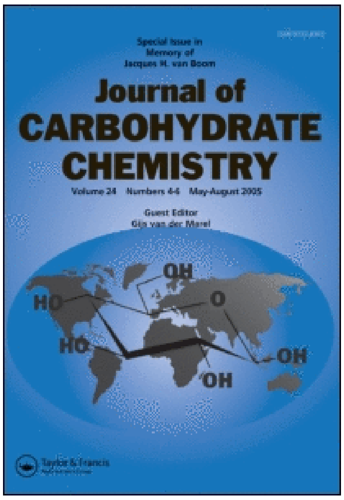

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Oligosaccharide synthesis using aminosugars requires the presence of a suitable amino protecting group. A number of protecting groups are currently used, and while many display favorable properties, most agents available still suffer from certain disadvantages. This report details the use of a hydrazine labile aminosugar protecting group, *N*-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl] (Dde), which can be introduced and removed in a facile and cost-effective manner.

Keywords Carbohydrates, Vinylogous amides, Protecting group

INTRODUCTION

Aminosugars are important constituents of various glycoconjugates and biologically relevant oligosaccharides.[1] Examples include peptidoglycans, mucopolysaccharides, glycopeptides and proteins, oligosaccharides of human milk, and blood group determinants. Aminosugars are also often encountered in bacterial and tumor-associated carbohydrate antigens.[2]

There have been various methods reported for the formation of 2-deoxy 2-*N*-protected carbohydrate donors for the synthesis of 1,2-*trans*-glycosides.

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2-Deoxyphthalimido donors were the most commonly used in 1980s.[3] More recently, tetrachlorophthaloyl (TCP),[4] pentenoyl,[5] dithiasuccinoyl (Dts),[6] allyloxycarbonyl (Alloc),[7,8] 2,2,2-trichloroethyloxycarbonyl (Troc),[9] *N,N*-diacetyl,[10] 2,5-dimethylpyrrole,[11] and dimethylmaleoyl (DMM)[12] protection has been used for 1,2-*trans*-glycosylation of aminosugars.

There has been to date an absence of suitable *N*-protecting groups for 1,2-*cis*-glycosylation of aminosugars. The azide group has proven effective as a masked nonparticipating amino functionality, thereby allowing the synthesis of 1,2-cis-linked 2-amino-2-deoxy glycosides.[13] However, there are various problems associated with the preparation of 2-azido-2-deoxy sugars.[14–19] Other nonparticipating groups that have been reported include 2,4-dinitrophenyl and *p*-methoxybenzylimino, both of which result in loss of the desired product.[20]

In solid-phase peptide synthesis (SPPS), *N*-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl] (Dde) has been used effectively as a lysine side chain amino protecting group.[21] Further, a derivatized Dde group has demonstrated efficacy as a linker for both solid-phase carbohydrate and peptide synthesis.[22] With similar structural characteristics to Dde, the recently reported (1,3-dimethyl-2,4,6(1H,3H,5H)-trioxopyrimidine-5-ylidene)methyl (DTPM) protecting group has displayed some nonparticipating characteristics.[23]

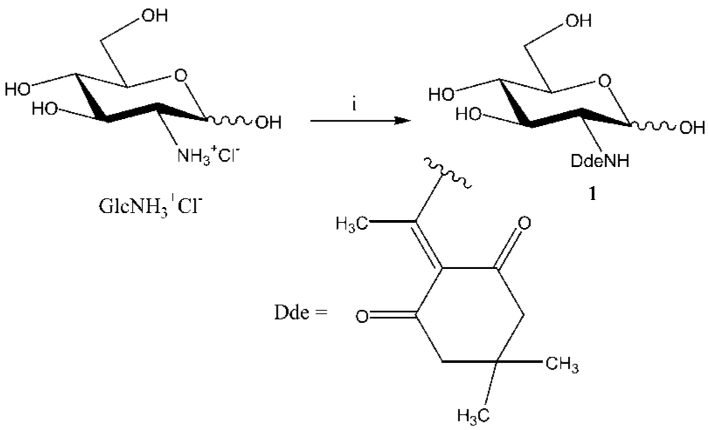
Herein, we report the investigations in our laboratory directed toward determining the efficacy of the Dde group as an amino sugar protecting group. Furthermore, a short study on the potential nonparticipating effect of the Dde group for the synthesis of amino-sugar containing glycoconjugates has been carried out.[24]

RESULTS AND DISCUSSION

Dde Protection of Aminosugars

Generally, Dde-type vinylogous amide protection of aminosugars can be achieved in good yield by refluxing an unprotected aminosugar with the commercially available 2-acetyldimedone in alcohol. If required, secondary and tertiary bases can catalyse the reaction. Typically, glucosamine hydrochloride was Dde protected by refluxing with 2-acetyldimedone in methanol to give compound **1** (Sch. 1).

As mentioned, it was of interest to examine the stability of the Dde protecting group to common carbohydrate chemistries, as well as the protecting group's influence on the outcome of various glycosylation reactions. To this end several suitably protected Dde-containing donor sugars were synthesized. Compound **1** was acetylated with acetic anhydride in pyridine to give glucopyranose **2** as a crystalline solid in 86% yield. Peracetate **2** was



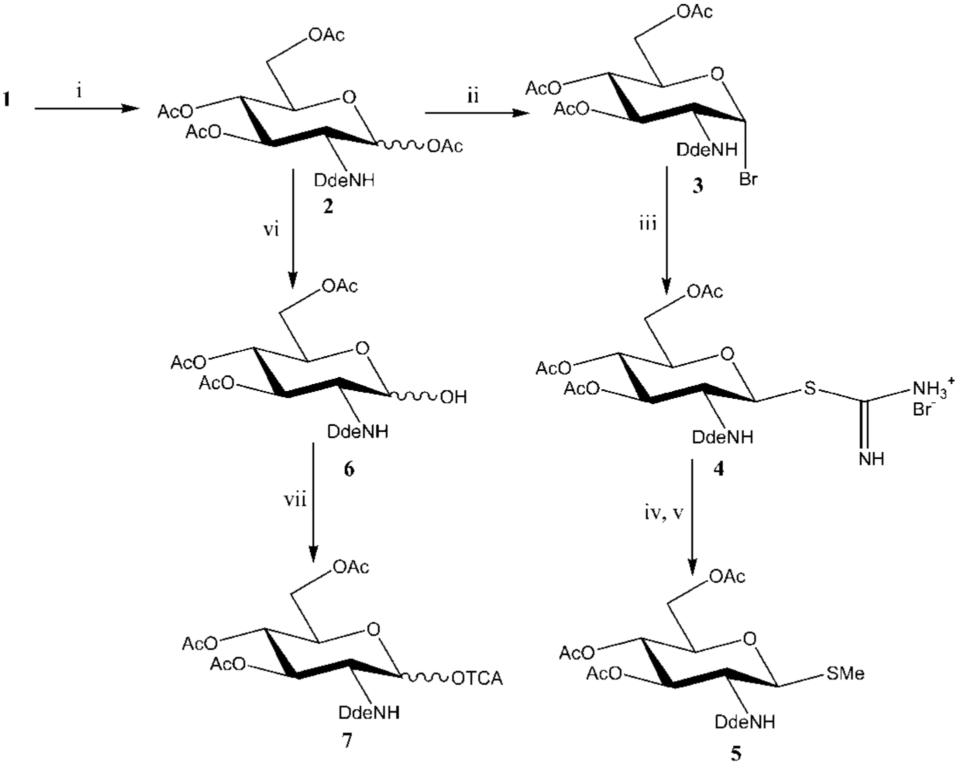
Scheme 1: *Conditions*: i. 2-Acetyldimedone/MeOH (78%).

treated with 45% HBr/AcOH at rt to give the solid glycosyl bromide **3** in good yield. Bromosugar **3** was also found to be a stable crystalline solid at rt. Bromosugar **3** was refluxed in acetone with thiourea to give the isothiouronium salt **4**. Under phase-transfer conditions uronium salt **4** was treated with $Na_2S_2O_5$ followed by reaction with methyl iodide (MeI) in methanol to give thiomethyl glycoside **5**. In an alternative sequence, peracetate **2** was converted with piperidine to hemiacetal **6**. Subsequent treatment of hemiacetal **6** with trichloroacetonitrile in the presence of 1,8-diazabicyclo(5.4.0)-undec-7-ene (DBU) gave the trichloroacetimidate **7** in an α/β ratio of 12/1 (Sch. 2).

