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First Direct Glycosylation of Unprotected Nonreducing Mono- and Disaccharides

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The first single-step random-glycosylation methodology for fully unprotected glycosyl acceptors is reported by random glycosylation leading to all possible regioisomers. For such systems conventional glycosylation methods such as Koenigs–Knorr glycosylation, Schmidt's trichloroacetimidate glycosylation and reactions employing glycosyl fluoride donors fail entirely. Starting from unprotected nonreducing saccharides, the glycosylation of β-glucosylated and β-galactosylated monosaccharides (Glc, Gal), symmetric disaccharides (e.g. α,α-trehaloses) as well as unsymmetric disaccharides (e.g. sucrose) were studied. The influence of base type and concentration were examined. Several libraries of di- and trisaccharides were generated. All regioisomers were formed in approximately equal proportions, and their partial separation was achieved by flash column chromatography. Even though it appears that overall yields are lower when comparing to classical protecting-group chemistry, this synthetic effort may be superior especially for access to higher saccharides.

Introduction

To advance access for the formation of complex carbohydrate derivatives and mimetics, a fast and simple synthetic approach is desired. With respect to carbohydrate combinatorial chemistry, there are only a few studies concerned with reactions at glycosyl acceptor moieties, in which the reducing end was blocked with a voluminous apolar aglycon bearing only some free hydroxy groups.[1–7] An alternative approach used the split-mix synthesis, whereby the glycosyl donors and glycosyl acceptors reacted at first with each other. The reaction product is then mixed with other products. Further splitting into smaller portions, followed by selective deprotection forms a "second-generation glycosyl acceptor" which can be used in subsequent glycosylation steps with other glycosyl donors.[8–12] However, a drawback common to all methods, are the sequential protecting-group schemes involved, even though less demanding compared to those employed for the total synthesis of complex oligosaccharide targets. To the best of our knowledge, there is no example to date of a direct glycosylation methodology of an entirely unprotected nonreducing saccharide.

Prior to the Koenigs–Knorr method, the use of acetohalo sugar derivatives for glycosylation could only be employed to alkali salts of different phenols to arrive at a variety of phenyl glycopyranosides.[13–16] In contrast, there were never any reports on the use of alkali salts of aliphatic glycosyl acceptors. Even though this could be considered a trivial or an obvious approach, it is completely unknown whether this could be elaborated into an alternative method by fine-tuning of the reaction conditions for appropriate donor and acceptor systems.

In the present work a monosaccharide (methyl α-glycopyranoside), a nonreducing disaccharide with inherent symmetry (α,α-trehalose) and an unsymmetric disaccharide (sucrose) were employed as examples for direct glycosylation as proof of concept.

Results and Discussion

Initially, a number of commonly used glycosylation methods were tested using a model reaction. Surprisingly, the well-established procedures such as the Koenigs–Knorr glycosylation, Schmidt's trichloroacetimidate glycosylation and reactions employing glycosyl fluoride donors failed.[17] Further, the trehalose glycosylation was tested using Hindsgaul et al.'s adaptation of a combinatorial glycosylation of a partial protected glycosyl acceptor.[4,12] However, for entirely unprotected acceptors, this approach did not lead to the desired products since under none of these reaction conditions glycosylation occurred. The main difficulty appeared to be poor solubility of the unprotected acceptor in commonly used solvents such as dichloromethane or acetonitrile.

Scheme 1 depicts a summary of this simple and widely applicable methodology for direct glycosylations of unprotected nonreducing mono- and disaccharides. In order to control the stereoselectivity of the newly formed glycosidic bonds, both α-acetochloroglucose (**1**) and α-acetochloroga-

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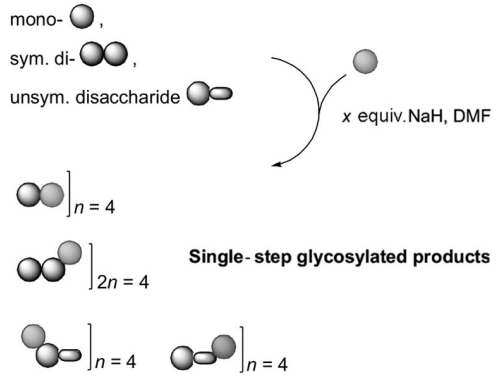
lactose (**2**) were chosen as glycosyl donors with acetyl protecting groups leading to β-glycopyranosides exclusively. Corresponding approaches can be considered for the formation of α-glycosides. Aim was to design a glycosylation method that ensures the most versatile application, hence leading to the largest possible variety of products. Using this direct glycosylation, mono- and higher glycosylation products are accessible. Readily available 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose and 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose were quantitatively converted in only 10 min into the desired 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl chloride (**1**) and 2,3,4,6-tetra-*O*-acetyl-α-D-galactopyranosyl chloride (**2**) donors using a microwave reactor thus shortening the reaction time and enhancing the yield compared to the conventional method.[18]



Scheme 1. Direct glycoslylation of unprotected nonreducing saccharides using monosaccharide glycosides (Gal, Glc), a symmetric disaccharide (α,α-trehalose) and an unsymmetric disaccharide (sucrose) as examples.

Starting from monosaccharides it was intended to prepare initially all theoretically possible branched disaccharides in a single step. The reactions were stopped after 2 h, and on average a total yield of 20–30% of predominantly monosubstituted products (disaccharides) were obtained. The analysis of a heteromeric random glycosylation of Gal with Glc showed under all tested reaction conditions an about equal amount of self-glycosylation of the donor (Figure 1) reducing the overall yield. In this particular system for yet unknown reasons the product distribution lacked only 2-linked derivatives. For a homomeric donor/acceptor couple, Gal with Gal self-glycosylation does only lead to indistinguishable products displaying all branched derivatives. In this system, the 1→4-linked derivative could not be identified and only traces of the 1→3,6-branched ones were observed (Figure 2).

Random glycosylations of disaccharides appear to be advantageous when using heteromeric donor/acceptor couples. Self-glycosylation initiated by cleavage of ester functions in the donor moiety would only lead to disaccharides, whereas disaccharides lead to trisaccharides. Subsequently, α,α-trehalose and sucrose were studied.

