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N-Trichloroethoxycarbonyl-glucosamine derivatives as glycosyl donors [1]

Wulf Dullenkopf, Julio C. Castro-Palomino, Leonardo Manzoni, Richard R. Schmidt *

Fakultät für Chemie, Universität Konstanz, Postfach 5560 M 725, D-78434 Konstanz, Germany

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Abstract

D-Glucosamine can be readily transformed into 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-D-glucopyranose (**2**). From this intermediate valuable glycosyl donors can be obtained; reaction with ethanethiol in the presence of boron trifluoride etherate afforded ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranoside (**4**) which gave, upon *N*-acetylation, the *N*-acetyl-*N*-trichloroethoxycarbonyl derivative (**5**). Selective removal of the 1-*O*-acetyl group in **2** followed by treatment with trichloroacetonitrile in the presence of base afforded 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-α-D-glucopyranosyl trichloroacetimidate (**6**). Reaction of **5** with five selectively protected glycosides as glycosyl acceptors in the presence of *N*-iodosuccinimide/trifluoromethanesulfonic acid as the promoter system furnished the corresponding β-glycosides in good yields, thus exhibiting the valuable glycosyl donor properties of **5**. Reductive removal of the trichloroethoxycarbonyl (Teoc) group afforded the corresponding *N*-acetyl-protected saccharides in high yields. The imidate **6** reacted with three of the above acceptors in the presence of catalytic amounts of trimethylsilyl trifluoromethanesulfonate to give the β-linked disaccharides in even better yields. The direct replacement of the *N*-Teoc group by the *N*-acetyl group using zinc/acetic anhydride, via the free amines as transient intermediates, adds to the high efficiency and convenience of this methodology. © 1996 Elsevier Science Ltd.

Keywords: Oligosaccharide synthesis; Thioglycosides; Glycosyl trichloroacetimidates; *N*-Trichloroethoxycarbonyl; Deprotection

* Corresponding author.

[1] Glycosyl imidates, part 77. For part 76, see Ref. [1].

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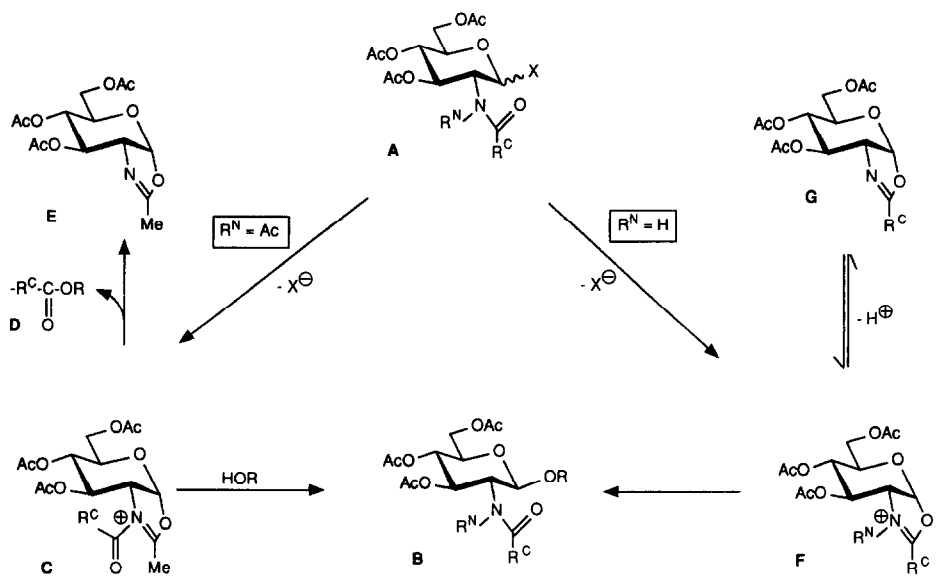
1. Introduction

D-Glucosamine is an important constituent of various glycoconjugates [2]. Most frequently it is *N*-acetylated and found in β-glycosidic linkage. Glycoside bond formation with donors derived from *N*-acetyl-D-glucosamine occurs generally via neighboring group participation to give an oxazoline intermediate [3]; these oxazolines do not exert strong glycosyl donor properties because the methyl-substituted *N*-protonated oxazolinium system is rather stable. Therefore, various alternative glucosamine donors have been investigated, amongst which the phthalimido group [2,3] and the azido group [2–5] have gained wide use. The azido group serves as an excellent latent functionality for the amino group [2,5]; however, the preparation of the required azidodeoxyglucose is still not very economical [5]. Phthalimido sugars can be readily obtained from amino sugars and, for instance, in combination with trichloroacetimidate activation, good glycosyl donors are available for β-glycoside bond formation via reactive *N*-acylated oxazolinium intermediates [2,5]. However, cleavage of the phthalimido group requires basic conditions which often result in partial product decomposition [6] (Improvements have recently been reported [7].) Therefore, tetrachlorophthalimido(TCP)-protected glycosyl donors were recently employed [8,9], which exhibit high glycosyl donor properties and permit removal of the TCP group under very mild nonbasic conditions [1,9].

For various applications the intermediate generation of a free amino group — especially under basic conditions — leads to undesired side reactions. Therefore, methods retaining the *N*-acetyl functionality (or an equivalent) in the glycosyl donor are in great demand. A convenient solution of this problem is the formation of *N*,*N*-diacetyl



Scheme 1.