The stability of the Dde group to other common protecting group manipulations was also examined (Sch. 3). Under Zemplen conditions, thioglycoside **5** was converted to triol **8** in good yield. Experience in our laboratories has shown that the Dde group shows far greater stability to Zemplen conditions than, for example, the phthalimido group. Treatment of **8** with α,α-dimethoxytoluene (α,α-DMT) and catalytic *p*-toluenesulphonic acid (*p*-TsOH) in acetonitrile provided benzylidene protected **9**, which was further derivatized by reaction with biphenylcarbonylchloride to give the fully protected derivative **10**. The benzylidene ring of derivative **10** was then cleaved with *p*-TsOH in MeCN/MeOH to give diol **11**. Triol **8** was also treated with *t*-butyldiphenylsilylchloride in the presence of imidazole to give diol **12**. Similarly, triol **8** was treated with trityl chloride in pyridine to give compound **13**. Triol **8** was then regenerated from compounds **12** and **13** by treatment with tetrabutylammoniumfluoride and *p*-TsOH, respectively.

Glycosylation Studies with Dde Protected Aminosugars

Introductory glycosylation studies were carried out with the previously formed Dde-protected donor sugars: peracetate **2**, bromosugar **3**, thioglycoside **5**,

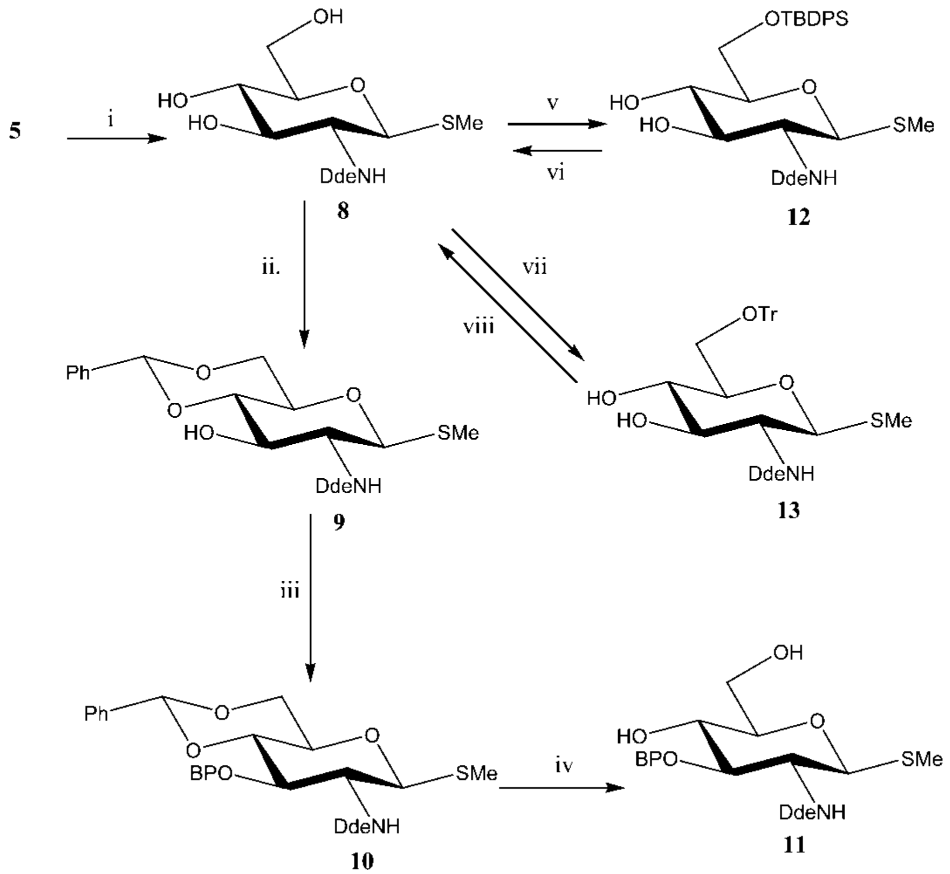


Scheme 2: *Conditions*: i. Ac_2O/Py; ii. HBr/AcOH, DCM; iii. Thiourea, Acetone; iv. $Na_2S_2O_5$, 1,2-DCE; v. K_2CO_3, Acetone/Water, MeI; vi. Piperidine, DMF; vii. Trichloroacetonitrile, DBU.

and trichloroacetimidate **7** and 3 acceptors (methanol, 4-phenylbenzylalcohol, and 1,2-3,4-di-*O*-isopropylidene-α-D-galactopyranose). Surprisingly, sugars **2** and **5** were unable to be activated using standard conditions and were recovered after the coupling reaction (Sch. 4). Although a disappointing result, this failure to activate thiomethyl glycosides does open up interesting opportunities in armed/disarmed-type glycosylations, whereby the Dde group is employed to effectively mask a thiomethylglycoside leaving group.

More successful glycosylations were carried out with the Dde-protected bromosugar and trichloroacetimidate. Bromosugar **3** was reacted with 4-phenylbenzylalcohol, methanol, and 1,2-3,4-di-*O*-isopropylidene-α-D-galactopyranose employing silver triflate as a promoter. Similarly, trichloroacetimidate **7** was reacted with 4-phenylbenzylalcohol and 1,2-3,4-di-*O*-isopropylidene-α-D-galactopyranose under borontrifluorideetherate activation (Sch. 5, results provided in Table 1).

Results in Table 1 indicate that there is considerable nonparticipating characteristics to both Dde donor sugars **3** and **7**.

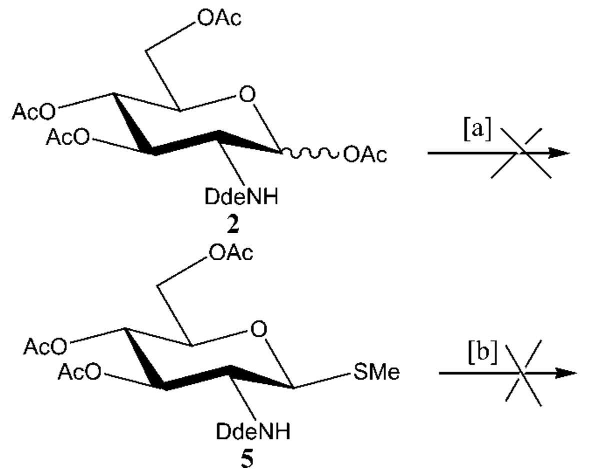


Scheme 3: *Conditions*: i. NaOMe/MeOH; ii. α,α-DMT, MeCN, *p*-TsOH; iii. Biphenylcarbonylchloride, DMAP, 1,2-DCE; iv. MeCN/MeOH, *p*-TsOH; v. TBDPS-Cl, Imidazole, 1,2-DCE; vi. TBAF, THF; vii. Trityl chloride, Pyridine; viii. *p*-TsOH, MeCN, MeOH.

