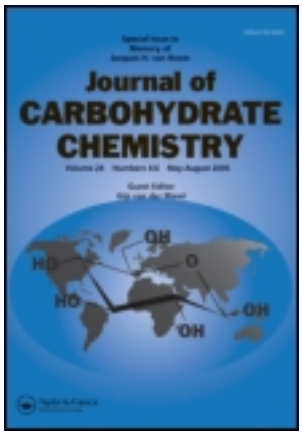

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2,4-DIMETHOXYBENZYL: AN AMIDE PROTECTING GROUP FOR 2-ACETAMIDO GLYCOSYL DONORS

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2,4-DIMETHOXYBENZYL: AN AMIDE PROTECTING GROUP FOR 2-ACETAMIDO GLYCOSYL DONORS[1]

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Dedicated to Professor Joachim Thiem.

ABSTRACT

2,4-Dimethoxybenzyl (Dmob) was used as an amide protecting group for 2-acetamido glycosyl donors. The *N*-Dmob group was introduced by imine formation between 2,4-dimethoxybenzaldehyde and D-glucosamine, followed by per-*O*-acylation, reduction to form the amine, and finally *N*-acetylation to give 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(2,4-dimethoxybenzylacetamido)-β-D-glucopyranose. Selective 1-*O*-deacetylation and treatment with trichloroacetonitrile gave the corresponding trichloroacetimidate glycosyl donor. Lewis acid-promoted glycosylations of the model substrate 3-nitrobenzyl alcohol gave exclusively the β-glycoside product, either with or without the Dmob protecting group remaining depending on the reagent and conditions employed. The *N*-Dmob protected 1-*O*-acetate glucosyl donor gave higher glycosylation yields than the corresponding 2-acetamido glucosyl donor without Dmob protection.

Key Words: Carbohydrates; Glycosides; Glycosylations; Stereoselective synthesis; Dimethoxybenzyl

*Corresponding author.

INTRODUCTION

Glycoconjugates play crucial roles in the development, growth, and proper functions of an organism.[2] Amino sugars are found in many biologically important poly- and oligosaccharides, *e.g.*, in glycans of *O*- and *N*-glycoproteins and -peptides, lipochitin nodulation factors, and amino glycoside antibiotics such as streptomycin. Synthesis of oligosaccharides provides an important tool for glycobiology, but the synthesis of glycosides of amino sugars such as D-glucosamine and D-galactosamine involves special problems.[3] Glycosyl donors with a 2-acylamino group give, upon electrophilic activation of an anomeric (C-1) leaving group, an oxocarbenium ion which by neighbouring group participation forms an oxazolinium ion. Abstraction of the amide proton then gives a relatively stable oxazoline. To avoid this stable and thus rather unreactive intermediate, the 2-amino group should be protected with either one bivalent, or one or two monovalent protecting groups. Bivalent protecting groups used include phthaloyl (Phth),[3] tetrachlorophthaloyl (TCP),[4] dithiasuccinoyl (Dts),[5] dimethylmaleoyl (DMM),[6] and thiodiglycoloyl (TDG).[7] Monovalent protecting groups used for single protection include trichloroacetyl (TCA).[8] trichloroethoxycarbonyl (Troc),[9] trifluoroacetyl (TFA),[10] and allyloxycarbonyl (Alloc),[11] whereas double protection has been achieved with diacetyl,[12] Ac/Troc,[9b] and dibenzyl.[13] Of these approaches, the Ac/Troc strategy retains the acetamido functionality, whereas the TCA strategy relies on a masked acetamido functionality. The protecting groups can then be cleaved by base, reduction, palladium catalysed transfer or thiolysis, sometimes requiring harsh conditions for removal. Backbone amide protection with an acidolyzable 2,4-dimethoxybenzyl (Dmob) moiety has been developed for peptide synthesis,[14] and the Dmob moiety can been removed by treatment with concd TFA.[14] Herein, we report preliminary results on the synthesis of novel *N*-Dmob protected 2-acetamido glucosyl donors and their use in model glycosylations.

RESULTS AND DISCUSSION

Synthesis of *N*-Dmob protected glucosyl donors began with condensation of D-glucosamine hydrochloride **1** with 2,4-dimethoxybenzaldehyde, **2**, in the presence of aq sodium hydroxide[15] to give imine **3** in 70% yield (Scheme 1). Imine **3** was then *O*-acetylated with acetic anhydride in pyridine to give the 1-*O*-β -acetate **4** exclusively. Washing imine **3** with ethanol and ensuring that the solid was thoroughly dried was essential to give consistent acetylation results. If this was not done, then large amounts of 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose, **5**, were formed due to hydrolysis of the imine bond followed by acetylation of the amino group.

