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Catalytic Iron(III) Chloride Mediates Site-Selective Protection of Mono- and Disaccharides and one Trisaccharide

Alexandra Gouasmat,[a] Aurélie Lemétais,[a] Julien Solles,[a] Yann Bourdreux*[a] and Jean-Marie Beau*[a,b]

Dedication ((optional))

Abstract: Synthetic transformations of mono- and oligosaccharidic substrates necessitate the regioselective differentiation of the hydroxyl groups to yield the desired building blocks usable for a selective synthetic construction. Herein, we show that iron(III) chloride hexahydrate catalyzes tandem protection of mono- and disaccharides, providing, in a one-pot procedure, carbohydrate building units with a site-selective protecting group pattern. This tandem protocol was successfully applied to a trisaccharide. The procedure is easy to perform and it is shown that every particular carbohydrate substrate required a fine-tuning of the operating one-pot conditions for optimal results.

Introduction

During the last two decades, much attention has been given to "one-pot" multiple transformations followed by a single workup stage.[1,2] This sequence of one-pot transformations may also be induced advantageously by catalytic reagents. Such approaches have been used to transform carbohydrates e.g. in the selective synthesis of complex oligosaccharides or bioactive compounds. Lewis acids-catalyzed tandem protocols for the regioselective acetalation-alkylation-acylation on carbohydrate templates were recently developed using copper(II) triflate [$Cu(OTf)_2$],[3,4] trimethylsilyltriflate (TMSOTf),[5,6] iron(III) choride hexahydrate ($FeCl_3$•$6H_2O$)[7] and trifluoromethanesulfonic acid (triflic acid, TfOH) on molecular sieves.[8]

The procedures are notably convenient for the site-selective reductive alkylation (benzylation) of carbohydrates. Most of the tandem processes reported have been applied to monosaccharides, and only few have been described with disaccharides.[6b,7] Other approaches have been developed for the regioselective alkylation of diols or polyols, of which benzylation is the most commonly used, with tin,[9] and boron derivatives,[10] and silver(I)[11] or nickel(II) salts.[12] Recently, Dong has developed an excellent route to selectively monoalkylate diverse diol-containing structures with an iron(III) catalyst that should favorably replace the toxic organotin reagents.[13] These alternative methods apply to diols and polyols in monosaccharides containing *cis*-diol units with the equatorial hydroxy groups adjacent to an axial hydroxyl group being selectively benzylated (alkylated). It excludes the important glucopyranosyl moiety where these procedures are not selective with one exception on the recently described regioselective benzylation of 1,2-*trans* diol.[13].

In a preliminary account we reported that $FeCl_3$•$6H_2O$ is an effective catalyst for the regioselective protection of mono- and disaccharides, with the examples of trehalose and maltose.[7] Moreover, we recently applied this $FeCl_3$•$6H_2O$-promoted tandem protocol to trehalose for the synthesis of sulfoglycolipid analogues, important metabolites from *Mycobacterium tuberculosis*.[14] We describe herein an extension of this procedure to other mono- and disaccharides and to a trisaccharide, all containing D-glucopyranosyl units. It revealed unexpected site-selective reductive benzylation induced by the substrate structures themselves.

Results and Discussion

In our initial studies,[7] per-*O*-silylated α-methyl-D-glucopyranoside **1** was used as a model compound. The procedure consisted of adding at 0°C, 3 equiv of benzaldehyde, 1 equiv of triethylsilane and 5 mol% of $FeCl_3$•$6H_2O$ to a solution of substrate **1** which, after 1.5 h at room temperature, provided compound **4** in 77% yield. From the different iron catalysts tested, $FeCl_3$•$6H_2O$ was the best choice, although anhydrous $FeCl_3$ was equally effective but the hydrated salt was selected because of its easiness to handle being not air sensitive. The reductive etherification reaction of the tandem procedure provided a very good 3-*O* selectivity, as observed with $Cu(OTf)_2$[3] and TMSOTf[5]. These standard conditions were also efficiently applied to β-thiophenyl-D-glucopyranoside **2**, leading to **5** with the same benzylation selectivity (scheme 1).[7] These preliminary results might suggest that the anomeric configuration had no influence on the benzylation regioselectivity. However, the same conditions applied to the per-*O*-silylated β-methyl-D-glucopyranoside **3**, induced a significant decrease in yield with only 44% yield of the 3-*O*-benzylated compound **6**.

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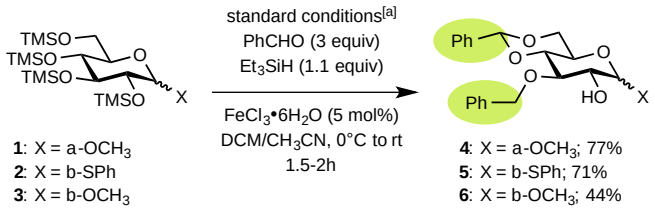
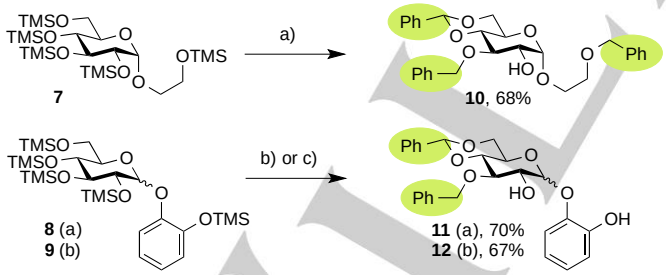


Scheme 1. $FeCl_3$•$6H_2O$-catalyzed regioselective protection of glucopyranosides **1**-**3**. [a] See ref 7. Ph = phenyl; TMS = trimethylsilyl.

This is a result of a decrease in regioselectivity for the etherification step. The 2-*O*-mono- and 2,3-di-*O*-benzylated derivatives were unexpectedly formed in 9 and 21% yields respectively.

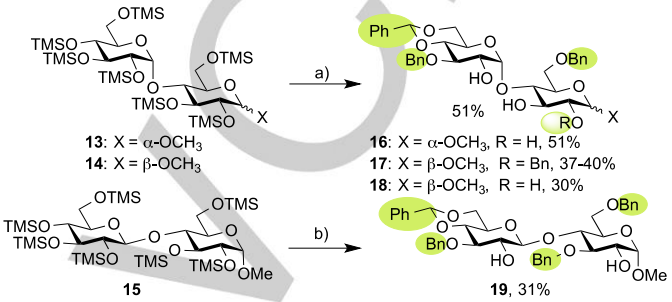
Compounds **7**-**9** with functional aglycone moieties were next evaluated. For these compounds, modifications of our standard conditions were required. The derivative **7** was less reactive, and a higher amount of reagents and an increase in the reaction time and temperature were necessary to provide compound **10** in 68% yield. This compound was benzylated at the primary aglycone hydroxyl group and at *O*-3 of the glucose unit (scheme 2). Compounds **8** and **9** also required an excess of PhCHO and Et_3SiH, and 10 mol% of the catalyst instead of 5 mol% under the standard conditions. A possible complexation of the catechol moiety with the catalyst may reduce the activity of $FeCl_3$•$6H_2O$. Both anomers **8** and **9** led to the 4,6-*O*-benzylidene-3-*O*-benzyl protecting pattern in compounds **11** and **12** in 70% and 67% yields, respectively. With these substrates, 2,3-di-*O*-benzylated compounds were also formed as by-products, but mono-*O*-benzylated derivatives at C-2 were not detected (scheme 2). For these anomers **8**/**9**, and in contrast with the anomers **1**/**3**, the anomeric configuration had no effect on the regioselectivity of the reductive etherification.