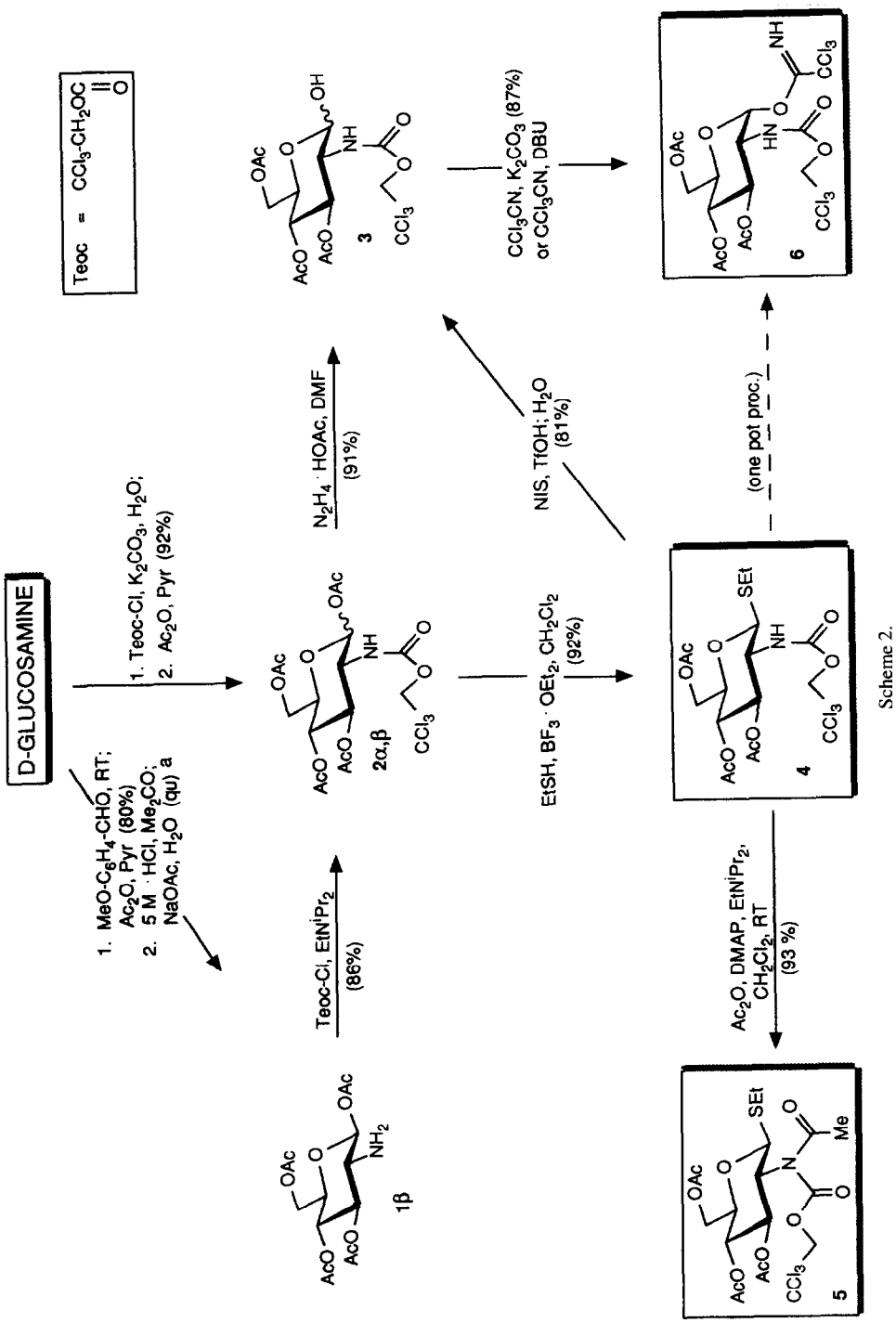
derivatives [10]. Thus, thioglycosides of *N*,*N*-diacetyl-D-glucosamine (Scheme 1, **A**: $R^N = Ac$, $R^C = Me$, $X = SMe$) turned out to be excellent glycosyl donors for very reactive acceptors (HOR), giving β-glycosides **B** (presumably via **C**) in high yields. However, for less reactive acceptors acetyl transfer from the donor to the acceptor ($\rightarrow$ **D** + **E**) turned out to be a competing side reaction [10]. Therefore, we initiated a program to replace one of the *N*-acetyl groups by a readily removable alkoxycarbonyl moiety, thus lowering the *N*-acetyl transfer character of the glycosyl donor [11]. Because alkoxycarbonyl residues participating in the formation of oxazolinium systems of type **C** can undergo cleavage to an alkylcarbonium ion, the inductively electron-withdrawing trichloroethoxycarbonyl (Teoc) moiety was chosen (**A**: $R^N = Ac$, $R^C = OCH_2CCl_3$), thus avoiding this undesired side reaction and increasing the glycosyl donor properties of intermediate **C** [2]. For comparison reasons the corresponding *N*-deacetyl compound (**A**: $R^N = H$, $R^C = OCH_2CCl_3$) was investigated, which, as has already been shown [11,13,14], can be obtained with trichloroacetimidate as leaving group; this compound exhibited, in the few cases thus far applied, good glycosyl donor properties due to the strong electron-withdrawing effect of the R^C substituent in the oxazolinium intermediate **F** (or in **G**).

2. Results and discussion

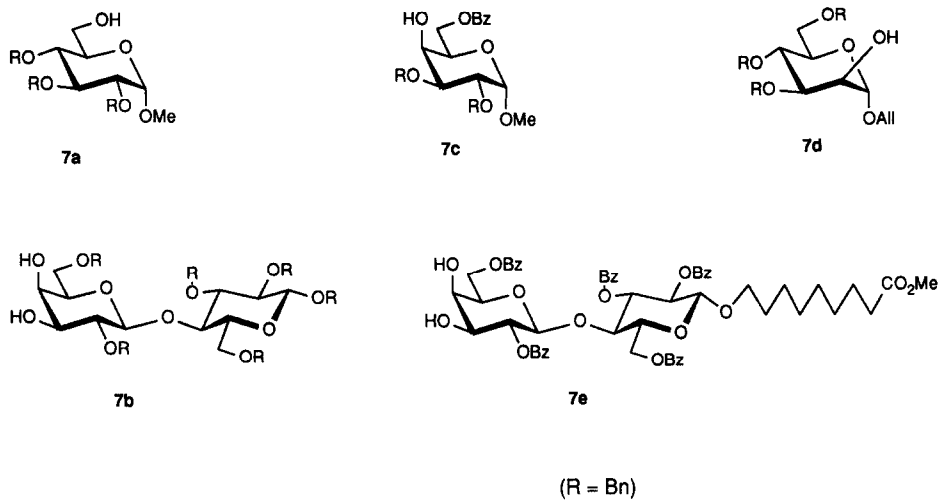
For the synthesis of the known *N*-Teoc-protected *O*-acetyl-glucosamine **2β** [15] (Scheme 2) the free amine **1** was prepared [16] which was then transformed with trichloroethoxycarbonyl chloride (Teoc-Cl) into **2β**; reaction with ethanethiol in the presence of boron trifluoride etherate gave, as described by Kunz et al. [17], thioglycoside **4** in good yield which has also been investigated as a glycosyl donor [17,18]. Reaction of **4** with acetic anhydride in the presence of 4-dimethylaminopyridine (DMAP) and Hünig base afforded the desired *N*-acetyl-*N*-Teoc-protected glucosamine donor **5**. For the synthesis of trichloroacetimidate **6** transformation of **4** with *N*-iodosuccinimide (NIS)/trifluoromethanesulfonic acid (TfOH) in the presence of water provides the 1-*O*-unprotected glucosamine derivative **3** which can be transformed into **6** in very high yield either by treatment with trichloroacetonitrile in the presence of potassium carbonate [13] or in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as base. The synthesis of **3** can be performed much more efficiently by direct reaction of D-glucosamine with Teoc-Cl in the presence of aqueous sodium hydrogen carbonate and then per-*O*-acetylation, furnishing **2α,β** in almost quantitative yield. Regioselective hydrazinolysis of the anomeric *O*-acetyl group could be carried out even in the presence of the quite reactive Teoc group, thus leading to **3** in three steps in high overall yield. Because transformation of **2** into **6** can also be performed in a one-pot procedure in high yield, the synthesis of glycosyl donor **6** is very straightforward and efficient.

The investigation of the glycosylation potential of donors **5** and **6** was performed with glycosides **7a–e** (Scheme 3) which represent a broad scale of different acceptor

[2] In equilibrium reactions with the acceptor, ortho-acid derivatives could also be formed [12].