Next, reduction of imine **4** was investigated. Use of sodium borohydride resulted in over-reduction whilst sodium triacetoxyborohydride did not fully reduce the imine bond and often gave capricious results. However, use of sodium cyanoborohydride in either THF-H_2O or THF-MeOH gave the desired amine **6** in a moderate yield with a small amount of an easily removed by-product. Finally,

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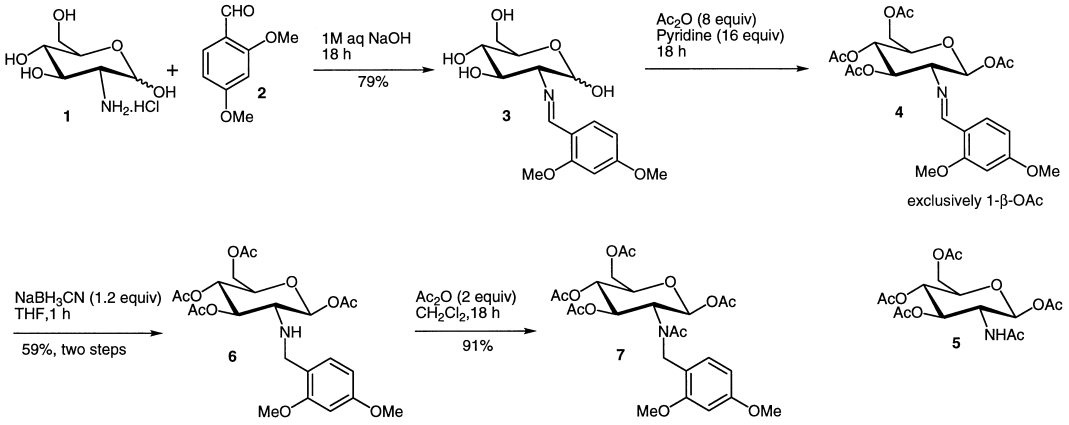
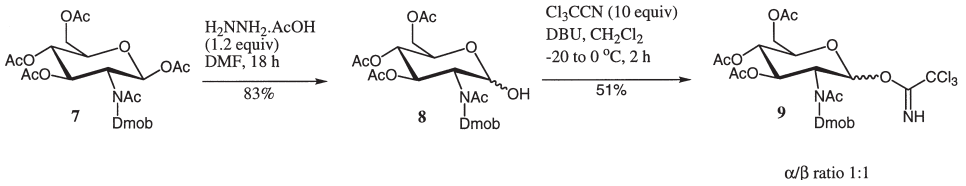


Scheme 1. Synthesis of *N*-Dmob protected 2-acetamido glycosyl donor **7**.

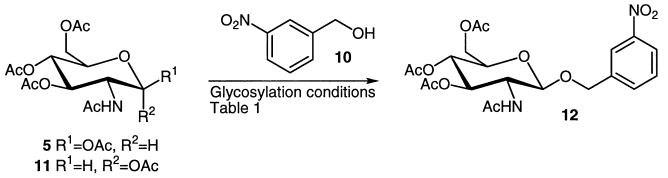
N-acetylation with acetic anhydride gave the glycosyl donor **7** in quantitative yield. Although the amide **7** was practically pure by HPLC and TLC, purification by vacuum liquid chromatography (VLC) or preparative HPLC was carried out to guarantee comparative results in the glycosylation experiments. The more reactive trichloroacetimidate was accessed by a regioselective hydrazinolysis[16] of the 1-*O*-acetyl of **7** to give **8** in good yield and subsequent treatment with trichloroacetonitrile[17] to give the trichloroacetimidate **9** (Scheme 2). An ~1:1 mixture of the α- and β-anomers of **9** was obtained in 51% after VLC purification. The pure α-trichloroacetimidate **9**α could be obtained by preparative HPLC. Rotamers were observed in the ^{1}H and ^{13}C NMR spectra of all *N*-acetylated compounds, *e.g.*, in **7**. However, purity and product type could easily be determined by analytical photodiode array (PDA) HPLC.

As a model glycosyl acceptor we chose 3-nitrobenzyl alcohol (**10**) for its characteristic UV spectrum easily identified by PDA-HPLC. To provide a comparison for glycosylations with Dmob protected glycosyl donors, we first studied the glycosylation of **10** with 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-β-D-glucopyranose (**5**)[18] and its α-anomer, **11**[19] (Scheme 3). Glycosylations were carried out in either toluene or CH_2Cl_2 using equimolar amounts of donor and acceptor, and $BF_3.OEt_2$ or TMSOTf as the Lewis acid (Table 1).

Glycosylations in CH_2Cl_2, at 40 °C, gave up to 56% yield, while higher yields were obtained in toluene, at 100 °C. The α-anomer **11** gave slightly higher yields, as did the use of $BF_3.OEt_2$ as Lewis acid, resulting in up to 69% yield of the gly-



Scheme 2. Synthesis of *N*-Dmob protected 2-acetamido trichloroacetimidate **9**.