Scheme 2. $FeCl_3$•$6H_2O$-catalyzed regioselective protection of glucopyranosides **7**-**9**. Reagents and conditions: a) PhCHO (4 equiv), Et_3SiH (3 equiv), $FeCl_3$•$6H_2O$ (5 mol%), CH_3CN, 50°C, overnight; b) Starting from **8**: PhCHO (4 equiv), Et_3SiH (2.2 equiv), $FeCl_3$•$6H_2O$ (10 mol%), DCM/CH_3CN 4/1, rt, overnight; c) Starting from **9**: PhCHO (6 equiv), Et_3SiH (3 equiv), $FeCl_3$•$6H_2O$ (10 mol%), DCM/CH_3CN 4/1, rt, overnight.

Application to disaccharides

This tandem protocol was first applied to silylated trehalose,[7] a step which was advantageously incorporated into total synthetic schemes of bioactive glycolipids.[14] With per-*O*-silylated α-methyl maltoside **13**, optimized conditions led to the regioselectively protected derivative **16**[7] in a good 51% yield (three reactions catalyzed in one pot). The disaccharide was benzylated at O-6 of the reducing unit and at O-3 of the non-reducing unit (scheme 3). The major product formed under optimized conditions was often accompanied with unidentified by-products, complicating the purification procedure.

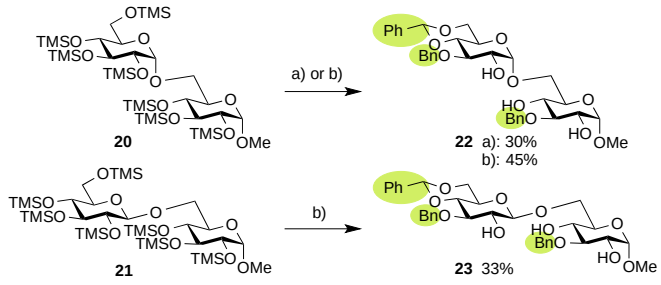


Scheme 3. Iron(III)-catalyzed tandem protocol applied to 1,4-disaccharides **13**-**15**. Reagents and conditions: a) PhCHO (8 equiv), Et_3SiH (4 equiv), $FeCl_3$•$6H_2O$ (15 mol%), DCM/CH_3CN 4/1, rt, overnight; b) PhCHO (6 equiv), Et_3SiH (4 equiv), $FeCl_3$•$6H_2O$ (10 mol%), DCM/CH_3CN 4/1, rt, overnight. Bn = benzyl.

The same tandem procedure, examined on the β-anomer **14**, provided derivative **17** in a 37% or 40% yield under slightly modified reaction conditions (6 equiv of PhCHO, 4 equiv of Et_3SiH and 10 mol% $FeCl_3$•$6H_2O$). Compound **17** was tri-*O*-benzylated at *O*-3 of the terminal unit and *O*-2 and *O*-6 of the reducing unit. The major identified byproduct **18** exhibited the benzylation pattern of the α-anomer **13** (dibenzylation at *O*-6 of the reducing unit and at *O*-3 of the terminal unit) (30% yield).[15]

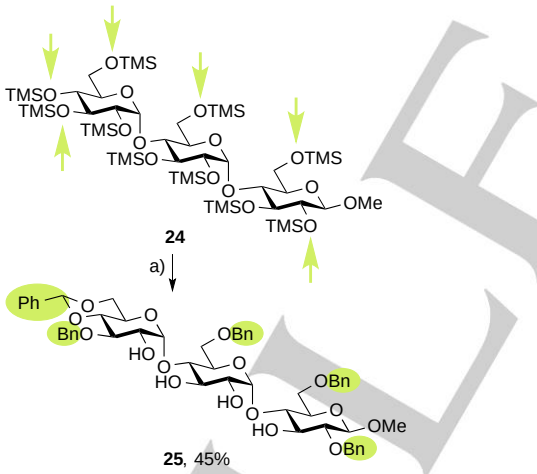
The per-*O*-silylated α-methyl cellobioside **15** furnished a complex mixture of *O*-benzylated derivatives. The best result was obtained under conditions b (scheme 3) giving the tri-*O*-benzylated compound **19** as the major product in a moderate 31% yield. In this case, both positions 3 of the two glucose units were *O*-benzylated, as well as the primary position of the reducing unit.[16]

We next studied substrates with 1,6-interglycosydic linkages. The conditions used for α-methyl maltoside **13**, applied to the α-methyl isomaltoside **20**, (α-1,6 linkage) led to compound **22**, benzylated at both *O*-3 of the two glucose units in 30% yield, increased to 45% under optimized conditions (scheme 4).[17] Under the same conditions, the per-*O*-silylated gentiobioside **21** (β-1,6 linkage) led to the di-*O*-benzylated disaccharide **23** in 33% yield, a low yield resulting from the formation of a mixture of byproducts, indicating a decrease in selectivity with a β-interglycosidic bond. With these two 1,6-dimers, the major products were benzylated at both *O*-3.



Scheme 4. Iron(III)-catalyzed tandem protocol applied to 1,6-disaccharides **20** and **21**. Reagents and conditions: a) PhCHO (8 equiv), Et_3SiH (4 equiv), $FeCl_3$•$6H_2O$ (15 mol%), DCM/CH_3CN 4/1, rt, overnight; b) PhCHO (4 equiv), Et_3SiH (2.2 equiv), $FeCl_3$•$6H_2O$ (10 mol%), DCM/CH_3CN 4/1, rt, overnight.

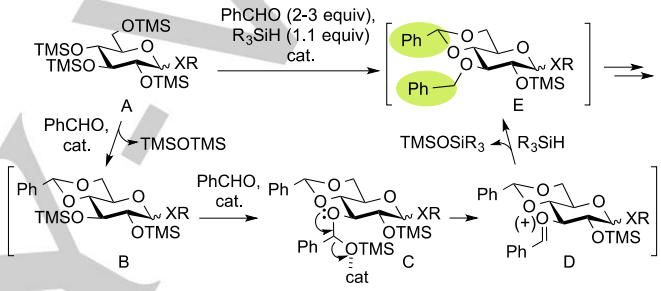
We next evaluated the one-pot procedure with β-methyl maltotrioside **24**. With this compound, and based on the above observations on disaccharides, the formation of a 4,6-*O*-benzylidene-3-*O*-benzyl protection pattern on the terminal unit, di-*O*-benzylation of the two primary positions of the two other units, and a selective 2-*O*-benzylation of the reducing unit were expected. This anticipated protection pattern is shown as green arrows in Scheme 5. Under the indicated conditions, the "expected" 4,6-*O*-benzylidene-tetra-*O*-benzylated derivative **25** was indeed formed as the major product in a 45% yield.