D-GLUCOSAMINE
1. MeO-C6H4-CHO, RT;
Ac2O, Pyr (80%)
2. 5 M · HCl, Me2CO;
NaOAc, H2O (qu) a
1. Teoc-Cl, K2CO3, H2O;
2. Ac2O, Pyr (92%)
Teoc-Cl, EtN(iPr)2
(86%)
N2H4 · HOAc, DMF
(91%)
EtSH, BF3 · OEt2, CH2Cl2
(92%)
NIS, TfOH; H2O
(81%)
CCl3CN, K2CO3 (87%)
or CCl3CN, DBU
(one pot proc.)
Ac2O, DMAP, EtN(iPr)2,
CH2Cl2, RT
(93 %)
Teoc = CCl3-CH2OC
O
1β
2α,β
3
4
5
6

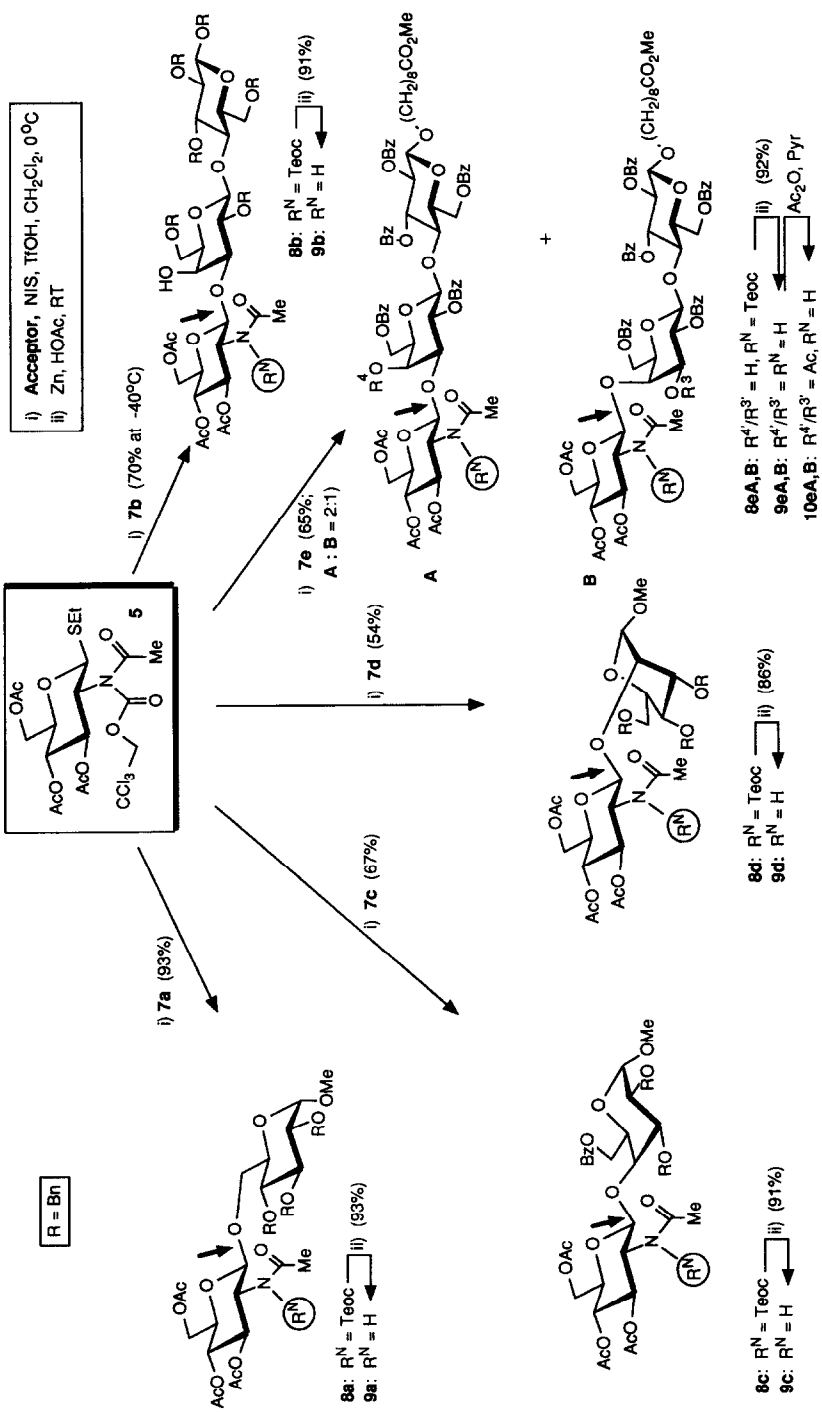
Scheme 2.



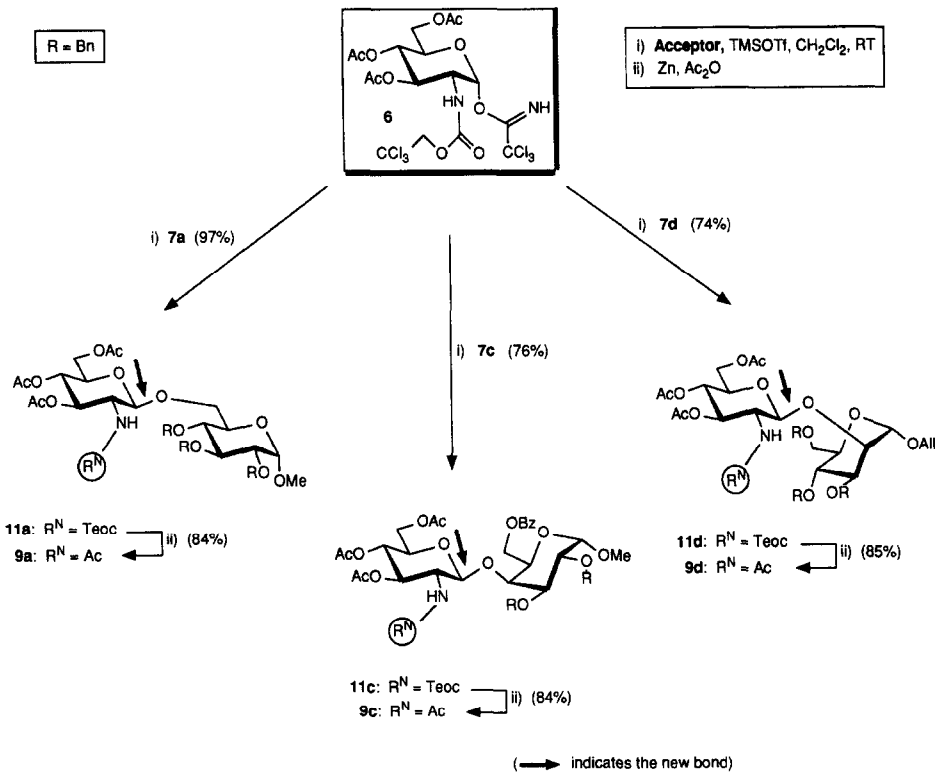
Scheme 3.