Scheme 3. Glycosylations with 2-acetamido 1-*O*-acetates **5** and **11**.

coside product **12** (Table 1, entry 5). No reaction was achieved using the β-anomer **5** and $BF_3.OEt_2$ in CH_2Cl_2 (Table 1, entry 3).

With the new Dmob protected glycosyl donors in hand, glycosylations with *N*-Dmob protected 1-*O*-acetate **7** were then studied (Scheme 4). Using equimolar amounts of donor and acceptor, and the same conditions as employed before for the 2-acetamido glycosyl donors **5** and **11**, the Dmob group was cleaved and the β-glycoside **12** was isolated in good yield (Table 2, entries 1, 2, and 4).

As expected, the reaction proceeded with high stereoselectivity and only the β-anomer was observed. In this case, the use of TMSOTf as the Lewis acid gave higher yields of β-glycoside **12**. A small amount of the 1-α-acetate **13** was also formed when using TMSOTf in CH_2Cl_2 (Table 2, entry 4) which was probably due to the attack of water on the oxazolinium intermediate. With $BF_3.OEt_2$ in CH_2Cl_2 (Table 2, entry 3), **12** was obtained together with β-glycoside **14** in which the Dmob was still present. To increase the yield of the latter, 3 equiv of donor **7** were used in the glycosylation reactions (Table 2, entries 5–8). Surprisingly, the yield of the *N*-Dmob protected β-glycoside **14** did not change when using the same conditions of $BF_3.OEt_2$ in CH_2Cl_2 (Table 2, entry 7 vs. 3). However, increasing the temperature to 100 °C and lowering the amount of catalyst increased the yield of β-glycoside **14** to an excellent 94% (Table 2, entry 5). Reversing the ratios and using 3 equiv of acceptor **10** to donor **7**, gave a 45% yield of β-glycoside **14** (Table 2, entry 9).

Table 1. Glycosylation of 3-nitrobenzyl Alcohol (**10**) with Donors **5** and **11**[a]

Entry	Donor	Lewis Acid	Equiv of Lewis Acid	Solvent[b]	Yield[c]
1	**5**	$BF_3{\cdot}OEt_2$	0.1	PhMe	51% **12**
2	**5**	TMSOTf	0.1	PhMe	33% **12**
3	**5**	$BF_3{\cdot}OEt_2$	1.0	CH_2Cl_2	NR[d]
4	**5**	TMSOTf	1.0	CH_2Cl_2	56% **12**
5	**11**	$BF_3{\cdot}OEt_2$	0.1	PhMe	69% **12**
6	**11**	TMSOTf	0.1	PhMe	63% **12**
7	**11**	$BF_3{\cdot}OEt_2$	1.0	CH_2Cl_2	43% **12**
8	**11**	TMSOTf	1.0	CH_2Cl_2	13% **12**

[a] The reactions were carried out in the presence of molecular sieves 3Å under argon for 18 h using 1 equiv of donor.
[b] Reactions in PhMe were run at 100°C and those in CH_2Cl_2 were run at 40°C.
[c] All yields are of isolated, pure products.
[d] No reaction.

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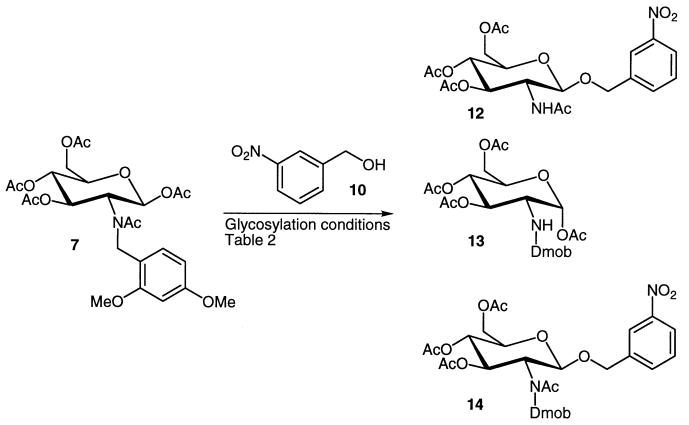

Scheme 4. Glycosylations with *N*-Dmob protected 2-acetamido glycosyl donor **7**.

In a further effort to increase the yield of the glycoside product without concomitant cleavage of the Dmob group, glycosylations with the *N*-Dmob protected amine **6** were attempted. Since the nitrogen was not acetylated, the Lewis acidic conditions presumably would not cleave the Dmob group and so, a 'safety-catch' system was anticipated.[20] However, the use of TMSOTf or $BF_3.OEt_2$ in toluene, as described before, only gave decomposition of acetate **6**, and in CH_2Cl_2 no reaction was observed.

