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Glycosylation with *N*-Troc-protected glycosyl donors

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Abstract

N-Troc-protected (Troc = 2,2,2-trichloroethoxycarbonyl) glucosamine and galactosamine glycosyl donors (1-*O*-acetyl sugar, bromo sugar, and thioglycoside) were compared with the corresponding *N*-Phth-protected derivatives in glycosylations of 2-(trimethylsilyl)ethanol, 2-bromoethanol, methyl 3-mercaptopropionate, *N*-Fmoc-protected serine, and 2-(trimethylsilyl)ethyl 6-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside. The *N*-Troc-protected donors gave pure β-glycosides in somewhat higher yields than the *N*-Phth-protected counterparts. The *N*-Troc protecting group can be removed by reduction with zinc, which allows selective *N*-deprotection in oligosaccharides containing both *N*-Troc and *N*-Phth groups.

Keywords: *N*-Troc-protected glycosyl donors; Glycosylation

1. Introduction

The chemical synthesis of β-glycosides of 2-acetamido-2-deoxy sugars normally requires that the glycosyl donor carries a participating group on the nitrogen, or the use of a 1,2-oxazoline donor [1]. *N*-Phthaloyl (*N*-Phth)-protected donors usually give the desired β-glycoside in high yield and stereoselectivity, but the later removal of the phthaloyl group can be difficult to perform in high yield. The alternative participating 2,2,2-trichloroethoxycarbonylamino (*N*-Troc [2]) group has been used in glycosylations primarily with the corresponding glycosyl halides [3]; a few examples of Lewis acid promoted glycosylation with 1-*O*-acetyl sugars [4], and ethyl 1-thioglycosides [5] have

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Table 1
Reaction types and reagents that are compatible with the N-Troc protecting group

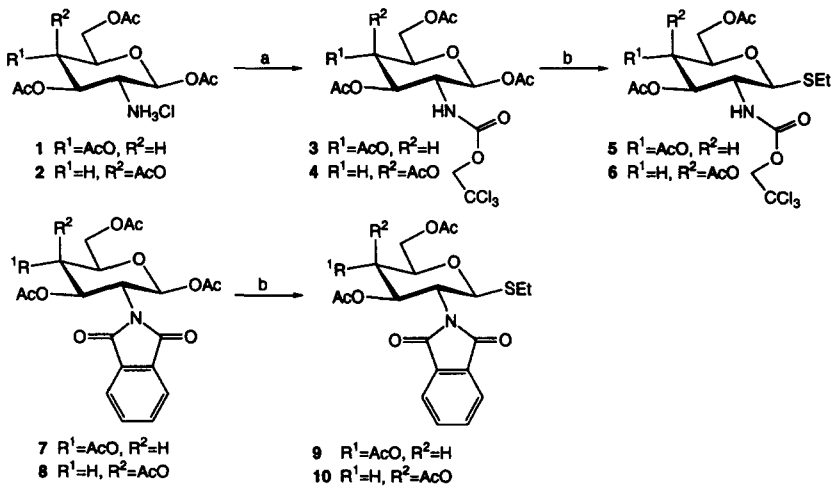
Type of reaction	Reagents	Reference
Glycoside synthesis	$CF_3SO_3SiMe_3$	[7,16]
	Hg-salts	[3,7,11,17]
	$ZnCl_2$, Ph_3CCl	[18]
	$ZnBr_2$, Me_3SiBr	[19,20]
	$(CF_3SO_3)_2Sn$	[4]
	$AgClO_4$	[18]
	DMTST	[5]
	$BF_3 \cdot Et_2O$	
	MeSBr, AgOTf	
Bromination	HBr, HOAc	[3,11,18,21]
Acylation	RCOOH, DCC, DMAP	[3,11]
Acetylation	Ac_2O, pyridine	[3,17,21]
Deacetylation	HCl, dioxane	[2]
Hydrogenation	H_2, Pd–C or PtO_2	[2]
Oxidation	3-Cl-$C_6H_4CO_3H$ or CH_3CO_3H	[22]
Isopropylidenation	Me_2CO, H_2O	[16]
	$(MeO)_2CMe_2$, p-$MeC_6H_4SO_3H$	[3]
Deisopropylidenation	HOAc, 90 °C	[21]
Allylation	$H_2C{=}CHCH_2OH$, HCl	[3]
Deallylation	$[Ir(COD)(PMePh_2)_2]PF_6$, I_2	[3,21]
Trichloroacetimidoylation	Cl_3CCN, K_2CO_3	[16]

also appeared (Table 1). The Troc group can be reductively removed in high yield by zinc powder under acidic conditions [2]. In addition, the Troc group is stable under a range of standard conditions used for carbohydrate synthesis as shown in Table 1. It is sensitive to alcoholysis under basic conditions, which permits convenient transformations into other carbamates.