reactivities. Reaction of **5** with the highly reactive primary hydroxy group of **7a** [19] under typical conditions for the activation of thioglycosides (1–2 equivalents of NIS and 0.1–0.2 equivalent of TfOH at 0 °C [20]) afforded the β-linked disaccharide **8a** in practically quantitative yield (Scheme 4). Immediate reductive removal of the *N*-Teoc group with zinc in acetic acid [21] to afford the *N*-acetyl derivative **9a** could be performed in 93% yield. The 3′,4′-*O*-unprotected lactose derivative **7b** is also an excellent glycosyl acceptor [22]. Because of the high overall acceptor reactivity, high regioselectivity for 3′-*O* attack could only be achieved at −30 °C, thus affording **8b** in 70% yield, which was again immediately transformed into **9b**. Axial hydroxy groups generally exhibit lower acceptor reactivity. Therefore, the 4-*O*-unprotected galactose derivative **7c** [23] was treated with **5**; under standard conditions disaccharide **8c** and hence **9c** were obtained in very good yields. Also the 2-*O*-unprotected mannose derivative **7d** [24] could be transformed into disaccharide **8d**, though in lower yield; **9d** formation was again high-yielding. Finally, the 3′,4′-*O*-unprotected *O*-benzoyl-protected lactose derivative **7e** [25] was employed as acceptor. Obviously, the *O*-benzoyl groups not only lower the glycosyl acceptor properties but also the regioselectivity in the reaction with **5**, thus furnishing a 2:1 mixture of **8eA,B** in 65% overall yield. For the structural assignment, removal of the *N*-Teoc group under standard conditions (→ **9eA, B**), then *O*-acetylation, and separation provided **10eA** and **10eB** (^{1}H NMR; **10eA**: δ 5.28, H-4′; **10eB**: δ 3.99, H-4′; 4.93, H-3′).

We then turned our attention to glycosyl donor **6**, because transformation of *N*-Teoc-protected compounds into the corresponding *N*-acetyl derivatives could be performed directly with zinc and acetic anhydride in high yield [26], thus generating free amines as intermediates only in low concentrations. Reaction of **6** with **7a** in the presence of catalytic amounts of trimethylsilyl trifluoromethanesulfonate (TMSOTf) (0.01 equivalent), applying the inverse procedure [27], furnished the β-linked disaccha-


i) Acceptor, NIS, TfOH, CH_2Cl_2, 0°C
ii) Zn, HOAc, RT
R = Bn
5
i) 7a (93%)
i) 7b (70% at -40°C)
i) 7c (67%)
i) 7d (54%)
i) 7e (65%; A : B = 2:1)
8a: R^N = Teoc
9a: R^N = H
ii) (93%)
8b: R^N = Teoc
9b: R^N = H
ii) (91%)
8c: R^N = Teoc
9c: R^N = H
ii) (91%)
8d: R^N = Teoc
9d: R^N = H
ii) (86%)
A
B
8eA,B: R^4/R^3 = H, R^N = Teoc
9eA,B: R^4/R^3 = R^N = H
10eA,B: R^4/R^3 = Ac, R^N = H
ii) (92%)
Ac_2O, Pyr
(—▲— indicates the new bond)

Scheme 4.



Scheme 5.

ride **11a** in practically quantitative yield (Scheme 5); thus the excellent properties of **6** as a glycosyl donor are exhibited [17,18,28]. Subsequent replacement of the *N*-Teoc group in **11a** by the *N*-acetyl group with zinc and acetic anhydride furnished **9a** in 84% yield. The less reactive acceptors **7c** and, as already reported [13], **7d** gave with **6** under the same reaction conditions excellent yields of **11c** and **11d**; replacement of the *N*-Teoc group using zinc and acetic anhydride readily afforded the desired *N*-acetyl derivatives **9c** and **9d**.

In conclusion, the *N*-acetyl-*N*-Teoc-protected thioglycoside **5** is a good glycosyl donor for acceptors of very different reactivity; the convenient and selective removal of the *N*-Teoc group in the products in the presence of various protecting groups by zinc and acetic acid provides a generally applicable method for the synthesis of β-glycosides of *N*-acetyl-D-glucosamine. The ease of formation of the *N*-Teoc-protected trichloroacetimidate **6**, the simple activation by catalytic amounts of TMSOTf, the very high glycosylation yields, and the high-yielding direct replacement of the *N*-Teoc group by the *N*-acetyl group with zinc and acetic anhydride make this method even more efficient. It is therefore a valuable addition to the available repertoire of glycoside bond-forming reactions in glycoconjugate synthesis.

3. Experimental

Solvents were purified in the usual way; boiling range of the petroleum ether (PE) used: 35–60 °C. ^{1}H NMR spectra: Bruker AC 250 (250 MHz) and Bruker DRX 600 (600 MHz); solvent, $CDCl_3$; internal standard, Me_4Si; chemical shifts and coupling constants were partially obtained from COSY spectra. Flash chromatography: silica gel (Baker: particle size 40 μm). Thin-layer chromatography (TLC): foil plates, Silica Gel 60 F_{254} (Merck; layer thickness, 0.2 nm). Optical rotations: Perkin–Elmer polarimeter 241 MC; 1-dm cell; temperature, 20 °C. Elemental analyses: Heraeus CHN-O-rapid.

*1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-α,β-*D*-glucopyranose* (**2α,β**).—(*a*) *From* **1**. Transformation of **1β** [16] into **2β** was performed as previously described [15].

(*b*) *Directly from* D-*glucosamine yielding* **2α,β**. Trichloroethoxycarbonyl chloride (8.1 mL, 60 mmol) was added dropwise at room temperature to a vigorously stirred solution of D-glucosamine hydrochloride (10.8 g, 50 mmol) and $NaHCO_3$ (12.6 g, 150 mmol) in water (100 mL). The mixture was stirred for 1 h, then neutralized with 1 M HCl, concentrated, and dried in vacuo. A solution of the residue in pyridine (50 mL) and Ac_2O (25 mL) was stirred overnight at room temperature and then concentrated. The residue was eluted from a column of silica gel with 4:1 hexane–EtOAc to give **2α,β** (21.2 g, 92%) as a colorless oil which was identical to previously obtained material [15].

*3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-α,β-*D*-glucopyranose* (**3**).—(*a*) *From* **2**. A solution of **2** (2.0 g, 3.82 mmol) and hydrazinium acetate (458 mg, 4.97 mmol) in DMF (20 mL) was stirred for 20 min at room temperature, then diluted with EtOAc (80 mL), washed with satd. aq NaCl (2 × 30 mL) and water (2 × 30 mL), dried ($MgSO_4$), and concentrated. The residue was eluted with 2:1 toluene–EtOAc to give **3** as a white foam (1.55 g, 83%); ^{1}H NMR (250 MHz, $CDCl_3$): δ 2.01–2.21 (m, 9 H, 3 × Ac), 3.65 (s, 1 H, OH), 4.01–4.29 (m, 4 H, H-2, H-5, H-6a, H-6b), 4.61–4.83 (m, 2 H, CH_2CCl_3), 5.09–5.48 (m, 4 H, H-1, H-3, H-4, NH).