Glycosylation with trichloroacetimidate **9** was then attempted with an equimolar amount of 3-nitrobenzyl alcohol **10** at −20 °C using 0.1 equiv of either TMSOTf or $BF_3.OEt_2$ in CH_2Cl_2. However, no reaction was observed after 1 h at this temperature. Warming to rt and using $BF_3.OEt_2$ as the catalyst, only 10% of

Table 2. Reaction of Glycosyl Donor **7** with 3-nitrobenzyl Alcohol **10**[a]

Entry	Equiv of Donor	Lewis Acid	Equiv of Lewis Acid[b]	Solvent[c]	Yield[d]
1	1	$BF_3{\cdot}OEt_2$	0.1	PhMe	57% **12**
2	1	TMSOTf	0.1	PhMe	64% **12**
3	1	$BF_3{\cdot}OEt_2$	1.0	CH_2Cl_2	20% **12** 24% **14**
4	1	TMSOTf	1.0	CH_2Cl_2	71% **12** 21% **13**
5	3	$BF_3{\cdot}OEt_2$	0.1	PhMe	94% **14**
6	3	TMSOTf	0.1	PhMe	5% **14**
7	3	$BF_3{\cdot}OEt_2$	1.0	CH_2Cl_2	25% **14**
8	3	TMSOTf	1.0	CH_2Cl_2	9% **14**
9	0.33	$BF_3{\cdot}OEt_2$	0.1	PhMe	45% **14**
10	0.33	$BF_3{\cdot}OEt_2$	1.0	CH_2Cl_2	27% **14**

[a] The reactions were carried out in the presence of molecular sieves under argon for 18 h.
[b] Equiv relative to acceptor.
[c] Reactions in PhMe were run at 100°C and those in CH_2Cl_2 were run at 40°C.
[d] All yields are of isolated, pure products.

the desired glycoside **14** was obtained together with 33% of the rearranged acetate **13**. However, using TMSOTf, 26% of the desired glycoside **14** was obtained together with 47% of acetate **13**.

CONCLUSION

In conclusion, new *N*-Dmob protected 2-acetamido glucosamine acetate and trichloroacetimidate glycosyl donors have been prepared. The *N*-Dmob protected acetate **7** was found efficient for the glycosylation of the model acceptor 3-nitrobenzyl alcohol. Depending on the glycosylation conditions, the Dmob moiety was either retained or cleaved.

EXPERIMENTAL

General Methods. ^{1}H NMR spectra were recorded at 499.87 MHz and ^{13}C NMR spectra at 125.70 MHz on a Varian Inova 500 spectrometer equipped with a z− (single axis) PFG inverse detection C—H—P probe. Chemical shifts, δ, were measured in ppm and coupling constants, *J*, in Hz. For NMR spectra in deuterated solvents, the solvent peak was used as reference ($CDCl_3$: δ 7.27 for ^{1}H, 77.00 for ^{13}C; acetone-d_6: δ 2.05 for ^{1}H). When necessary, NMR data was assigned using ^{1}H—^{1}H correlated spectra. Melting points are uncorrected. Specific rotations were measured on a Perkin-Elmer 241 polarimeter. IR spectra were recorded on a Perkin-Elmer 1720 FTIR spectrometer. Mass spectra were recorded on Micromass LCT or PE Sciex API 150EX instruments. TLC was performed on Merck $60F_{254}$ precoated silica plates and spots were detected by immersing the plate in sulphuric acid (2 M) then charring. Vacuum liquid chromatography[21] (VLC) was performed with silica gel 60 H (Merck, 5–40 μm). The product was pre-dried onto silica gel 60 (Merck, 40–63 μm, 1 g of silica per gram substrate) then loaded onto the VLC column before elution with an increasing concentration of ethyl acetate in hexanes. Sinter funnel filtrations were performed with silica gel 60 (Merck, 40–63 μm). Analytical HPLC was performed on a Waters system equipped with a 600E pump and a 996 PDA detector on a Nova-Pak C18 (3.9×50 mm, 4 μm, 60 Å) column. The program used was run at 2 mL/min in water-acetonitrile with the following linear gradient: initial 92:8; 1 min 92:8; 7 min 65:35; 12.5 min 5:95; 13 min 5:95; 13.5 min 92:8; 20 min 92:8. Preparative HPLC was performed on a Waters system with a Delta 600 pump and 996 PDA detector on a stack of three Prep Nova-Pak H C18 (40×100 mm, 6 μm, 60 Å) RCM units. Unless stated otherwise, the program used water-acetonitrile with the following linear gradient: initial 95:5 at 0 mL/min; 1 min 95:5 at 30 mL/min; 69 min 20:80 at 30 mL/min; 79 min 20:80 at 30 mL/min; 80 min 20:80 at 0 mL/min. Fractions were collected every 40 s and the product was extracted into ethyl acetate, dried over $MgSO_4$, filtered and concentrated *in vacuo*. All solvents for reactions were dried and distilled before use. Crystallizations were from CH_2Cl_2-hexane.