α,α-Trehalose (**3**) was dissolved in *N*,*N*-dimethylformamide and, in order to test the product distribution, varying excess amounts of sodium hydride were added to form the

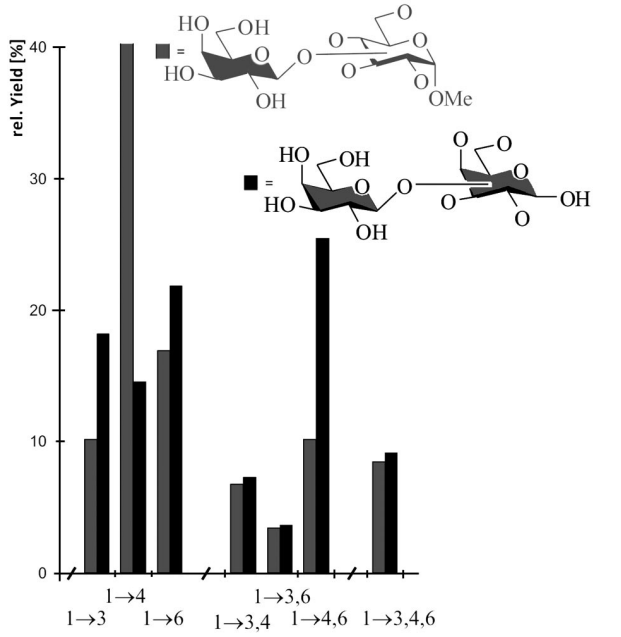


Figure 1. Results for heteromeric glycosylation couples (grey bars) and self-glycosylation of **2** (black columns).

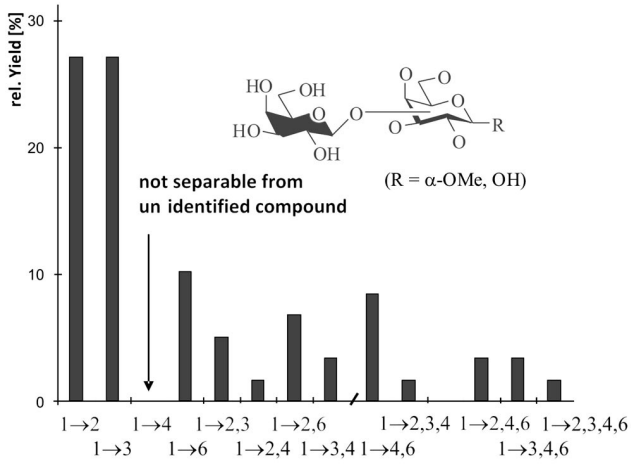
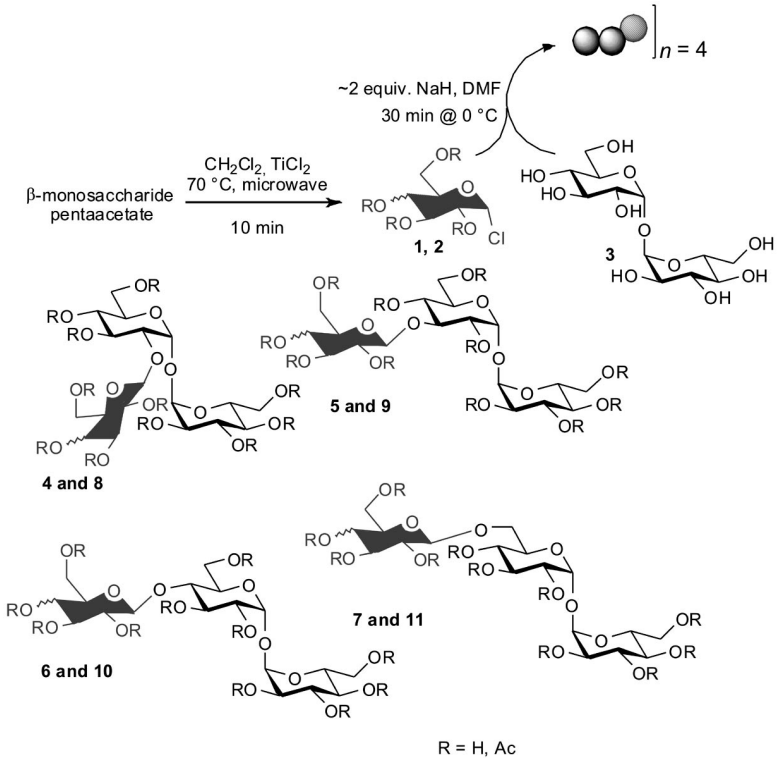


Figure 2. Result for a homomeric glycosylation of **2**.

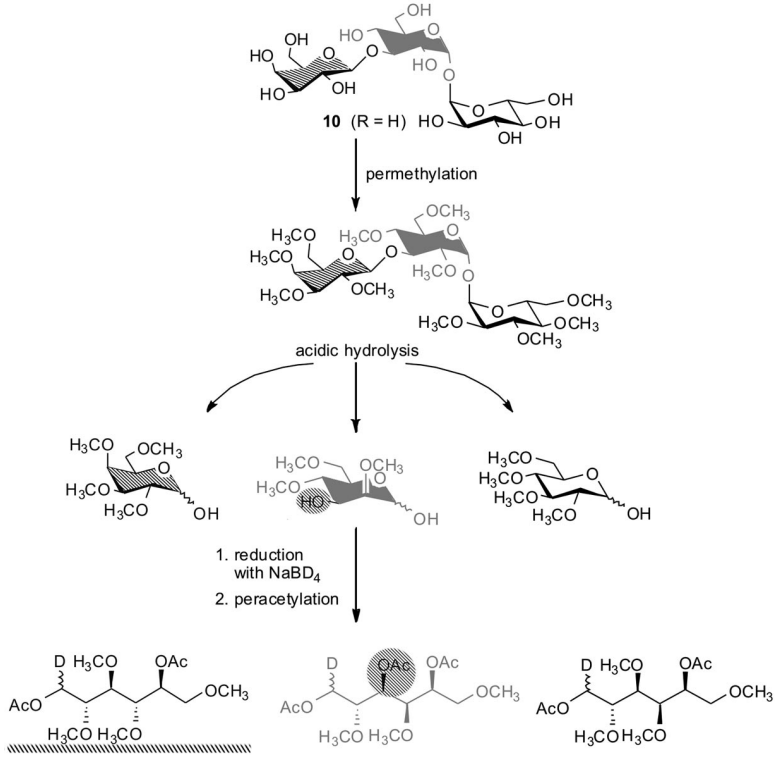
alkoxide(s). The glycosyl donors **1** and **2** were predissolved in DMF and a solution of the acceptor in DMF carefully added under cooling. Using this very simple preparation, the glycosyl acceptor was glycosylated up to 20% overall yield. After 2 h, the reaction was stopped, and monosubstituted products (trisaccharides) with only traces of higher glycosylation could be detected by MALDI-TOF mass spectra. The glycosylation proceeded stereoselectively to give the β-glycopyranosides throughout; α-glycopyranosides could not be detected. After subsequent peracetylation of the product mixture, the trisaccharides were separated from starting materials using a single flash-chromato-



Scheme 2. Random glucosylation (series **4**–**7**) and galactosylation (series **8**–**11**) of α,α-trehalose (**3**).

graphic purification step (Scheme 2). Characterisation of regioisomeric oligosaccharides containing various amounts of impurities was done by NMR spectroscopy.