Scheme 5. Iron(III) chloride-catalyzed tandem protection of persilylated β-methyl maltotrioside **24**. The green arrows show the expected regioselective protection pattern of methyl β-D-maltotrioside. Reagents and conditions: a) PhCHO (15 equiv), Et_3SiH (8 equiv), $FeCl_3$•$6H_2O$ (15 mol%), CH_3CN, 50°C, overnight.

In these one-pot multi-step protocols from silylated substrates, glucopyranosyl monomers and all non-reducing units in the di- and trisaccharides are acetalized at the 4,6-positions. This is the initial catalytic cycle on silylated **A** providing the 4,6-*O*-benzylidene derivative **B** and TMSOTMS [18] from benzaldehyde and the 4,6-di-*O*-TMS motif (Scheme 6). A second catalytic cycle follows, the catalyst likely promoting the site-selective formation of the open mixed acetal at *O*-3 **C** with a second equivalent of benzaldehyde, activated by the catalyst to oxonium **D** which is reduced by R_3SiH to the benzyl ether **E** and $TMSOSiR_3$).

This 3-*O*-selectivity, first established in a single reductive alkylation (benzylation) step on methyl 2,3-di-*O*-trimethylsilyl-4,6-O-benzylidene-α-D-glucopyranoside,[19] is promoted in the above sequence by all the different Lewis acids tested (TMSOTf, $Cu(OTf)_2$ or $FeCl_3$•$6H_2O$), indicating that the regioselectivity was controlled by the substrate. When some of the structural characteristics of the glucopyranosyl substrate are changed, the site-selectivity is perturbed or lost probably arising from a change of the steric (including chiral) and electronic environment. It is difficult, at the present, to rationalize the origin of the regioselectivities observed for the reductive benzylation steps.



Scheme 6. Possible starting catalytic cycles for the site-selective reductive benzylation catalyzed by Lewis acids at the non-reducing glucopyranosyl unit of the substrates. cat = TMSOTf, $Cu(OTf)_2$ or $FeCl_3$•$6H_2O$; X = alkyl, aryl or glucopyranosyl.

A few experimental rules may however be deduced from this study:

- the 3-*O*-selectivity reported above was high with α-alkyl, α-aryl (as in **8**), α-glucosyl (as in all oligomers) and β-aryl (as in **9**) and β-thioaryl (as in **5**) derivatives but not with β-alkyl (as in **3**) or β-glucosyl substrates (as in dimers **15**, **21**),

- whenever stable acetalization was not possible, all primary hydroxyl groups were benzylated (as in **7** and all oligosaccharides),

- a phenolic hydroxyl group was not benzylated (as in **8**, **9**),

- an α-1,4 interglycosidic linkage between two glucose units prevented the 3-*O*-benzylation of the reducing moiety, as in the maltobioside **13** (Scheme 3). This was also noticed with the TMSOTf-catalyzed benzylation, pointing again on a substrate-controlled site-selectivity.[15] With a β-methyl anomer of the disaccharide (as in **14**), a 2-*O*-benzylation on the reducing unit was possible instead. The 3-*O*-benzylation of the reducing moiety was partly restored with a β-1,4 interglycosidic linkage (as in cellobioside **15**).

- these "experimental rules" are indeed useful to predict the site-selective benzylation on new substrates, as realized above with the benzylation pattern on β-methyl maltotrioside **24**.

Conclusions

In this work, we have collected more extensive results on the iron(III) chloride-catalyzed site-selective acetalation/benzylation of mono- and disaccharides. We have demonstrated that the nature of the interglycosidic linkage and the anomeric configuration of the reducing unit have a strong effect on the protective patterns. The tandem protection of a trisaccharide was also successfully predicted and performed. The procedure, using a single iron(III) catalyst in a single reaction vessel is an attractive method for the synthesis of regioselectively functionalized building blocks en route to complex glycoconjugates. We are currently working on other substrates in order to gain insights into the origin of the site-selective FeCl3•6H2O-catalyzed benzylation of mono- and oligosaccharides.

Experimental Section

General methods: All air sensitive reactions were carried out in oven-dried glassware under a slight positive pressure of argon. Dichloromethane and acetonitrile were distilled from CaH_2 or by filtration through a column of activated alumina using equipment from Glass Technology® (dry solvent station GT S100). TLC (Silica Gel 60 F_{254}) were visualized under UV (254 nm) and by staining in a 5% ethanolic sulfuric acid or orcinol solutions. Silica gel SDS 60 ACC 35-70 μm was used for column chromatography. Melting points were measured on a Stuart SMP10 apparatus and are uncorrected. NMR spectra were recorded on Bruker DRX 300 or AV 360 or DPX 250 NMR spectrometers. Chemical shifts (in ppm) were determined relative to residual undeuterated solvent as an internal reference. Abbreviations of multiplicity were as follows: s (singlet), d (doublet), dd (doublet of doublet), t (triplet), at (apparent triplet), m (multiplet), b (broad). Coupling constants in hertz (Hz) were measured from one-dimensional spectra. High-resolution mass spectra (positive mode ESI) were performed on a Bruker Daltonics micrOTOF-QII spectrometer. Optical rotations were measured on a Perkin Elmer 341 Polarimeter (*c* in g / 100 mL). The regioselectivities of reductive etherifications were determined through chemical correlation after acetylation of the hydroxyl functions, or by HMBC experiments. For the synthesis of per-*O*-silylated starting materials, see supporting information.

Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside 6: To a solution of per-*O*-silylated compound **3** (100 mg, 0.207 mmol) in dichloromethane (360 µL) was added benzaldehyde (63 µL, 0.621 mmol, 3 equiv) at room temperature. Then, triethylsilane (36 µL, 0.228 mmol, 1.1 equiv) and a solution of $FeCl_3$•$6H_2O$ in acetonitrile (90 µL of a 118 mM solution, 5 mol%) were added at 0°C. The reaction was stirred for 1h30 at room temperature. The mixture was then diluted with ethyl acetate and neutralized with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate: 9/1 to 1/1) to afford compound **6** (24.2 mg, 35%). Analytical data were in agreement with those previously reported. [20]