2. Results and discussion

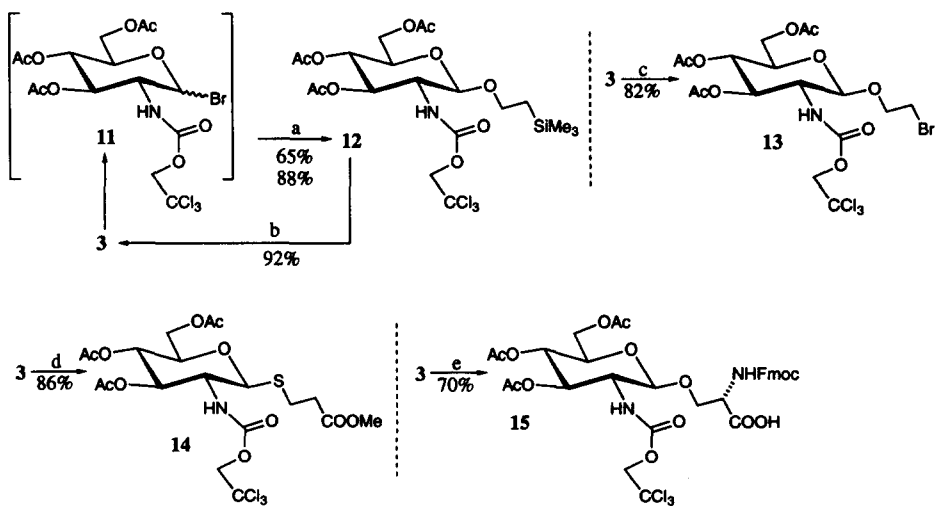
In order to develop stable *N*-Troc-protected donors for the synthesis of oligosaccharides containing 2-acetamido-2-deoxy sugars, we have investigated the synthesis and use of the corresponding 1-*O*-acetyl sugars and thioglycosides. The *N*-Troc- and *N*-Phth-protected thioglycoside donors **5**, **6**, **9**, and **10** were synthesized as depicted in Scheme 1. Briefly, the acetylated glucosamine and galactosamine derivatives [6] **1** and **2** were treated with 2,2,2-trichloroethoxycarbonyl chloride (TrocCl) in pyridine to yield the *N*-Troc-protected compounds **3** [7] (66%) and **4** [4a] (99%). Treatment with ethanethiol and boron trifluoride etherate gave the thioglycosides **5** [5] (92%) and **6** (78%) with high selectivity for the β anomers. In similar reactions, the *N*-Phth-protected compounds [8,9] **7** and **8** gave the β-thioglycosides **9** [10] and **10** (82%) suitable as glycosyl donors, as exemplified by the syntheses of the disaccharides **18**–**21** (see Scheme 3 below).

The possibility of varying the nature of the aglycon in *N*-Troc-protected amino sugars adds flexibility to the planning of oligosaccharide syntheses. Thus, the 2-(tri-