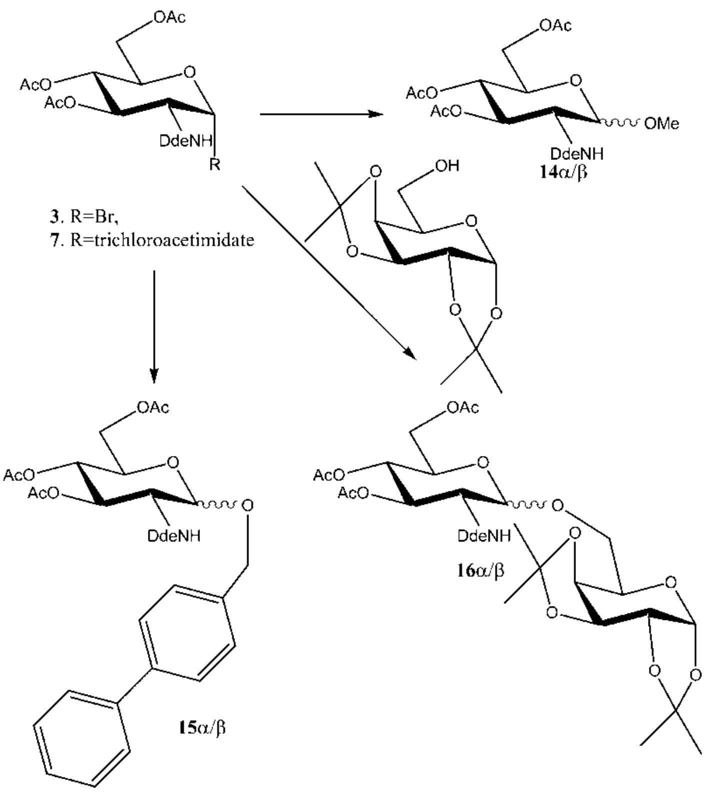
So far only methanol, di-*O*-isopropylidene-D-galactose, and a benzylic alcohol have been successfully employed as glycosylation acceptors. Some less reactive acceptors such as compound **9** were trialed without success. Experiments with less reactive acceptors were typically low yielding ($\sim$15%) with an α/β ratio favoring 1,2-*trans*-glycoside formation.

Deprotection of Dde-Protected Aminosugars

The Dde group is labile to ammonia, hydrazine, and primary amines (ethanolamine, ethylenediamine, n-butylamine, hydroxylamine, etc.) at rt. The Dde group also exhibits some lability toward aqueous hydroxides and under some conditions is susceptible to alkylation. Unwanted alkylation of the Dde group was shown to deactivate it to the conditions required for cleavage. The



Scheme 4: *Conditions*: (a) (i) $SnCl_4$ or (ii) TMSOTf and primary or secondary alcohol acceptor, (b) (i) DMTST or (ii) DMTSB or (iii) MeOTf and primary or secondary alcohol acceptor.



Scheme 5: Glycosylation reactions.

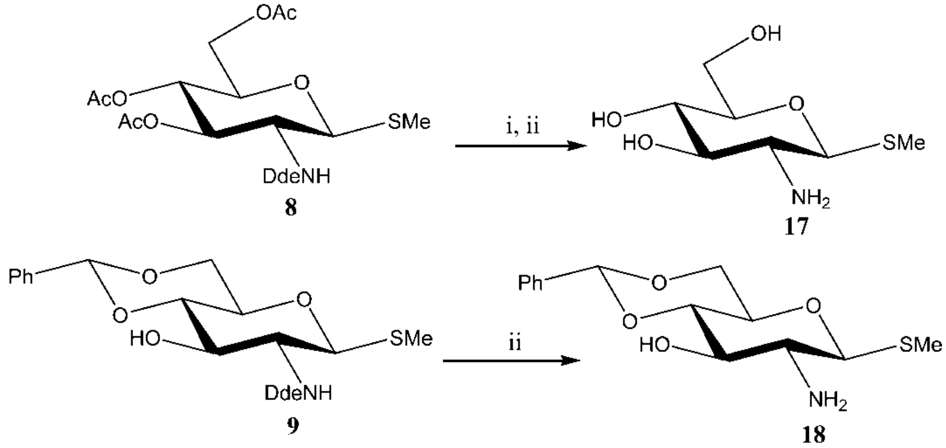
Table 1: Results of glycosylations with Dde protected aminosugar donors.

Entry	Donors	Acceptors	Products	Yields	α/β Ratio
1	**3**	Methanol	**14**α/β	81	13 : 1
2	**3**	4-Phenylbenzylalcohol	**15**α/β	72	7 : 10
3	**3**	1,2-3,4-di-*O*-Isopropylidene-α-D-galactopyranose	**16**α/β	86	1 : 1.75
4	**7**	4-Phenylbenzylalcohol	**15**α/β	74	2 : 3
5	**7**	1,2-3,4-Di-*O*-isopropylidene-α-D-galactopyranose	**16**α/β	48	1 : 2

following scheme (Sch. 6) provides an example of Dde cleavage by treatment with ammonia/methanol solution, resulting in amines **17** and **18** in high yield.

CONCLUSION

The results of our investigations have shown that the Dde-protecting group is stable to a wide range of carbohydrate chemistries. The excellent crystalline characteristics that the Dde group imparts to carbohydrate building blocks and the ease of its introduction and cleavage make it an ideal protecting group for the facile synthesis of monosaccharide donor sugars and derivatives. At this stage the capabilities of Dde as a nonparticipating group for the synthesis of 1,2-*cis*-glycosidic linkages have not been comprehensively explored; however, initial results indicate that in most cases the 1,2-*trans*-glycoside i.e.



Scheme 6: *Conditions*: i. MeOH/NaOMe; ii. NH_3/MeOH.

the beta anomer formed preferentially. The complete deactivation of thioglycoside donor sugars by Dde was unexpected but may prove to be useful in the coupling of complex oligosaccharides to aglycons and supports. Similarly, such deactivation may prove useful in the synthesis of repeating oligosaccharide motifs. So far the Dde group has proven to be a valuable tool in carbohydrate synthesis.

EXPERIMENTAL

General Methods

Purification was achieved by flash chromatography on silica gel (0.0404-0.063 mm, Amicon), using mobile phases as stated. Reaction progress was monitored by thin layer chromatography (TLC) on Kiesegel 60 F_{254} (Merck) using mobile phases as stated with detection by UV light and/or charring with 5% sulfuric acid. Solvents were evaporated under reduced pressure with a rotary evaporator. ^{1}H NMR and COSY spectra were obtained with a Bruker AM 500 instrument operating at a field of 500 MHz, a Brucker ARX 500 MHz, or a Varian Mercury 400 broadband spectrometer (internal standard Me_4Si, $\delta = 0.00$). Chemical shifts are reported in ppm (δ) referenced from solvent. Mass spectra were run with a VG analytical ZAB-SE instrument using fast atom bombardment (FAB) techniques -20 kV Cs^+ ion bombardment, with 2 μL of appropriate matrix, either 3-nitrobenzyl alcohol or thioglycerol with NaI (MeOH) solution, added when necessary to produce natriated species when no protonated molecular ions were observed, or on a PE SCIEX API 3000 MS SHIMADZU SLC/LC-10A HPLC gradient system.