(*b*) *From* **4** [17,28]. To a mixture of **4** (1.66 g, 3.17 mmol), water (114 μL, 6.34 mmol), and NIS (0.79 g, 3.49 mmol) in CH_2Cl_2 (15 mL) was added TfOH (20 μL, 0.22 mmol). After 30 min the reaction mixture was diluted with CH_2Cl_2 (15 mL), washed successively with satd. aq $NaHCO_3$, satd. aq $Na_2S_2O_3$, and water, dried ($MgSO_4$), filtered, and concentrated. The residue was eluted from a column of silica gel with 2:1 toluene–EtOAc to give **3** as a white foam (1.25 g, 81%).

*Ethyl 3,4,6-tri-*O*-acetyl-2-[*N*-acetyl-*N*-(2,2,2-trichloroethoxycarbonylamino)]-2-deoxy-1-thio-β-*D*-glucopyranoside* (**5**).—A solution of ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranoside (**4**) [17,28] (1.74 g, 3.31 mmol) in dry CH_2Cl_2 (15 mL) was stirred for 72 h at room temperature and then concentrated. The residue was eluted from a column of silica gel with 6:1 toluene–EtOAc to give syrupy **5** (1.71 g, 93%); $[\alpha]_D$ −7.7° (*c* 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$; 2 rotamers, 2:1 a–b): (a) δ 1.20–1.23 (m, 3 H, SCH_2CH_3), 1.93–2.05 (m, 9 H, 3 × Ac), 2.51 (s, 3 H, NHAc), 2.61–2.66 (m, 2 H, SCH_2CH_3), 3.68–3.70 (m, 1 H, H-5), 4.07–4.10 (m, 1 H, H-6a), 4.20–4.24 (m, 1 H, H-6b), 4.82 (d, 1 H, J_{gem} 7.4 Hz, CH_2CCl_3), 4.96 (d, 1 H, J_{gem} 7.4 Hz, CH_2CCl_3), 4.98 (dd, 1 H, $J_{1,2}$ 10.3, $J_{2,3}$ 9.5 Hz, H-2), 5.14 (dd, 1 H, $J_{3,4} = J_{4,5} = 9.5$ Hz, H-4), 5.32 (d, 1 H, $J_{1,2}$ 10.3 Hz, H-1), 5.74

(dd, 1 H, $J_{2,3} = J_{3,4} = 9.5$ Hz, H-3); (b) δ 1.20–1.23 (m, 3 H, SCH_2CH_3), 1.93–2.05 (m, 9 H, 3 × Ac), 2.43 (s, 3 H, NHAc), 2.61–2.66 (m, 2 H, SCH_2CH_3), 3.75–3.78 (m, 1 H, H-5), 4.07–4.10 (m, 1 H, H-6a), 4.20–4.24 (m, 1 H, H-6b), 4.39 (dd, 1 H, $J_{1,2} = J_{2,3} = 9.8$ Hz, H-2), 4.80 (d, 1 H, J_{gem} 11.9 Hz, CH_2CCl_3), 4.88 (d, 1 H, J_{gem} 11.9 Hz, CH_2CCl_3), 5.02 (dd, 1 H, $J_{3,4} = J_{4,5} = 9.5$ Hz, H-4), 5.50 (d, 1 H, $J_{1,2}$ 9.8 Hz, H-1), 5.78 (dd, 1 H, $J_{2,3}$ 9.8, $J_{3,4}$ 9.5 Hz, H-3). Anal. Calcd for $C_{13}H_{26}Cl_3NO_{10}S$ (566.8): C, 40.25; H, 4.26; N, 2.47. Found: C, 40.16; H, 4.78; N, 2.94.

*3,4,6-Tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-*α*-*D*-glucopyranosyl trichloroacetimidate* (**6**).—(*a*) *From* **3**. A solution of **3** (2.01 g, 4.01 mmol), trichloroacetonitrile (4 mL, 40 mmol), and DBU (0.15 mL, 1 mmol) in CH_2Cl_2 (12 mL) was stirred at room temperature for 20 min and then concentrated. The residue was eluted from a column of silica gel with 2:1 hexane–EtOAc containing 0.1% of triethylamine to afford **6** as a white solid (1.98 g, 73%); it was identical to material previously obtained from **3** with K_2CO_3 as base [13].

(*b*) *From* **2** *in a one-pot procedure*. A solution of **2** (1 g, 1.9 mmol) and hydrazinium acetate (0.19 g, 2.1 mmol) in DMF (8 mL) was stirred for 20 min at room temperature, then diluted with EtOAc (50 mL), washed with water, then with satd. aq $NaHCO_3$, and again with water, dried ($MgSO_4$), and concentrated. A solution of the residue, trichloroacetonitrile (1 mL, 10 mmol), and DBU (0.15 mL, 1 mmol) in CH_2Cl_2 (10 mL) was stirred for 30 min at room temperature and then concentrated. Workup was performed as described above to yield **6** (0.90 g, 76%).

Compounds **7a–e** were obtained following literature procedures: **7a** [19], **7b** [22], **7c** [23], **7d** [24], **7e** [25].

Methyl O-*(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-D-glucopyranosyl)-(1 → 6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside* (**9a**).—(*a*) *Synthesis of* **8a**. TfOH (34 μL of a 0.1 M solution of TfOH in dry CH_2Cl_2, 3.4 μmol) was added to a stirred solution of **5** (200 mg, 0.343 mmol), methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (**7a**) [19] (122 mg, 0.263 mmol), and NIS (89 mg, 0.395 mmol) in dry CH_2Cl_2 (2 mL). The mixture was stirred at room temperature under dry Ar for 2 h, then diluted with CH_2Cl_2 (20 mL), washed with satd. aq $NaHCO_3$, aq $Na_2S_2O_3$ (0.5 M), and satd. aq NaCl, dried ($MgSO_4$), and concentrated in vacuo. The residue was eluted from a column of silica gel with 9:1 toluene–EtOAc to give syrupy **8a** (236 mg, 93%).

