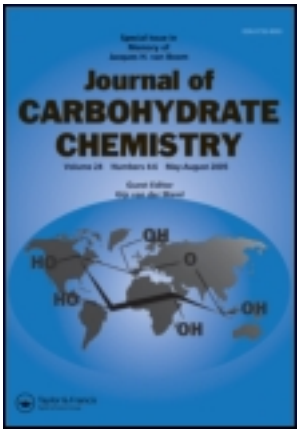

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A New Method for Selective Deprotection of Anomeric N,O-Dimethylhydroxylamine Promoted by TMSCl

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A New Method for Selective Deprotection of Anomeric *N,O*-Dimethylhydroxylamine Promoted by TMSCl

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TMSCl was shown to be an efficient reagent for selective deprotection of the anomeric position protected as *N*,*O*-dimethylhydroxylamine glycoside. This deprotection condition was proved to be compatible with a number of protecting groups, such as the TBDPS, acetyl, benzyl, benzylidene, and benzoyl groups.

Keywords TMSCl; *N,O*-dimethylhydroxylamine; Anomeric protection; Anomeric deprotection

INTRODUCTION

Synthetic carbohydrate chemistry has significantly promoted the understanding of the important roles that oligosaccharides and glycoconjugates have played in various biological processes, such as bacterial infections, cell growth, and immune response.[1–3] In the synthesis of complex oligosaccharides, selective protection and deprotection of the sugar anomeric positions are commonly involved. An ideal anomeric protecting group should be easy to install, stable under various conditions, and able to be selectively and efficiently removed to afford the desirable hemiacetals under mild conditions. *N,O*-dimethylhydroxylamine as a potentially useful anomeric protecting group has been explored in carbohydrate synthesis.[4] The advantage of this protecting group is

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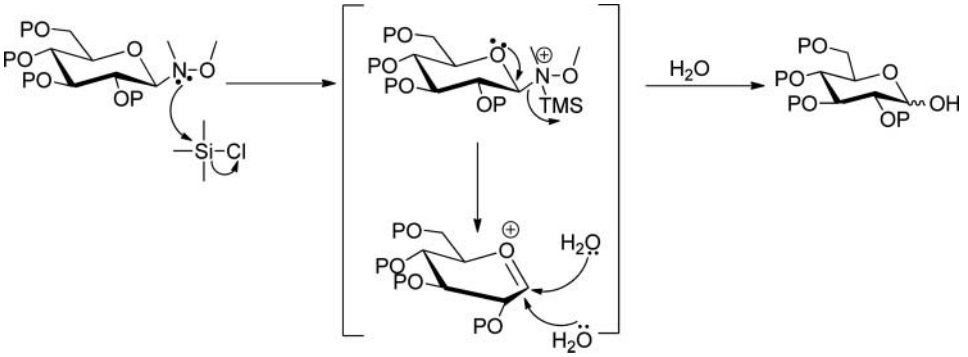
that it can be directly and selectively introduced to mono- and oligosaccharide anomeric positions in aqueous solution without extensive sugar protection or a special activation procedure, which can reduce the number of synthesis steps required in oligosaccharide synthesis.[5] Acids such as AcOH/H_2O (4:1), $FeCl_3$, THF/H_2O (9:1), etc.,[5] have been used to hydrolyze these types of *N*-glycosides, but most processes led to low yields of the desired hemiacetals.[6]

Noting the broad application of trimethylsilyl chloride (TMSCl) to various organic transformations, including the hydrolysis of *N*-glycosides and esterification of carboxylic acids under milder conditions without affecting various protecting groups,[7] we envisioned that TMSCl may be employed to deprotect *N,O*-dimethyl-hydroxylamine glycosides. The reaction should also be compatible with a wide variety of organic solvents.[8] To test the hypothesis, we investigated the deprotection of *N,O*-dimethyl-hydroxylamine glycosides in the presence of TMSCl under various conditions.