Since it was not in the focus of this study, further purification was not attempted but can be achieved according to Ajisaka et al.[19] Qualitative and quantitative analysis of the



Scheme 3. Principles of linkage-type analyses using methylation and sodium deuteride reduction to alditols. Formation of their acetates and assignment by GC-MS fingerprint fragmentation (exemplary depiction for **10**, R = H).

product composition was done by a modified methylation analysis and subsequent GC-MS quantification of the methylated alditol acetates (Scheme 3).[20–22]

In order to evaluate the influence of base, lithium hydride and potassium hydride were tested as well. Both, lithium hydride and potassium hydride did not lead to useful yields (ca. 3–5% total yield) suitable for analyses; hence, the reactions were not further evaluated.

Furthermore, it was examined whether differences in the product distribution of regioisomeric trisaccharides **4**–**7** would be obtained with varying amounts of sodium hydride applied (Figure 3A) and were tested up to 6 equiv. of NaH (data shown for 0.85–2.5 equiv.). No significant alteration of the product composition was observed.

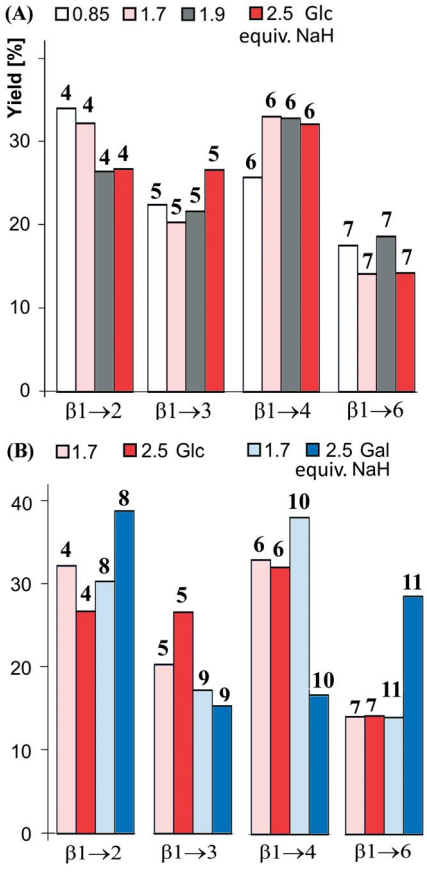


Figure 3. (A) Comparison of the relative average yield [%] at varying NaH concentrations for the four βGlcp-trehalose products (**4**–**7**). (B) Comparison of yields of βGlcp-trehaloses **4**–**7** and βGalp-trehaloses **8**–**11**.

Comparison of the relative yields for corresponding reaction conditions for glucosylation vs. galactosylation (Figure 3B) showed a similar trend of the product composition. Only in the case of galactosylation using 2.5 equiv. of sodium hydride did the amount of the β1→6-linked trisaccharide **11** increase to 30% relative yield at the expense of the β1→4 isomer **10** (15% relative yield). Considering the complexity of the obtained trisaccharides, such yields are at least comparable if not superior to a total synthetic approach which would require, e.g., a six-step synthesis to form such trisaccharides. This way, in only few glycosylation steps, libraries of mono- and multiple-glycosylated oligosaccharides are accessible.

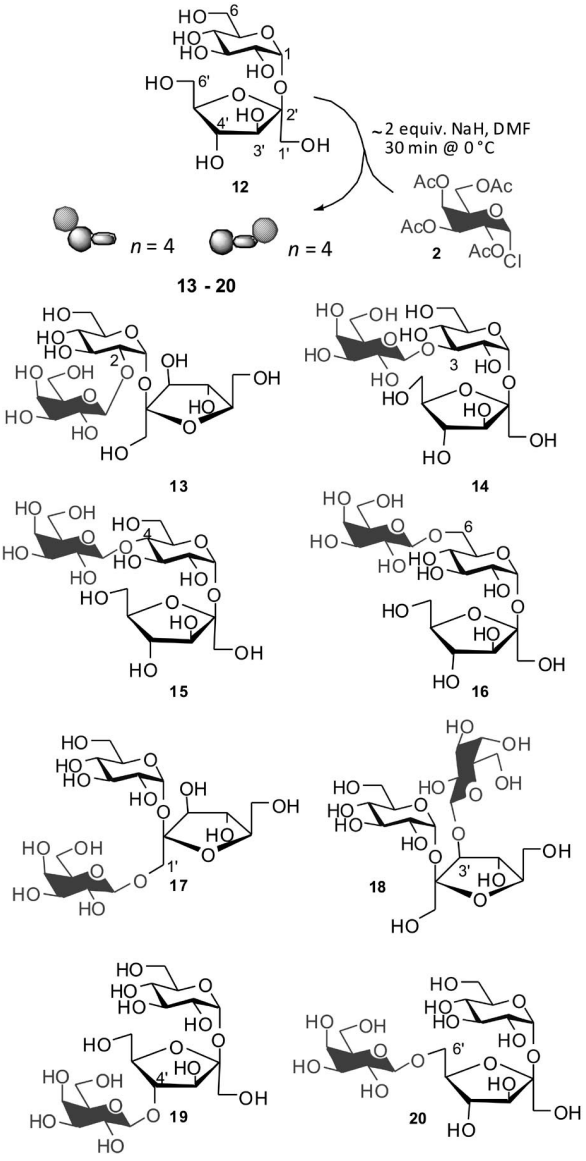
All procedures and analytical data for the characterisation of the product composition of **4**–**11** determined by NMR and methylation analysis can be found in the Experimental Section. Surprisingly, the relative yield of individual trisaccharide components revealed that each was formed in about similar amounts. However, significant differences in their yields would have been expected, due to differences in the reactivities of primary relative to secondary hydroxy groups, and thus their domination in the product mixture.[23] The most noticeable difference in the relative yield observed was by the factor 2.5, comparing the highest and the lowest relative yield. Generally, both steric demand and nucleophilicity of the glycoside bond-forming hydroxy group have to be considered. In this case, the basicity of the hydroxy protons and the stability of the initially formed alkoxide may play a more dominant role then anticipated.

Under the assumption that basicity and nucleophilicity of the acceptor hydroxy groups are affiliated, the more basic groups should also react more readily in glycoside formation. It is well documented, that hydroxy groups in position 2 exhibit an increased nucleophilicity for α-configured anomers apparently associated with hydrogen-bond formation.[24–26] Therefore, one would have expected a preference for certain branched trisaccharides. Surprisingly, under none of these combinatorial glycosylation conditions any preference was detected. It could be shown that the amount of sodium hydride had no significant influence on the product distribution. Even less than 1 equiv. of sodium hydride relative to glycosyl donor led to a rather uniform product distribution (Figure 3A and B). Therefore, under the present conditions a fast equilibrium of nucleophilic alkoxides competing for the electrophiles can be assumed.