2-Deoxy-2-*N*-(1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl)-D-glucopyranose (1)

To a mixture of sodium (143 mg, 6.21 mmol) completely dissolved in anhydrous methanol (30 mL), was added D-glucosamine hydrochloride (1.34 g, 6.21 mmol). The reaction mixture was stirred at rt for 5 min. 2-Acetyldimedone (1.69 g, 9.32 mmol) was added, and the reaction mixture was refluxed for 5 h. The reaction mixture was cooled and the product was precipitated by the addition of ether (200 mL) and collected by filtration to yield **1** as single anomer (1.66 g, 78%). R_f 0.37 (MeCN/H_2O 10:0.5); ^{1}H NMR (D_2O) δ 5.12 (d, 1H, $J_{1,2}$ 3.6 Hz, H-1), 3.60 (m, 6H, H-2, H-3, H-4, H-5, H-6a, H-6b), 2.38, 2.36 (2s, 3H, CH_3), 2.28, 2.27 (2s, 4H, 2 CH_2), 0.85 (s, 6H, 2 CH_3). HRMS (TOF) Calcd for $C_{16}H_{25}NO_{17}$: 343.1631. Found: 344.1676 $[M + H]^+$.

1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-*N*-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl]-α-D-glucopyranose (2)

A mixture of **1** (1.55 g, 4.51 mmol), pyridine (11 mL), and acetic anhydride (20 mL) was stirred at rt overnight. The reaction mixture was evaporated, and the product crystallized from MeOH (10 mL, −15°C) to afford **2** (1.95 g, 86%). R_f 0.35 (Hexane/EtOAc 1 : 1); ^{1}H NMR ($CDCl_3$) δ 13.70 (d, 1H, NH), 6.22 (d, 1H, $J_{1,2}$ 3.8 Hz, H-1), 5.44 (t, 1H, $J_{3,4}$ 9.9 Hz, H-3), 5.19 (t, 1H, $J_{4,5}$ 10.0 Hz, H-4), 4.39 (dd, 1H, $J_{6a,6b}$ 12.2 Hz, H-6b), 4.25 (m, 1H, $J_{5,6a}$ 1.2 Hz, $J_{5,6b}$ 3.9 Hz, H-5), 4.13 (dd, 1H, $J_{2,3}$ 9.8 Hz, H-2), 4.06 (dd, 1H, $J_{6a,6b}$ 12.2 Hz, H-6a), 2.58 (s, 3H, CH_3–C(NH–)=C<), 2.35 (s, 4H, 2 CH_2), 2.09, 2.03, 1.97 (3s, 9H, 3 CH_3 acetyl), 1.00 (s, 6H, 2 CH_3); HRMS (TOF) Calcd for $C_{24}H_{33}NO_{11}$: 511.2054. Found: 512.2145 $[M + H]^+$.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-*N*-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl]-α-D-glucopyranosyl bromide (3)

A mixture of **2** (2 g, 3.9 mmol) in DCM (5 mL) and HBr in acetic acid (45%) (5.0 mL) was stirred at rt for 1 h. The reaction mixture was diluted with cold CH_2Cl_2 (50 mL), and washed with cold H_2O (50 mL), cold saturated $NaHCO_3$ solution (50 mL), and cold H_2O (50 mL). The organic phase was dried over $MgSO_4$ and evaporated to afford **3** (1.88 g, 91%); R_f 0.35 (hexane/EtOAc 1 : 1); ^{1}H NMR ($CDCl_3$) δ 13.83 (d, 1H, NH), 6.45 (d, 1H, $J_{1,2}$ 3.7 Hz, H-1), 5.55 (t, 1H, $J_{3,4}$ 9.7 Hz, H-3), 5.23 (t, 1H, $J_{4,5}$ 9.9 Hz, H-4), 4.41 (m, 2H, H-6b, H-2), 4.26 (m, 1H, $J_{5,6a}$ 1.3 Hz, $J_{5,6b}$ 4.0 Hz, H-5), 4.14 (dd, 1H, $J_{6a,6b}$ 11.9 Hz, H-6b), 4.09 (dd, 1H, H-6a), 2.62 (s, 3H, CH_3–C(NH–)=C<), 2.41 (s, 4H, 2 × CH_2), 2.11, 2.04, 1.96 (3s, 9H, 3 CH_3 acetyl), 1.02 (s, 6H, 2 × CH_3); HRMS (TOF) Calcd for $C_{22}H_{29}BrNO_9$: 531.3767. Found: 532.1146 $[M + H]^+$.

Methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-*N*-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl]-1-thio-β-D-glucopyranoside (5)

Thiourea (280 mg, 3.37 mmol) was added to a solution of **3** (2.05 g, 3.85 mmol) in acetone (10 mL). The mixture was refluxed for 30 min and then concentrated. The residue was purified by column chromatography ($CHCl_3$/MeOH, 5:1) yielding *S*-[3,4,6-tri-*O*-acetyl-2-Deoxy-2-*N*-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl]-β-D-glucopyranosyl]-isothiouronium bromide 4 (1.72 g, 85%); R_f 0.46 ($CHCl_3$/MeOH 5:1). To **4** (1.7 g, 3.25 mmol) was added a solution of $Na_2S_2O_5$ (538 mg, 0.225 mmol) in water (0.2 mL) and 1,2-dichloroethane (0.24 mL). The reaction mixture was kept under reflux at 85°C for 20 min. After dilution with CH_2Cl_2 (5 mL) the layers were separated. The organic phase was washed with water (3 mL), dried over $MgSO_4$, concentrated under reduced pressure, and purified by column chromatography (ether/MeOH 10 : 1) to yield the thioglycoside precursor to **5** (1.41 g, 87%). Then to a solution of the thioglycoside (1.17 mg, 2.4 mmol) in acetone (2.5 mL) was added K_2CO_3 (400 mg) in water (2.5 mL), followed by methyliodide (370 mg, 2.6 mmol). After 2 h the reaction mixture was concentrated under reduced pressure and dissolved in CH_2Cl_2 (50 mL) and the layers were separated. The organic phase was washed twice with water (50 mL), dried over $MgSO_4$, and evaporated. The residue was purified by chromatography (EtOAc/petroleum ether 2 : 1) to yield 5 (947 mg, 58%); R_f 0.44 (EtOAc/petroleum ether 2 : 1); ^{1}H NMR ($CDCl_3$) δ 13.96 (d, 1H, NH), 5.24 (t, 1H, $J_{3,4}$ 9.4 Hz, H-3), 5.09 (t, 1H, $J_{4,5}$ 9.8 Hz, H-4), 4.64 (d, 1H, $J_{1,2}$ 10.0 Hz, H-1), 4.30 (dd, 1H, $J_{1,2}$ 9.8 Hz, H-2), 4.01 (m, 3H, H-6a, H-6b, H-5), 2.60 (s, 3H, CH_3–C(NH–)=C<), 2.42 (s, 4H, 2 CH_2), 2.20 (s, 3H, SCH_3), 2.09, 2.02, 1.96 (3s, 9H, 3 AcO), 1.03 (s, 6H, 2 CH_3). HRMS (TOF) Calcd for $C_{23}H_{33}NO_9S$: 499.1876. Found: 500.1917 $[M+H]^+$.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-*N*-(1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl)-α-D-glucopyranose (6)

