Hz, H-1''), 5.03 (t, 1H, $J_{2', 3'}$ = 7.7 Hz, H-2'), 5.01 (d, 1H, $J_{1, 2}$ = 3.3 Hz, H-1), 4.94 (t, 1H, $J_{4', 5'}$ = 8.8 Hz, H-4'), 4.90 (d, 1H, $J_{1''', 2'''}$ = 7.7 Hz, H-1'''), 4.58 (dd, 1H, $J_{5, 6b}$ = 2.3 Hz, H-6b), 4.41 (dd, 1H, $J_{5, 6a}$ = 4.9 Hz, $J_{6a, 6b}$ = 11.8 Hz, H-6a), 4.37 (d, 1H, $J_{1', 2'}$ = 7.7 Hz, H-1'), 4.30-4.25 (m, 1H, H-5), 4.21 (t, 1H, $J_{3', 4'}$ = 8.8 Hz, H-3'), 4.11 (dd, 1H, $J_{5''', 6'''a}$ = 2.1 Hz, $J_{6'''a, 6'''b}$ = 8.7 Hz, H-6'''a), 4.00 (dd, 1H, $J_{5', 6'b}$ = 5.5 Hz, H-6'b), 3.98-3.82 (m,

4H, H-5'', 5''', 6''b, 6'''b), 3.77 (dd, 1H, $J_{5', 6'a}$ = 8.2 Hz, $J_{6'a, 6'b}$ =12.1 Hz, H-6'a), 3.72-3.69 (m, 1H, H-5'), 3.35 (dd, 1H, $J_{5'', 6''a}$ = 6.6 Hz, $J_{6''a, 6''b}$ = 12.6 Hz, H-6''a), 3.04 (s, 3H, OMe) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.8, 166.5, 166.3, 166.2, 166.1, 165.9, 165.8, 165.7, 165.6, 164.7, 134.0, 133.8, 133.7, 133.5, 133.4, 130.5, 130.4, 130.3, 130.0, 130.0, 130.0, 129.9, 129.8, 129.7, 129.7, 129.6, 129.5, 129.4, 129.3, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 101.9, 101.4, 97.1, 75.4, 74.1, 73.5, 73.3, 72.8, 72.7, 72.5, 72.3, 70.9, 70.4, 70.2, 70.1, 69.2, 68.9, 68.6, 63.8, 55.7, 30.3; ESI-TOF HRMS (*m/z*) calcd for $C_{116}H_{96}O_{34}Na^+$: 2055.5675; Found: 2055.5672.

Methyl 6-*O*-(6-*O*-(6-*O*-(3,6-di-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,4-di-*O*-benzoyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzoyl-β-D-glucopyranosyl)-3-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-2,4-*O*-benzoyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzoyl-α-D-glucopyranoside (14)

A solution of the glycosyl donor **5** (185 mg, 0.24 mmol), BSP (63 mg, 0.29 mmol) and MS4Å (500 mg) was stirred in dry CH_2Cl_2 (4 mL) at room temperature for 30 min under nitrogen atmosphere. The reaction mixture was cooled to -78 ºC, and stirred at same temperature for 15 min after addition of Tf_2O (0.29 mmol, 49 μL). Then a solution of glycosyl acceptor **6** (109 mg, 0.06 mmol) in dry CH_2Cl_2 (2 mL) was added to the reaction mixture. It was allowed to slowly warm to -40 ºC with stirring overnight (two dimensional TLC, hexane/EtOAc, (1/1, v/v) and toluene/EtOAc (5/1, v/v)), then quenched with Et_3N and diluted $CHCl_3$, filtered, washed with sat. aq. $NaHCO_3$, and brine. After drying ($MgSO_4$) and concentration the residue was purified by repeated column chromatography with (hexane/EtOAc (1/1, v/v), followed by toluene/EtOAc 10/1, v/v)) to provide **14** (98 mg, 47%) and hexaglucosides (72 mg,