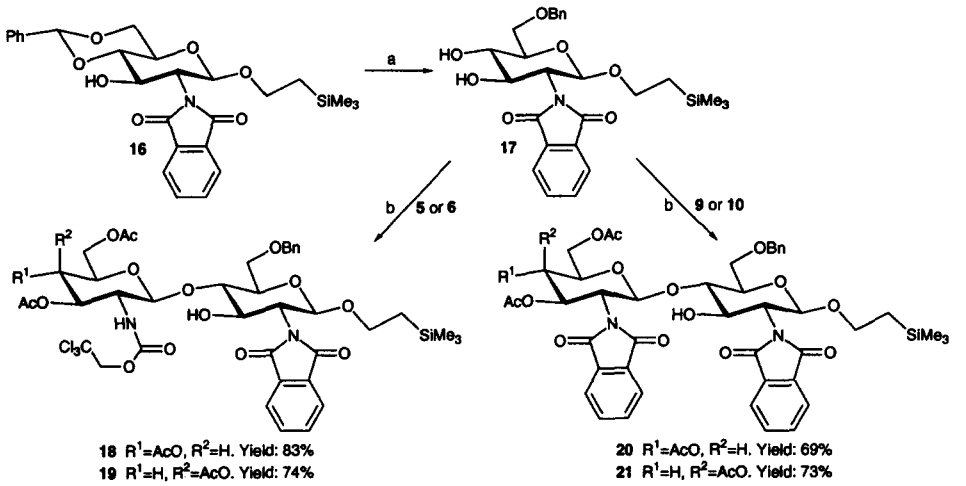


Scheme 1. (a) Cl_3CCH_2OCOCl, pyr. (b) EtSH, $BF_3 \cdot Et_2O$, CH_2Cl_2, 0 °C, Ar.

methylsilyl)ethyl (TMSEt) glycoside **12** was prepared via the glycosyl bromide [11] **11** (65% and 88%) by treatment with mercury salts and silver silicate, respectively. Treatment of **12** with boron trifluoride etherate–acetic anhydride gave the β-1-acetate **3** (92%), devoid of the α anomer (Scheme 2). This transformation adds to the already known usefulness of the TMSEt group for anomeric protection [12] and makes com-



Scheme 2. (a) $Me_3SiCH_2CH_2OH$, $Hg(CN)_2$, $HgBr_2$, MeCN, −30 °C → 22 °C; alternative method: $Me_3SiCH_2CH_2OH$, Ag/SiO_2, CH_2Cl_2, 22 °C. (b) Ac_2O, $BF_3 \cdot Et_2O$, CH_2Cl_2, Ar. (c) $BrCH_2CH_2OH$, $BF_3 \cdot Et_2O$, CH_2Cl_2, Ar. (d) $MeOOCCH_2CH_2SH$, $BF_3 \cdot Et_2O$, CH_2Cl_2, Ar. (e) N^{α}-Fmoc-L-Serine, $BF_3 \cdot Et_2O$, CH_2Cl_2.



Scheme 3. (a) $NaBH_3CN$, HCl/Et_2O, THF, 0 °C. (b) MeSBr, CF_3SO_3Ag, MeCN, CH_2Cl_2, −45 °C, Ar.

pounds such as **12** potentially useful as precursors of glycosyl acceptors, when manipulation at the anomeric position is required in the final steps of glycoconjugate syntheses [13].

Additional examples of spacer glycosides, suitable for coupling to such carriers as proteins, particles, and surfaces, are found in compounds **13–15**. The *N*-Troc-protected β-1-acetate **3** was treated with 2-bromoethanol, methyl 3-mercaptopropionate, and Fmoc-protected serine, with boron trifluoride etherate as promoter, to give the 2-bromoethyl glycoside **13** (82%), the thioglycoside ester **14** (86%), and the amino acid glycoside **15** (70%). Compound **15** was used for solid-phase synthesis of glycopeptides [14]. It was very rewarding to find that the *N*-Troc-protected β-1-acetates **3** and **4** were as efficient glycosyl donors as the corresponding *N*-Phth-protected acetates **7** and **8**, as witnessed by the high-yielding boron trifluoride etherate-mediated transformations into both thioglycosides (**5**, **6**, **14**) and *O*-glycosides (**13**, **15**).

As a final efficiency test (Scheme 3), the *N*-Troc-protected thioglycosyl donors **5** and **6** were compared with the *N*-Phth-protected counterparts **9** and **10** for regioselective glycosylation of the acceptor **17** (obtained by a standard route from the known [12a] TMSEt glycoside **16**). It should be noted that **17** has two unprotected hydroxyl groups and that HO-4 in this case is much more reactive than HO-3, leading to practically complete regio (and stereo)-selection. The regioselectivity in the glycosylation reaction was confirmed by acetylation of the unprotected hydroxyl group in the disaccharides **18–21** and determination of the NMR data of the acetylated derivatives, using homonuclear correlation spectroscopy (COSY) and conventional analysis of coupling patterns (see Experimental).