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1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(2,4-dimethoxybenzylidenamino)-β-D-glucopyranose (4): D-Glucosamine (21.56 g, 100 mmol) and 2,4-dimethoxybenzaldehyde (16.62 g, 100 mmol) were shaken in aq sodium hydroxide (100 mL, 1.0 M, 100 mmol) for 18 h at rt.[15,22] The white solid was filtered and washed with ice cold water (100 mL), ethanol (100 mL) and ether (100 mL) then dried under high vacuum for 4 h. The resultant white powder was crushed and then dried under high vacuum for an additional 1 h to yield 2-deoxy-2-(2,4-dimethoxybenzylidenamino)-D-glucopyranose **3** (25.8 g, 79%) which was used in the next reaction.

A solution of crude **3** (6.54 g, 20.0 mmol) in pyridine (32 mL, 400 mmol), cooled to 0 °C, and acetic anhydride (19 mL, 200 mmol) was added dropwise. The reaction was stirred for 18 h at rt then ethyl acetate (100 mL) was added. The product was washed with excess saturated aq $NaHCO_3$ solution, brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. Toluene (2×100 mL) was added and the mixture concentrated *in vacuo* to give title compound **4** as a viscous pale orange oil, which was contaminated with about 10% of 2,4-dimethoxybenzaldehyde; the product was used directly in the next reaction. A pure sample of the imine could be prepared by VLC, eluting with ethyl acetate in hexanes (0:1 to 1:1): $[\alpha]_D^{22}$ +59.9° (*c* 1.0 CH_2Cl_2); ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.90 (s, 3H), 2.02 (s, 3H), 2.03 (s, 3H), 2.09 (s, 3H), 3.45 (dd, 1H, *J* = 9.6, 8.3 Hz, H-2), 3.82 (s, 3H), 3.84 (s, 3H), 3.96 (ddd, 1H, *J* = 10.0, 4.6, 2.1 Hz, H-5), 4.13 (dd, 1H, *J* = 12.4, 2.1 Hz, H-6), 4.36 (dd, 1H, *J* = 12.4, 4.6 Hz, H-6′), 5.14 (dd, 1H, *J* = 10.0, 8.8 Hz, H-4), 5.40 (dd, 1H, *J* = 9.6, 8.8 Hz, H-3), 5.95 (d, 1H, *J* = 8.3 Hz, H-1), 6.42 (d, 1H, *J* = 2.3 Hz), 6.49 (dd, 1H, *J* = 8.7, 2.3 Hz), 7.81 (d, 1H, *J* = 8.7 Hz), 8.56 (s, 1H, N—H); ^{13}C NMR (125 MHz, $CDCl_3$): _ 20.23, 20.41, 20.46, 20.52, 55.25, 55.37, 61.65, 67.88, 72.52, 72.75, 73.05, 93.09, 97.67, 105.35, 116.99, 128.83, 160.14, 160.37, 163.52, 168.52, 169.31, 169.57, 170.34; HRMS (FAB): *m/z* calcd for $C_{23}H_{30}NO_{11}$ $[M+H]^+$ 496.1819; found 496.1819; analytical HPLC, 11.12 min.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(2,4-dimethoxybenzylamino)-β-D-glucopyranose (**6**): Sodium cyanoborohydride (1.51 g, 24 mmol) was added to crude **4**, (from the previous reaction) in THF-H_2O (50 mL, 20:1) and the reaction was stirred at rt under argon for 60 min. Saturated aq ammonium chloride solution (20 mL) was added and the reaction mixture stirred for 5 min, next 1.0 M aq HCl was added until pH 5. The mixture was stirred for 5 min, then neutralised with saturated aq $NaHCO_3$ solution. The product was extracted with ethyl acetate (3×100 mL), and the organic phase washed with brine, then dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a yellow oil. Purification by column chromatography eluting with hexanes and ethyl acetate or by preparative HPLC (program used water-acetonitrile with the following gradient: initial 92:8 at 0 mL/min; 1 min 92:8 at 30 mL/min; 79 min 20:80 at 30 mL/min; 80 min 20:80 at 0 mL/min) gave title compound **6** as a white foam (5.91g, 59%, two steps): $[\alpha]_D^{22}$ +29.5° (*c* 1.0 CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 1.94 (s, 3H), 1.98 (s, 3H), 2.04 (s, 3H), 2.14 (s, 3H), 2.88 (dd, 1H, *J* = 9.8, 8.5 Hz, H-2), 3.64 (d, 1H, *J* = 13.2 Hz, C*h*H′-Ar), 3.75 (ddd, 1H, *J* = 9.8, 4.7, 2.4 Hz, H-5), 3.76 (s, 3H), 3.78 (s, 3H), 4.04 (dd, 1H, *J* = 12.4, 2.1 Hz, H-6), 4.27 (dd, 1H, *J* = 12.4, 4.7 Hz, H-6′), 4.98 (m, 1H, H-4), 5.03 (m, 1H,