RESULTS AND DISCUSSION

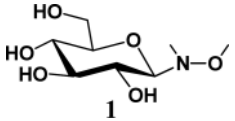
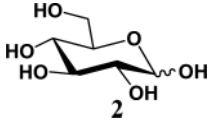
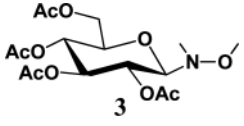
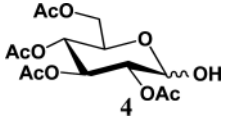
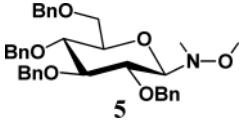
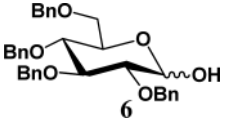
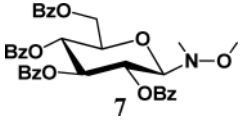
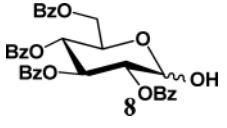
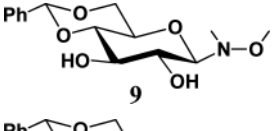
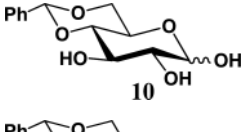
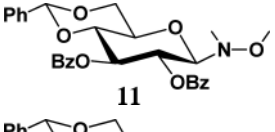
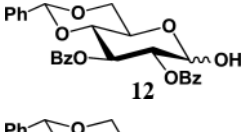
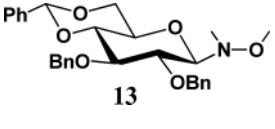
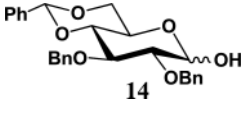
Our initial study used *N,O*-dimethyl-N-(*β-D*-glucopyranosyl)-hydroxylamine (**1**) as the model compound, which when treated with 2.0 eq. of TMSCl in THF/MeOH (9:1) at 50°C afforded the corresponding hemiacetal (**2**) in 93% yield after chromatographic purification (Table 1, entry 1). After exploring a number of solvents, we found that THF/MeOH (9:1) was the best solvent for this procedure. Moreover, addition of a few drops of acetic acid to the reaction mixture could further improve the reaction.

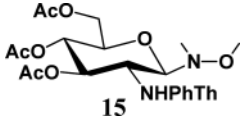
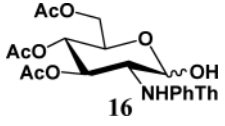
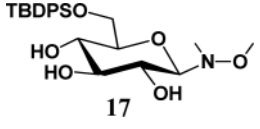
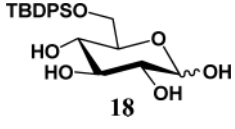
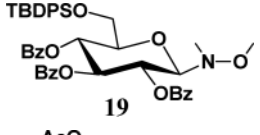
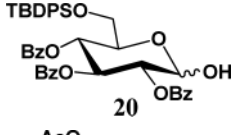
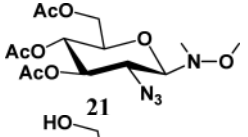
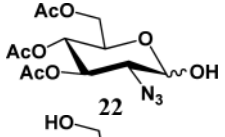
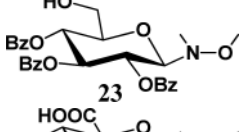
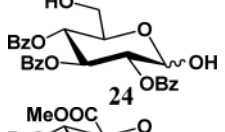
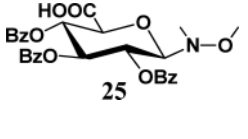
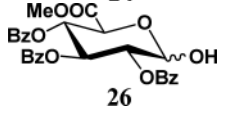
Scheme 1 outlines the proposed mechanism for this deprotection reaction. The lone-pair electrons on the nitrogen atom of the *N*-glycoside can react with TMSCl to promote the formation of an oxonium ion, which is then hydrolyzed to furnish the desirable hemiacetal. Alternatively, water molecules may directly attack the TMS-ated (N-glycosides-TMS complex) intermediate to afford the deprotection product.



Scheme 1: Plausible mechanism for the hydrolysis of *N*-glycosides.