(*b*) **9a** *from* **8a**. A solution of **8a** (303 mg, 0.319 mmol) and freshly activated Zn-powder (300 mg) was stirred for 5 h in AcOH (5 mL), diluted with toluene, filtered, and concentrated in vacuo. The residue was eluted from a column of silica gel with 1:1 toluene–EtOAc to give syrupy **9a** (239 mg, 93%); $[\alpha]_D$ +5.2° (*c* 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.79–2.00 (4 s, each 3, 4 × Ac), 3.33 (s, 3 H, OCH_3) 3.45 (dd, 1 H, $J_{3,4} = J_{4,5} = 9.6$ Hz, H-4), 3.50 (dd, 1 H, $J_{1,2}$ 3.5, $J_{2,3}$ 9.6 Hz, H-2), 3.62–3.66 (m, 1 H, H-5′), 3.69 (dd, 1 H, $J_{5,6a}$ 4.2, $J_{6a,6b}$ 10.6 Hz, H-6a), 3.71–3.75 (m, 1 H, H-5), 3.82 (ddd, 1 H, $J_{1',2'}$ 8.4, $J_{2',NH}$ 9.0, $J_{2',3'}$ 9.5 Hz, H-2′), 3.95 (dd, 1 H, $J_{2,3} = J_{3,4} = 9.6$ Hz, H-3), 4.02 (dd, 1 H, $J_{5,6b}$ 1.4 Hz, H-6b), 4.07 (dd, 1 H, $J_{5',6'a}$ 2.4, $J_{6'a,6'b}$ 12.6 Hz, H-6′a), 4.19 (dd, 1 H, $J_{5',6'b}$ 4.7 Hz, H-6′b), 4.57 (d, 1 H, H-1), 4.65 (d, 1 H, H-1′), 4.53–4.96 (m, 6 H, 3 × CH_2Ph), 5.01 (t, 1 H, $J_{3',4'} = J_{4',5'} = 9.5$ Hz, H-4′), 5.24 (t, 1 H, $J_{2',3'} = J_{3',4'} = 9.5$ Hz, H-3′), 5.37 (d, 1 H, $J_{2',NH}$ 9.0 Hz, NH), 7.25–7.32 (m, 15 H, Ph).

Anal. Calcd for $C_{42}H_{51}NO_{14}$ (793.8): C, 63.54; H, 6.47; N, 1.76. Found: C, 63.03; H, 6.54; N, 2.32.

(*c*) **9a** *from* **11a**. To a solution of **11a** (170 mg, 0.181 mmol) in Ac_2O (5 mL) was added freshly activated Zn-powder (300 mg); the mixture was stirred at room temperature for 5 h, then diluted with toluene, filtered, and concentrated in vacuo. The residue was eluted from a column of silica gel with 1:1 toluene–EtOAc to give **9a** as a syrup (121 mg, 84%) which was identical with the material obtained from **8a**.

Benzyl O-*(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-*D*-glucopyranosyl)-(1 → 3)-*O*-(2,6-di-*O*-benzyl-β-*D*-galactopyranosyl)-(1 → 4)-2,3,6-tri-*O*-benzyl-β-*D*-glucopyranoside* (**9b**).—(*a*) *Synthesis of* **8b**. A solution of benzyl *O*-(2,6-di-*O*-benzyl-β-D-galactopyranosyl)-(1 → 4)-2,3,6-tri-*O*-benzyl-β-D-glucopyranoside (**7b**) [22] (200 mg, 0.226 mmol), **5** (154 mg, 0.271 mmol), NIS (66 mg, 0.283 mmol), and molecular sieves 4 Å in dry CH_2Cl_2 (3 mL) was stirred for 1 h under dry Ar and then cooled to −30 °C. TMSOTf (10 μL, 0.056 mmol) was added and the mixture was stirred for 3 h at −30 °C, then diluted with CH_2Cl_2 (20 mL), washed with satd. aq $NaHCO_3$ (10 mL), aq $Na_2S_2O_3$ (10 mL, 0.5 M), and satd. aq NaCl, dried ($MgSO_4$), and concentrated. The residue was eluted from a column of silica gel with 6:1 toluene–EtOAc to give syrupy **8b** (220 mg, 70%).

(*b*) **9b** *from* **8b**. A solution of **8b** (180 mg, 0.129 mmol) in AcOH (4 mL) was treated as described for the preparation of **9a**. The residue was eluted from a column of silica gel with 1:1 toluene–EtOAc to give amorphous **9b** (145 mg, 91%); $[\alpha]_D$ −3.6° (*c* 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.50, 1.95–2.03 (4 s, each 3 H, 4 × Ac), 2.59 (b, 1 H, OH), 3.30–3.32 (m, 1 H, H-5′), 3.42–3.59 (m, 6 H, H-3, H-5, H-6a, H-2′, H-3′, H-2″), 3.58 (dd, 1 H, $J_{1,2}$ 8.3, $J_{2,3}$ 7.8 Hz, H-2), 3.68–3.76 (m, 5 H, H-6b, H-6′a, H-6′b, H-2″, H-5″), 3.90–4.00 (m, 2 H, H-4, H-4′), 4.13 (dd, 1 H, $J_{5'',6''a}$ 2.16, $J_{6''a,6''b}$ 11.8 Hz, H-6″a), 4.19 (dd, 1 H, $J_{5'',6''b}$ 5.4 Hz, H-6″b), 4.31–5.02 [m, 17 H, H-1, H-1′, H-1″, H-4″, NH, 6 × CH_2Ph (d, 1 H, $J_{1'',2''}$ 8.4 Hz, H-1″)], 5.12 (dd, 1 H, $J_{2'',3''} = J_{3'',4''}$ = 10.4 Hz, H-3″), 7.21–7.25 (m, 30 H, Ph). Anal. Calcd for $C_{68}H_{77}NO_{19}$ (1212.4): C, 67.36; H, 6.40; N, 1.15. Found: C, 67.38; H, 6.45; N, 1.38.

Methyl O-*(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-*D*-glucopyranosyl)-(1 → 4)-6-*O*-benzoyl-2,3-di-*O*-benzyl-α-*D*-galactopyranoside* (**9c**).—(*a*) A mixture of methyl 6-*O*-benzoyl-2,3-di-*O*-benzyl-α-D-galactopyranoside (**7c**) [23] (159 mg, 0.332 mmol), **5** (443 mg, 0.781 mmol), and NIS (177 mg, 0.797 mmol) was treated as described for the preparation of **9a**. The residue was eluted from a column of silica gel with 6:1 toluene–EtOAc to give syrupy **8d** (218 mg, 67%).

(*b*) **9c** *from* **8c**. A solution of **9a** (165 mg, 0.168 mmol) in AcOH (4 mL) was treated as described for the preparation of **9a**. The residue was eluted from a column of silica gel with 1:1 toluene–EtOAc to give syrupy **9c** (124 mg, 91%); $[\alpha]_D$ +15.2° (*c* 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.51, 1.93, 1.96, 2.00 (4 s, each 3 H, 4 × Ac), 3.26 (s, 3 H, OCH_3), 3.53–3.55 (m, 1 H, H-5′), 3.78 (dd, 1 H, $J_{1,2}$ 3.3, $J_{2,3}$ 9.9 Hz, H-2), 3.92–4.09 (m, 6 H, H-3, H-4, H-5, H-2′, H-6′a, H-6′b), 4.28 (dd, 1 H, $J_{5,6a}$ 11.8, $J_{6a,6b}$ 7.1 Hz, H-6a), 4.55–4.69 [m, 8 H, H-1, H-6b, H-1′, H-3′, 2 × CH_2Ph (d, 1 H, $J_{1',2'}$ 9.0 Hz, H-1′)], 4.99 (dd, 1 H, $J_{3',4'} = J_{4',5'} = 9.7$ Hz, H-4′), 5.59 (dd, 1 H, $J_{2',NH}$ 9.6 Hz, NH), 7.24–7.97 (m, 15 H, Ph). Anal. Calcd for $C_{42}H_{49}NO_{15}$ (807.8): C, 62.44; H, 6.11; N, 1.73. Found: C, 62.07; H, 6.12; N, 1.72.