2-Benzyloxyethyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside 10: To a solution of persilylated glucopyranoside **7** (3 g, 5.126 mmol) in acetonitrile (10 mL) was added benzaldehyde (2.1 mL, 20.5 mmol, 4 equiv) at room temperature. Then, a solution of iron(III) chloride hexahydrate in acetonitrile (1 mL of a 256 mM solution in acetonitrile, 5 mol%) and thiethylsilane (2.5 mL, 15.4 mmol, 3 equiv) were added dropewise. The reaction was stirred for 3 hours at 50°C. The mixture was then diluted with ethyl acetate and neutralized with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted twice with ethyl acetate and the combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate: 9/1 to 1/1) to yield to the expected product **10** (1.706 g, 3.46 mmol, 68%) as a white solid. R_f = 0.67 (Ethyl acetate/cyclohexane: 75/25); $[\alpha_D]^{20}$ = + 46.3 (*c* 1, $CHCl_3$); mp: 92-94°C; ^{1}H NMR ($CDCl_3$, 300MHz) δ (ppm): 7.55-7.28 (m, 15H, H_{ar}), 5.60 (s, 1H, CHPh), 4.99 (d, 1H, $J_{1,2}$ = 3.7 Hz, H_1), 4.99 (d, 1H, *J* = 11.6 Hz, CH_2Ph), 4.86 (d, 1H, *J* = 11.6 Hz, CH_2Ph), 4.60 (s, 2H, CH_2Ph), 4.29 (dd, 1H, $J_{6a,6b.}$ = 10.3 Hz, $J_{6a,5}$ = 4.9 Hz, H $_{6a}$), 3.97 (ddd, 1H, $J_{5,4}$ = 9.1 Hz, $J_{5,6a}$ = 4.9 Hz, $J_{5,6b}$ = 10 Hz, H_5), 3.91 (m, 1H, O*C*H_2-CH_2), 3.87 (at, 1H, $J_{3,2}$ = $J_{3,4}$ = 9.1 Hz, H_3), 3.79-3.69 (m, 5H, H_{6b}, H_2, 1H of O*C*H_2-CH_2, C*H*$_2$-OBn), 3.66 (at, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.1 Hz, H_4), 2.37 (bs, 1H, OH); ^{13}C NMR ($CDCl_3$, 75MHz) δ (ppm): 138.6, 137.9, 137.4 (C_q-Ar), 128.9, 128.4, 128.3, 128.2, 127.9, 127.8, 127.6, 126.1 (CH-Ar), 101.3 (CHPh), 99.3 (C_1), 81.8 (C_4), 79.1 (C_3), 74.7, 73.3 (2 CH_2Ph), 72.7 (C_2), 69.0 (O*C*H_2-CH_2), 68.9 (C_6), 67.7 (*C*H_2OBn), 62.8 (C_5); ESI HRMS for $C_{29}H_{32}NaO_7$ $[M+Na]^+$: cacld 515.2040, found 515.2042.

2-Hydroxyphenyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside 11: To a solution of persilylated compound **8** (100 mg, 0.158 mmol) in dichloromethane (250 µL) was added benzaldehyde (64 µL, 0.632 mmol, 4 equiv) at room temperature. Then, triethylsilane (56 µL, 0.348 mmol, 2.2 equiv) and a solution of $FeCl_3$•$6H_2O$ in acetonitrile (63 µL of a 252 mM solution, 10 mol%) were added at 0°C. The reaction was stirred for 12 hours at room temperature. The mixture was then diluted with ethyl acetate and neutralized with water. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate: 9/1 to 1/1) to afford compound **11** (53 mg, 74%) as a white solid. R_f = 0.74 (cyclohexane/ethyl acetate: 6/4); $[\alpha_D]^{20}$ = + 123.7 (*c* 0.6, $CHCl_3$); mp: 185-187°C; ^{1}H NMR ($CDCl_3$, 360MHz) δ (ppm): 7.6-7.1 (m, 10H, H_{ar}), 7.06-6.8 (m, 4H, H_{ar}), 5.63 (s, 1H, CHPh), 5.13 (d, 1H, $J_{1,2}$ = 3.6 Hz, H_1), 5.06 (d, 1H, *J* = 11.4 Hz, CH_2Ph), 4.73 (d, 1H, *J* = 11.4 Hz, CH_2Ph), 4.41 (dd, 1H, $J_{6,5}$ = 5 Hz, $J_{6,6'}$ = 10.0 Hz, H_6), 4.28 (ddd, 1H, $J_{5,4}$ = 9.5 Hz, $J_{5,6'}$ = 10.0 Hz, $J_{5,6}$ = 5 Hz, H_5), 4.16 (at, 1H, $J_{2,3}$ = $J_{3,4}$ = 9.5 Hz, H_3), 3.84 (dd, 1H, $J_{2,1}$ = 3.6 Hz, $J_{2,3}$ = 9.5 Hz, H_2), 3.83 (at, 1H, $J_{6',5}$ = $J_{6,6'}$ = 10.0 Hz, $H_{6'}$), 3.76 (at, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.5 Hz, H_4); ^{13}C NMR ($CDCl_3$, 90MHz) δ (ppm): 148.4, 144.9, 138.1, 137.2 ($C_{q\text{-}Ar}$), 129.1, 128.6, 128.6, 128.3, 128.3, 128.2, 128.2, 128.1, 126.1, 126.1, 125.4, 120.2, 120.0, 116.4 (CH_{Ar}), 101.5 (CHPh), 101.4 (C_1), 82.0 (C_4), 78.1 (C_3), 75.1 (CH_2Ph), 71.7 (C_2), 68.8 (C_6), 63.7 (C_5); ESI HRMS for $C_{26}H_{26}NaO_7$ $[M+Na]^+$: cacld 473.1571, found 473.1583.

2-Hydroxyphenyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside 12: To a solution of persilylated compound **9** (100 mg, 0.158 mmol) in dichloromethane (250 µL) was added benzaldehyde (96 µL, 0.948 mmol, 6 equiv) at room temperature. Then, triethylsilane (77 µL, 0.474 mmol, 3 equiv) and a solution of $FeCl_3$•$6H_2O$ in acetonitrile (63 µL of a 252 mM solution, 10 mol%) were added at 0°C. The reaction was stirred for 12 hours at room temperature. The mixture was then diluted with ethyl acetate and neutralized with water. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate: 9/1 to 1/1) to afford compound **12** (48 mg, 67%) as a white solid. R_f = 0.59 (cyclohexane/ethyl acetate: 6/4); $[\alpha_D]^{20}$ = - 11.2 (*c* 1.6, $CHCl_3$); mp: 182-184°C; ^{1}H NMR ($CDCl_3$, 360MHz) δ (ppm): 7.53-7.30 (m, 10H, H_{ar}), 7.17-6.80 (m, 4H, H_{ar}), 5.62 (s, 1H, CHPh), 5.02 (d, 1H, *J* = 11.5 Hz,

CH_2Ph), 4.73 (d, 1H, J = 11.5 Hz, CH_2Ph), 4.69 (d, 1H, $J_{1,2}$ = 8.2 Hz, H_1), 4.38 (dd, 1H, $J_{6,5}$ = 5 Hz, $J_{6,6'}$ = 10.4 Hz, H_6), 3.87 (at, 1H, $J_{6',5}$ = $J_{6',6}$ = 10.4 Hz, $H_{6'}$), 3.82 (dd, 1H, $J_{2,1}$ = 8.2 Hz, $J_{2,3}$ = 9.1 Hz, H_2), 3.87 (at, 1H, $J_{4,3}$ = $J_{4,5}$ = 9.1 Hz, H_4), 3.70 (at, 1H, $J_{3,4}$ = $J_{3,2}$ = 9.1 Hz, H_3), 3.40 (ddd, 1H, $J_{4,5}$ = 9.1 Hz, $J_{5,6'}$ = 10.4 Hz, $J_{5,6}$ = 5 Hz, H_5). ^{13}C NMR ($CDCl_3$/CD_3OD, 90MHz) δ (ppm): 147.8, 144.9, 138.2, 137.1 ($C_{q\text{-}Ar}$), 129.1, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 127.8, 126.1, 125.2, 120.3, 120.1, 119.6, 116.6 (C_{Ar}), 104.5 (C_1), 101.3 (CHPh), 81.1 (C_4), 80.5 (C_3), 74.9 (CH_2Ph), 73.8 (C_2), 68.6 (C_6), 66.5 (C_5); ESI HRMS for $C_{26}H_{26}O_7$ $[M+Na]^+$: cacld 473.1571, found 473.1566.

Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl-(1→4)-2,6-di-*O*-benzyl-β-D-glucopyranoside 17: To a solution of per-*O*-silylated maltoside **14** (83 mg, 0.096 mmol) and benzaldehyde (59 µL, 0.576 mmol, 6 equiv) in dichloromethane (160 µL) at 0°C were added a solution of $FeCl_3$•$6H_2O$ in acetonitrile (40 µL of a 239 mM solution, 10 mol%) and triethylsilane (61 µL, 0.384 mmol, 4 equiv). The reaction was stirred overnight at room temperature. The mixture was then diluted with ethyl acetate and neutralized with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate: 70/30 to ethyl acetate 100%) to yield the expected product **17** as a colourless oil (27 mg, 40%). R_f = 0.53 (cyclohexane/ethyl acetate: 60/40); $[\alpha_D]^{20}$ = + 34 (*c* 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 7.51-7.27 (m, 20H, H_{ar}), 5.55 (s, 1H, CH-Ph), 5.16 (d, $J_{1',2'}$ = 3.6 Hz, 1H, $H_{1'}$), 4.96 (d, J = 11.5 Hz, 1H, CH_2Ph), 4.91 (d, J = 11.5 Hz, 1H, CH_2Ph), 4.76 (d, J = 11.5 Hz, 1H, CH_2Ph), 4.72 (d, J = 11.5 Hz, 1H, CH_2Ph), 4.62 (d, J = 12.0 Hz, 1H, CH_2Ph), 4.57 (d, J = 12.0 Hz, 1H, CH_2Ph), 4.31 (d, $J_{1,2}$ = 7.6 Hz, 1H, H_1), 4.12 (dd, $J_{6'b,5'}$ = 5.0 Hz, $J_{6'b,6'a}$ = 10.1 Hz, 1H, $H_{6'b}$), 3.92 (m, 1H, $H_{5'}$), 3.84 (at, $J_{3',2'}$ = $J_{3',4'}$ = 9.2 Hz, 1H, $H_{3'}$), 3.81 (dd, $J_{6b,6a}$ = 10.8 Hz, $J_{6b,5}$ = 1.8 Hz 1H, H_{6b}), 3.76-3.63 (m, 5H, $H_{3'}$, $H_{2'}$, H_{6a}, $H_{6'a}$, H_4), 3.62 (at, $J_{4',3'}$ = $J_{4',5'}$ = 9.2 Hz, 1H, $H_{4'}$), 3.57 (s, 3H, OCH_3), 3.46 (ddd, $J_{5,4}$ = 9.3 Hz, $J_{5,6a}$ = 4.3 Hz, $J_{5,6b}$ = 1.8 Hz 1H, H_5), 3.29 (dd, $J_{2,1}$ = 7.6 Hz, $J_{2,3}$ = 9.4 Hz, 1H, H_2); ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm): 138.6, 138.6, 138.3, 137.5 (4C, C_q-Ar), 129.1, 128.6, 128.6, 128.5, 128.4, 128.2, 128.1, 127.9, 127.8, 127.8, 126.2 (20C, CH-Ar), 104.5 (C_1), 102.0 ($C_{1'}$), 101.5 (CH-Ph), 82.0 ($C_{4'}$), 81.2 (C_4), 80.8 (C_2), 78.6 ($C_{3'}$), 76.2 (C_3), 74.9 (CH_2Ph), 74.5 (CH_2Ph), 74.4 (C_5), 73.8 (CH_2Ph), 73.3 ($C_{2'}$), 69.1, 69.0 (C_6 , $C_{6'}$), 63.9 ($C_{5'}$), 57.2 (OCH_3); ESI HRMS for $C_{41}H_{46}O_{11}$ $[M+Na]^+$: Calcd 737.2932, Found 737.2919.

Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl-(1→4)-6-*O*-benzyl-β-D-glucopyranoside 18: The derivative **18** was obtained in 30% yield as a by-product during the protocol described above. ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 7.50-7.26 (m, 20H, H_{ar}), 5.56 (s, 1H, CH-Ph), 5.16 (d, $J_{1',2'}$ = 4.0 Hz, 1H, $H_{1'}$), 4.99 (d, J = 11.5 Hz, 1H, CH_2Ph), 4.74 (d, J = 11.5 Hz, 1H, CH_2Ph), 4.63 (d, J = 12.0 Hz, 1H, CH_2Ph), 4.57 (d, J = 12.0 Hz, 1H, CH_2Ph), 4.22 (d, $J_{1,2}$ = 7.8 Hz, 1H, H_1), 4.12 (dd, $J_{6'b,6'a}$ = 10.0 Hz, $J_{6'b,5'}$ = 4.8 Hz, 1H, $H_{6'a}$), 3.92 (ddd, $J_{5',6'b}$ = $J_{5',4'}$ = 10.0 Hz, $J_{5',6'a}$ = 4.8 Hz, , 1H, $H_{5'}$), 3.87 (t, $J_{3',2'}$ = $J_{3',4'}$ = 9.3 Hz, 1H, $H_{3'}$), 3.82 (dd, $J_{6a,6b}$ = 10.6 Hz, $J_{6a,5}$ = 1.7 Hz, 1H, H_{6a}), 3.75 (dd, $J_{2',3'}$ = 9.3 Hz, $J_{2',1'}$ = 4.0 Hz, 1H, $H_{2'}$), 3.73-3.63 (m, 4H, H_{6b}, H_3, $H_{6'b}$ & $H_{4'}$), 3.61 (at, $J_{4,3}$ = $J_{4,5}$ = 9.1 Hz, 1H, H_4), 3.53 (s, 3H, OCH_3), 3.51 (ddd, $J_{5,4}$ = 9.1 Hz, $J_{5,6b}$ = 4.8 Hz, $J_{5,6a}$ = 1.7 Hz, 1H, H_5), 3.43 (dd, $J_{2,1}$ = 7.8 Hz, $J_{2,3}$ = 9.1 Hz, 1H, H_2); ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm): 138.6, 138.2, 137.4 (3C, C_q-Ar), 129.1, 128.5, 128.3, 128.1, 127.9, 127.8, 127.7, 126.1 (15C, CH-Ar), 103.6 (C_1), 102.1 ($C_{1'}$), 101.4 (CH-Ph), 81.9 ($C_{4'}$), 81.5 (C_4), 78.6 ($C_{3'}$), 76.5 (C_3), 74.9 (Ph-CH_2)-$C_{3'}$, 74.5 (C_5), 73.7 (Ph-CH_2)-C_6, 73.2 (C_2), 72.8 ($C_{2'}$), 69.2 (C_6), 68.9 ($C_{6'}$), 63.8 ($C_{5'}$), 57.2 (O-CH_3); ESI HRMS for $C_{34}H_{40}O_{11}$ $[M+Na]^+$: Calcd 647.2468, Found 647.2452.

Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranosyl-(1→4)-3,6-di-*O*-benzyl-α-D-glucopyranoside 19: To a solution of per-*O*-silylated cellobioside **15** (163 mg, 0.189 mmol) and benzaldehyde (153 µL, 1.51 mmol, 8 equiv) in dichloromethane (150 µL) at 0°C were added a solution of $FeCl_3$·$6H_2O$ in acetonitrile (40 µL of a 697 mM solution, 15 mol%) and triethylsilane (120 µL, 0.756 mmol, 4 equiv). The reaction was stirred overnight at room temperature. The mixture was then diluted with ethyl acetate and neutralized with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate: 70/30 to ethyl acetate 100%) to give the expected product **19** a colourless oil (41 mg, 31%). R_f = 0.16 (cyclohexane/ethyl acetate: 60/40); ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 7.50-7.26 (m, 20H, H_{ar}), 5.49 (s, 1H, CHPh), 4.96 (d, J = 11.0 Hz, 1H, CH_2-Ph), 4.95 (d, J = 11.5 Hz, 1H, CH_2-Ph), 4.80 (d, $J_{1,2}$ = 3.2 Hz, 1H, H_1), 4.79 (d, J = 11.0 Hz, 1H, CH_2-Ph), 4.77 (d, J = 11.5 Hz, 1H, CH_2-Ph), 4.72 (d, J = 11.9 Hz, 1H, CH_2-Ph), 4.54 (d, $J_{1',2'}$ = 7.9 Hz, 1H, $H_{1'}$), 4.52 (d, J = 11.9 Hz, 1H, CH_2-Ph), 4.09 (dd, $J_{6'a,5'}$ = 5.0 Hz, $J_{6'a,6'b}$ = 10.4 Hz, 1H, $H_{6'a}$), 4.05-3.97 (m, 2H, H_{6a}, H_4), 3.80 (m, 1H, H_5), 3.76-3.70 (m, 3H, H_{6b}, H_2, H_3), 3.62-3.45(m, 4H, $H_{6'b}$, $H_{4'}$, $H_{3'}$, $H_{2'}$), 3.43 (s, 3H, OCH_3), 3.14 (m, 1H, $H_{5'}$), 2.92 (bs, 1H, OH), 2.26 (bs, 1H, OH); ^{13}C NMR ($CDCl_3$, 90 MHz) δ (ppm): 139.1, 138.6, 137.9, 137.5 (C_q-Ar), 129.1, 128.6, 128.6, 128.5, 128.4, 128.3, 128.1, 127.9, 127.7, 127.2, 126.2 (20C, CH-Ar), 103.4 ($C_{1'}$), 101.4 (CH-Ph), 99.4 (C_1), 81.7 (C_3), 81.5 ($C_{4'}$), 80.5 ($C_{3'}$), 76.7 (C_4), 75.2 ($C_{2'}$), 75.1 (CH_2-Ph), 74.6 (CH_2-Ph), 73.8 (CH_2-Ph), 72.6 (C_2), 70.3 (C_5), 68.8 ($C_{6'}$), 68.5 (C_6), 66.5 ($C_{5'}$), 55.4 (O-CH_3); ESI HRMS for $C_{41}H_{46}O_{11}$ $[M+Na]^+$: Calcd 737.2938, Found 737.2935.

Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl-(1→6)-3-*O*-benzyl-α-D-glucopyranoside 22: To a solution of per-*O*-silylated isomaltoside **20** (100 mg, 0.116 mmol) and benzaldehyde (47 µL, 0.464 mmol, 4 equiv) in dichloromethane (200 µL) at 0°C were added a solution of $FeCl_3$·$6H_2O$ in acetonitrile (50 µL of a 460 mM solution, 10 mol%) and triethylsilane (41 µL, 0.255 mmol, 2.2 equiv). The reaction was stirred overnight at room temperature. The mixture was then diluted with ethyl acetate and neutralized with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate: 9/1 to 1/1) to give the expected product **22** a colourless oil (33 mg, 45%). R_f = 0.80 (ethyl acetate); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.50-7.28 (m, 15H, H_{ar}), 5.56 (s, 1H, CH-Ph), 5.00 (d, J = 11.5 Hz, 1H, CH_2-Ph), 4.96 (d, J = 11.9 Hz, 1H, CH_2-Ph), 4.94 (d, $J_{1',2'}$ = 3.2 Hz, 1H, $H_{1'}$), 4.79 (d, J = 11.5 Hz, 1H, CH_2-Ph), 4.77 (d, J = 11.9 Hz, 1H, CH_2-Ph), 4.74 (d, $J_{1,2}$ = 3.2 Hz, 1H, H_1), 4.28 (dd, $J_{6'a,5'}$ = 4.7 Hz, $J_{6'a,6'b}$ = 10.0 Hz, 1H, $H_{6'a}$), 4.00 (dd, $J_{6a,5}$ = 4.5 Hz, $J_{6a,6b}$ = 10.4 Hz, 1H, H_{6a}), 3.92 (m, 1H, $H_{5'}$), 3.81 (at, $J_{3',2'}$ = $J_{3',4'}$ = 9.2 Hz, 1H, $H_{3'}$), 3.80-3.53 (m, 8H, H_2, H_3, H_4, H_5, H_{6b}, $H_{2'}$, $H_{4'}$, $H_{6b'}$), 3.42 (s, 3H, OCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 138.6, 138.5, 137.3, (C_q-Ar), 129.0, 128.7, 128.6, 128.6, 128.4, 128.4, 128.3, 128.1, 128.1, 128.0, 128.0, 127.8, 127.7, 126.0 (18C, CH-Ar), 101.3 (CH-Ph), 99.5 (C_1), 99.2 ($C_{1'}$), 82.7 (C_3), 81.8 ($C_{4'}$), 79.0 ($C_{3'}$), 75.1 (CH_2Ph), 74.8 (CH_2Ph), 72.7 (C_5), 72.4 ($C_{2'}$), 70.7 (C_4), 69.6 (C_2), 69.0 ($C_{6'}$), 68.0 (C_6), 62.9 ($C_{5'}$), 55.5 (OCH_3); ESI HRMS for $C_{34}H_{40}O_{11}$ $[M+Na]^+$: Calcd 647.2468, Found 647.2483.

Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranosyl-(1→6)-3-*O*-benzyl-α-D-glucopyranoside 23: To a solution of per-*O*-silylated gentiobioside **21** (100 mg, 0.116 mmol) and benzaldehyde (47 µL, 0.464 mmol, 4 equiv) in dichloromethane (200 µL) at 0°C were added a solution of $FeCl_3$·$6H_2O$ in acetonitrile (50 µL of a 460 mM solution, 10 mol%) and triethylsilane (41 µL, 0.255 mmol, 2.2 equiv). The reaction was stirred overnight at room temperature. The mixture was then diluted with ethyl acetate and neutralized with a saturated aqueous $NaHCO_3$ solution. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under