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H-3), 5.55 (d, 1H, J = 8.5 Hz, H-1), 6.41 (2H, m), 7.05 (m, 1H); ^{13}C NMR ($CDCl_3$): _ 20.49, 20.54, 20.59, 20.93, 47.38, 55.18, 55.26, 59.53, 61.72, 68.39, 72.31, 73.78, 95.26, 98.65, 103.75, 120.47, 130.47, 158.47, 160.21, 168.88, 169.54, 170.49, 170.52; IR $_{max}$ (cm^{-1}) 3472, 2938, 1752, 1614, 1589, 1508, 1368, 1225, 1157, 1069, 1042; HRMS (FAB): *m/z* calcd for $C_{23}H_{30}NO_{11}$ $[M+H]^+$ 498.1975; found 498.1960; analytical HPLC, 10.69 min.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(*N*-(2,4-dimethoxybenzyl)-acetamido)-β-D-glucopyranose (7). Compound **6** (6.30 g, 12.67 mmol) and acetic anhydride (2.4 mL, 25 mmol) were stirred together in CH_2Cl_2 (25 mL) for 18 h at rt. The reaction mixture was diluted with CH_2Cl_2 (25 mL), then washed with saturated aq sodium bicarbonate solution (2×30 mL), brine (30 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a white foam. The product was over 95% pure by TLC and analytical HPLC, but purification by preparative HPLC was normally carried out to give title compound **7** as a white foam (6.20 g, 91%); mp 133–134.5 °C; $[\alpha]_D^{25}$ +14.7° (*c* 1.0 CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 1.82 (s, 1H), 1.93 (br. s, 4H), 2.00 (s, 1H), 2.01 (s, 2H), 2.04 (s, 1H), 2.06 (s, 2H), 2.07 (s, 1H), 2.17 (br. s, 2H), 2.31 (s, 1H), 3.28 (br. s, 0.5H), 3.73 (ddd, 0.5H, J = 10.2, 4.5, 2.1 Hz), 3.77 (s, 1H), 3.81 (s, 1.5H), 3.81 (m, 0.5H), 3.82 (s, 2.5H), 3.88 (s, 1H), 3.92 (m, 0.5H), 4.04 (m, 1H), 4.23 (d, 0.67H, J = 16.2 Hz), 4.29 (m, 0.5H), 4.35 (dd, 0.5H, J = 12.6, 4.5 Hz), 4.46 (d, 0.67H, J = 16.2 Hz), 4.87 (d, 0.5H, 15.8 Hz), 5.01 (m, 0.5H), 5.10 (dd, 0.5H, J=10.2, 9.0 Hz), 5.45 (d, 0.5H, J = 8.7 Hz), 5.55 (dd, 0.5H, J = 10.7, 9.0 Hz), 6.16 (m, 0.67H), 6.43 (m, 2H), 6.65 (br. s, 0.5H), 7.11 (br. s, 0.67H), 7.23 (m, 0.33H); HRMS (FAB): *m/z* calcd for $C_{25}H_{34}NO_{12}$ $[M+H]^+$ 540.2081; found 540.2098; analytical HPLC: 10.36 min.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-(*N*-(2,4-dimethoxybenzyl)-acetamido)-D-glucopyranose (8). Compound **7** (10.0 mmol, 5.38 g) and hydrazinium acetate (1.10 g, 12.0 mmol) were stirred together in DMF (20 mL) for 18 h, at rt, under argon. The reaction mixture was diluted with ethyl acetate (100 mL), then washed sequentially with water (2×100 mL), saturated aq $NaHCO_3$ (30 mL) and brine (30 mL), then dried over $MgSO_4$, filtered and concentrated *in vacuo* to give a white foam (4.86 g, 98%). The product was pure apart from a small amount of DMF, which could be removed by flash column chromatography, eluting with chloroform (100 mL) to give pure title compound **8** as a white foam (4.13g, 83%): mp 73–74.5 °C; $[\alpha]_D^{25}$ +19.2° (*c* 1.0 CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 2.00 (br. s, 3H), 2.02 (s, 3H), 2.06 (s, 3H), 2.23 (br. s, 3H), 3.81 (s, 3H), 3.83 (s, 3H), 4.01 (dd, 1H J = 12.0, 1.7 Hz), 4.07 (m, 1H), 4.21 (dd, 0.5H, J = 12.0, 4.9 Hz), 4.32 (m, 1.5H), 4.70 (d, 1H, J = 15.6 Hz), 4.80 (m, 1H), 5.03 (m, 1H), 6.15 (br. s, 1H), 6.47 (2H, m), 7.07 (m, 1.5H), 7.23 (m, 0.5H); HRMS (FAB): *m/z* calcd for $C_{25}H_{33}NO_{12}$ $[M+H]^+$ 498.1975; found 498.1975; analytical HPLC: 8.86 and 9.29 min (equilibrating anomeric mixture)