In comparing glycosylations with the glucose and galactose donors **1** and **2**, differences in the relative yields could be explained in terms of differences in their reactivity. The more reactive galactose donor reacted predominantly with the sterically most accessible hydroxy groups. This may explain the enhanced relative yield of the β1→6-linked trisaccharide **11** with 2.5 equiv. of sodium hydride. Under these conditions, several hydroxy groups were deprotonated indicating a more kinetically controlled transformation process. By using 1.7 equiv. of sodium hydride, this effect was not observed due to fewer deprotonated hydroxy groups. Furthermore, stabilizing effects of intermolecular hydrogen bonds may be taken into consideration to contribute. The influence of the polar hydrogen bond-forming solvent DMF is presently uncertain.

Direct glycosylation of the unsymmetric disaccharide sucrose **12** led to all possible branched sucrose derivatives **13**–**20** (total yield of 18%). Again, ^{1}H NMR studies and permethylation/GC-MS analyses allowed for assignments of seven out of the possible eight isomeric galactopyranosyl sucrose product components. Except trisaccharide **19**, all galactopyranosyl sucroses could be identified but not always quantified, due to the fact that the furanosides were

partly degraded (Scheme 4). The furanoside ring of sucrose was partly unstable towards methylation analysis, which is a common problem.[27] The methodology for such systems has not yet been developed.



Scheme 4. Formation of galactopyranosyl sucroses **13**–**20**.

The present study demonstrated the first method suitable for combinatorial glycosylation of fully unprotected symmetric and unsymmetric nonreducing saccharides providing facile access to trisaccharides and potentially higher saccharides in uniform product distributions. Exemplarily, a combinatorial glycosylation of two glycosyl donors with *gluco* and *galacto* configuration using monosaccharide glycosides, α,α-trehalose and sucrose as acceptors were tested. GC-MS analyses were done on the corresponding alditol acateates revealing linkage types quantitalively.

The concentration of sodium hydride had no significant impact on the product distribution. Separation was achieved by flash chromatography. Stability towards intramolecular acetyl migration promoting self-glycosylation of the donor appeared to be an issue for monosaccharides only. For higher saccharides self-glycosylation is not relevant since self-glycosylated products lead only to disaccharides, which can be separated. The method and its application to other systems leading to defined libraries and potentially higher oligosaccharides are attractive and will be further elaborated.

Conclusions

This contribution demonstrates exemplarily the synthesis of complex di- and trisaccharides by using a simple glycosylation methodology leading in a single glycosylation step to a variety of products. Prior to flash-column separation of the resulting glycosides, further selective functionalization, degradation and assaying is envisioned and under current investigation.

Experimental Section

General Remarks: Commercially available starting materials were used without further purification, unless explicitly stated. Solvents were dried according to standard methods. Purifications of the products were carried out by column chromatography using Merck silica gel 60 (230–400 mesh). The nuclear magnetic resonance spectra were recorded with Bruker AMX-400 (100.62 MHz for ^{13}C) or DRX-500 (125.83 MHz for ^{13}C). All chemical shifts are quoted in ppm downfield from TMS or referred to the characteristic signals of the used solvents $CHCl_3$ in $CDCl_3$ (δ = 7.24 ppm), [D_3]methanol in [D_4]methanol (δ = 3.35 ppm) or HDO in D_2O (δ = 4.63 ppm). NMR analyses of trisaccharides were done on the peracetylated derivatives. Mass spectra were recorded with Bruker MALDI-Tof Biflex III using 2,5-dihydroxybenzoic acid (DHB). Microwave-assisted synthesis was performed in a CEM Microwave, Type "Discover" with a max. power output of 300 W. Reactions were carried out in closed vessels, using an infrared-sensor temperature control. Gas chromatography was done with an HP 6890, using a separation column HP-5 (30 m length), with an inner diameter (i.d.) of 0.32 mm, film thickness (f.th.) of 0.25 μm, and H_2 as a carrier. The temperature program used was: 40 °C for 2 min, 30 °C/min to 60 °C, 5 °C/min to 300 °C; temperature-programmable injector (PTV): 50 °C for 0.2 min, 300 °C/min to 250 °C; and standard FID detector unit. The HP 6890 GC was coupled to a HP 5890-A MS instrument from Hewlett Packard, California.

2,3,4,6-Tetra-*O*-acetyl-α-D-hexopyranosyl Chloride (1 and 2): 2,3,4,6-Tetra-*O*-acetyl-β-D-hexopyranose (10.0 g, 25.6 mmol) was dissolved in dry dichloromethane (50 mL). To this solution titanium tetrachloride (3 mL) was added, and the yellow precipitate was dissolved by shaking and heating at 70 °C for 10 min using a closed microwave reactor at 100 W. After cooling to room temperature, the solution was poured into ice/water (100 mL), and the product was extracted three times with dichloromethane (100 mL). The combined organic phases were dried with sodium sulfate, filtered and concentrated. The remaining syrup was recrystallized from diethyl ether/petroleum ether to give colorless crystals. Yield of **1**: 8.70 g, 93%; m.p. 72 °C; $[\alpha]_D^{20}$ = +163 (*c* = 1, $CHCl_3$) [ref.[28] m.p. 75–76 °C; $[\alpha]_D^{20}$ = +166 ($CHCl_3$)]. ^1H NMR (400 MHz, CDCl3): δ = 6.29 (d, 1 H, 1-H), 5.55 (vt, 1 H, 3-H), 5.13 (vt, 1 H, 4-H), 5.01 (dd, 1 H, 2-H), 4.30 (m, 2 H, 5-H, 6-Ha), 4.12 (dd, 1 H, 6-Hb), 2.10, 2.09, 2.04,2.03 (4 s, 4 × 3 H, 4 CH_3) ppm; $J_{1,2}$ = 3.9,

$J_{2,3}$ = 10.0, $J_{3,4}$ = 9.7, $J_{4,5}$ = 10.1, $J_{5,6b}$ = 6.4, $J_{6a,6b}$ = 11.5 Hz. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.96, 170.30 (2 ×), 169.89, (C=O), 90.49 (C-1), 71.15 (C-5), 71.80 (C-2), 69.83 (C-3), 67.82 (C-4), 61.53 (C-6), 21.10, 21.05, 21.01, 20.98 (CH_3) ppm. Yield of **2**: 8.89 g, 95%; m.p. 82 °C; $[\alpha]_D^{20}$ = +83 (c = 1, $CHCl_3$) [ref.[29] m.p. 86–87 °C; $[\alpha]_D^{20}$ = +115 ($CHCl_3$)]. ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 2.00, 2.05, 2.10, 2.14 (s, 3 H, CH_3 acetyl), 4.09 (dd, 1 H, 6-Ha), 4.16 (dd, 1 H, 6-Hb), 4.50 (t, 1 H, 5-H), 5.24 (dd, 1 H, 4-H), 5.41 (dd, J = 10.3 Hz, 1 H, 2-H), 5.51 (dd, J = 10.3 Hz, 1 H, 3-H), 6.36 (d, 1 H, 1-H) ppm; $J_{1,2}$ = 4.1, $J_{2,3}$ = 10.3, $J_{3,4}$ = 1.3, $J_{4,5}$ < 1, $J_{5,6a}$ = 6.9, $J_{5,6b}$ = 6.9, $J_{6a,6b}$ = 11.5 Hz. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 21.0, 21.0, 21.1, 21.1 (CH_3 acetyl), 61.4 (C-6), 67.5 (C-2), 67.6 (C-3), 68.3 (C-4), 69.8 (C-5), 91.5 (C-1), 170.2, 170.4, 170.6, 170.8 (C=O) ppm.