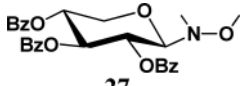
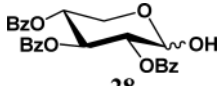
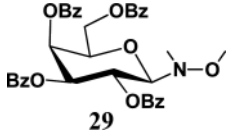
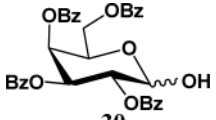
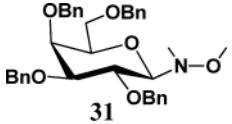
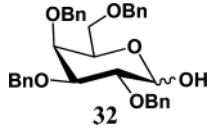
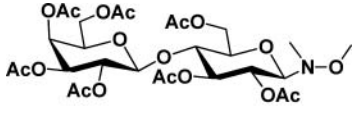
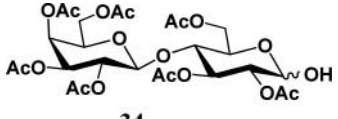
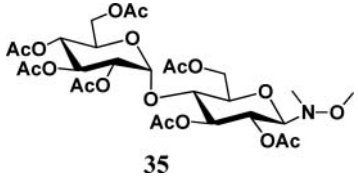
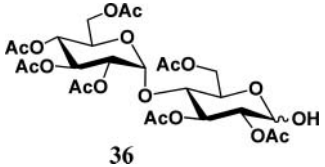
Table 1: Results of TMSCl-promoted hydrolysis of *N,O*-dimethylhydroxylamine glycosides[a]

Entry	Starting material	Product	Time (h)	Yield (%)[b]	Ref
1	 1	 2	1	93	(5)
2	 3	 4	1	91	(9)
3	 5	 6	1	90	(5)
4	 7	 8	1	90	(10)
5	 9	 10	1	81	(5)
6	 11	 12	1	77	(10)
7	 13	 14	1	79	(5)

8	 15	 16	1	83	(11)
9	 17	 18	1	81	(12)
10	 19	 20	1	80	(10)
11	 21	 22	1	90	(5)
12	 23	 24	1	90	(13)
13	 25	 26	2	92	(7)

(Continued on next page)

Table 1: Results of TMSCl-promoted hydrolysis of *N,O*-dimethylhydroxylamine glycosides[a] *(Continued)*

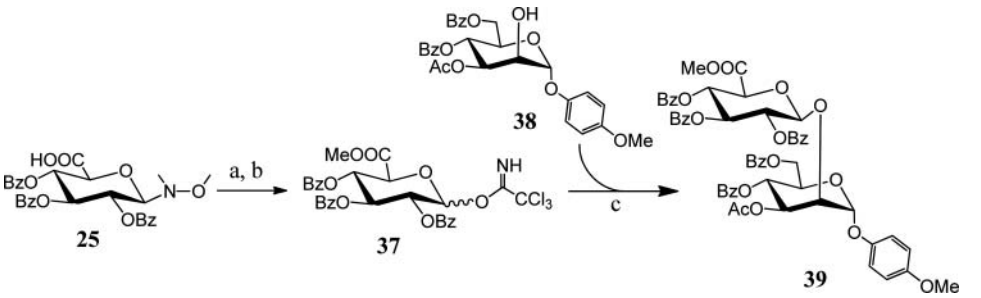
Entry	Starting material	Product	Time (h)	Yield (%)[b]	Ref
14	 **27**	 **28**	1	91	(10)
15	 **29**	 **30**	1	89	(10)
16	 **31**	 **32**	1	92	(5)
17	 **33**	 **34**	1	85	(9)
18	 **35**	 **36**	1	83	(9)

[a]All compounds were characterized by NMR spectroscopy and mass spectrometry.
[b]Yields are those after chromatographic purification.

Inspired by the excellent result of this deprotection method, we then evaluated its application to a diverse range of carbohydrate derivatives that bear various protecting groups. As shown in Table 1, the method was generally effective, and most of the reactions went to completion within 1 h at 50°C as monitored by TLC. The method was compatible with most common protecting groups used in carbohydrate synthesis, including acetyl, azido, *t*-butyldimethylsilyl, benzoyl, benzyl, benzylidene, and phthalyl groups. It is worth mentioning that in the presence of benzylidene protection (entries 5–7), the reaction yields dropped slightly, probably due to partial deprotection of the benzylidene.

