NIS/TFA

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Note

NIS/TFA: a general method for hydrolyzing thioglycosides

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Abstract—A variety of thioglycosides are chemoselectively hydrolyzed to the corresponding 1-hydroxy glycosides using equimolar amounts of NIS/TFA as promoter systems.

Keywords: Thioglycosides; NIS; Hydrolysis; Hemiacetal

Thioglycosides are versatile building blocks in synthetic carbohydrate chemistry. Installing an aryl- or alkylthio functionality at the anomeric center of most common monosaccharides is easily accomplished, starting from the corresponding peracylated sugars.[1,2] Anomeric thio functionalities are compatible with many protective group manipulations inherent to carbohydrate synthesis practice, thereby allowing their introduction at an early stage of an oligosaccharide synthesis route. Thioglycosides can be activated by a number of reagent systems, the most prominent of which are the *N*-iodosuccinimide/trimethylsilyl trifluoromethanesulfonic acid (NIS/TMSOTf)[3] and the sulfoxide (both 1-benzenesulfinylpiperidine and diphenylsulfoxide)/triflic anhydride reagent systems.[4,5] As such, thioglycosides are often employed as carbohydrate donors in oligosaccharide and glycoconjugate synthesis.[6] A further advantageous property of thioglycosides, enabling their use in chemoselective glycosylation strategies, is their relative inertness toward activating systems other than those directed to anomeric thio functions.[7]

A relative shortcoming of anomeric thio functionalities is the difficulty often encountered in their removal. The numerous reported procedures for the hydrolysis of thioglycosides include heavy metal salts, *N*-bromosuccinimide (NBS) or NIS in wet acetone,[8–10] $AgNO_3$ in wet acetone,[11,12] NBS/$NaHCO_3$ (aq) or $CaCO_3$ (aq) in THF,[6] NBS/HCl,[13] $^nBu_4NIO_4$/$TrB(C_6H_5)_4$, $^nBu_4NIO_4$/trifluoromethanesulfonic acid (TfOH), $^nBu_4NIO_4$/$HClO_4$,[14] $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$–$H_2O_2$ with $HClO_4$/NH_4Br,[15] V_2O_5–H_2O_2/NH_4Br,[16] chloramine-T[17] and NIS/TfOH.[18] In our experience none of these methods is fail-safe in their application on different thioglycosides and it is a common practice in our laboratory to select and try a few on a given thioglycoside to achieve the desired anomeric deblocking. This is unfortunate, because it limits the use of thio functionalities as anomeric protecting groups. Based on their excellent glycosylation properties, one would think that thioglycosides are easily hydrolysable by executing a standard thioglycoside mediated glycosylation protocol, but with H_2O as an acceptor instead of an acceptor glycoside. With this reasoning in mind, we set out to study the NIS mediated hydrolysis under acidic conditions of a set of diversely functionalized thioglycosides.

In an initial set of experiments, phenyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (**1**) was treated with 1 equiv NIS in wet methylene chloride ($CH_2Cl_2/H_2O = 10{:}1$) in the presence of either a catalytic amount of TfOH or an equimolar amount of trifluoroacetic acid (TFA) (Scheme 1).

Both reaction mixtures were stirred for 30 min at 0 °C and subsequently quenched by the addition of an aqueous solution of sodium thiosulfate. The protocol involving triflic acid proved to be unproductive: next to trace

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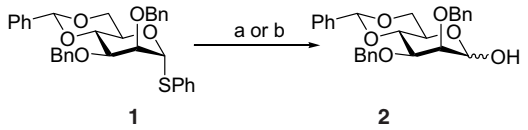


1 2

Scheme 1. Hydrolysis of phenyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-1-thio-α-D-mannopyranoside (**1**). Reagents and conditions: (a) NIS, TfOH (cat), CH_2Cl_2, 0 °C, 30 min, traces of **2**; (b) NIS, TFA, CH_2Cl_2, 0 °C, 30 min, 75% of **2**.

amounts of the desired hydrolysis product both self-condensation products and benzylidene cleavage products were formed, as detected by LC–MS. In contrast, the NIS/TFA conditions afforded the target mannose derivative **2** in 75% yield (Table 1, entry 1). The outcome of these two experiments led us to make several observations. First, the conditions involving catalytic triflic acid are too acidic for the benzylidene protective group to withstand. Second, the occurrence of self-condensation in the TfOH experiment, but not in the TFA experiment, indicates the existence of two separate reaction pathways for the two processes. It should be noted here that apart from the nature and equivalents of acid used, the reaction conditions (concentration, excess of water, temperature, running time) were identical in both experiments. One possible explanation for the observed difference in product formation is the involvement of the anomeric trifluoroacetate as intermediate in the second experiment.