Exemplary Glycosylation Methodology: Under argon α,α-trehalose (**3**, 2.00 g, 5.84 mmol) was dissolved in anhydrous *N*,*N*-dimethylformamide (50 mL) and the mixture stirred with freshly activated molecular sieves (3 Å, 2.00 g) for 1 h. Subsequently, sodium hydride (60% suspension in paraffin) was added, and the mixture stirred at 22 mbar and room temperature for 1 h until gas development had ceased. The mixture was cooled to 0 °C, and a solution of the α-acetochloro sugar (**1** or **2**, 2.15 g, 5.84 mmol), dissolved in anhydrous *N*,*N*-dimethylformamide (5 mL), was added and the mixture stirred at 0 °C for 30 min. The solvent was removed under vacuum (40 °C, 2 mbar) and the remaining syrup taken up in pyridine (25 mL) and cooled to 0 °C. After addition of acetic anhydride (15 mL), the mixture was stirred overnight. Pyridine was removed under vacuum and by codistilling with toluene. The remaining residue was purified using flash-column chromatography (toluene/acetone, 6:1) to separate the trisaccharides from remaining peracetylated donor and acceptor. The subsequent analysis of the trisaccharide mixture by MALDI-TOF (DHB, positive mode) showed the corresponding peak at m/z = 988.5 [M + Na$^+$], 1004.4 [M + K$^+$].

Exemplary Methylation Analysis: The mixture of peracetylated trisaccharides **4**–**7** or **8**–**11** (200 mg, 0.2 mmol) was dissolved in dry methanol (10 mL) and a spatula tip of sodium methoxide added (pH = 8). The solution was stirred for 24 h and then neutralized using DOWEX-50, filtered and methanol removed under vacuum. The residue was redissolved in dimethyl sulfoxide (20 mL) and methyl iodide (1 mL) added, followed by sodium hydroxide solution (4 mL, 50%). After stirring at room temperature for 30 min, the solution was diluted with water (20 mL) and then extracted three times with purified dichloromethane (30 mL). The combined organic phases were washed with water, dried with sodium sulfate, and then filtered. The solvent was removed under reduced pressure and the residue dried in a stream of nitrogen. The remaining material (10 mg) was treated with trifluoroacetic acid (5 mL, 2.5 N) and heated in a microwave reactor to 120 °C for 1 h. Then the solution was cooled to room temperature, dried in a stream of nitrogen, and co-distilled twice with dry acetonitrile. The residue was dissolved with sodium tetradeuteridoborate (41 mg, 1.0 mmol) in a solution of aqueous ammonia (0.272 mL, 25%) and bi-distilled water (1.73 mL, 0.5 M $NaBD_4$ in 2 M NH_3 solution). The solution was stirred at 60 °C for 1 h, followed by addition of acetone (2 mL) and further stirring for 20 min. Acetonitrile (5 mL) was added and the solution dried in a stream of nitrogen and this repeated a second time. The residue was dissolved in a mixture of glacial acetic acid (2 mL), ethyl acetate (1 mL) and acetic anhydride (3 mL) and agitated. Finally, perchloric acid (0.1 mL, 70%) was added and the solution stirred for 5 min, then cooled to 0 °C, quenched with water (10 mL) and 1-methylimidazole (0.2 mL) and stirred for an additional 5 min. The solution was extracted by addition of dichloromethane (1 mL), subsequent vigorous agitation and phase separation. The methylated alditol acetate mixture was kept at –26 °C prior to GC-MS separation and analysis.[20–22]

Purification: The individual peracetylated trisaccharides were sufficiently enriched by flash-column chromatography on silica using toluene/acetone (6:1) to be characterized by NMR, GC-MS methylation analysis and matrix-assisted laser desorption ionization/time of flight (MALDI-TOF). The resulting fractions were characterized by NMR spectroscopy. The newly formed glycosidic bonds were identified by characteristic shifts in the ^{1}H and ^{13}C NMR signals and by typical long-range coupling in the HMBC NMR spectra.

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl-(1→2)-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranoside (4): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.45 (vt, 2 H, 3-H, 3′-H), 5.26 (d, 1 H, 1-H), 5.22 (d, 1 H, 1′-H), 5.15 (vt, 2 H, 4-H, 4′-H), 4.85 (dd, 1 H, 2′′-H), 4.64 (d, 1 H, 1′′-H), 3.93 (dd, 1 H, 2′-H), 2.10–1.98 (m, 33 H, CH_3) ppm; $J_{1'',2''}$ = 7.9, $J_{2'',3''}$ = 9.8, $J_{1',2'}$ = 3.8, $J_{2',3'}$ = 9.9, $J_{3',4'}$ = 9.5, $J_{4',5'}$ = 9.5, $J_{1,2}$ = 3.8, $J_{2,3}$ = 10.0, $J_{3,4}$ = 9.5, $J_{4,5}$ = 9.5 Hz. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 101.86 (C-1′′), 95.17 (C-1), 93.66 (C-1′), 76.01 (C-2′) ppm.

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl-(1→3)-2,4,6-tri-*O*-acetyl-α-D-glucopyranosyl 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranoside (5): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.55 (vt, 1 H, 3-H), 5.28 (d, 1 H, 1′-H), 5.20 (d, 1 H, 1-H), 5.03 (dd, 1 H, 2-H), 4.95 (m, 2 H, 4-H, 4′-H), 4.76 (d, 1 H, 1′′-H), 4.45 (dd, 1 H, 6′′-Ha), 4.15 (m, 1 H, 3′-H), 3.87 (m, 1 H, 5′-H), 2.10–1.98 (m, 33 H, CH_3) ppm; $J_{1'',2''}$ = 7.9, $J_{5'',6''a}$ = 3.8, $J_{6''a,6''b}$ = 12.6, $J_{1',2'}$ = 4.0, $J_{1,2}$ = 4.0, $J_{2,3}$ = 10.1 Hz.