Treatment of **17** with the *N*-Troc-protected thioglycoside donors **5** or **6** and methylsulfenyl bromide/silver triflate [15] gave the disaccharides **18** (83%) and **19** (74%). The corresponding *N*-Phth-protected donors **9** or **10** gave, under identical conditions, the

disaccharides **20** (69%) and **21** (73%). Not only did the *N*-Troc-protected donors compare well with the *N*-Phth-donors, but the use of *N*-Troc-protection gave disaccharide derivatives with different *N*-protection patterns, thus enabling further selective manipulations.

In summary, *N*-Troc-protected glycosyl donors give high yields and high β/α-stereoselectivity, and removal of the Troc group by zinc-reduction is often simpler and more high-yielding than hydrazinolysis of the Phth group.

3. Experimental

General methods.—Melting points are uncorrected. Optical rotations were measured with a Perkin–Elmer 141 polarimeter. ^{1}H-NMR spectra were measured with Varian XL-300 and Bruker ARX-500 instruments. High-resolution FAB mass spectra (HRMS) were recorded with a JEOL SX-120 mass spectrometer. Chemical shifts are given in ppm downfield from the signal for Me_4Si, with reference to internal $CHCl_3$ (7.26 ppm). Dichloromethane and MeCN were dried by distillation from CaH_2, and THF from Na–benzophenone, immediately before use. Methylsulfenyl bromide was prepared [15] and kept intact as a solution in 1,2-dichloroethane in a sealed ampoule under Ar at −20 °C for several months. TLC was performed on SiO_2 (Matrex LC-gel; 60A, 35-70MY, Grace).

Compounds **1–2**, **7–9**, and **16** were synthesized as described: **1** [6], **2** [6], **7** [8], **8** [9], **9** [10], **16** [12a].

*1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-*D*-glucopyranose* (**3**).—(a) Compound **1** (14.83 g, 3.86 mmol) was dissolved in dry pyridine (100 mL) and TrocCl (12 mL, 9.65 mmol) was added. The mixture was stirred for 1 h, then MeOH (3 mL) was added, and the mixture was concentrated, chromatographed (SiO_2, 2:1 heptane–EtOAc), and recrystallized (EtOAc–heptane) to give pure **3** (13.30 g, 68%); mp 125–126 °C; $[\alpha]_D^{20}$ +14.0° (*c* 0.9, $CHCl_3$); lit. [7] mp 122–123 °C; $[\alpha]_D^{20}$ +15° (*c* 3.2, $CHCl_3$); ^{1}H-NMR data ($CDCl_3$): δ 5.73 (d, 1 H, *J* 8.8 Hz, H-1), 5.22 (t, 1 H, *J* 9.2 Hz, H-3), 5.11 (t, 1 H, *J* 9.3 Hz, H-4), 5.14 (d, 1 H, *J* 9.11 Hz, NH), 4.72 (s, 2 H, Cl_3CCH_2), 4.29, 4.10 (ABq, 1 H each, *J* 12.7, 4.6, 2.2 Hz, H-6), 3.93 (q, 1 H, *J* 9.5 Hz, H-2), 3.81 (ddd, 1 H, *J* 9.5, 4.7, 2.4 Hz, H-5), 2.10, 2.08, 2.03 (3 s, 12 H, 4 × Ac).

(b) Compound **12** (40 mg, 0.07 mmol) was dissolved in dry CH_2Cl_2 (2 mL). Acetic anhydride (0.300 mL, 3.2 mmol) and BF_3 etherate (0.027 mL, 0.21 mmol) were added and the mixture was stirred for 2 h. Dichloromethane (50 mL) was added and the mixture was washed with saturated aq $NaHCO_3$, dried (Na_2SO_4), and concentrated. The residue was chromatographed (SiO_2, 2:1 heptane–EtOAc) to give **3** (33 mg, 92%). The NMR spectrum was identical with that of **3** obtained via the procedure above.