Table 1. Hydrolyses of thioglycosides using NIS/TFA[a]

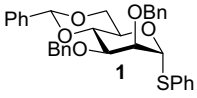
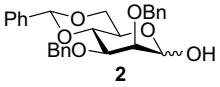
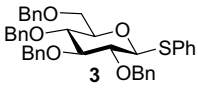
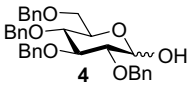
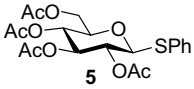
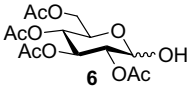
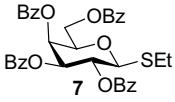
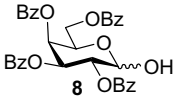
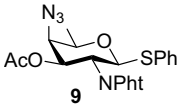
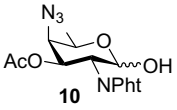
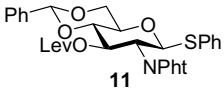
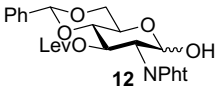
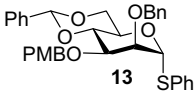
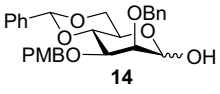
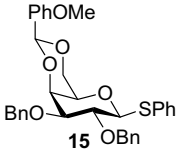
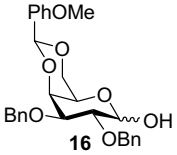
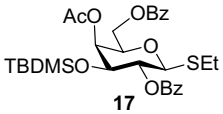
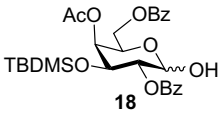
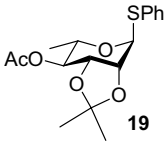
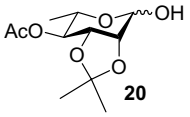
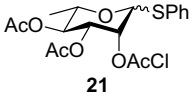
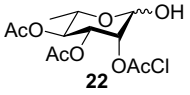
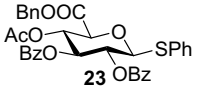
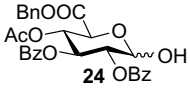
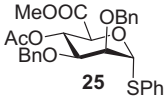
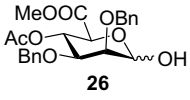
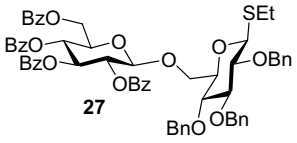
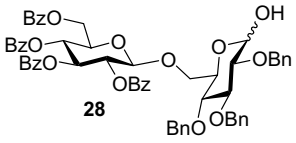
Entry	Thioglycoside	Product	Time (min)	Yield (%)
1	 **1**	 **2**	30	75
2	 **3**	 **4**	30	90
3	 **5**	 **6**	30	88
4	 **7**	 **8**	60	92
5	 **9**	 **10**	15	79
6	 **11**	 **12**	120	85
7	 **13**	 **14**	30	80
8	 **15**	 **16**	20	70
9	 **17**	 **18**	40	85

Table 1 (*continued*)

Entry	Thioglycoside	Product	Time (min)	Yield (%)
10	 **19**	 **20**	30	83
11	 **21**	 **22**	30	86
12	 **23**	 **24**	60	82
13	 **25**	 **26**	30	74
14	 **27**	 **28**	30	70

[a] NIS/TFA equimolar, CH_2Cl_2/H_2O (10/1) 0.1 M, at 0 °C.

The outcome of the NIS/TFA mediated hydrolysis of a diverse set of thioglycosides is presented in Table 1. Invariably, productive yields (70–90%) were obtained irrespective of the nature of the starting thioglycoside concerning its substitution pattern and the nature of the protective groups. Most reactions went to completion within 30 min at 0 °C, as monitored by TLC. In some instances a somewhat prolonged reaction time was required, as indicated in the table. Important to notice is the number of different protective groups that are compatible with the hydrolysis conditions, ranging from acid labile (benzylidene, silyl ether, *p*-methoxybenzyl, isopropylidene) to base-labile ester functionalities and including standard amine protective groups (azide, phthaloyl). Moreover, the nature of the parent glycoside (glucose, mannose, galactose, rhamnose) including deoxysugars and uronic acid derivatives appear to have no influence on the outcome of the anomeric deprotection. In the case of thiomannuronic acid (Table 1, entry 13), a prolonged quenching time had to be employed. In the first attempt, we isolated the corresponding anomeric trifluoroacetate as the main product. This result is of interest in itself, as it points toward the occurrence of anomeric trifluoroacetates as important reaction intermediates. The last entry involving the anomeric deblocking of a thiodisaccharide (Table 1, entry 14) holds promise for the future use of thio functionalities as temporary anomeric protective groups in the construction of oligosaccharides.