3,4,6-Tri-*O*-acetyl-2-deoxy-2-(*N*-(2,4-dimethoxybenzyl)-acetamido)-α-D-glucopyranosyl trichloroacetimidate (9). A solution of hemiacetal **8** (1.49 g, 3.0 mmol) and trichloroacetonitrile (3.0 mL, 30 mmol) in CH_2Cl_2 (15 mL) under ar-

gon in the presence of molecular sieves, was cooled to −20 °C, and DBU (112 μL, 0.75 mmol) was added dropwise. After stirring for for 30 min at −20 °C, the solution was warmed to rt over 30 min. The reaction was filtered through a pad of Celite eluting with CH_2Cl_2 (20 mL) and concentrated *in vacuo* to give a dark brown oil which was purified by column chromatography eluting with 10–50% ethyl acetate in hexanes affording title compound **9** as a white powder (986 mg, 51%) with anα/β ratio of ~1:1. Purification by preparative HPLC gave the α-anomer as the sole product; mp 64.5–65.5 °C; $[\alpha]_D^{25}$ +85.0° (*c* 1.0 CH_2Cl_2); ^{1}H NMR (acetone-d_6): δ 1.74 (s, 3H), 1.92 (s, 3H), 1.95 (s, 3H), 1.99 (s, 3H), 3.77 (s, 3H), 3.81 (s, 3H), 4.09 (dd, 1H, J = 12.4, 2.1 Hz, H-6), 4.25 (dd, 1H, J = 12.4, 4.7 Hz, H-6′), 4.30 (ddd, 1H, J = 10.2, 4.7, 2.1 Hz, H-5), 4.47 (d, 1H, J = 19.2 Hz), 4.61 (d, 1H, J = 19.2 Hz), 5.16 (dd, 1H, J = 10.2, 8.8 Hz, H-4), 5.34 (dd, 1H, J = 11.7, 3.4 Hz, H-2), 5.61 (dd, 1H, J = 11.7, 8.8 Hz, H-3), 6.51 (m, 2H), 6.53 (d, 1H, J = 3.4 Hz, H-1), 6.91 (m, 1H), 9.4 (s, N—H); calcd for $C_{25}H_{31}Cl_3N_2O_{11}$ [M]: 640.10 (monoisotopic), 641.88 (average), [M—C_2NCl_3]: 497.1897 (monoisotopic), [M—C_2HONCl_3]: 480.1870 (monoisotopic); negative ion ESMS found *m/z* 641.0 $[M—H]^-$; positive ion ESMS found *m/z*: 498.23, 480.28; analytical HPLC: 11.73 min.

General procedure for glycosylation with acetates 5, 7, and 11 in CH_2Cl_2 or toluene. The glycosyl donor (0.5 mmol) and 3-nitrobenzyl alcohol (**10**, 0.5 mmol) were stirred together in CH_2Cl_2 or toluene (5 mL), respectively, at rt under argon in the presence of molecular sieves. After 10 min, TMSOTf (0.5 mmol) or $BF_3.OEt_2$ (0.5 mmol) was added, and the reaction was heated to 100 °C under argon for 18 h. The reaction was cooled to rt, and water (0.5 mL) and CH_2Cl_2 (25 mL) were added. The organic phase was dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give an oil. Purification was achieved by preparative HPLC. Tables 1 and 2 summarise the data.

General procedure for glycosylation with trichloroacetimidates in CH_2Cl_2. The trichloroacetimidate donor **9** (128 mg, 0.20 mmol) and 3-nitrobenzyl alcohol (**10**, 31 mg, 0.20 mmol) were dissolved in CH_2Cl_2 (5 mL) at −20 °C, under argon, and TMSOTf (0.02 mmol) or $BF_3.OEt_2$ (0.02 mmol) in CH_2Cl_2 (0.1 mL) was added. The reaction was stirred at −20 °C to −10°C for 1 h (TLC indicated no reaction at this temperature), then stirred at rt for 18 h. Water (1mL) was added, and the product extracted with ethyl acetate (2×10mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give an oil. The product was purified by column chromatography eluting with 0–100% ethyl acetate in hexanes to give the products as described in the text.