We have further proved that in addition to glucosides, the *N,O*-dimethylhydroxylamine glycosides of other sugars, including glucuronic acid (entry 13), xylose (entry 14), galactose (entries 15 and 16), and disaccharides (entries 17 and 18), were also effectively deprotected under the same condition. These results also suggest that this deprotection method would not affect natural glycosidic linkages (see entries 17 and 18). Interestingly, we observed that the deprotection of glucuronic acid glycoside (entry 13) was easier than that of other glycosides, as the former completed within 2 h at rt while the others had no reaction under this condition.

To demonstrate the applicability of the current method, it was employed to synthesize a disaccharide **39** from **25** (Sch. 2). After the anomeric position of **25** was deprotected, the resultant **26** was conveniently converted to its trichloroacetimidate derivative **37** via reacting with trichloroacetonitrile and DBU at 0°C. Trichloroacetimidate **37** was then used as a glycosyl donor to glycosylate **38** in the presence of TMSOTf to afford disaccharide **39** in a good yield (75%).



Scheme 2: Reagents and conditions: (a) TMSCl, THF/MeOH (9:1), rt; (b) CCl_3CN, DBU, CH_2Cl_2, 0°C; (c) TMSOTf, CH_2Cl_2, −20°C.

In conclusion, we have demonstrated a new and efficient method for the deprotection of *N,O*-dimethylhydroxylamine glycosides. The method was proved to be generally applicable to various sugars and compatible with a wide range

of commonly used protecting groups. Furthermore, we have demonstrated the synthetic applicability of the method in the synthesis of oligosaccharide **39**.

EXPERIMENTAL

General Methods

^{1}H NMR spectra were obtained using a Bruker Avance (300 MHz) NMR spectrometer. Chemical shifts (δ) are expressed in ppm with tetramethylsilane (TMS) as the internal standard if not specified otherwise. ESI-MS data were collected with a Finngan LCQ Deca XP Max instrument. Thin-layer chromatography (TLC) was performed on silica gel GF254 plates with UV detection or by charring with a 5% H_2SO_4 solution in EtOH. Anhydrous solvents were obtained from a solvent purification system, while commercial anhydrous reagents were used without further purification.

General Experimental Protocol for the Preparation of *N*-Glycosides

Mono- or disaccharide (5 mmol) was dissolved in water (8 mL) in a round-bottomed flask. *N,O*-dimethylhydroxylamine hydrochloride (732 mg, 7.5 mmol) and sodium acetate (615 mg, 7.5 mmol) were dissolved in 1 mL of water, and the solution was then added slowly to the saccharide solution at 0°C. The reaction was allowed to stir for 20 h at rt, at which time TLC analysis showed complete conversion of the starting material to a faster moving product. Water was evaporated in vacuo, and the crude product was purified by flash column chromatography eluted with CH_2Cl_2:MeOH to give the desired *N*-glycoside.

General Procedure for the Hydrolysis of *N*-glycosides

To a stirred solution of an *N*-glycoside (1 mmol) dissolved in THF:MeOH (3 mL, 9:1) was added TMSCl (0.25 mL, 2 mmol) at rt, and the solution was then warmed to 50°C. The mixture was stirred at this temperature until TLC showed complete conversion to a slower-moving product. Solvents were evaporated in vacuo, and the crude oil product was purified by column chromatography to afford corresponding pure hemiacetal (Table 1).

2,3,4,6-tetra-*O*-acetyl-D-glucopyranose (4): Colorless syrup (91% yield). Flash column chromatography using petroleum ether–EtOAc (2:1) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.53 (t, J = 9.8 Hz, 1 H), 5.25 (t, J = 9.5 Hz, 1 H), 5.08 (t, 1 H), 4.94–4.84 (m, 1H), 4.31–4.05 (m, 3 H), 3.69 (s, 1 H), 2.09–2.02 (4 s, 12 H, 4 × COCH_3). ESI-MS: $[M + Na]^+$: 371.08.

2,3,4,6-tetra-*O*-benzyl-D-glucopyranos (6): A white solid (90% yield). Flash column chromatography using petroleum ether–EtOAc (4:1) as eluent.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.36 (m, 20 H, Ar*H*); 5.21 (d, $J = 3.4$ Hz, 1 H), 4.95–4.46 (m, 8 H, 4 × CH_2Bn), 4.03 (d, $J = 8.4$ Hz, 1 H), 3.98 (t, 1 H), 3.54–3.70 (m, 4 H), 3.26 (br s, 1 H, OH). ESI-MS: $[M + Na]^+$: 563.23.