Having established the use of the NIS/TFA combination of reagents in the hydrolysis of a number of thioglycosides, we arrived at the hypothesis that the NIS/TFA combination of reagents can effectuate an efficient glycosylation of thioglycoside donors.[19,20] Accordingly, in a pilot experiment we treated ethyl 2,3,4,6-tetra-*O*-benzoyl-1-thio-β-D-galactopyranoside (**7**) with equimolar amounts of NIS and TFA at 0 °C and added acceptor glycoside methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside. After workup, only traces of disaccharide could be obtained. Instead, acceptor and hydrolyzed donor were isolated, indicating that NIS/TFA is not a useful alternative thioglycoside activating system for oligosaccharide synthesis purposes.

In conclusion, we have demonstrated an efficient and generally applicable protocol for the hydrolysis of thioglycosides, which nicely complements existing literature procedures.

1. Experimental

1.1. General methods

CH_2Cl_2 was heated at reflux over P_2O_5 and distilled before use. Trifluoroacetic acid was treated with trifluoroacetic anhydride and distilled. All chemicals (Acros, Fluka, Merck, Schleicher & Schue) were used as received. Column chromatography was performed on

Merck silica gel 60 (0.040–0.063 mm). TLC analysis was conducted on DC-fertigfolien (Schleicher & Schuell, F1500, LS254) or HPTLC aluminum sheets (Merck, silica gel 60, F245). Compounds were visualized by UV absorption (245 nm), by spraying with 20% H_2SO_4 in ethanol or with a solution of $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ 25 g/L, $(NH_4)_4Ce(SO_4)_4{\cdot}2H_2O$ 10 g/L, 10% H_2SO_4 in H_2O followed by charring at ±140 °C. ^1H and ^{13}C NMR spectra were recorded with a Bruker AV 400 (400 and 100 MHz, respectively), AV 500 (500 and 125 MHz, respectively) or a Bruker DMX 600 (600 and 150 MHz, respectively). NMR spectra were recorded in $CDCl_3$ with chemical shift (δ) relative to tetramethylsilane unless stated otherwise. High resolution mass spectra were recorded on a LTQ-FT (thermoelectron). IR spectra were recorded on a Shimadzu FTIR-8300 and are reported in cm^{-1}.

1.2. General procedure

To a vigorously stirred solution of thioglycoside (0.50 mmol) in CH_2Cl_2 (5 mL) and H_2O (0.5 mL) was added at 0 °C NIS (112 mg, 0.50 mmol) and TFA (39 μL, 0.50 mmol). After TLC analysis showed complete consumption of starting material, the reaction was quenched with satd aq $Na_2S_2O_3$ (unless noted otherwise) and washed with satd aq $NaHCO_3$. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. Purification by column chromatography yielded the corresponding 1-hydroxy glycosides.

1.2.1. 2,3-Di-*O*-benzyl-4,6-*O*-benzylidene-D-mannopyranose (2).[10] The reaction mixture was quenched after 30 min. Column chromatography yielded **2** (0.166 g, 75%) as a colorless oil. IR (neat): 1028, 1093, 1373, 2870 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.09 (d, 1H, $J = 3.6$ Hz, OH), 3.79 (br s, 1H, H-2), 3.85 (d, 1H, $J = 10.1$ Hz, H-6), 3.99 (m, 2H, H-5, H-3), 4.22 (m, 2H, H-4, H-6), 4.64 (d, 1H, $J = 12.2$ Hz, C*H*HBn), 4.68 (d, 1H, $J = 12.2$ Hz, C*H*HBn), 4.78 (d, 1H, $J = 12.1$ Hz, CH*H*Bn), 4.81 (d, 1H, $J = 12.1$ Hz, CH*H*Bn), 5.12 (d, 1H, $J = 2.1$ Hz, H-1), 5.63 (s, 1H, C*H*Ph), 7.24–7.50 (m, 15H, H_{arom}); ^{13}C NMR (125 MHz): δ 64.2 (*C*-5), 68.8 (*C*-6), 73.1 (*C*H_2Bn), 73.5 (*C*H_2Bn), 75.8 (*C*-3), 76.7 (*C*-2), 79.1 (*C*-4), 94.1 (*C*-1), 101.4 (*C*HPh), 126.0–129.1 (*C*H_{arom}), 137.5, 138.1, 138.5 (C_q Bn, C_q CHPh); HRMS *m*/*z* calcd for $C_{27}H_{28}O_6Na$ $[M+Na]^+$: 471.17781. Found 471.17779.