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranoside (6): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.46 (2 vt, 2 H, 3-H, 3′-H), 5.27 (d, 1 H, 1-H), 5.23 (d, 1 H, 1′-H), 4.99 (m, 2 H, 2-H, 2′-H), 4.51 (d, 1 H, 1′′-H), 3.70 (vt, 1 H, 4′-H), 3.67 (ddd, 1 H, 5′′-H), 2.10–1.98 (m, 33 H, CH_3) ppm; $J_{1'',2''}$ = 7.9, $J_{1',2'}$ = 3.8, $J_{1,2}$ = 4.1, $J_{2',3'}$ = 10.0, $J_{2,3}$ = 10.1, $J_{3',4'}$ = 9.5, $J_{3,4}$ = 9.4 Hz. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 101.44 (C-1′′), 92.04 (2 C, C-1, C-1′), 77.29 (C-4′) ppm.

2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl-(1→6)-2,3,4-tri-*O*-acetyl-α-D-glucopyranosyl 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranoside (7): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.47 (d, 1 H, 1′′-H), 3.45 (dd, 1 H, 6′′-Ha) ppm; $J_{1'',2''}$ = 8.0, $J_{5'',6''a}$ = 6.5, $J_{6''a,6''b}$ = 10.6 Hz. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 68.03 (C-6′′) ppm.

2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl-(1→2)-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranoside (8): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.46 (vt, 1 H, 3-H), 5.44 (vt, 1 H, 3′-H), 5.39 (dd, 1 H, 4′′-H), 5.25 (d, 1 H, 1′-H), 5.20 (m, 1 H, 4′-H), 5.19 (m, 1 H, 4-H), 5.18 (d, 1 H, 1-H), 4.95 (m, 3 H, 2′′-H, 3′′-H, 2-H), 4.57 (d, 1 H, 1′′-H), 4.53 (dd, 1 H, 6′-Ha), 4.40 (ddd, 1 H, 5-H), 4.34 (dd, 1 H, 6′-Hb), 4.15 (m, 1 H, 5′-H), 4.13 (m, 2 H, 6′′-Ha, 6′′-Hb), 4.10 (m, 2 H, 6-Ha, 6-Hb), 3.87 (m, 1 H, 2′-H), 2.15–1.96 (m, 3 H, CH_3) ppm; $J_{1'',2''}$ = 7.6, $J_{3'',4''}$ = 2.2, $J_{4'',5''}$ < 1, $J_{1',2'}$ = 3.8, $J_{2',3'}$ = 10.1, $J_{3',4'}$ = 10.7, $J_{5',6'a}$ = 1.9, $J_{5'6'b}$ = 5.0, $J_{6'a,6'b}$ = 12.7, $J_{1,2}$ = 4.1, $J_{2,3}$ = 9.1, $J_{3,4}$ = 10.7, $J_{4,5}$ = 10.1, $J_{5,6a}$ = < 1, $J_{5,6b}$ < 1 Hz. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.48–170.47 (m, C=O), 102.34 (C-1′′), 95.76 (C-1′), 94.31 (C-1), 75.98 (C-2′), 72.25 (C-3′), 71.62 (C-3), 67.35 (C-4′′), 70.96, 70.86, 70.83, 68.75, 68.56, 68.22, 68.04, 67.83, 62.11, 61.48, 61.32 (C-2, C-2′′, C-3′′, C-4, C-4′, C-5, C-5′, C-5′′, C-6, C-6′, C-6′′) ppm.

2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl-(1→3)-2,4,6-tri-*O*-acetyl-α-D-glucopyranosyl 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranoside (9): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.55 (vt, 1 H, 3-H), 5.37 (dd,

1 H, 4′′-H), 5.29 (d, 1 H, 1-H), 5.21 (d, 1 H, 1′-H), 5.10 (dd, 1 H, 2′′-H), 5.04 (m, 1 H, 2-H), 5.01 (m, 1 H, 4-H), 4.99 (m, 1 H, 3′′-H), 4.96, (m, 1 H, 2′-H), 4.93 (vt, 1 H, 4-H), 4.40 (d, 1 H, 1′′-H), 4.21 (m, 1 H, 5-H), 4.13 (vt, 1 H, 3′-H), 4.08 (m, 2 H, 6′′-Ha, 6′′-Hb), 4.01 (m, 2 H, 6′-Ha, 6′-Hb), 4.00 (m, 2 H, 6-Ha, 6-Hb), 3.95 (vt, 1 H, 5′-H), 3.87 (vt, 1 H, 5′′-H), 1.98–2.11 (m, 3 H, CH_3) ppm; $J_{1'',2''}$ = 7.9, $J_{2'',3''}$ = 10.4, $J_{3'',4''}$ = 2.4, $J_{4'',5''} < 1$, $J_{5'',6''a}$ = 6.3, $J_{5'',6''b}$ = 6.6, $J_{1',2'}$ = 4.1, $J_{2',3'}$ = 9.5, $J_{3',4'}$ = 9.4, $J_{4',5'}$ = 10.1, $J_{5',6'a}$ = 6.3, $J_{5',6'b}$ = 6.0, $J_{6'a,6'b}$ = 11.9, $J_{1,2}$ = 3.8, $J_{2,3}$ = 9.8, $J_{3,4}$ = 9.8 Hz. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.48–170.47 (m, C=O), 101.61 (C-1′′), 91.96 (C-1′), 91.81 (C-1), 75.92 (C-3′), 71.11 (C-5′′), 70.50 (C-3), 67.18 (C-4′′), 62.38 (C-6′′), 61.52 (C-6), 61.05 (C-6′), 21.16–20.92 (m, CH_3) ppm.