2,3,4,6-tetra-*O*-benzoyl-D-glucopyranos (8): A white solid (90% yield). Flash column chromatography using petroleum ether–EtOAc (2:1) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07–7.29 (m, 20 H, Ar*H*), 6.30 (t, $J = 9.9$ Hz, 1 H), 5.76 (d, $J = 3.0$ Hz, 1 H), 5.73 (t, 1 H), 5.28 (dd, $J = 3.6$, 10.4 Hz, 1 H), 4.62 (m, 2 H), 4.46 (m, 1 H). ESI-MS: $[M + Na]^+$: 619.21.

4,6-*O*-benzylidene-D-glucopyranose (10): Colorless syrup (81% yield). Flash column chromatography using CH_2Cl_2-MeOH (10:1) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50–7.39 (m, 5 H, Ar*H*), 5.53 (s, 1 H, PhC*H*), 5.12 (d, $J = 3.8$ Hz, 1 H), 4.60 (d, $J = 7.7$ Hz, 1 H), 4.19 (dd, $J = 4.0$, 10.0 Hz, 1 H), 3.92 (dd, $J = 3.5$, 13.0 Hz, 1 H), 3.86 (t, 1 H), 3.62 (t, 1 H), 3.50–3.39 (m, 1 H), 3.23 (dd, $J = 7.7$, 8.7 Hz, 1 H). ESI-MS: $[M + Na]^+$: 291.09.

4,6-*O*-benzylidene-2,3-di-*O*-benzoyl-D-glucopyranose (12): Colorless foam (77% yield). Flash column chromatography using petroleum ether–EtOAc (3:1) as eluent. ^{1}H NMR (300MHz, $CDCl_3$): δ 8.12–7.28 (m, 15 H, Ar*H*), 6.14 (t, 1 H), 5.87 (t, 1 H), 5.70 (br s, 1 H), 5.57 (s, 1 H, C*H*Ph), 5.31 (dd, $J = 4.8$, $J =$ 9.3 Hz, 1 H), 4.39 (m, 1 H), 3.97–3.85 (m, 3 H), 3.45 (br s, 1 H, OH). ESI-MS: $[M + Na]^+$: 499.18.

4,6-*O*-benzylidene-2,3-di-*O*-benzyl-D-glucopyranose (14): Colorless syrup (79% yield). Flash column chromatography using petroleum ether–EtOAc (3:1) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55–7.28 (m, 15 H, Ar*H*), 5.60 (s, 1 H, PhC*H*), 5.21 (d, $J = 3.0$ Hz, 1 H), 5.00–4.73 (4 d, $J =$ 11.4 Hz, 4 H, 2 × CH_2Ph), 4.06 (t, 1 H), 3.78 (t, 1 H), 3.73–3.61 (m, 3 H), 3.45 (m, 1 H). ESI-MS: $[M + Na]^+$: 471.21.

3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-D-glucopyranose (16): Colorless syrup (83% yield). Flash column chromatography using petroleum ether–EtOAc (2:1) as eluent. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.89–7.69 (m, 4 H, Ar*H*), 5.82 (dd, $J = 8.4$, $J = 9.3$ Hz, 1 H), 5.63 (d, $J = 8.4$ Hz, 1 H), 5.16 (m, 2H), 4.40–4.09 (m, 2H), 3.92 (m, 1 H), 2.08, 2.02, 1.84 (3 s, 9 H, 3 × COCH_3). ESI-MS: $[M + Na]^+$: 636.23.

6-*O*-tert-butyl-diphenylsilyl-D-glucopyranose (18): Colorless syrup (81% yield). Flash column chromatography using CH_2Cl_2-MeOH (10:1) as eluent. ^{1}H NMR (300MHz, $CDCl_3$): δ 7.80–7.35 (m, 10 H, Ar*H*), 5.14 (d, $J = 3.6$ Hz, 1 H), 4.49 (d, $J = 7.8$ Hz, 1 H), 3.97–3.82 (m, 2 H), 3.69 (t, 1 H), 3.49 (t, 1 H), 3.37 (m, 1 H), 3.15 (dd, $J = 7.8$, 8.9 Hz, 1 H), 1.03 (s, 9 H). ESI-MS: $[M + Na]^+$: 441.16.