1.2.2. 2,3,4,6-Tetra-*O*-benzyl-D-glucopyranose (4).[9] The reaction mixture was quenched after 30 min by addition of Et_3N after which satd aq $Na_2S_2O_3$ was added. Column chromatography yielded **4** (0.243 g, 90%) as a white solid. IR (neat): 1026, 1045, 1074, 1085, 1145, 1356, 1452, 1497 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.26 (br s, 1H, OH), 3.54–3.70 (m, 4H, H-6, H-6, H-2), 3.98 (t, 1H, $J = 9.3$ Hz, H-3), 4.03 (d, 1H, $J = 8.4$ Hz, H-5), 4.46–4.50 (m, 2H, C*H*HBn), 4.58 (d, 1H, $J = 12.2$ Hz, C*H*HBn), 4.68 (d, 1H, $J = 11.9$ Hz, C*H*HBn), 4.75 (d, 1H, $J = 11.8$ Hz, CH*H*Bn), 4.80 (m, 2H, CH*H*Bn), 4.95 (d, 1H, $J = 10.9$ Hz, CH*H*Bn), 5.21 (d, 1H, $J = 3.4$ Hz, H-1), 7.26–7.36 (m, 20H, H_{arom} Bn); ^{13}C NMR (125 MHz): δ 68.5 (*C*-6), 70.2 (*C*-5), 73.2 (*C*H_2Bn), 73.4 (*C*H_2Bn), 75.0 (*C*H_2Bn), 75.7 (*C*H_2Bn), 77.7 (*C*-4), 79.9 (*C*-2), 81.7 (*C*-3), 91.3 (*C*-1), 127.6–128.5 (*C*HBn), 137.8 (C_q Bn), 138.1 (C_q Bn), 138.6 (C_q Bn); HRMS *m*/*z* calcd for $C_{34}H_{36}O_6Na$ $[M+Na]^+$: 563.24041. Found 563.24251.

1.2.3. 2,3,4,6-Tetra-*O*-acetyl-D-glucopyranose (6).[21] The reaction mixture was quenched after 30 min. Column chromatography yielded **6** (0.153 g, 88%) as a colorless oil. IR (neat): 1032, 1213, 1367, 1740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.03 (s, 3H, CH_3Ac), 2.04 (s, 3H, CH_3Ac), 2.09 (s, 3H, CH_3Ac), 2.10 (s, 3H, CH_3Ac), 4.15 (t, 1H, $J = 11.5$ Hz, H-6), 4.26 (m, 2H, H-5, H-6), 4.89 (dd, 1H, $J = 3.0$, 9.5 Hz, H-2), 5.09 (m, 1H, H-4), 5.46 (d, 1H, $J = 2.5$ Hz, H-1), 5.54 (t, 1H, $J = 9.5$ Hz, H-3); ^{13}C NMR (125 MHz): δ 20.6 (*C*H_3Ac), 20.7 (*C*H_3Ac), 20.8 (*C*H_3Ac), 20.9 (*C*H_3Ac), 61.9 (*C*-6), 67.1 (*C*-5), 68.4 (*C*-4), 69.7 (*C*-3), 73.0 (*C*-2), 90.0 (*C*-1), 169.6 (*C*=O Ac), 170.2 (*C*=O Ac), 170.7 (*C*=O Ac), 170.9 (*C*=O Ac); HRMS *m*/*z* calcd for $C_{14}H_{20}O_{10}Na$ $[M+Na]^+$: 371.09487. Found 371.09519.

1.2.4. 2,3,4,6-Tetra-*O*-benzoyl-D-galactopyranose (8).[22] The reaction mixture was quenched after 60 min. Column chromatography yielded **8** (0.274 g, 92%) as a colorless oil. IR (neat): 1026, 1069, 1093, 1263, 1724 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.63 (s, 1H, OH), 4.38 (m, 1H, H-6), 4.61 (m, 1H, H-6), 4.87 (t, 1H, $J = 6.6$ Hz, H-5), 5.71 (dd, 1H, $J = 3.0$, 10.0 Hz, H-2), 5.85 (s, 1H, H-1), 6.08 (m, 2H, H-3, H-4), 7.22–8.15 (m, 20H, H_{arom}Bz); ^{13}C NMR (125 MHz): δ 62.4 (*C*-6), 66.8 (*C*-5), 68.0 (*C*-4), 69.2 (*C*-2), 69.5 (*C*-3), 91.1 (*C*-1), 128.2–128.6 (*C*HBz), 129.1–129.4 (C_q Bz), 129.7–129.9 (*C*HBz), 133.1–133.6 (*C*HBz), 165.6 (*C*=O Bz), 166.1 (*C*=O Bz); HRMS *m*/*z* calcd for $C_{34}H_{28}O_{10}Na$ $[M+Na]^+$: 619.15747. Found 619.15892.