To a solution of **2** (0.5 g 0.98 mmol) in dry DMF (10 mL), piperidine (0.13 mL) was added. The reaction mixture was stirred at rt overnight, then concentrated under vacuum. The crude mixture was purified by chromatography (EtOAc/petroleum ether 2 : 1) to yield **6** (340 mg, 74%); R_f 0.44 ($CHCl_3$/EtOAc 1 : 1); ^{1}H NMR ($CDCl_3$) δ 13.81 (d, 1H, NH), 5.49 (t, 1H, $J_{3,4}$ 9.6 Hz, H-3), 5.28 (d, 1H, $J_{1,2}$ 3.3 Hz, H-1), 5.11 (t, 1H, $J_{4,5}$ 9.9 Hz, H-4), 4.42 (dd, 1H, $J_{2,3}$ 9.7 Hz, H-2), 4.39 (dd, 1H, $J_{6a,6b}$ 12.2 Hz, H-6b), 4.33 (dd, 1H, H-6a), 4.25 (m, 1H, $J_{5,6a}$ 1.2 Hz, $J_{5,6b}$ 3.9 Hz, H-5), 2.59 (s, 3H, CH_3–C(NH–)=C<), 2.37 (s, 4H, 2 CH_2), 2.10, 2.03, 1.96 (3s, 9H, 3 CH_3 acetyl), 1.01 (s, 6H, 2 CH_3). HRMS (TOF) Calcd for $C_{22}H_{31}NO_{10}$: 469.1948. Found: 470.1984 $[M+H]^+$.

2-Deoxy-2-*N*-(1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl)-3,4,6-tri-*O*-acetyl-α,β-D-glucopyranosyl trichloroacetimidate (7)

A mixture of **6** (1.7 g, 3.62 mmol) and trichloroacetonitrile (2.2 mL, 21.74 mmol) in CH_2Cl_2 (12 mL) was cooled to 0°C and 1,8-diazabicyclo(5.4.0)-undec-7-ene (108 μL, 0.72 mmol) added. The reaction mixture was stirred at 0°C for 1.5 h and at rt for 2 h. The solution was evaporated, and the residue purified by column chromatography yielding **7** (880 mg, 40%, $\alpha:\beta$, 12 : 1); R_f 0.61 ($CHCl_3$/EtOAc 1 : 1); ^{1}H NMR ($CDCl_3$) δ 13.74 (d, 1H, NH), 8.85, (s, 1H, NH), 6.48 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 5.55 (t, 1H, $J_{3,4}$ 10.0 Hz, H-3), 5.24

(t, 1H, $J_{4,5}$ 10.0 Hz, H-4), 4.26 (m, 4H, H-2, H-6a, H-6b, H-5), 2.67 (s, 3H, CH_3–C(NH–)=C<), 2.36 (s, 4H, 2 CH_2), 2.11, 2.08, 2.00 (3s, 9H, 3 CH_3 acetyl), 1.02, 1.04 (2 × s, 6H, 2 × CH_3). HRMS (TOF) Calcd for $C_{24}H_{31}Cl_3N_2O_{10}$: 613.8816. Found: 614.8947 $[M + H]^+$.

Methyl 2-deoxy-2-*N*-(1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl)-1-thio-β-D-glucopyranoside (8)

Sodium (10 mg, 0.44 mmoL) was reacted with anhydrous MeOH (25 mL), and then to the solution was added compound **5** (720 mg, 1.44 mmoL). The reaction mixture was stirred at rt overnight and then neutralized to pH 7 using Amberlite resin IR 120 (H^+). The resin was filtered out and the residue was concentrated under vacuum to yield compound **8** as a white powder (496 mg, 92%). R_f 0.1 (EtOAc/petroleum ethers 4 : 1); ^1H NMR ($CDCl_3$) δ 13.64 (d, 1H, NH), 4.68 (d, 1H, $J_{1,2}$ 9.8 Hz, H-1), 3.85 (t, 1H, $J_{2,3}$ 8.9 Hz, H-2), 3.79 (dd, 1H, $J_{5,6a}$ 1.3 Hz, $J_{6a,6b}$ 11.4, Hz, H-6a), 3.62 (dd, 1H, $J_{5,6b}$ 3.8 Hz H-6b), 3.59 (t, 1H, $J_{3,4}$ 9.7 Hz, H-3), 3.41 (m, 2H, H-4, H-5), 2.41 (s, 1H, SCH_3), 2.31 (s, 4H, 2 CH_2), 2.07 (s, 3H, CH_3–C(NH–)=C<), 0.88 (2 × s, 6H, 2 × CH_3). HRMS (TOF) Calcd for $C_{17}H_{27}NO_6S$: 373.1559. Found: 374.1602 $[M + H]^+$; $[\alpha]_D$—193.21°C ($c = 1.00$, MeOH).

Methyl 4,6-*O*-benzylidene-2-deoxy-2-*N*-(1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl)-1-thio-β-D-glucopyranoside (9)

Compound **8** (1 g, 2.68 mmol) and *p*-TsOH (10 mg, 52.6 μmol) were dissolved in dry acetonitrile (10 mL) and heated to 60°C. After equilibrium was reached α,α-dimethoxytoluene (600 mg, 4.02 mmol) was added to the reaction flask. The reaction was stirred at 60°C for 12 h after which additional *p*-TsOH (10 mg, 52.6 μmol) and α,α-dimethoxytoluene (200 mg, 1.34 mmol) were added to the reaction mixture. After a further 6 h the reaction mixture was neutralized with triethylamine (250 μL) and the solvent removed in vacuo. The reaction mixture was taken up in EtOAc (100 mL) and washed with saturated $NaHCO_3$ solution (3 × 100 mL). The organic layer was dried over Na_2SO_4 and the solvent removed in vacuo. The residue was purified by column chromatography (EtOAc/Petroleum ether 1:1) to afford compound **9** (900 mg, 81%); R_f 0.55 (EtOAc/Petroleum ether 2:1), ^{1}HNMR δ 13.78 (d, 1H, NH), 5.59 (s, 1-H, Ar-CH), 4.58 (d, 1H, $J_{1,2}$ 9.6 Hz, H-1), 4.42 (dd, 1H, $J_{4,5}$ 10.5 Hz, H-4), 3.92 (m, 2H, H-6a, H-6b), 3.81 (t, 1H, $J_{3,4}$ 10.2 Hz, H-3), 3.64 (t, 1H, $J_{2,3}$ 9.0 Hz, H-2), 3.60 (m, 1H, $J_{5,6a}$ 1.4 Hz, $J_{5,6b}$ 3.6 Hz, H-5), 2.67 (s, 3H, CH_3–C(NH–)=C<), 2.38 (s, 3H, 2 × CH_2), 2.23 (s, 3H, S-CH_3), 1.05 (s, 6H, 2 × CH_3). HRMS (TOF) Calcd for $C_{24}H_{31}NO_6S$: 461.1872. Found: 462.1895 $[M + H]^+$; $[\alpha]_D$−177.95°C ($c = 1.00$, MeOH).