2,3,4-tri-*O*-benzoyl-6-*O*-tert-butyldiphenylsilyl-D-glucopyranose (20): A white solid (80% yield). Flash column chromatography using petroleum ether–EtOAc (5:1) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.03–7.18 (m, 25 H, Ar*H*), 6.21 (t, 1 H), 5.74 (t, 1 H), 5.32 (m, 1 H), 4.42 (d, $J = 10.1$ Hz, 1 H), 3.93–3.86 (m, 3 H), 3.39 (s, 1 H). ESI-MS: $[M + Na]^+$: 515.43.

3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-D-glucopyranose (22): A white solid (90% yield). Flash column chromatography using petroleum ether–EtOAc (3:1) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.49 (d, J = 2.4 Hz, 1 H), 5.42–5.39 (m, 1 H), 5.28 (s, 1 H), 4.37–4.16 (m, 4 H), 3.56 (s, 1 H), 2.11 (s, 9 H). ESI-MS: $[M + Na]^+$: 354.11.

2,3,4-tri-*O*-benzoyl-D-glucopyranose (24): A white solid (90% yield). Flash column chromatography using petroleum ether–EtOAc (1:1) as eluent. ^{1}H NMR (300MHz, $CDCl_3$): δ 8.01–7.25 (m, 15 H, Ar*H*), 6.32 (t, 1 H), 5.84 (d, J = 2.7 Hz, 1 H), 5.51 (t, 1 H), 5.34 (dd, J = 3.5, 10.2 Hz, 1 H), 5.10 (s, 1 H), 4.40 (d, J = 10.0 Hz, 1 H), 3.94–3.66 (m, 3 H). ESI-MS: $[M + Na]^+$: 515.45.

Methyl 2,3,4-tri-*O*-benzoyl-D-glucuronic acid ester (26): A white solid (92% yield). Flash column chromatography using petroleum ether–EtOAc (4:1) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.94–7.29 (m, 15 H, Ar*H*), 6.27 (t, 1 H), 5.87 (s, 1 H), 5.67 (t, 1 H), 5.35 (dd, J = 2.5, 9.7 Hz, 1 H), 4.89 (d, J = 9.8 Hz, 1 H), 4.16 (s, 1 H), 3.65 (s, 3 H). ESI-MS: $[M + Na]^+$: 543.13.

2,3,4-tri-O-benzoyl-D-xylopyranose (28): A white solid (91% yield). Flash column chromatography using petroleum ether–EtOAc (4:1) as eluent. ^{1}H NMR (300MHz, $CDCl_3$): δ 8.02–7.30 (m, 15 H, Ar*H*), 6.22 (t, 1 H), 5.69 (t, 1 H), 5.42 (d, J = 7.1 Hz, 1 H), 5.31 (t, 1 H), 4.14 (d, J = 7.8 Hz, 2 H), 3.25 (s, 1 H, OH). ESI-MS: $[M + Na]^+$: 485.19

2,3,4,6-tetra-*O*-benzoyl-D-galactopyranose (30): Colorless syrup (92% yield). Flash column chromatography using petroleum ether–EtOAc (4:1) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22–8.15 (m, 20 H, Ar*H*), 6.08 (m, 2 H), 5.85(s, 1 H), 5.71 (dd, J = 3.0, 10.0 Hz, 1 H), 4.87 (t, 1 H), 4.61–4.38 (m, 2 H), 3.63 (s, 1 H, OH). ESI-MS: $[M + Na]^+$: 619.15.

2,3,4,6-tetra-*O*-benzyl-D-galactopyranose (32): Colorless syrup (92% yield). Flash column chromatography using petroleum ether–EtOAc (4:1) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.26–7.34 (m, 20 H), 5.24 (brs, 1 H), 4.98 (m, 1 H), 4.48–4.88 (4dd, J = 11.6, 12.3 Hz, PhCH_2O-, 8 H), 3.97 (m, 2 H), 3.63 (m, 3 H). ESI-MS: $[M + Na]^+$: 563.66.