1.2.5. 3-*O*-Acetyl-4-azido-2,4,6-trideoxy-2-phthalimido-D-galactopyranose (10). The reaction mixture was quenched after 15 min. Column chromatography yielded **10** (0.142 g, 79%) as a colorless oil. IR (neat): 1044, 1242, 1383, 1708, 2108 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.37 (d, 3H, $J = 11$ Hz, CH_3 C-6), 1.98 (s, 3H, CH_3Ac), 3.97 (d, 1H, $J = 6$ Hz, H-5), 3.99 (d, 1H, $J = 4$ Hz, H-4), 4.49 (dd, 1H, $J = 9$ Hz, 11 Hz, H-2), 5.38 (d, 1H, $J = 9$ Hz, H-1), 5.89 (dd, 1H,

$J = 3$ Hz, 11 Hz, H-3), 7.72–7.87 (m, 4H, H_{arom}Phth); ^{13}C NMR (125 MHz): δ 17.4 (*C*-6), 20.3 (CH_3Ac), 53.0 (*C*-2), 63.2 (*C*-4), 69.3 (*C*-5), 70.3 (*C*-3), 92.3 (*C*-1), 123.5 (*C*HPhth), 123.6 (*C*HPhth), 131.3 (C_q Phth), 131.4 (C_q Phth), 134.3 (*C*HPhth), 134.4 (*C*HPhth), 168.0 (*C*=O Phth), 168.3 (*C*=O Phth), 170.1 (*C*=O Ac); HRMS *m*/*z* calcd for $C_{16}H_{16}O_6Na$ $[M+H]^+$: 361.11426. Found 361.15307.

1.2.6. 4,6-*O*-Benzylidene-2-deoxy-3-*O*-levulinoyl-2-phthalimido-D-glucopyranose (12). The reaction mixture was quenched after 120 min. Column chromatography yielded **12** (0.210 g, 85%) as a white solid. IR (neat): 1076, 1386, 1716 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.86 (s, 3H, CH_3 Lev), 2.35–2.56 (m, 4H, CH_2 Lev), 3.81 (m, 3H, H-6, H-5, H-4), 4.25 (dd, 1H, $J = 8.5$, 10.0 Hz, H-2), 4.25 (dd, 1H, $J = 4.0$, 10.0 Hz, H-6), 5.54 (s, 1H, C*H*Ph), 5.63 (d, 1H, $J = 8.5$ Hz, H-1), 5.93 (t, 1H, $J = 10.0$ Hz, H-3), 7.35 (m, 3H, H_{arom}CHPh), 7.45 (m, 2H, H_{arom}CHPh), 7.67 (m, 2H, H_{arom}Phth), 7.81 (br s, 2H, H_{arom}Phth); ^{13}C NMR (125 MHz): δ 27.7 (CH_2 Lev), 29.3 (CH_3 Lev), 37.6 (CH_2 Lev), 56.5 (*C*-2), 66.3 (*C*-5), 68.5 (*C*-6), 69.5 (*C*-3), 79.2 (*C*-4), 93.1 (*C*-1), 101.4 (*C*HPh), 123.4–136.8 (CH_{arom}), 168.1 (*C*=O Phth), 171.9 (*C*=O Lev), 206.0 (*C*=O Lev); HRMS *m*/*z* calcd for $C_{26}H_{25}O_9NNa$ $[M+Na]^+$: 518.14215. Found 518.14428.