Methyl 4,6-*O*-benzylidene-2-deoxy-2-*N*-(1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl)-3-*O*-(4-phenylbenzoyl)-1-thio-β-D-glucopyranoside (10)

A solution of biphenylcarbonylchloride (667 mg, 3.1 mmol) and 4-dimethylaminopyridine (378 mg, 3.1 mmol) in dry 1,2-DCE (5 mL) was stirred at rt for 10 min. Compound **9** (1.3 g, 2.8 mmol) was added portion-wise. The mixture was stirred at rt for 40 min and then cooled in a water and ice bath. The resultant suspension was filtered, the filtrate and diluted with DCM (25 mL) and washed with saturated $KHSO_4$ solution (200 mL) and water (200 mL). The organic phase was dried over $MgSO_4$ and the solvent removed in vacuo. The residue was crystallized from dichloromethane, diethylether to give **10** (1.5 g, 84%), R_f 0.60 (EtOAc/petroleum ether 1:1), ^{1}H NMR δ 13.84 (d, 1H, NH), 8.27 (m, 2H, Ar-BP), 7.63 (m, 5H, Ar-BP), 7.47 (m, 2H, Ar-BP), 7.41 (m, 2H, Ar), 7.33 (m, 3H, Ar), 5.66 (t, 1H, $J_{3,4}$ 9.6 Hz, H-3), 5.57 (s, 1H, benzylidene), 4.76 (d, 1H, $J_{1,2}$ 9.9 Hz, H-1), 4.48 (dd, 1H, $J_{4,5}$ 9.5 Hz, H-4), 4.20 (dd, 1H, $J_{2,3}$ 9.8 Hz, H-2), 3.91 (2 × t, 2H, H-6a, H-6b), 3.76 (m, 1H, H-5), 2.60 (s, 3H, CH_3–C(NH–)=C<), 2.38 (s, 3H, 2 × CH_2), 2.28 (s, 3H, S–CH_3), 1.03, 0.96 (2 × s, 4H, 2 × CH_2). HRMS (TOF) Calcd for $C_{37}H_{39}NO_7S$: 641.2512. Found: 642.2525 $[M+H]^+$; $[\alpha]_D$ −139.87°C ($c = 1.04$, MeOH).

Methyl 2-deoxy-2-*N*-(1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl)-3-*O*-(4-phenylbenzoyl)-1-thio-β-D-glucopyranoside (11)

A mixture of **10** (1 g, 1.56 mmol) in acetonitrile/methanol (24 mL, 1/1) with a catalytic amount of *p*-TsOH (5 mg) was stirred at 100°C for 24 h. The reaction mixture was cooled to rt, and concentrated in vacuo and any trace solvents removed by coevaporation with toluene (25 mL). The residue was taken up with DCM (25 mL) and washed two times with saturated $NaHCO_3$ solution (250 mL) and saturated brine solution (250 mL). The organic phase was dried over $MgSO_4$ and the solvent removed in vacuo to give a white solid **11**, (810 mg, 94%), R_f 0.09 (EtOAc/petroleum ether 3:1), ^{1}H–NMR δ 13.91 (d, 1H, NH), 8.02 (m, 2H, Ar), 7.63 (m, 5H, Ar), 7.49 (m, 2H, Ar), 5.38 (t, 1H, $J_{3,4}$ 9.5 Hz, H-3), 4.75 (d, 1H, $J_{1,2}$ 9.9 Hz, H-1), 4.12 (dd, 1H, $J_{4,5}$ 9.3 Hz, H-4), 4.05 (dd, 1H, $J_{6a,6b}$ 9.7 Hz, H-6a), 4.97 (m, 2H, H-2, H-6b), 3.66 (m, 1H, $J_{5,6a}$ 1.3 Hz, $J_{5,6b}$ 2.9 Hz H-5), 2.64 (s, 3H, CH_3–C(NH–)=C<), 2.35 (s, 3H, 2 × CH_2), 2.27 (s, 3H, S–CH_3), 1.01, 0.91 (2 × s, 4H, 2 × >CH_2). HRMS (TOF) Calcd for $C_{30}H_{35}NO_7S$: 553.2206. Found: 554.2182 $[M+H]^+$.

Methyl 6-*tert*-butyldiphenylsilyl-2-deoxy-2-*N*-(1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl)-1-thio-β-D-glucopyranoside (12)

To a solution of compound **8** (1 g, 2.7 mmol) in 1,2-DCE (12 mL) was added TBDPSCl (411 mg, 1.5 mmol) and DMAP (183 mg, 1.5 mmol). The reaction mixture was stirred at 80°C for 24 h and then cooled in a water and ice bath. The resultant suspension was filtered and the filtrate diluted with DCM (25 mL) and washed twice with saturated $KHSO_4$ solution (20 mL) and water (20 mL). The organic phase was dried over $MgSO_4$ and the solvent removed in vacuo. The residue was purified by column chromatography (EtOAc/ petroleum ether 3 : 1) to afford compound **12** (1.11 mg, 68%). R_f 0.62 (EtOAc/ Toluene 3 : 1), ^{1}H-NMR δ 13.88 (d, 1H, NH), 7.70 (m, 4H, Ar), 7.43 (m, 6H, Ar), 4.45 (d, 1H, $J_{1,2}$ 9.6 Hz, H-1), 3.95 (m, 2H, H-6b, H-6b), 3.77 (dd, 1H, $J_{2,3}$ 9.5 Hz, H-2), 3.76 (t, 1H, $J_{4,5}$ 9.8 Hz, H-4), 3.66 (t, 1H, $J_{3,4}$ 9.5 Hz, H-3), 3.48 (m, 1H, H-5), 2.62 (s, 3H, CH_3–C(NH–)=C<), 2.21 (s, 3H, S–CH_3), 1.07 (s, 9H, C–$(CH_3)_3$), 1.03 (s, 4H, 2 × >CH_2), 0.03 (s, 6H, 2 × CH_3). HRMS (TOF) Calcd for $C_{33}H_{45}NO_6Ssi$: 611.2835. Found: 612.2815 $[M+H]^+$; $[\alpha]_D$– 94.23°C ($c = 1.00$, MeOH).

Methyl 2-deoxy-2-*N*-(1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl)-6-*O*-trityl-1-thio-β-D-glucopyranoside (13)

Compound **8** (250 mg, 0.669 mmol) was dissolved in anhydrous pyridine (10 mL) and stirred with trityl chloride (560 mg, 2 mmol) at 50°C for 48 hours. The solvent was evaporated and trace amounts of pyridine removed by coevaporation with toluene (20 mL). The crude product was dissolved in $CHCl_3$ (50 mL) and washed with H_2O (50 mL), 10% citric acid solution (50 mL), saturated $NaHCO_3$ solution (50 mL) and saturated brine solution (50 mL). The aqueous washings were back extracted with $CHCl_3$ (50 mL) and the organic layers combined, dried over $MgSO_4$, filtered, and evaporated to dryness. The residue was chromatographed (EtOAc/toluene 3:1) to yield the desired product **13** (270 mg, 65%). R_f 0.25 (EtOAc/toluene 3 : 1), ^{1}H-NMR δ 13.68 (d, 1H, NH), 7.38 (m, 4H, Ar), 7.19 (m, 1H, Ar), 4.32 (d, 1H, $J_{1,2}$ 9.6 Hz, H-1), 3.74 (dd, 1H, $J_{2,3}$ 9.8 Hz, H-2), 3.56 (m, 2H, H-3, H-4), 4.38 (m, 3H, H-5, H-6a, H-6b), 2.56 (s, 3H, CH_3–C(NH–)=C<), 2.28 (s, 3H, 2 × CH_2), 2.12 (s, 3H, S-CH_3), 1.50 (s, 9H, C–$(CH_3)_3$), 0.97 (s, 4H, 2 × >CH_2). HRMS (TOF) Calcd for $C_{33}H_{45}NO_6SSi$: 611.2835. Found: 612.2815 $[M+H]^+$; $[\alpha]_D$–153,69°C ($c = 1.01$, MeOH).

Methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-*N*-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl]-α,β-D-glucopyranoside (14α, 14β)

To a solution of **3** (60 mg, 0.11 mmol) in dichloromethane (5 mL−15°C), was added silver trifluoromethanesulphonate (43 mg, 0.16 mmol) in MeOH (1 mL). The reaction mixture was stirred overnight and filtered and the filtrate evaporated. The residue was washed with saturated $NaHCO_3$ solution, dried over $MgSO_4$, and evaporated. The residue was purified by chromatography to yield methyl 3,4,6-tri-*O*-acetyl- 2-deoxy-2-*N*-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl]-*α*-D-glucopyranoside **14α** (40 mg, 75%); R_f 0.35 (hexane/EtOAc, 1 : 1); ^{1}H NMR ($CDCl_3$) δ 13.55 (d, 1H, NH), 5.40 (t, 1H, $J_{3,4}$ 9.7 Hz, H-3), 5.08 (t, 1H, $J_{4,5}$ 9.7 Hz, H-4), 4.82 (d, 1H, $J_{1,2}$ 3.4 Hz, H-1), 4.32 (dd, 1H, $J_{2,3}$ 9.4 Hz, H-2), 4.12 (m, 3H, H-5, H-6a, H-6b), 3.53 (s, 3H, OCH_3), 2.58 (s, 3H, CH_3–C(NH–)=C<), 2.41 (s, 4H, 2 CH_2), 2.11, 2.02, 1.94 (3s, 9H, 3 × CH_3 acetyl), 1.02 (s, 6H, 2 × CH_3), and methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-*N*-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl]-*β*-D-glucopyranoside **14β** (3 mg, 6%); R_f 0.33 (Hexane/EtOAc 1:1); ^{1}H NMR ($CDCl_3$) δ 13.84 (d, 1H, NH), 5.20 (t, 1H, $J_{3,4}$ 9.8 Hz, H-3), 5.09 (t, 1H, $J_{4,5}$ 9.9 Hz, H-4), 4.41 (d, 1H, $J_{1,2}$ 8.2 Hz, H-1), 4.32 (dd, 1H, $J_{2,3}$ 9.8 Hz, H-2), 4.09 (m, H, H-6a), 3.95 (m, 1H, H-6b), 3.75 (m, 1H, H-5), 3.48 (s, 3H, OCH_3), 2.57 (s, 3H, CH_3), 2.37 (s, 4H, 2 CH_2), 2.09, 2.03, 1.96 (3s, 9H, 3 CH_3(O)–), 1.02 (s, 6H, 2 × CH_3). HRMS (TOF) Calcd for $C_{23}H_{33}NO_{10}$: 483.2104. Found: 484.2145 $[M+H]^+$.

4-Phenylbenzyl-3,4,6-tri-*O*-acetyl-2-deoxy-2-*N*-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl]-α/β-D-glucopyranoside (15α, 15β)

From donor 3: Under an atmosphere of nitrogen compound **3** (200 mg, 376 μmmol), 4-phenylbenzyl alcohol (66 mg, 358 μmol) and 4 Å molecular sieves (200 mg) were combined in anhydrous DCM (2 mL). The reagents were stirred at rt for 4 h and cooled to 0°C, at which time silver triflate (138 mg, 537 μmol) was added. The reaction mixture was allowed to return to rt and stirred for a further 1.5 h. The reaction was neutralized by the addition of solid $NaHCO_3$, diluted with chloroform (50 mL), filtered through Celite, washed with saturated $NaHCO_3$ solution (2 × 50 mL) and saturated brine solution (50 mL), and dried over $MgSO_4$. The organic phase was evaporated and the resulting residue purified by column chromatography (1,2-DCE/EtOAc 6 : 1) to yield 4-phenylbenzyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-*N*-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl]-*α*/*β*-D-glucopyranoside (**15α**, **15β**) as a white solid (170 mg, 72%, (*α*:*β*, 7 : 10), R_f 0.35 (DCE-EtOAc 7-3). A small amount of each anomer could be purified: ^{1}H NMR (4-phenylbenzyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-*N*-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl]-*α*-D-glucopyranoside) **15α**, ($CDCl_3$)

δ 13.72 (d, 1H, NH), 7.43 (m, 9H, Ar), 5.48 (t, 1H, $J_{3,4}$ 9.3 Hz, H-3), 5.12 (t, 1H, $J_{4,5}$ 9.6 Hz, H-4), 5.00 (d, 1H, $J_{1,2}$ 3.5 Hz, H-1), 4.80 (2 × d, 2H, CH_2-Ar), 4.34 (dd, 1H, $J_{6a,6b}$ 9.9 Hz, H-6a), 4.14 (m, 3H, H-2, H-5, H-6b), 2.57 (s, 3H, CH_3–C(NH–)=C<), 2.19 (s, 4H, 2 × CH_2), 2.14, 2.04, 1.97 (3 × s, 9H, 3 × CH_3(CO)-), 1.06 (s, 6H, 2 × CH_3); (4-phenylbenzyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-*N*-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl]-β-D-glucopyranoside) **15β**, ($CDCl_3$) δ 13.85 (d, 1H, NH), 7.44 (m, 9H, Ar), 5.25 (t, 1H, $J_{3,4}$ 9.4 Hz, H-3), 5.15 (t, 1H, $J_{4,5}$ 9.6 Hz, H-4), 4.8 (2d, 2H, CH_2-Ar), 4.62, (d, 1H, $J_{1,2}$ 8.3 Hz, H-1), 4.37, (dd, 1H, $J_{6a,6b}$ 12.3 Hz, H-6a), 4.21 (dd, 1H, H-6b), 4.06 (m, 1H, $J_{2,3}$ 9.8 Hz, H-2), 3.77 (m, 1H, $J_{5,6a}$ 2.1 Hz, $J_{5,6b}$ 4.5 Hz, H-5), 2.63 (s, 3H, CH_3–C(NH–)=C<), 2.35 (s, 4H, 2 × CH_2), 2.14, 2.05, 1.99, (3s, 9H, 3 × CH_3(CO)), 1.05 (s, 6H, 2 × CH_3). HRMS (TOF) Calcd for $C_{35}H_{41}NO_{10}$: 635.2730. Found: 636.2796 $[M+H]^+$.

From donor 7: Under an atmosphere of nitrogen compound **7** (100 mg, 163 μmol), 4-phenylbenzyl alcohol (45 mg, 245 μmol) and 4 Å molecular sieves (150 mg) were combined in anhydrous DCM (1.5 mL). The reaction mixture was stirred at rt for 1 h; the reaction mixture was then cooled to 0°C and TMSOTf (10 μL, 543 μmol) was added. The reaction mixture was allowed to return to rt and stirred for a further 2 h. The reaction was neutralized with triethylamine, diluted with chloroform (50 mL), filtered through Celite, washed with saturated $NaHCO_3$ solution (2 × 50 mL), and dried over $MgSO_4$. The organic phase was evaporated and the resulting residue chromatographed (DCE/EtOAc 6:1) to yield 4-phenylbenzyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-*N*-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)-ethyl]-α/β-D-glucopyranoside as a white solid (76 mg; 74% (α:β, 2:3); R_f 0.35 (DCE-EtOAc 7:3). HRMS (TOF) and ^{1}H-NMR ($CDCl_3$), see experiment **15** above.