*1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-*D*-galactopyranose* (**4**).—Compound **2** (549 mg, 1.43 mmol) was treated as in (a) above (**1** → **3**) to give **4** (743 mg, 99%) (compound **4** was reported [4a] without experimental details); $[\alpha]_D^{20}$ +9.6° (*c* 1.1, $CHCl_3$); ^{1}H-NMR data ($CDCl_3$): δ 5.75 (d, 1 H, *J* 8.8 Hz,

H-1), 5.39 (d, 1 H, *J* 2.5 Hz, H-4), 5.13 (dd, 1 H, *J* 11.4, 3.1 Hz, H-3), 5.0–5.10 (m, 1 H, NH), 4.72 (s, 2 H, Cl_3CCH_2), 4.0–4.2 (m, 4 H, H-2,5,6), 2.16, 2.11, 2.04, 2.00 (4 s, 3 H each, 4 × Ac).

Ethyl 3,4,6-tri-O-acetyl-2-deoxy-1-thio-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranoside (**5**).—Compound **3** [7] (3.0 g, 5.74 mmol) and ethanethiol (0.570 mL, 7.5 mmol) were dissolved in dry CH_2Cl_2 (12 mL). The mixture was cooled to 0 °C and then BF_3 etherate (0.970 mL, 7.5 mmol) was added during 5 min. The mixture was stirred for 40 min at 0 °C and then for 45 min at room temperature. The reaction was quenched by addition of triethylamine (1 mL), and the mixture was concentrated and chromatographed (SiO_2, 2:1 heptane–EtOAc) to give **5** (2.76 g, 92%). Recrystallization (Et_2O–heptane) gave pure **5** (2.51 g, 83%); mp 136–137 °C; $[\alpha]_D^{20}$ −15.1° (*c* 1.0, $CHCl_3$); ^{1}H-NMR data ($CDCl_3$): δ 5.23 (dd, 1 H, *J* 10.1, 9.5 Hz, H-3), 5.12 (d, 1 H, *J* 9.0 Hz, NH), 5.09 (dd, 1 H, *J* 10.0, 9.5 Hz, H-4), 4.81, 4.67 (ABq, 1 H each, *J* 12.0 Hz, Cl_3CCH_2), 4.63 (d, 1 H, *J* 10.4 Hz, H-1), 4.26, 4.13 (dABq, 1 H each, *J* 12.1, 5.1, 2.4 Hz, H-6), 3.77 (q, 1 H, *J* 10.4 Hz, H-2), 3.65–3.75 (m, 1 H, H-5), 2.73 (m, 2 H, SCH_2CH_3), 2.08, 2.03, 2.01 (3 s, 3 H each, 3 × Ac), 1.28 (m, 3 H, SCH_2CH_3). HRMS: Calcd for $C_{17}H_{24}Cl_3NO_9S$ (M + 1): *m/z* 524.0316. Found: *m/z* 524.0316.

Ethyl 3,4,6-tri-O-acetyl-2-deoxy-1-thio-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-galactopyranoside (**6**).—Compound **4** [4a] (0.500 g, 0.95 mmol) was treated as above (**3** → **5**) to give **6** (390 mg, 78%, α/β 1:11); $[\alpha]_D^{20}$ −11.2° (*c* 1.1, $CHCl_3$); ^{1}H-NMR data ($CDCl_3$): δ 5.40 (d, 1 H, *J* 3.2 Hz, H-4), 5.18 (bd, 1 H, *J* 9.6 Hz, NH), 5.00 (bd, 1 H, *J* 10.7 Hz, H-3), 4.80, 4.68 (ABq, 1 H each, *J* 13.1 Hz, Cl_3CCH_2), 4.67 (d, 1 H, *J* 10.4 Hz, H-1), 4.18, 4.11 (dABq, 1 H each, *J* 11.4, 6.9, 6.4 Hz, H-6), 3.96 (q, 1 H, *J* 9.8 Hz, H-2), 3.93 (t, 1 H, *J* 6.4 Hz, H-5), 2.65 (m, 2 H, SCH_2CH_3), 2.16, 2.05, 1.99 (3 s, 3 H each, 3 × Ac), 1.29 (m, 3 H, SCH_2CH_3). HRMS: Calcd for $C_{17}H_{24}Cl_3NO_9S$ (M + Na): *m/z* 546.0135. Found: *m/z* 546.0107.