2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α-D-glucopyranosyl 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranoside (10): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.50 (vt, 1 H, 3-H), 5.47 (vt, 1 H, 3′-H), 5.35 (d, 1 H, 4′′-H), 5.26 (d, 1 H, 1′-H), 5.22 (d, 1 H, 1-H), 5.12 (dd, 1 H, 2′′-H), 5.04 (m, 1 H, 2′-H), 5.03 (m, 1 H, 4′-H), 4.96 (dd, 1 H, 3′′-H), 4.95 (m, 1 H, 2-H), 4.50 (d, 1 H, 1′′-H), 4.32 (d, 1 H, 6-Hb), 4.21 (m, 1 H, 6′-Hb), 4.15 (m, 1 H, 6-Ha), 4.13 (m, 1 H, 6′′-Ha), 4.10 (m, 1 H, 6′′-Hb), 4.03 (m, 1 H, 6′-Ha), 4.02 (m, 1 H, 5′-H), 3.94 (m, 1 H, 5-H), 3.90 (vt, 1 H, 5′′-H), 3.73 (vt, 1 H, 4-H), 2.16, 2.10, 2.08, 2.07, 2.06, 2.06, 2.05, 2.05, 2.02, 2.02, 1.96 (11 s, 11 × 3 H, 11 CH_3) ppm; $J_{1'',2''}$ = 7.9, $J_{2'',3''}$ = 10.1, $J_{3'',4''}$ = 3.2, $J_{4'',5''} < 1$, $J_{5'',6''a}$ = 7.2, $J_{5'',6''b}$ = 5.3, $J_{1',2'}$ = 3.8, $J_{2',3'}$ = 10.1, $J_{3',4'}$ = 10.1, $J_{5',6'b}$ = 5.5, $J_{6'a,6'b}$ = 11.7, $J_{1,2}$ = 3.8, $J_{2,3}$ = 9.1, $J_{3,4}$ = 9.5, $J_{4,5}$ = 9.8, $J_{5,6a} < 1$, $J_{6a,6b}$ = 11.7 Hz. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.02, 170.81, 170.59, 170.51, 170.35, 170.20, 170.06, 169.70, 169.67, 169.30, 169.28 (11 × C=O), 101.80 (C-1′′), 92.14 (2 C, C-1′, C-1), 77.28 (C-4), 71.47 (C-5′′), 71.11 (C-2), 70.66 (C-3′′), 70.40, 70.36 (C-3′, C-3), 70.24 (C-2′), 69.69 (C-2′′), 69.39 (C-4′), 68.95 (C-5), 68.49 (C-5′), 66.93 (C-4′′), 62.23 (C-6′), 62.18 (C-6), 61.14 (C-6′′), 21.11–20.94 (m, CH_3) ppm.

2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-acetyl-α-D-glucopyranosyl 2,3,4,6-Tetra-*O*-acetyl-α-D-glucopyranoside (11): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.48 (vt, 1 H, 3′-H), 5.46 (vt, 1 H, 3-H), 5.41 (dd, 1 H, 4-H), 5.27 (d, 1 H, 1′-H), 5.23 (d, 1 H, 1-H), 5.15 (m, 1 H, 2-H), 5.12 (dd, 1 H, 2′′-H), 5.04 (m, 1 H, 3-H), 5.02 (vt, 1 H, 4-H), 4.96 (m, 1 H, 4′-H), 4.94 (m, 1 H, 2′-H), 4.73 (d, 1 H, 1′′-H), 4.18 (m, 1 H, 5-H), 4.11 (m, 1 H, 5′-H), 4.06 (m, 2 H, 6-Ha, 6-Hb), 4.03 (m, 3 H, 5′′-H, 6′′-Ha, 6′′-Hb), 3.92 (dd, 1 H, 6′-Hb), 3.44 (dd, 1 H, 6′-Ha), 2.11–1.98 (m, 33 H, CH_3) ppm; $J_{1'',2''}$ = 7.9, $J_{2'',3''}$ = 10.4, $J_{3'',4''}$ = 2.2, $J_{1',2'}$ = 3.4, $J_{2',3'}$ = 9.9, $J_{3',4'}$ = 9.9, $J_{5',6'a}$ = 6.3, $J_{5',6'b}$ = 1.9, $J_{6'a,6'b}$ = 10.4, $J_{1,2}$ = 3.5, $J_{2,3}$ = 10.1, $J_{3,4}$ = 9.9, $J_{4,5}$ = 9.6 Hz. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.48–170.47 (C=O), 101.28 (C-1′′), 93.09 (C-1), 92.63 (C-1′), 71.14 (C-5′′), 70.47 (C-3), 70.46 (C-3′), 68.04 (C-6′), 67.31 (C-4′′), 62.47 (C-6′′), 62.28 (C-6), 21.16–20.92 (m, CH_3) ppm. Further signals of a mixture of **9** and **11**: ^{13}C NMR (100 MHz, $CDCl_3$): δ = 72.41, 71.50, 70.89, 70.80, 70.46, 70.18, 69.68, 69.48, 69.32, 69.22, 68.98 (2 C), 68.90, 68.84, 68.69, 68.54 ppm.

2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl-(1→2)-3,4,6-tri-*O*-acetyl-α-D-glucopyranosyl 1,3,4,6-Tetra-*O*-acetyl-β-D-fructofuranoside (13): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.62 (d, 1 H, 3′-H), 5.53 (d, 1 H, 1-H), 5.43 (vt, 1 H, 4′-H), 5.38–5.34 (m, 2 H, 3-H, 4′′-H), 5.27 (dd, 1 H, 2′′-H), 4.93–4.96 (m, 2 H, 4-H, 3′′-H), 4.55 (d, 1 H, 1′′-H), 4.04–4.40 (m, 8 H, 5-H, 6-Ha, 6-Hb, 1′-Ha, 1′-Hb, 5′-H, 6′-Ha, 6′-Hb), 3.81 (dd, 1 H, 2-H), 2.17, 2.14, 2.13, 2.11, 2.10, 2.07, 2.07, 2.06, 2.05, 1.96, 1.96 (11 s, 11 × 3 H, 11 CH_3) ppm; $J_{1,2}$ = 3.5, $J_{2,3}$ = 9.8, $J_{3',4'}$ = 7.9, $J_{4',5'}$ = 7.3, $J_{1'',2''}$ = 7.8, $J_{2'',3''}$ = 10.6 Hz. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.11, 171.00, 170.83, 170.70, 170.55, 170.49, 170.47, 170.19, 170.12, 169.97, 169.21 (11 C=O), 104.10 (C-2′), 102.16 (C-1′′), 92.12 (C-1), 79.00 (C-5), 75.59 (C-2), 75.16 (C-4′), 74.98 (C-3′), 71.93 (C-4′′), 71.48 (C-5′′), 71.02 (C-3′′), 68.98 (C-5), 68.76 (C-4), 68.14 (C-2′′), 67.16 (C-3), 65.48, 63.04, 62.48, 61.63 (C-6, C-1′, C-6′, C-6′′), 21.20–20.73 (m, CH_3) ppm.

2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl-(1→3)-2,4,6-tri-*O*-acetyl-α-D-glucopyranosyl 1,3,4,6-Tetra-*O*-acetyl-β-D-fructofuranoside (14), 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl-(1→3)-2,4,6-tri-*O*-acetyl-α-D-glucopyranosyl 1,3,4,6-Tetra-*O*-acetyl-β-D-fructofuranoside (15), and 2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl-(1→6)-2,3,4-tri-*O*-acetyl-α-D-glucopyranosyl 1,3,4,6-Tetra-*O*-acetyl-β-D-fructofuranoside (16): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.74 (d, 1 H, 1-H), 4.63 (d, 1 H, 1-H), 4.78 (d, 1 H, 1-H) ppm. GC-MS fragmentation.