1.2.7. 2-*O*-Benzyl-4,6-*O*-benzylidene-3-*O*-*p*-methoxybenzyl-D-mannopyranose (14). The reaction mixture was quenched after 30 min. Column chromatography yielded **14** (0.191 g, 80%) as a colorless oil. IR (neat): 1026, 1090, 1512, 1612 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 3.45 (d, 1H, $J = 3.5$ Hz, OH), 3.75 (s, 3H, CH_3OMe), 3.77 (m, 1H, H-2), 3.82 (t, 1H, $J = 10.5$ Hz, H-6), 3.97 (dd, 2H, $J = 3.0$ Hz, 10.5 Hz, H-5, H-3), 4.19 (m, 2H, H-4, H-6), 4.56 (d, 1H, $J = 12$ Hz, C*H*HBn), 4.65 (d, 1H, $J = 12$ Hz, C*H*HBn), 4.71 (d, 1H, $J = 12$ Hz, CH*H*Bn), 4.74 (d, 1H, $J = 12$ Hz, CH*H*Bn), 5.07 (s, 1H, H-1), 5.61 (s, 1H, C*H*Ph), 6.82 (d, 2H, $J = 8.5$ Hz, H_{arom}PMB), 7.29 (m, 12H, H_{arom}); ^{13}C NMR (125 MHz): δ 55.1 (CH_3 PMB), 64.1 (*C*-5), 68.8 (*C*-6), 72.6 (CH_2Bn), 73.4 (CH_2Bn), 75.4 (*C*-3), 76.5 (*C*-2), 79.0 (*C*-4), 93.9 (*C*-1), 101.4 (*C*HPh), 113.6 (CH_{arom}PMB), 126.0–129.5 (CH_{arom}), 130.6 ($C_{q\,arom}$), 137.6 ($C_{q\,arom}$), 138.0 ($C_{q\,arom}$), 159.0 (C_q PMB); HRMS *m*/*z* calcd for $C_{28}H_{30}O_7Na$ $[M+Na]^+$: 501.18837. Found 501.18893.

1.2.8. 2,3-Di-*O*-benzyl-4,6-*O*-*p*-methoxybenzylidene-D-galactopyranose (16). The reaction mixture was quenched after 20 min. Column chromatography yielded **16** (0.168 g, 70%) as a colorless oil. IR (neat): 1028, 1051, 1093, 1248, 1517, 1614 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 2.90 (br s, 1H, OH), 3.73 (s, 3H, CH_3–*p*-OMePhCH), 3.76 (d, 1H, $J = 1.0$ Hz, H-5), 3.88 (dd, 1H, $J = 4.5$, 12.5 Hz, H-3), 3.92 (dd, 1H, $J = 2.5$, 16.5 Hz, H-6), 3.98 (dd, 1H, $J = 4.5$, 12.5 Hz, H-2), 4.13 (m, 2H, H-4, H-6), 4.62 (d, 1H, $J = 14.5$ Hz, C*H*HBn), 4.69 (d, 2H, $J = 5$ Hz, C*HH*Bn), 4.71 (d, 1H, $J = 14.5$ Hz, CH*H*Bn), 5.29 (d, 1H, $J = 4.5$ Hz, H-1), 5.37 (s, 1H, C*H*–*p*-OMePhCH), 6.79 (d, 2H, $J = 6.0$ Hz, H_{arom}–*p*-OMePhCH), 7.19–7.22 (m, 14H, H_{arom}); ^{13}C NMR (125 MHz): δ 55.3 (CH_3–*p*-OMePhCH), 62.8 (*C*-5), 69.4 (*C*-6), 71.7 (CH_2Bn), 73.9 (CH_2Bn), 74.3 (*C*-4), 75.7 (*C*-2,3), 92.3 (*C*-1), 101.0 (*C*H–*p*-OMePhCH), 113.5 (*C*H–*p*-OMePhCH), 127.7–128.4 (CH_{arom}), 130.4 (C_q *p*-OMePhCH), 138.3 (C_q Bn), 138.5 (C_q Bn), 160.0 (C_q *p*-OMePhCH); HRMS *m*/*z* calcd for $C_{28}H_{30}O_7NH_4$ $[M+NH_4]^+$: 496.23298. Found 496.23303.

1.2.9. 4-*O*-Acetyl-2,6-di-*O*-benzoyl-3-*O*-*tert*-butyldimethylsilyl-D-galactopyranose (18). The reaction mixture was quenched after 40 min. Column chromatography yielded **18** (0.231 g, 85%) as a colorless oil. IR (neat): 1112, 1270, 1451, 1723 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 0.02 (s, 3H, CH_3–Me–TBDMS), 0.13 (s, 3H, CH_3–Me–TBDMS), 0.76 (s, 9H, CH_3–*t*Bu–TBDMS), 2.19 (s, 3H, CH_3Ac), 3.40 (s, 1H, OH), 4.33 (m, 1H, H-6), 4.46 (m, 2H, H-3, H-6), 4.60 (t, 1H, $J = 6$ Hz, H-5), 5.39 (d, 1H, $J = 7.5$ Hz, H-2), 5.51 (s, 1H, H-4), 5.89 (s, 1H, H-1), 7.46 (m, 4H, H_{arom}), 7.58 (m, 2H, H_{arom}), 8.08 (m, 4H, H_{arom}); ^{13}C NMR (125 MHz): δ −5.0 (CH_3–Me–TBDMS), −4.8 (CH_3–Me–TBDMS), 17.7 (CH_3Ac), 25.3 (CH_3–*t*Bu–TBDMS), 62.9 (*C*-6), 66.6 (*C*-3), 67.0 (*C*-5), 71.0 (*C*-4), 71.7 (*C*-2), 91.1 (*C*-1), 128.3–133.4 (*C*HBz), 166.0 (*C*=O Bz), 166.2 (*C*=O Bz), 170.3 (*C*=O Ac); HRMS *m*/*z* calcd for $C_{28}H_{36}O_9SiNa$ $[M+Na]^+$: 567.20208. Found 567.20453.