vacuum. The crude product was purified by silica gel chromatography (cyclohexane/ethyl acetate: 9/1 to 1/1) to give the expected product **23** a colourless oil (24 mg, 33%). R_f = 0.78 (ethyl acetate); ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 7.50-7.27 (m, 15H, H_{ar}), 5.55 (s, 1H, CH-Ph), 4.97 (d, J = 11.6 Hz, 1H, CH_2-Ph), 4.97 (d, J = 11.8 Hz, 1H, CH_2-Ph), 4.82 (d, J = 11.6 Hz, 1H, CH_2-Ph), 4.78 (d, $J_{1,2}$ = 3.0 Hz, 1H, H_1), 4.76 (d, J = 11.8 Hz, 1H, CH_2-Ph), 4.40 (d, $J_{1',2'}$ = 7.3 Hz, 1H, $H_{1'}$), 4.33 (dd, $J_{6'a,5'}$ = 4.8 Hz, $J_{6'a,6'b}$ = 10.4 Hz, 1H, $H_{6'a}$), 4.10 (dd, $J_{6a,5}$ = 1.8 Hz, $J_{6a,6b}$ = 10.7 Hz, 1H, H_{6a}), 3.82 (m, 1H, H_{6a}), 3.79 (at, $J_{6'b,5'}$ = $J_{6'b,6'a}$ = 10.4 Hz, 1H, $H_{6'b}$), 3.75-3.64 (m, 4H, H_2, H_4, H_5, $H_{4'}$), 3.63-3.52 (m, 3H, H_3, $H_{3'}$, $H_{2'}$), 3.41 (s, 3H, OCH_3), 3.40 (m, 1H, $H_{5'}$); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 138.8, 138.4, 137.4 (Cq-Ar), 129.1, 128.7, 128.6, 128.4, 128.2, 128.1, 128.0, 128.0, 126.2 (15C, CH-Ar), 104.0 ($C_{1'}$), 101.4 (CHPh), 99.7 (C_1), 82.7 (C_3), 81.4 ($C_{4'}$), 80.4 ($C_{3'}$), 75.1 (CH_2-Ph), 74.7 (CH_2-Ph), 74.4 ($C_{2'}$), 72.8 (C_2), 70.3 (C_5), 70.0 (C_4), 69.7 (C_6), 68.8 ($C_{6'}$), 66.7 ($C_{5'}$), 55.6 (OCH_3); ESI HRMS for $C_{34}H_{40}O_{11}$ [M+Na]$^+$: Calcd 647.2468, Found 647.2467.

Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranosyl-(1→4)-6-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,6-di-*O*-benzyl-β-D-glucopyranoside 25: To a solution of persilylated compound **24** (74 mg, 0.0596 mmol) in acetonitrile (120 µL) was added benzaldehyde (90 µL, 0.895 mmol, 15 equiv) at room temperature. Then, triethylsilane (77 µL, 0.477 mmol, 8 equiv) and a solution of $FeCl_3$•$6H_2O$ in acetonitrile (30 µL of a 296 mM solution, 15 mol%) were added at 0°C. The reaction was stirred overnight at 50°C. The mixture was then diluted with ethyl acetate and neutralized with water. The aqueous layer was extracted twice with ethyl acetate. The combined organic layers were dried over Na_2SO_4, filtered and concentrated under vacuum. The crude product was purified by silica gel chromatography (dichloromethane/methanol: 100/1 then 100/5 then 1/1) to afford compound **25** (26 mg, 45%). R_f = 0.51 (dichloromethane/methanol: 95/5); $[\alpha_D]^{20}$ = + 52.6 (*c* 1.1, $CHCl_3$); mp: 69-71 °C; ^{1}H NMR ($CDCl_3$, 360 MHz) δ (ppm): 7.50-7.20 (m, 25H, H_{ar}), 5.56 (s, 1H, CHPh), 5.13 (d, 1H, $J_{1'',2''}$ = 3.6 Hz, $H_{1''}$), 5.11 (d, 1H, $J_{1',2'}$ = 3.6 Hz, $H_{1'}$), 4.99 (d, 1H, J = 11.4 Hz, CH_2Ph), 4.91 (d, 1H, J = 11.4 Hz, CH_2Ph), 4.76 (d, 1H, J = 11.4 Hz, CH_2Ph), 4.72 (d, 1H, J = 11.4 Hz, CH_2Ph), 4.64 (d, 1H, J = 12.3 Hz, CH_2Ph), 4.55 (d, 1H, J = 11.8 Hz, CH_2Ph), 4.50 (d, 1H, J = 11.8 Hz, CH_2Ph), 4.48 (d, 1H, J = 12.3 Hz, CH_2Ph), 4.31 (d, 1H, $J_{1,2}$ = 7.7 Hz, H_1), 4.10 (dd, 1H, $J_{6''a,6''b}$ = 10.0 Hz, $J_{6''a,5}$ = 4.5 Hz, $H_{6''a}$), 3.95-3.79 (m, 5H, H_{6a}, $H_{3'}$, $H_{5'}$, $H_{3''}$, $H_{5''}$), 3.78-3.66 (m, 5H, H_3, H_{6b}, $H_{6'a}$, $H_{2''}$, $H_{6''a}$) 3.65-3.55 (m, 5H, H_4, $H_{2'}$, $H_{4'}$, $H_{6b'}$, $H_{4''}$) 3.56 (s, 3H, OCH_3), 3.53-3.44 (m, 1H, H_5), 3.29 (dd, 1H, $J_{2,3}$ = 9.1 Hz, $J_{2,1}$ = 7.7 Hz, H_2); ^{13}C NMR (CD_3OD, 75 MHz) δ (ppm): 140.2, 139.8, 139.7, 139.6, 139.3 (5C, $C_{q\text{-}ar}$), 134.1, 130.8, 130.1, 129.5, 129.3, 129.1, 129.0, 128.8, 128.6, 127.5 (25C, C_{ar}), 105.7 (C_1), 103.6 ($C_{1''}$), 102.8 ($C_{1'}$), 102.7 (CHPh), 83.1 ($C_{4''}$), 82.7 ($C_{2'}$), 81.6 ($C_{2''}$), 81.4 (C_2), 80.1 ($C_{3''}$), 77.6 (C_3), 75.8, 75.5, 75.0, 74.4 (4 CH_2Ph), 75.4, (C_5), 75.1, 74,4, 73.8, 72.2 (C_4, $C_{3'}$, $C_{4'}$, $C_{5'}$), 70.4, 70.4, 69.9 (C_6, $C_{6'}$, $C_{6''}$), 65.1 ($C_{5''}$), 57.5 (OCH_3); ESI HRMS for $C_{54}H_{62}NaO_{16}$ [M+Na]$^+$: cacld 989.3936, found 989.3970.

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Keywords: carbohydrates; iron(III) chloride; regioselective protection; tandem catalysis; one-pot procedure

[1] Selected reviews: a) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115-136; b) S. E. Denmark, A. Thorarensen, *Chem. Rev.* **1996**, *96*, 137-165; c) P. J. Parsons, C. S. Penkett, A. J. Shell, *Chem. Rev.* **1996**, *96*, 195-206; d) J.-C. Wasilke, S. J. Obrey, R. T. Baker, G. C Bazan, *Chem. Rev.* **2005**, *105*, 1001-1020; e) K. C. Nicolaou, D. J. Edmonds, P. G. Bulger, *Angew. Chem.* **2006**, *118*, 7292-7344; *Angew. Chem. Int. Ed.* **2006**, *45*, 7134-7186; f) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590-1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570-1581; g) H. Pellissier, *Chem. Rev.* **2013**, *113*, 442-524.