Ethyl 3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-galactopyranoside (**10**).—Compound **8** [9] (1.00 g, 2.09 mmol) was treated as above (**3** → **5**) to give **10** (0.821 g, 82%); $[\alpha]_D^{20}$ +17.6° (*c* 1.0, $CHCl_3$); ^{1}H-NMR data ($CDCl_3$): δ 7.70–7.90 (m, 4 H, NPhth), 5.84 (dd, 1 H, *J* 11.0, 3.4 Hz, H-3), 5.52 (bd, 1 H, *J* 3.2 Hz, H-4), 5.47 (d, 1 H, *J* 10.6 Hz, H-1) 4.61 (t, 1 H, *J* 10.7 Hz, H-2), 4.10–4.25 (m, 3 H, H-5,6), 2.60–2.75 (m, 2 H, SCH_2CH_3), 2.20, 2.06, 1.86 (3 s, 3 H each, 3 × Ac), 1.20 (m, 3 H, SCH_2CH_3). HRMS: Calcd for $C_{22}H_{25}NO_9S$ (M + 1): *m/z* 480.1328. Found: *m/z* 480.1338.

2-(Trimethylsilyl)ethyl 3,4,6-tri-O-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-glucopyranoside (**12**).—(a) Compound **3** (261 mg, 0.50 mmol) was dissolved in AcOH (1 mL). Acetic anhydride (0.15 mL) and HBr solution (1 mL, 33% HBr in AcOH) were added and the mixture was stirred for 1 h at room temperature. The mixture was diluted with CH_2Cl_2 and washed with saturated aq $NaHCO_3$. The organic phase was dried (Na_2SO_4) and concentrated to give crude **11** (266 mg) that was used without further purification. Compound **11** (257 mg, 0.47 mmol) was dissolved in dry MeCN (1 mL) and 2-(trimethylsilyl)ethanol (88 mL, 0.56 mmol), $Hg(CN)_2$ (167 mg, 0.66 mmol), and $HgBr_2$ (1 mg, catalytic amount) were added at −30 °C. The temperature was gradually raised to room temperature. After 2 h, the mixture was filtered through a short column of silica gel, the eluate was concentrated, and the residue

was chromatographed (SiO_2, 3:1 heptane–EtOAc) to give **12** (178 mg, 65%); $[\alpha]_D^{20}$ +4.1° (*c* 1.0, $CDCl_3$); ^{1}H-NMR data ($CDCl_3$): δ 5.33 (t, 1 H, *J* 9.8 Hz, H-3), 5.09 (m, 1 H, NH), 5.08 (t, 1 H, *J* 10.0 Hz, H-4), 4.79, 4.65 (ABq, 1 H each, *J* 11.8 Hz, Cl_3CCH_2), 4.67 (d, 1 H, *J* 8.0 Hz, H-1), 4.29, 4.13 (dABq, 1 H each, *J* 12.2, 4.8, 2.4 Hz, H-6), 3.96 (dt, 1 H, *J* 9.3, 7.0 Hz, $OCH_2CH_2SiMe_3$), 3.70 (m, 1 H, H-5), 3.50–3.62 (m, 2 H, H-2, $OCH_2CH_2SiMe_3$), 2.08, 2.03 (2 s, 9 H, 3 × Ac), 0.94 (m, 2 H, $OCH_2CH_2SiMe_3$), 0.00 (s, 9 H, $SiMe_3$). HRMS: Calcd for $C_{20}H_{32}NO_{10}Si$ (M + Na): *m/z* 602.0759. Found: *m/z* 602.0750.

(b) Compound **11** [470 mg, 0.82 mmol; prepared as in (a) above] was dissolved in dry CH_2Cl_2 (4 mL). Activated molecular sieve (4Å, 500 mg) and 2-(trimethylsilyl)ethanol (0.11 mL, 0.83 mmol) were added and the mixture was stirred at 22 °C for 30 min. Silver silicate (500 mg) was added, the mixture was protected from light, a second portion of 2-(trimethylsilyl)ethanol (0.44 mL, 3.3 mmol) was added, and the mixture was stirred overnight. The mixture was filtered (Celite) and concentrated, and the residue was chromatographed (SiO_2, 1:1 heptane–EtOAc) to give **12** (443 mg, 88%).