(*c*) **9c** *from* **11c**. To a solution of **11c** (80 mg, 0.081 mmol) in Ac_2O (5 mL) was added freshly activated Zn-powder (300 mg); the mixture was stirred at room temperature for 5 h and then worked up as described for **9a** to yield **9c** as syrup (55 mg, 84%).

Allyl O-*(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-*D*-glucopyranosyl)-(1 → 2)-3,4,6-tri-*O*-benzyl-α-*D*-mannopyranoside* (**9d**).—(*a*) *Synthesis of* **8d**. A solution of allyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (**7d**) [24] (175 mg, 0.377 mmol), **5** (320 mg, 0.564 mmol), and NIS (135 mg, 0.603 mmol) was treated as described for the preparation of **9a**. The residue was eluted from a column of silica gel with 6:1 toluene–EtOAc to give syrupy **8d** (197 mg, 54%).

(*b*) **9d** *from* **8d**. A solution of **8d** (197 mg, 0.204 mmol) in AcOH (4 mL) was treated as described for the preparation of **9a**. The residue was eluted from a column of silica gel with 1:1 toluene–EtOAc to give syrupy **9d** (139 mg, 86%); $[\alpha]_D$ +14.6° (*c* 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.73, 1.98, 1.99, 2.01 (4 s, each 3 H, 4 × Ac), 3.27 (ddd, 1 H, $J_{1',2'}$ 8.2, $J_{2',NH}$ 7.3, $J_{2',3'}$ 9.5 Hz, H-2′), 3.63–4.14 (m, 10 H, H-2, H-3, H-4, H-5, H-6a, H-6b, H-5′, H-6′a, $CH_2CH=CH_2$), 4.24 (dd, 1 H, $J_{5',6'b}$ 5.2, $J_{6'a,6'b}$ 12.2 Hz, H-6′b), 4.45–4.91 (m, 6 H, 3 × CH_2Ph), 4.77 (d, 1 H, $J_{1,2}$ 1.2 Hz, H-1), 5.00–5.22 [m, 3 H, H-1′, $CH_2CH=CH_2$ (d, 1 H, H-1′)], 5.44 (b, 1 H, NH), 5.73 (dd, 1 H, $J_{2',3'}=J_{3',4'}=9.5$ Hz, H-3′), 5.81–5.85 (m, 1 H, $CH_2CH=CH_2$), 7.21–7.34 (m, 15 H, Ph). Anal. Calcd for $C_{44}H_{53}NO_{14}$ (828.9): C, 63.75; H, 6.44; N, 1.68. Found: C, 63.81; H, 6.48; N, 1.55.

(*c*) **9d** *from* **11d**. To a solution of **10d** (310 mg, 0.297 mmol) in Ac_2O (5 mL) was added freshly activated Zn-powder (300 mg); the mixture was stirred at room temperature for 6 h and then worked up as described for **9a** to yield **9d** as syrup (209 mg, 85%).

8-(Methoxycarbonyl)octyl O-*(2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-β-*D*-glucopyranosyl)-(1 → 3)-(4-*O*-acetyl-2,6-di-*O*-benzoyl-β-*D*-galactopyranosyl)-(1 → 4)-2,3,6-tri-*O*-benzoyl-β-*D*-glucopyranoside* (**10eA**) *and 8-(methoxycarbonyl)octyl* O-*(2-acetamido-3,4,6-*O*-tri-*O*-acetyl-2-deoxy-β-*D*-glucopyranosyl)-(1 → 4)-(3-*O*-acetyl-2,6-di-*O*-benzoyl-β-*D*-galactopyranosyl)-(1 → 4)-2,3,6-tri-*O*-benzoyl-β-*D*-glucopyranoside* (**10eB**).—(*a*) *Synthesis of* **8e**. A mixture of 8-(methoxycarbonyl)octyl *O*-(2,6-di-*O*-benzoyl-β-D-galactopyranosyl)-(1 → 4)-2,3,6-tri-*O*-benzoyl-β-D-glucopyranoside (**7e**) [25] (160 mg, 0.157 mmol), **5** (142 mg, 0.251 mmol), and NIS (58 mg, 0.264 mmol) was treated as described for the preparation of **9a**. The residue was eluted from a column of silica gel with 3:1 toluene–EtOAc to give syrupy **8eA** and **8eB** (164 mg, 65%).

(*b*) **9eA,B** *from* **8eA,B**. A solution of **8eA,B** (164 mg, 0.101 mmol) in AcOH (5 mL) was treated as described for the preparation of **9a**. The residue was eluted from a column of silica gel with 2:3 toluene–EtOAc to give amorphous **9eA,B** (134 mg, 92%).

(*c*) **10eA** *and* **10eB** *from* **9eA,B**. A mixture of **9eA,B** (134 mg, 0.093 mmol) in pyridine (5 mL) and Ac_2O (3 mL) was stirred for 3 h at room temperature and then concentrated. The residue was eluted from a column of silica gel with 1:1 toluene–EtOAc to give syrupy **10eA** and **10eB** (127 mg, 92%; **10eA**: 89 mg; **10eB**: 38 mg); ^{1}H NMR (600 MHz, $CDCl_3$): **10eA**: δ 1.04–2.22 [m, 29 H, $(CH_2)_7CH_2COOCH_3$, 5 × Ac], 3.34–3.64 [m, 11 H, H-5, H-3′, H-5′, H-6′a, H-2″, H-5″, $(CH_2)_7CH_2COOCH_3$, OCH_3), 3.85 (dd, 1 H, $J_{5',6'b}$ 5.4, $J_{6'a,6'b}$ 9.5 Hz, H-6′b), 4.00 (dd, 1 H, $J_{5'',6''a}$ 4.4, $J_{6''a,6''b}$ 12.1 Hz, H-6″a), 4.08 (dd, 1 H, $J_{5'',6''b}$ 2.2, $J_{6''a,6''b}$ 12.1 Hz, H-6″b), 4.12 (dd, 1 H, $J_{3,4}=J_{4,5}=9.5$ Hz, H-4), 4.37 (dd, 1 H, $J_{5,6a}$ 4.3, $J_{6a,6b}$ 12 Hz, H-6a), 4.49 (dd, 1 H,