1.2.10. 4-*O*-Acetyl-2,3-*O*-isopropylidene-L-rhamnopyranose (20).[23] The reaction mixture was quenched after 30 min. Column chromatography yielded **20** (0.102 g, 83%) as a white solid. IR (neat): 1045, 1130, 1221, 1375, 1740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.16 (d, 3H, $J = 6.3$ Hz, H-6), 1.36 (s, 3H, CH_3 isoprop), 1.57 (s, 3H, CH_3 isoprop), 2.11 (s, 3H, CH_3Ac), 3.21 (d, 1H, $J = 2.9$ Hz, OH), 3.97 (dq, 1H, H-5, $J = 6.3$ Hz, 10.0 Hz, H-5), 4.18 (d, 1H, $J = 5.4$ Hz, H-2), 4.22 (dd, 1H, $J = 5.4$ Hz, 7.7 Hz, H-3), 4.87 (dd, 1H, $J = 7.7$ Hz, 10.0 Hz H-4), 5.42 (d, 1H, $J = 2.2$ Hz, H-2); ^{13}C NMR (125 MHz): δ 17.0 (*C*-6), 21.0 (CH_3Ac), 26.4 (CH_3 isoprop), 27.6 (CH_3 isoprop), 64.2 (*C*-5), 74.4 (*C*-4), 75.5 (*C*-3), 76.1 (*C*-2), 91.8 (*C*-1), 109.8 (C_q isoprop), 170.2 (*C*=O Ac).

1.2.11. 3,4-Di-*O*-Acetyl-2-*O*-chloroacetyl-L-rhamnopyranose (22). The reaction mixture was quenched after 30 min. Column chromatography yielded **22** (0.139 g, 86%) as a colorless oil. IR (neat): 1049, 1219, 1371, 1740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.22 (d,

3H, $J = 5.8$ Hz, H-6), 2.00 (s, 3H, CH_3Ac), 2.06 (s, 3H, CH_3Ac), 3.21 (s, 1H, OH), 4.18 (m, 3H, H-5, CH_2Cl–ClAc), 5.11 (t, 1H, $J = 9.5$ Hz, H-4), 5.20 (s, 1H, H-1), 5.36 (s, 1H, H-2), 5.39 (m, 1H, H-3); ^{13}C NMR (125 MHz): δ 17.4 (*C*-6), 20.7 (*C*H_3Ac), 20.8 (*C*H_3Ac), 40.7 (*C*H_2Cl–ClAc), 66.4 (*C*-5), 68.6 (*C*-3), 70.9 (*C*-4), 71.9 (*C*-2), 91.8 (*C*-1), 166.8 (*C*=O ClAc), 170.0 (*C*=O Ac).

1.2.12. Benzyl 4-*O*-acetyl-2,3-di-*O*-benzoyl-D-glucopyranuronate (24). The reaction mixture was quenched after 60 min. Column chromatography yielded **24** (0.220 g, 82%) as a colorless oil. IR (neat): 906, 1261, 1450, 1674, 1724 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 1.68 (s, 3H, CH_3Ac), 4.09 (d, 1H, $J = 2.5$ Hz, OH), 4.76 (d, 1H, $J = 10$ Hz, H-5), 5.11 (d, 1H, $J = 12$ Hz, C*H*HBn), 5.17 (d, 1H, $J = 12$ Hz, CH*H*Bn), 4.60 (dd, 1H, $J = 3.5$ Hz, 10 Hz, H-2), 5.46 (t, 1H, $J = 9.5$ Hz, H-4), 5.78 (s, 1H, H-1), 6.04 (t, 1H, $J = 10$ Hz, H-3), 7.36 (m, 9H, H_{arom}), 7.49 (m, 2H, H_{arom}), 7.94 (m, 4H, H_{arom}); ^{13}C NMR (125 MHz): δ 20.2 (*C*H_3Ac), 67.9 (*C*H_2Bn), 68.3 (*C*-5), 69.3 (*C*-4), 69.6 (*C*-3), 71.6 (*C*-2), 90.4 (*C*-1), 128.4-134.6 (*C*H_{arom}), 165.6 (*C*=O Bz), 165.7 (*C*=O Bz), 168.0, 169.6 (*C*=O Ac, *C*OOBn); HRMS *m*/*z* calcd for $C_{29}H_{26}O_{10}Na$ $[M+Na]^+$: 557.14182. Found 557.14287.