3,4,6-Tri-*O*-acetyl-2-deoxy-2-*N*-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl]-α/β-D-glucopyranosyl-(1 → 6)-1,2-3,4-di-*O*-isopropylidene galactopyranoside (16α/16β)

From donor 3: Compound **3** (300 mg, 56.4 mmol), 1,2-3,4-di-*O*-isopropylidene galactopyranose (100 mg, 37.6 mmol), and 4 Å molecular sieves (350 mg) were combined under nitrogen in DCM (5 mL) and stirred at rt for 2 h. The reaction was cooled in a dry ice/acetone bath silver triflate (193 mg, 75.2 mmol) was added, and the resulting mixture stirred for 1.5 h. $NaHCO_3$ (s) was added and the mixture diluted with chloroform (50 mL), filtered through Celite, washed with saturated $NaHCO_3$ solution (2 × 50 mL) and saturated brine solution (50 mL) and dried over $MgSO_4$. The organic phase was evaporated and the resulting residue chromatographed (DCE/EtOAc 7 : 3) to yield 3,4,6-tri-*O*-acetyl-2-deoxy-2-*N*-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene) ethyl]-α/β-D-glucopyranosyl-(1 → 6)-1,2-3,4-di-*O*-isopropylidene-α-D-galactopyranose (**16α/16β**) as a white solid (230 mg, 86%, α:β; 1:1.75), R_f 0.35 (DCE/EtOAc 7 : 3). Only a small amount of pure anomer β could be purified: ^{1}H NMR ($CDCl_3$) for **16**β, δ 13.85 (d, 1H, NH) 5.38 (d, 1H, $J_{1,2}$ 5.0 Hz, H-1) 5.26 (t, 1-H, $J_{3',4'}$ 9.8 Hz, H-3′), 5.11 (t, 1H, $J_{4',5'}$ 5.0 Hz, H-4′), 4.55 (d, 1H, J $_{1',2'}$ 7.6, H-1′), 4.55 (m, 1H, H-3), 4.36 (dd, 1H, $J_{6a,6b}$ 12.0 Hz, H-6a′), 4.26 (m, 1H, H-2), 4.12 (m, 2H, H-4, H-6b′), 4.02 (dd, 1H, $J_{6a,6b}$ 11.1 Hz, H-6a), 3.99 (m, 1H, H-2′), 3.83 (m, 1H, H-5), 3.75 (m, 1H, H-5′), 3.60 (dd, 1H, H-6b), 2.60 (s, 3H, CH_3–C(NH–)=C<) 2.40, 2.33 (2 × d, 4H, 2 × CH_2), 2.11, 2.04, 1.98 (3 × s, 9H, CH_3(CO)–), 1.44, 1.42, 1.31, 1.28 (4 × s, 12H, 4 × CH_3), 1.04, 1.01 (2 × s, 6H, 2 × CH_3). HRMS (TOF) Calcd for $C_{34}H_{49}NO_{15}$: 711.3102. Found: 712.3151 $[M + H]^+$. Only **16**β could be purified as a pure compound.

From donor 7: Under an atmosphere of nitrogen, compound **7** (185 mg, 302 μmol), 1,2-3,4-di-*O*-isopropylidene-α-D-galactopyranose (118 mg, 4.54 μmol), and 4 Å molecular sieves (400 mg) were combined in DCM (5 mL) and stirred at rt for 1 h. The reaction mixture was cooled to 0°C, at which time TMSOTf (20 μL, 110 μmol) was added. The resulting mixture was allowed to return to ambient temperature and stirred for 2 h. Pyridine (2 mL) and acetic anhydride (1 mL) were added and the reaction mixture stirred for a further 30 min. The solvent was removed in vacuo and the resulting residue azeotropically dried with toluene (2 × 30 mL). The residue was then taken up in chloroform (50 mL), filtered through Celite, washed with saturated $NaHCO_3$ solution (2 × 50 mL), and dried over $MgSO_4$. The organic phase was evaporated and the resulting residue was purified by column chromatography (DCE/EtOAc 7 : 3) to yield 3,4,6-tri-*O*-acetyl-2-deoxy-2-*N*-[1-(4,4-dimethyl-2,6-dioxocyclohex-1-ylidene)ethyl]-α/β-D-glucopyranosyl-(1 → 6)-1,2-3,4-di-*O*-isopropylidene galactopyranoside (**16α, 16β**) as a white film (104 mg, 48% (α/β; 1:2); Rf 0.35 (DCE/EtOAc 7:3). For ^{1}H-NMR and HRMS (TOF), see above.

Methyl 2-amino-2-deoxy-1-thio-β-D-glucopyranoside (17)

A mixture of compound **5** (12.03 g, 24.1 mmol) and NaOMe (100 mg, 1.85 mmol) in dry methanol (100 mL) was stirred at rt overnight. The reaction mixture was neutralized with Amberlite IR 120 (H^+), filtered, and evaporated. The residue was dissolved in NH_3/MeOH and stirred at 45°C for 2 h. The reaction mixture was reduced in vacuo and the resultant oil evaporated from benzene/ethanol (1 : 1, 3 × 150 mL). Crystallisation from ethanol/ether yielded compound **17** (4.61 g, 92%); R_f 0.21 (MeCN : H_2O, 9 : 1), ^{1}H NMR ($CDCl_3$) δ 4.22 (d, 1H, $J_{1,2}$ 9.6 Hz, H-1), 2.20 (s, 3H, CH_3), 2.65 (t, 1H, $J_{2,3}$ 8.6 Hz, H-2), 3.63 (dd, 1H, $J_{4,5}$ 9.0 Hz, H-4), 3.87 (apparent d, 1H, H-3), 3.27 (m, 3H, H-5, H-6a, H-6b). HRMS (TOF) Calcd for $C_7H_{15}NO_4S$: 209.0724. Found: 210.0712 $[M + H]^+$.

Methyl 2-amino-2-deoxy-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (18)

To a solution of aqueous ammonia in methanol (150 mL, 28% aqueous ammonia/MeOH, 1:1) was added compound **9** (5.30 g, 11.50 mmol). The suspension was stirred at rt overnight. The precipitate was collected and washed with diethylether and the washings discarded. The reaction mother liquor concentrated, azeotroped with toluene (3 × 100 mL), and suspended in diethyl ether (300 mL) and stirred for 2 h. The solid was collected and combined with the earlier precipitate to afford compound **18** (3.4 g, 99.5%); R_f 0.4 ($MeCN/H_2O$ 10:1); ^{1}H−NMR δ 7.41 (m, 5H, Ar), 5.60 (s, 1-H, Ar-CH), 4.35 (d, 1H, $J_{1,2}$ 9.8 Hz H-1), 4.19 (dd, 1H, $J_{4,5}$ 10.3 Hz, H-4), 3.70 (m, 1H, H-3), 3.44 (m, 2H, H-6a, H-6b), 3.31 (m, 1H, $J_{5,6a}$ 1.8 Hz, $J_{5,6b}$ 4.1 Hz, H-5), 2.61 (t, 1H, $J_{2,3}$ 8.9 Hz, H-2), 2.12 (s, 3-H, $S{-}CH_3$). HRMS (TOF) Calcd for $C_{14}H_{19}NO_4S$: 297.1035. Found: 298.1088 $[M+H]^+$.

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