$J_{5,6b}$ 1.2, $J_{6a,6b}$ 12.0 Hz, H-6b), 4.57 (d, 1 H, $J_{1',2'}$ 8.0 Hz, H-1'), 4.58 (d, 1 H, $J_{1,2}$ 7.9 Hz, H-1), 4.71 (d, 1 H, $J_{1'',2''}$ 8.2 Hz, H-1''), 4.91 (dd, 1 H, $J_{3'',4''} = J_{4'',5''} = 9.6$ Hz, H-4''), 4.95 (d, 1 H, $J_{2'',NH}$ 8.3 Hz, NH), 5.13 (t, 1 H, $J_{2'',3''} = J_{3'',4''} = 9.5$ Hz, H-3''), 5.28 (t, 1 H, $J_{3',4'} = J_{4',5'} = 3.4$ Hz, H-4'), 5.32 (dd, 1 H, $J_{1',2'}$ 8.0, $J_{2',3'}$ 9.6 Hz, H-2'), 5.37 (dd, 1 H, $J_{1,2}$ 7.9, $J_{2,3}$ 9.5 Hz, H-2), 5.69 (dd, 1 H, $J_{2,3} = J_{3,4} = 9.5$ Hz, H-3), 7.25–8.06 (m, 25 H, Ph); **10eB:** δ 0.97–2.20 [m, 29 H, $(CH_2)_7CH_2COOCH_3$, 5 × Ac], 3.53 (m, 1 H, H-2''), 3.54–3.78 [m, 10 H, H-5, H-5', H-6'a, H-5'', H-6''a, $(CH_2)_7CH_2COOCH_3$, OCH_3), 3.91 (dd, 1 H, $J_{5'',6''b}$ 4.4, $J_{6''a,6''b}$ 12.1 Hz, H-6''b), 3.99 (dd, 1 H, $J_{3',4'} = J_{4',5'} = 2.2$ Hz, H-4'), 4.12 (dd, 1 H, $J_{5',6'b}$ 6.0, $J_{6'a,6'b}$ 11.1 Hz, H-6'b), 4.21 (t, 1 H, $J_{3,4} = J_{4,5} = 9.5$ Hz, H-4), 4.35 (dd, 1 H, $J_{5,6a}$ 4.4, $J_{6a,6b}$ 12.0 Hz, H-6a), 4.56 (dd, 1 H, $J_{5,6b}$ 1.5, $J_{6a,6b}$ 12.0 Hz, H-6b), 4.60 (d, 1 H, $J_{1,2}$ 8.2 Hz, H-1), 4.65 (d, 1 H, $J_{1',2'}$ 7.8 Hz, H-1'), 4.81 (dd, 1 H, $J_{3'',4''} = J_{4'',5''} = 9.7$ Hz, H-4''), 4.93 (dd, 1 H, $J_{2',3'}$ 10.4, $J_{3',4'}$ 2.5 Hz, H-3'), 5.10 (d, 1 H, $J_{1'',2''}$ 8.0 Hz, H-1''), 5.38–5.39 (m, 2 H, H-2, H-2'), 5.68 (dd, 1 H, $J_{2,3} = J_{3,4} = 9.5$ Hz, H-3), 5.94 (dd, 1 H, $J_{2'',3''} = J_{3'',4''} = 10.5$ Hz, H-3''), 6.51 (d, 1 H, $J_{2'',NH}$ 6.5 Hz, NH), 7.34–8.03 (m, 25 H, Ph). **10eA**: $[\alpha]_D$ +25.5° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{73}H_{81}NO_{27}$ (1404.3): C, 62.43; H, 5.81; N, 0.95. Found: C, 62.90; H, 5.87; N, 1.12. **10eB**: $[\alpha]_D$ +32.9° (*c* 1, $CHCl_3$). Anal. Calcd for $C_{73}H_{31}NO_{27}$ (1404.3): C, 62.43; H, 5.81; N, 0.95. Found: C, 62.29; H, 6.00; N, 1.10.

Methyl O-[3,4,6-tri-O-acetyl-2-deoxy-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranosyl]-(1 → 6)-2,3,4-tri-O-benzyl-α-D-glucopyranoside (**11a**).—TMSOTf (47 μL of a 0.1 M solution of TMSOTf in dry CH_2Cl_2, 4.7 μmol) was added to a solution of **7a** [19] (170 mg, 0.366 mmol) and **6** (300 mg, 0.476 mmol) in dry CH_2Cl_2 (3 mL) under dry Ar at room temperature. The mixture was stirred for 15 min, neutralized with triethylamine, and concentrated in vacuo. The residue was eluted from a column of silica gel with 2:1 PE–EtOAc to give syrupy **11a** (329 mg, 97%); $[\alpha]_D$ +15.0° (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 1.99–2.04 (3 s, each 3 H, 3 × OAc), 3.36 (s, 3 H, OCH_3), 3.43–3.76 (m, 5 H, H-3, H-4, H-5, H-2', H-5'), 3.94–4.20 (m, 5 H, H-2, H-6a, H-6b, H-6'a, H-6'b), 4.39 (d, 1 H, $J_{1',2'}$ 8.3 Hz, H-1'), 4.52–5.02 (m, 11 H, H-1, H-4', CH_2CCl_3, 3 × CH_2Ph, NH), 5.19 (dd, 1 H, $J_{2',3'} = J_{3',4'} = 9.3$ Hz, H-3'), 7.30–7.39 (m, 15 H, Ph). Anal. Calcd for $C_{43}H_{50}Cl_3NO_{15}$ (927.2): C, 54.63; H, 5.33; N, 1.48. Found: C, 54.76; H, 5.41; N, 1.58.

Methyl O-[3,4,6-tri-O-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranosyl]-(1 → 4)-2,3-di-O-benzyl-6-O-benzoyl-α-D-galactopyranoside (**11c**).—A mixture of **7c** [21] (94 mg, 0.196 mmol) and **6** (155 mg, 0.255 mmol) was treated as described for the preparation of **11a**. The residue was eluted from a column of silica gel with 2:1 PE–EtOAc to give syrupy **11c** (141 mg, 76%); $[\alpha]_D$ +12° (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$): δ 1.97, 2.00, 2.03 (3 s, each 3 H, 3 × OAc), 3.31 (s, 3 H, OCH_3), 3.49–3.52 (m, 1 H, H-5'), 3.71 (ddd, 1 H, $J_{1',2'}$ 8.7, $J_{2',3'}$ 9.5, $J_{2',NH}$ 7.5 Hz, H-2'), 3.86–5.01 [m, 18 H, H-1, H-2, H-3, H-4, H-5, H-6a, H-6b, H-1', H-3', H-4', H-6'a, H-6'b, CH_2CCl_3, 2 × CH_2Ph, (d, 1 H, $J_{1',2'}$ 8.7 Hz, H-1')], 5.57 (d, 1 H, $J_{2',NH}$ 7.5 Hz, NH), 7.27–8.00 (m, 15 H, Ph). Anal. Calcd for $C_{43}H_{48}Cl_3NO_{16}$ (941.2): C, 53.91; H, 5.04; N, 1.48. Found: C, 53.95; H, 5.02; N, 1.72.

Allyl O-[3,4,6-tri-O-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranosyl]-(1 → 2)-3,4,6-tri-O-benzyl-α-D-mannopyranoside (**11d**).—This compound was obtained in the same yield as previously described [13].

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