*2-Bromoethyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-*D*-glucopyranoside* (**13**).—Compound **3** (52 mg, 0.10 mmol) was dissolved in dry CH_2Cl_2 (0.7 mL), and 2-bromoethanol (0.014 mL, 0.20 mmol) and BF_3 etherate (0.039 mL, 0.30 mmol) were added. The mixture was stirred for 3 h and then quenched by the addition of triethylamine (0.5 mL). The mixture was concentrated and the residue was chromatographed (SiO_2, 3:1 heptane–EtOAc) to give **13** (48 mg, 82%); $[\alpha]_D^{20}$ +9.1° (*c* 0.9, $CHCl_3$); ^{1}H-NMR data ($CDCl_3$): δ 5.32 (dd, 1 H, *J* 10.5, 9.6 Hz, H-3), 5.17 (dq, 1 H, *J* 8.8, 1.2 Hz, NH), 5.07 (dd, 1 H, *J* 10.0, 9.3 Hz, H-4), 4.77, 4.68 (ABq, 1 H each, *J* 11.9, 12.4 Hz, Cl_3CCH_2), 4.76 (d, 1 H, *J* 8.7 Hz, H-1), 4.27 (dd, 1 H, *J* 12.4, 4.9 Hz, H-6), 4.10–4.20 (m, 2 H, H-6, OCH_2CH_2Br), 3.84 (ddd, 1 H, *J* 11.3, 7.4, 6.4 Hz, OCH_2CH_2Br), 3.72 (m, 1 H, H-5), 3.64 (dt, 1 H, *J* 8.7, 8.3 Hz, H-2), 3.48 (d, 1 H, *J* 6.4 Hz, OCH_2CH_2Br), 3.46 (dd, 1 H, 6.1, 2.4 Hz, OCH_2CH_2Br), 2.10, 2.04, 2.03 (3 s, 3 H each, 3 × Ac). HRMS: Calcd for $C_{17}H_{23}BrCl_3NO_{10}$ (M + 1): *m/z* 585.9649. Found: *m/z* 585.9635.

*2-(Methoxycarbonyl)ethyl 3,4,6-tri-*O*-acetyl-2-deoxy-1-thio-2-(2,2,2-trichloroethoxycarbonylamino)-β-*D*-glucopyranoside* (**14**).—Compound **3** (52 mg, 0.10 mmol) was dissolved in dry CH_2Cl_2 (1.0 mL), and methyl 3-mercaptopropionate (0.022 mL, 0.20 mmol) and BF_3 etherate (0.063 mL, 0.50 mmol) were added. The mixture was stirred for 1 h and chromatographed (SiO_2, 2:1 heptane–EtOAc) to give **14** (50 mg, 86%); $[\alpha]_D^{20}$ −11.9° (*c* 1.0, $CHCl_3$); ^{1}H-NMR data ($CDCl_3$): δ 5.23 (t, 1 H, *J* 9.6 Hz, H-3), 5.20–5.30 (m, 1 H, NH), 5.08 (t, 1 H, *J* 9.6 Hz, H-4), 4.78, 4.67 (ABq, 1 H each, *J* 12.1, 11.8 Hz, Cl_3CCH_2), 4.71 (d, 1 H, *J* 10.3 Hz, H-1), 4.23, 4.13 (dABq, 1 H each, *J* 12.3, 5.0, 2.3 Hz, H-6), 3.77 (q, 1 H, *J* 10.0 Hz, H-2), 3.69 (s, 3 H, OMe), 3.65–3.85 (m, 1 H, H-5), 2.85–3.05 (m, 2 H, SCH_2CH_2COOMe), 2.65–2.75 (m, 2 H, SCH_2CH_2COOMe), 2.09, 2.03, 2.02 (3 s, 3 H each, 3 × Ac). HRMS: Calcd for $C_{19}H_{26}Cl_3NO_{11}S$ (M + Na): *m/z* 604.0190. Found: *m/z* 604.0192. Anal. Calcd for $C_{19}H_{26}Cl_3NO_{11}S$: C, 39.2; H, 4.5; N, 2.4. Found: C, 39.3; H, 4.3; N, 2.3.