2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl-(1→1′)-2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl 3,4,6-Tri-*O*-acetyl-β-D-fructofuranoside (17): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.67 (d, 1 H, 1-H), 5.41–5.45 (m, 2 H, 3′′-H, 4′′-H), 5.35 (m, 1 H, 3-H), 5.26 (d, 1 H, 4′-H), 5.16 (dd, 1 H, 2-′H), 5.02 (m, 1 H, 3′-H), 5.01 (m, 1 H, 4-H), 4.84 (dd, 1 H, 2-H), 4.53 (d, 1 H, 1′-H), 4.26–3.97 (m, 9 H, 5-H, 5′-H, 5′′-H, 6-Ha, 6′-Ha, 6′′-Ha, 6-Hb, 6′-Hb, 6′′-Hb), 3.75 (d, 1 H, 1′′-Ha), 3.46 (d, 1 H, 1′′-Hb), 2.15, 2.14, 2.12, 2.11, 2.09, 2.06, 2.06 2.04, 2.04, 2.03, 2.01 (11 s, 11 × 3 H, 11 CH_3) ppm; $J_{1,2}$ = 3.7, $J_{2,3}$ = 10.4, $J_{1'a,1'b}$ = 10.7, $J_{1'',2''}$ = 7.5, $J_{2'',3''}$ = 8.2, $J_{3'',4''} < 1$, $J_{4'',5''}$ = 3.0 Hz. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 101.21 (C-2′′), 101.95 (C-1′), 90.01 (C-1), 82.32 (C-5′′), 75.24 (C-3′′), 73.57 (C-4′′), 71.27 (C-3′), 71.09 (C-2), 71.03 (C-3), 70.32 (C-1′′), 69.12 (C-2′), 68.63 (C-4), 68.86 (C-5), 68.78 (C-5′), 67.36 (C-4′), 63.32, 62.01, 61.59 (C-6, C-6′, C-6′′), 171.10, 170.91, 170.64, 170.63, 170.56, 170.52, 170.47, 170.26, 170.18, 170.04, 169.95 (11 C=O), 21.10–21.03 (m, CH_3) ppm.

2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl-(1→3′)-2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl 1,4,6-Tri-*O*-acetyl-β-D-fructofuranoside (18): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.75 (d, 1 H, 1-H), 5.50 (vt, 4′-H), 5.43 (vt, 1 H, 3-H), 5.36 (d, 1 H, 4′′-H), 5.13 (dd, 1 H, 2′′-H), 5.07 (vt, 1 H, 4-H), 5.04 (dd, 1 H, 3′′-H), 4.95 (dd, 1 H, 2-H), 4.60 (d, 1 H, 1′′-H), 4.35 (d, 1 H, 1′-Ha), 4.32 (d, 1 H, 3′-H), 4.27–4.29 (m, 2 H, 5-H, 6-Ha), 4.04–4.19 (m, 7 H, 6-Ha, 1′-Ha, 5′-H, 6′-Ha, 6′-Hb, 6′′-Ha, 6′′-Hb), 3.92 (vt, 1 H, 5′′-H), 2.19, 2.15, 2.11, 2.11, 2.10, 2.09, 2.08, 2.05, 2.05, 2.00, 1.98 (11 s, 11 × 3 H, 11 CH_3) ppm; $J_{1,2}$ = 3.8, $J_{2,3}$ = 9.7, $J_{3,4}$ = 9.8, $J_{4,5}$ = 9.8, $J_{1'a,1'b}$ = 11.0, $J_{3',4'}$ = 7.9, $J_{4',5'}$ = 7.5, $J_{1'',2''}$ = 7.8, $J_{2'',3''}$ = 10.5, $J_{3'',4''}$ = 2.8, $J_{4'',5''} < 1$, $J_{5'',6''a}$ = 6.6, $J_{5'',6''b}$ = 6.6 Hz. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 103.32 (C-2′), 102.24 (C-1′′), 89.85 (C-1), 82.75 (C-3′), 79.01 (C-5), 74.23 (C-4′), 71.18 (C-3′′), 71.16 (C-5′′), 70.57 (C-3), 70.52 (C-2), 69.00 (C-2′′), 68.58 (C-4), 68.47 (C-5), 67.00 (C-4′′), 64.27, 63.34, 62.22, 61.08 (C-6, C-1′, C-6′, C-6′′), 20.93–21.25 (m, CH_3) ppm.

2,3,4,6-Tetra-*O*-acetyl-β-D-galactopyranosyl-(1→6′)-2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl 1,3,4-Tri-*O*-acetyl-β-D-fructofuranoside (20): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.59 (d, 1 H, 1-H), 5.48 (d, 1 H, 3′-H), 5.45 (vt, 1 H, 3-H), 5.39 (d, 1 H, 4′′-H), 5.30 (vt, 1 H, 3′-H), 5.17 (dd, 1 H, 2′′-H), 5.07 (vt, 1 H, 4-H), 5.05 (dd, 1 H, 3′′-H), 4.89 (dd, 1 H, 2-H), 4.60 (d, 1 H, 1′′-H), 4.38–4.25 (m, 3 H, 5-H, 6-Ha, 6-Hb), 4.20–4.05 (m, 5 H, 1′-Ha, 1′-Hb, 5′-H, 6′′-Ha, 6′′-Hb), 4.06 (m, 1 H, 6′-Hb), 3.97 (vt, 1 H, 5′′-H), 3.81 (dd, 1 H, 6′-Ha), 2.15, 2.14, 2.11, 2.10, 2.10, 2.08, 2.06, 2.03, 2.03, 2.01, 1.97 (11 s, 11 × 3 H, 11 CH_3) ppm; $J_{1,2}$ = 3.8, $J_{2,3}$ = 10.4, $J_{3,4}$ = 9.7, $J_{4,5}$ = 10.1, $J_{3',4'}$ = 7.3, $J_{4',5'}$ = 7.0, $J_{1'',2''}$ = 7.9, $J_{2'',3''}$ = 10.5, $J_{3'',4''}$ = 3.5, $J_{4'',5''} < 1$, $J_{5'',6''a}$ = 7.3, $J_{5'',6''b}$ = 7.3 Hz. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.10, 170.74, 170.70, 170.62, 170.53, 170.53, 170.46, 170.40, 170.30, 169.99, 169.93 (11 C=O), 103.90 (C-

1′), 102.14 (C-1′′), 90.29 (C-1), 80.06 (C-5′), 76.01 (C-3′), 74.97 (C-4′), 71.17 (C-3′′), 71.02 (C-6′), 70.98 (C-5′′), 70.60 (C-2), 69.91 (C-3), 69.14 (C-2′′), 68.93 (C-5), 68.63 (C-4), 67.35 (C-4′′), 63.48 (C-6), 62.21 (C-6′′), 61.32 (C-1′), 20.94–20.27 (m, CH_3) ppm.

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