1.2.13. Methyl 4-*O*-acetyl-2,3-di-*O*-benzyl-D-mannopyranuronate (26). The reaction mixture was quenched after 30 min by addition of Et_3N after which satd aq $Na_2S_2O_3$ was added. Column chromatography yielded **26** (0.189 g, 88%) as a colorless oil. IR (neat): 1042, 1118, 1229, 1371, 1744 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 2.01 (s, 3H, CH_3Ac), 3.60 (s, 3H, CH_3COOMe), 3.65 (br s, 1H, H-2), 3.89 (dd, 1H, $J = 6.6$ Hz, 2.9 Hz, H-3), 4.55 (d, 1H, $J = 12.0$ Hz, CH*H*Bn), 4.61 (d, 1H, $J = 12.0$ Hz, C*H*HBn), 4.63 (d, 1H, $J = 12.2$ Hz, CH*H*Bn), 4.73 (d, 1H, $J = 12.2$ Hz, C*H*HBn), 5.51–5.56 (m, 2H, $J = 6.6$ Hz, H-1, H-4), 7.23–7.49 (m, 10H, H_{arom}); ^{13}C NMR (125 MHz, $CDCl_3$): δ 20.7 (*C*H_3Ac), 52.3 (*C*H_3COOMe), 69.3 (*C*-4), 72.3 (*C*-5), 76.7 (*C*-2), 77.2 (*C*-3), 92.4 (*C*-1), 127.5–128.4 (*C*H_{arom}), 137.6 (C_q Bn), 137.9 (C_q Bn), 169.2, 169.8 (*C*=O Ac, *C*=O COOMe); HRMS *m*/*z* calcd for $C_{23}H_{26}O_8Na$ $[M+Na]^+$: 453.15199. Found 453.15220.

1.2.14. 2,3,4-Tri-*O*-benzyl-6-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-D-glucopyranose (28).[24] The reaction mixture was quenched after 30 min by addition of Et_3N after which satd aq $Na_2S_2O_3$ was added. Column chromatography yielded **28** (0.361 g, 70%) as a colorless oil. IR (neat): 1068, 1265, 1730, 2341, 2360 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.59 (d, 1H, $J = 2.4$ Hz, OH), 3.43 (m, 2H, H-2, H-4), 3.81 (dd, 1H, $J = 4.5$, 11 Hz, H-6), 3.89 (t, 1H, $J = 9.5$ Hz, H-3), 4.00 (dd, 1H, $J = 2.8$, 10 Hz, H-5), 4.23 (m, 2H, H-6, C*H*HBn), 4.40 (m, 2H, H-6′, C*H*HBn), 4.53 (d, 1H, $J = 11.2$ Hz, C*H*HBn), 4.69 (m, 3H, H-6′, CH*H*Bn), 4.80 (d, 1H, $J = 8.0$ Hz, H-1′), 4.87 (m, 2H, H-5′, CH*H*Bn), 5.09 (d, 1H, $J = 3.5$ Hz, H-1), 5.61 (dd, 1H, $J = 3.6$, 10.4 Hz, H-3′), 5.83 (dd, 1H, $J = 2.4$, 8 Hz, H-2′), 5.97 (d, 1H, $J = 3.2$ Hz, H-4′), 7.09–8.09 (m, 35H, H_{arom}); ^{13}C NMR (100 MHz): δ 61.9 (*C*-6′), 68.1 (*C*-5′), 68.7 (*C*-6), 69.8, 70.0 (*C*-4′, *C*-5), 71.3 (*C*-2′), 71.6 (*C*-3′), 73.2 (*C*H_2Bn), 74.7 (*C*H_2Bn), 75.5 (*C*H_2Bn), 77.3 (*C*-4), 79.9 (*C*-2), 81.5 (*C*-3), 91.1 (*C*-1′), 102.1 (*C*-1), 127.5–128.3 (*C*H_{arom}), 128.3–129.3 ($C_{q\,arom}$), 129.6–130.0 (*C*H_{arom}), 133.3–133.5 (*C*H_{arom}), 137.9–138.6 ($C_{q\,arom}$), 165.0 (*C*=O Bz), 165.5 (*C*=O Bz), 165.6 (*C*=O Bz), 166.0 (*C*=O Bz); HRMS *m*/*z* calcd for $C_{61}H_{56}O_{15}Na$ $[M+Na]^+$: 1051.35114. Found 1051.35269.

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