[2] a) D. E. Fogg, E. N. dos Santos, *Coord. Chem. Rev*. **2004**, *248*, 2365-2379 ; b) N. Shindoh, Y. Takemoto, K. Takasu, *Chem. Eur. J*. **2009**, *15*, 12168-12179;

[3] A. Français, D. Urban, J.-M. Beau, *Angew. Chem*. **2007**, *119*, 8816-8819; *Angew. Chem. Int. Ed*. **2007**, *46*, 8662-8665.

[4] A.-T. Tran, R.A. Jones, J. Pastor, J. Boisson, N. Smith, M. C. Galan, *Adv. Synth. Catal.* **2011**, *353*, 2593-2598.

[5] a) C.-C. Wang, J.-C. Lee, S.-Y. Luo, S. S. Kulkarni, Y.-W. Huang, C.-C. Lee, K.-L. Chang, S.-C. Hung, *Nature* **2007**, *446*, 896-899; b) C.-C. Wang, S. S. Kulkarni, J.-C. Lee, S.-Y. Luo, S.-C. Hung, *Nat. Protoc*. **2008**, *3*, 97-113; c) K.-L. Chang, M. M. L. Zulueta, X.-A. Lu, Y.-Q. Zhong, S.-C. Hung, *J. Org. Chem*. **2010**, *75*, 7424-7427; d) P. S. Patil, C.-C. Lee, Y.-W. Huang, M. M. L. Zulueta, S.-C. Hung, *Org. Biomol. Chem*. **2013**, *11*, 2605-2612; e) T.-Y. Huang, M. M. L. Zulueta, S.-C. Hung, *Org. Biomol. Chem*. **2014**, *12*, 376-382.

[6] a) R. Enugala, L. C. R. Carvalho, M. M. B. Marques, *Synlett* **2010**, 2711-2716; b) A. A. Joseph, V. P. Verma, X.-Y. Liu, C.-H. Wu, V. M. Dhurandhare, C.-C. Wang, *Eur. J. Org. Chem.* **2012**, 744-753.

[7] Y. Bourdreux, A. Lemétais, D. Urban, J.-M. Beau, *Chem. Commun.* **2011**, *47*, 2146-2148.

[8] G. Despras, D. Urban, B. Vauzeilles, J.-M. Beau, *Chem. Commun*. **2014**, *50*, 1067-1069.

[9] a) S. David, A. Thieffry, A. Forchioni, *Tetrahedron Lett*. **1981**, *22*, 2647-2650; b) H. Dong, Y. X. Zhou, X. L. Pan, F. C. Cui, W. Liu, J. Y. Liu, O. Ramström, *J. Org. Chem*. **2012**, *77*, 1457-1467; c) Y. X. Zhou, J. Y. Li, Y. J. Zhan, Z. C. Pei, H. Dong, *Tetrahedron* **2013**, *69*, 2693-2700; d) H. F. Xu, Y. C. Lu, Y. X. Zhou, B. Ren, Y. X. Pei, H. Dong, Z. C. Pei, *Adv. Synth. Catal.* **2014**, *356*, 1735-1740; e) M. Giordano, A. Iadonisi, *J. Org. Chem*. **2014**, *79*, 213-222; f) H. Xu, B. Ren, W. Zhao, X. Xin, Y. Lu, Y. Pei, H. Dong, Z. Pei, *Tetrahedron* **2016**, *72*, 3490-3499.

[10] a) L. N. Chan, M. S. Taylor, *Org. Lett*. **2011**, *13*, 3090-3093; b) D. Lee, C. L. Williamson, L. N. Chan, M. S. Taylor, *J. Am. Chem. Soc*. **2012**, *134*, 8260-8267.

[11] a) A. Bouzide, G. Sauvé, *Tetrahedron Lett*. **1997**, *38*, 5945-5948; b) S. Malik, V. A. Dixit, P. V. Bharatam, K. P. R. Kartha, *Carbohydr. Res.* **2010**, *345*, 559-564.

[12] U. B. Gangadharmath, A. V. Demchenko, *Synlett* **2004**, 2191-2193.

[13] B. Ren, O. Ramström, Q. Zhang, J. Ge, H. Dong, *Chem. Eur. J.* **2016**, *22*, 2481-2486.

[14] For applications of $FeCl_3$•$6H_2O$-catalyzed tandem protection of trehalose in the selective synthesis of glycolipids, see: a) A. Lemétais, Y. Bourdreux, P. Lesot, J. Farjon, J.-M. Beau, *J. Org. Chem*. **2013**, *78*, 7648-7657; b) B. Gau, A. Lemétais, M. Lepore, L. F. Garcia-Alles, Y. Bourdreux, L. Mori, M. Gilleron, G. De Libero, G. Puzo, J.-M. Beau, J. Prandi, *ChemBioChem* **2013**, *14*, 2413–2417; c) J.-M. Beau, Y. Bourdreux, F.-D. Boyer, S. Norsikian, D. Urban, G. Doisneau, B. Vauzeilles, A. Gouasmat, A. Lemétais, A. Mathieu, J.-F. Soulé, A. Stévenin and A. Xolin, in *Carbohydrate Chemistry*, The Royal Society of Chemistry, 2014, vol. 40, pp. 118-139.

[15] Wang and coworkers performed a TMSOTf-catalyzed tandem protection of β-*S*-tolyl maltoside (with only 3.3 equiv of PhCHO) and obtained a di-*O*-benzylated derivative at C-3 of the terminal unit and at C-6 of the reducing unit. See ref 6b.

[16] β-OMe cellobioside was also evaluated, but only complex mixtures were obtained, highlighting the strong influence of the glycosidic bond configuration on the benzylation regioselectivity.

[17] Less polar mixtures of *O*-benzylated derivatives were also detected by TLC.

[18] T. Tsunoda, M. Suzuki, R. Noyori, *Tetrahedron Lett*. **1980**, *21*, 1357-1358

[19] a) C.-C. Wang, J.-C. Lee, S.-Y. Luo, H.-F. Fan, C.-L. Pai, W.-C. Yang, L.-D. Lu, S.-C. Hung, *Angew. Chem.* **2002**, *114*, 2466-2468; *Angew. Chem. Int. Ed*. **2002**, *41*, 2360-2362; b) W.-C. Yang, X.-A. Lu, S. S. Kulkarni, S.-C. Hung, *Tetrahedron Lett*. **2003**, *44*, 7837-7840.

[20] J. G. M. van der Ven, J. C. H. M.Wijkmans, J. P. Kamerling, *Carbohydr. Res*. **1994**, *253*, 121-139.

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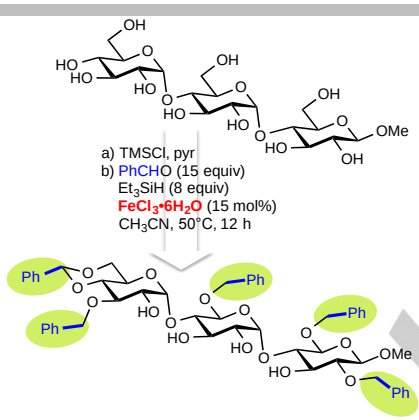

Regioselective Protection

Alexandra Gouasmat, Aurélie Lemétais, Julien Solles, Yann Bourdreux and Jean-Marie Beau**

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Catalytic Iron(III) Chloride Mediates Site-Selective Protection of Mono- and Disaccharides and one Trisaccharide