2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1$\rightarrow$4)-2,3,6-tri-O-acetyl-α-D-glucopyranose (34): Colorless syrup (85% yield). Flash column chromatography using petroleum ether–EtOAc (4:1) as eluent. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.45 (t, 1 H), 5.26 (brs, 2 H), 4.89 (dd, 1 H), 4.88 (dd, 1 H), 4.47 (m, 1 H), 4.37 (m, 2 H), 4.13 (m, 3 H), 4.03 (m, 1 H), 3.88 (m, 1 H), 2.08–1.88 (7 s, 21 H, 7 $\times$ COCH_3). ESI-MS: $[M + Na]^+$: 659.53.

2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl-(1$\rightarrow$4)-2,3,6-tri-O-acetyl-α-D-glucopyranose (36): Colorless syrup (83% yield). Flash column chromatography using petroleum ether–EtOAc (4:1) as eluent. ^{1}H NMR (300MHz, $CDCl_3$): δ 5.57 (d, J = 3.0 Hz, 1 H), 5.39 (m, 1 H), 5.33 (d, J = 3.0 Hz, 1 H), 5.03 (m, 1 H), 4.89 (m, 1 H), 4.70 (m, 1 H), 4.52 (m, 2 H), 3.90–4.15 (m, 5 H), 3.77 (m, 1 H), 2.18–1.92 (7 s, 21 H, 7 $\times$ COCH_3). ESI-MS: $[M + Na]^+$: 659.57.

4-Methoxyphenyl (methyl 2,3,4-tri-*O*-benzoyl-β-*D*-glucopyranosyluronate)-(1→2)-3-*O*-acetyl-4,6-di-*O*-benzoyl-α-*D*-mannopyranoside (39):[14] *N,O*-dimethyl-*N*-(2,3,4-tri-*O*-benzoyl-β-*D*-glucopyranosyluronic acid) hydroxylamine **25** (604 mg, 1.1 mmol) was dissolved in MeOH (5 mL) under an N_2 atmosphere. TMSCl (0.28 mL, 2.2 mmol) was added to the solution, and the mixture was stirred at rt. After a while, white solid started to precipitate, and 2 h later TLC showed the complete conversion of **25** to a slower-moving product. Filtration of the reaction mixture afforded **26** as a white solid. DBU (catalytic amount) was added to a solution of **26** (520 mg, 1 mmol) and CCl_3CN (1.0 mL, 10 mmol) in anhydrous CH_2Cl_2 (10 mL) and stirred under an N_2 atmosphere at 0°C. The reaction mixture was stirred for 1 h, at which point TLC (4:1 PE/EA) indicated that the reaction was complete. Concentration of the reaction mixture, followed by purification of the crude product on a silica gel column with 4:1 PE /EA as the eluent, afforded **37** (530 mg). A mixture of the resultant **37**, **38** (380 mg, 0.70 mmol), and MS 4 Å (1.0 g) in anhydrous CH_2Cl_2 (10 mL) was stirred under an N_2 atmosphere at rt for 1 h. After cooling to −20°C, TMSOTf (10 μL, 55 μmol) was added and the reaction was stirred for 30 min. Neutralization of the reaction mixture with triethylamine was followed by filtration through a Celite pad to remove MS, concentration in vacuum, and purification by silica gel column chromatography to afford disaccharide **39** (545 mg, 75%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.00–6.69 (m, 29 H, ArH), 6.09 (d, J = 4.8 Hz, 1 H), 5.75 (t, 1 H), 5.64 (t, 1 H), 5.53 (dd, J = 3.4, 10.1 Hz, 1 H), 5.47 (dd, J = 1.5, 7.6 Hz, 1 H), 5.37 (d, J = 1.7 Hz, 1 H), 4.78–4.75 (m, 1 H), 4.45 (dd, J = 2.0, 11.7 Hz, 1 H), 4.25 (ddt, J = 2.9, 5.8, 8.2 Hz, 3 H), 4.14 (dd, J = 2.0, 3.3 Hz, 1 H), 3.68 (s, 3 H, OMe), 3.58 (s, 3 H, COOMe), 1.92 (s, 3 H, CH_3CO). HRMS: calcd for $C_{57}H_{50}NaO_{19}$ $[M+Na]^+$: 1061.2946. Found 1061.2839.

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