3-Nitrobenzyl 2-Acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glycopyranoside (12). Mp 182–183°C; $[\alpha]_D^{25}$ −31.2° (*c* 1.0 CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 1.98 (s, 3H), 2.03 (s, 3H), 2.05 (s, 3H), 2.11 (s, 3H), 2.17 (s, 3H), 3.73 (ddd, 1H, J = 10.0, 4.7, 2.6 Hz, H-5), 4.09 (dt, 1H, J = 10.7, 8.5 Hz, H-2), 4.25 (dd, 1H, J = 12.4, 2.6 Hz, H-6), 4.38 (dd, 1H, J = 12.4, 4.7 Hz, H-6′), 4.64 (d, 1H, J = 12.8 Hz), 4.82 (d, 1H, J = 8.5 Hz, H-1), 4.99 (d, 1H, J = 12.8 Hz), 5.16 (dd, 1H, J = 10.0, 9.2 Hz, H-4), 5.25 (dd, 1H, J = 10.7, 9.2 Hz, H-3), 5.78 (s, 1H, J = 8.5

Hz, N—H), 7.52 (m, 1H), 7.63 (m, 1H), 8.17 (m, 2H); ^{13}C NMR ($CDCl_3$): δ 20.51, 20.56, 20.63, 23.12, 54.49, 62.01, 68.57, 69.11, 71.93, 72.12, 100.07, 122.07, 122.65, 129.34, 133.26, 139.49, 148.25, 169.29, 170.47, 170.58, 170.75; HRMS (FAB): *m/z* calcd for $C_{21}H_{27}N_2O_{11}$ $[M+H]^+$ 483.1615; found 483.1622; analytical HPLC: 8.88 min.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(2,4-dimethoxybenzylamino)-β-D-glucopyranose (13). Colourless oil; ^{1}H NMR ($CDCl_3$): δ 1.97 (s, 3H), 1.98 (s, 3H), 1.99 (s, 3H), 2.16 (s, 3H), 2.95 (dd, 1H, J = 10.7, 3.6 Hz, H-2), 3.70 (d, 1H, J = 13.6 Hz), 3.73 (d, 1H, J = 13.6 Hz), 3.78 (s, 3H), 3.82 (s, 3H), 3.97 (dd, 1H, J = 12.4, 2.6 Hz, H-6), 4.06 (ddd, 1H, J = 10.2, 4.3, 2.6 Hz, H-5), 4.21 (dd, 1H, J = 12.4, 4.3 Hz, H-6′), 4.98 (dd, 1H, J = 10.2, 9.4 Hz, H-4), 5.16 (dd, 1H, J = 10.7, 9.4 Hz, H-3), 6.13 (d, 1H, J = 3.6 Hz, H-1), 6.46 (m, 1H), 6.52 (m, 1H), 7.17 (m, 1H); analytical HPLC: 9.69 min.

3-Nitrobenzyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-(*N*-(2,4-dimethoxybenzyl)-acetamido)-δ-D-glucopyranoside (14). Colourless foam; $[\alpha]_D^{25}$ −25.3° (*c* 1.0 CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ 1.84 (br. s, 2H), 2.00 (br. s, 2H), 2.01 (s, 0.5H), 2.04 (s, 0.5H), 2.05 (s, 0.5H), 2.07 (s, 4H), 2.08 (s, 0.5H), 2.17 (s, 2H), 3.24 (br. s, 0.5H), 3.60 (ddd, 0.5H, J = 10.0, 4.7, 2.3 Hz), 3.65 (d, 0.5H, 11.7 Hz), 3.71 (s, 0.5H), 3.74 (s, 3H), 3.75 (br. s, 1.5H), 3.81 (m, 1H), 3.88 (s, 1H), 4.00 (dd, 0.5H, J = 10.7, 8.3 Hz), 4.08–4.5 (m, 4H), 4.58 (d, 0.5H, J = 11.5 Hz), 4.64 (br. s, 0.5H), 4.96 (m, 1.5H), 5.11 (dd, 0.5H, J = 10.0, 8.9 Hz), 5.62 (dd, 0.5H, J = 10.6, 8.9 Hz), 5.70 (br. s, 0.5H), 6.10 (br. s, 0.5H), 6.24 (m, 1H), 6.33 (br. s, 0.5H), 6.43 (d, 0.5H, J = 2.4 Hz), 7.11 (m, 0.5H), 7.49 (m, 2H), 7.99 (0.5H, m), 8.14 (1.5H, m); HRMS (FAB): *m/z* calcd for $C_{30}H_{37}N_2O_{13}$ $[M+H]^+$ 633.2296; found 633.2295; analytical HPLC: 11.85 min.

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