42%) as a colorless oil. Compound **14** had $[\alpha]_D^{24.6}$ = -14.4 (*c* 0.13, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.15-7.08 (m, 110H, CH_{arom}), 6.10 (t, 1H, $J_{3A', 4A'}$ = 9.9 Hz, H-3A'), 6.00 (t, 1H, $J_{3B, 4B}$ = 9.9 Hz, H-3B), 5.79 (t, H-1, $J_{3C, 4C}$ = 9.9 Hz, H-3C), 5.58 (dd, 3H, *J* = 9.3 Hz, *J* = 19.2 Hz, H-3A", 3A'", 4A'), 5.44-5.24 (m, 9H, H-2A', 2A", 2A'", 4A", 4A'", 2B, 4B, 2C, 4C), 5.18 (t, 1H, $J_{2D', 3D'}$ = 8.8 Hz, H-2D'), 5.03 (d, 1H, $J_{1A', 2A'}$ = 8.2 Hz, H-1A'), 4.98 (t, 1H, $J_{4D', 5D'}$ = 9.9 Hz, H-4D'), 4.97 (d, 1H, $J_{1B, 2B}$ = 3.7 Hz, H-1B), 4.95 (d, 1H, $J_{1A'", 2A'"}$ = 9.3 Hz, H-1A'"), 4.93 (d, 1H, $J_{1A", 2A"}$ = 7.7 Hz, H-1A"), 4.85 (t, 1H, $J_{2D", 3D"}$ = 8.8 Hz, H-2D"), 4.70 (t, 1H, $J_{4D", 5D"}$ = 8.8 Hz, H-4D"), 4.65 (d, 1H, $J_{1C, 2C}$ = 8.2 Hz, H-1C), 4.58 (dd, $J_{5A', 6\ A'b}$ = 2.2 Hz, H-6A'b), 4.41 (dd, 1H, $J_{5A', 6\ A'a}$ = 5.5 Hz, $J_{6\ A'a, 6\ A'b}$ = 14.8 Hz, H-6A'a), 4.35 (d, 1H, $J_{1D', 2D'}$ = 7.7 Hz, H-1D'), 4.37-4.31 (m, 1H, H-5A'), 4.26 (d, 1H, $J_{1D", 2D"}$ = 7.7 Hz, H-1D"), 4.26 (t, 1H, $J_{3D', 4D'}$ = 8.8 Hz, H-3D'), 4.22 (t, 1H, $J_{3D", 4D"}$ = 8.8 Hz, H-3D"), 4.19-4.08 (m, 2H, H-6A"a, 6A"b), 4.05-3.93 (m, 3H, H-5A", 5A'", 6A'"a), 3.87 (d, 1H, $J_{5D", 6D"b}$ = 11.5 Hz, H-6D"b), 3.82-3.71 (m, 5H, H-5B, 5C, 6Ba, 6Bb, 6Da), 3.70-3.52 (m, 4H, H-5D', 5D", 6Ca, 6D"a), 3.44 (dd, 1H, $J_{5D', 6D'b}$ = 7.7 Hz, H-6D'b), 3.25 (dd, 1H, $J_{5C, 6Cb}$ = 4.4 Hz, H-6Cb), 3.17 (dd, 1H, $J_{5B, 6Ba}$ = 3.8 Hz, $J_{6Ba, 6Bb}$ = 11.3 Hz, H-6Bb), 3.06 (s, 3H, OMe); ^{13}C NMR (75 MHz, $CDCl_3$): δ, 175.6, 165.9, 165.6, 165.4, 165.3, 165.1, 165.0, 164.9, 164.7, 164.7, 163.9, 134.1, 133.4, 133.0, 132.9, 132.8, 129.7, 129.6, 129.5, 129.4, 129.3, 129.2, 129.1, 129.0, 128.9, 128.7, 128.6, 128.4, 128.2, 128.1, 128.0, 100.9, 100.8, 100.7, 100.4, 100.1, 96.3, 81.6, 73.3, 72.9, 72.8, 72.7, 72.6, 72.0, 71.8, 70.2, 69.9, 69.7, 68.4, 63.2, 55.1, 52.8, 52.7, 51.5, 31.9; ESI-HRMS (*m/z*) calcd for $C_{197}H_{162}O_{58}Na^+$: 3477.9625; Found: 3477.9663.

Methyl 6-*O*-(3-*O*-(β-D-glucopyranosyl)-6-*O*-(6-*O*-(3,6-di-*O*-(β-D-glucopyranosyl)-β-D-glucopyranosyl)-β-D-glucopyranosyl)-β-D-glucopyranosyl)-

α-D-glucopyranoside (1)

To a solution of **14** (14 mg, 4.0 μmol) in MeOH (0.8 mL) and H_2O (0.7 mL) was added NaOMe (28 mg) at room temperature and the mixture was stirred at room temperature for 24 h, the reaction mixture was treated with Amberlite IR-120B ion exchange resin (H^+ form), to gave the title compound **1** (3.5 mg, 74%) as white solid. The spectroscopic data were consistent with the previous report.[2c, 3] ^{1}H NMR (600 MHz, D_2O, 300 K): δ 4.64 (d, 1H, *J* = 3.6 Hz), 4.57 (d, 1H, *J* = 7.8 Hz), 4.56 (d, 1H, *J* = 7.8 Hz), 4.39 (d, 1H, *J* = 7.2 Hz), 4.38 (d, 1H, *J* = 7.2 Hz), 4.37 (d, 1H, *J* = 7.2 Hz), 4.35 (d, 1H, *J* = 7.8 Hz), 3.80-3.10 (m, 41H); MALDI-TOF MS (*m/z*) calcd for $C_{43}H_{74}O_{36}Na^+$: 1189.4; Found: 1189.9.

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