N$^{\alpha}$*-(9-Fluorenylmethoxycarbonyl)-3-*O*-[3,4,6-tri-*O*-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-*D*-glucopyranosyl]-*L*-serine* (**15**).—Compound **3** (68.4 mg, 0.13 mmol) was dissolved in dry CH_2Cl_2 (2.5 mL), and *N*$^{\alpha}$-Fmoc-L-serine (51.7

mg, 0.16 mmol) and BF_3 etherate (0.050 mL, 0.39 mmol) were added. The mixture was stirred for 5 h, diluted with CH_2Cl_2 (8 mL), washed with aq HCl (1 M) and water, dried (Na_2SO_4), and concentrated. The residue was purified by HPLC (gradient, 40–100% B in A during 50 min; A = aq 0.1% trifluoroacetic acid, B = 0.1% trifluoroacetic acid in MeCN) to give **15** (72.6 mg, 70%); $[\alpha]_D^{20}$ +15.5° (*c* 1.0, $CHCl_3$); ^{1}H-NMR data (acetone-d_6): δ 7.86, 7.74, 7.42, 7.36 (m, 8 H, Fmoc), 7.03 (d, 1 H, *J* 9.0 Hz, CH_2OCONH), 6.52 (d, 1 H, *J* 8.0 Hz, NHFmoc), 5.29 (t, 1 H, *J* 9.4 Hz), 5.01 (t, 1 H, *J* 9.7 Hz, H-4), 4.94 (d, 1 H, *J* 8.5 Hz, H-1), 4.88, 4.55 (ABq, 1 H each, *J* 12.5, 12.2 Hz, Cl_3CCH_2), 4.50 (m, 1 H, Ser-H-α), 4.12 (dd, 1 H, *J* 12.2, 2.4 Hz, H-6), 3.88 (m, 1 H, H-5), 3.70 (q, 1 H, *J* 9.6 Hz, H-2), 2.01, 1.99, 1.93 (3 s, 3 H each, 3 × Ac); ^{13}C-NMR data (acetone-d_6): δ 157.0, 155.4 (OCON), 144.9, 142.0, 128.5, 128.0, 126.2, 120.8, 101.5, 96.8, 74.8, 73.3, 72.6, 69.7, 67.6, 62.8, 56.8, 54.8, 47.9, 20.6. HRMS: Calcd for $C_{33}H_{35}Cl_3N_2O_{14}$ (M + 1): *m/z* 789.1232. Found: *m/z* 789.1234.

*2-(Trimethylsilyl)ethyl 6-O-benzyl-2-deoxy-2-phthalimido-β-*D*-glucopyranoside* (**17**). —Compound **16** [12a] (2.28 g, 4.57 mmol) was dissolved in dry tetrahydrofuran (30 mL), and molecular sieve (2 g, 3A, activated) and $NaBH_3CN$ (1.62 g, 26 mmol) were added. The mixture was stirred for 50 min at room temperature, then cooled to 0 °C. An ice-cold, saturated solution of HCl in diethyl ether was added slowly until the pH (checked with a moist pH-paper) reached 2–3. The mixture was stirred for 30 min, CH_2Cl_2 (200 mL) was added, and the mixture was filtered (Celite). The filtrate was washed successively with saturated aq $NaHCO_3$, water, and brine, and then concentrated. The residue was chromatographed (SiO_2, 1:1 heptane–EtOAc) to give **17** (1.80 g, 79%); $[\alpha]_D^{20}$ −19.6° (*c* 0.8, $CHCl_3$); ^{1}H-NMR data ($CDCl_3$): δ 7.70–7.90 (m, 4 H, NPhth), 7.45 (m, 5 H, Ph), 5.24 (d, 1 H, *J* 8.3 Hz, H-1), 4.65, 4.58 (ABq, 1 H each, *J* 12.0, 12.2 Hz, OCH_2Ph), 4.26–4.36 (m, 1 H, H-5), 4.16 (dd, 1 H, *J* 10.9, 8.3 Hz, H-2), 3.94 (dt, 1 H, *J* 9.7, 4.7 Hz, $OCH_2CH_2SiMe_3$), 3.84 (dd, 1 H, *J* 14.1, 9.7 Hz, H-4), 3.82 (m, 1 H, H-3), 3.64 (m, 2 H, H-6), 3.49 (dt, 1 H, *J* 9.6, 6.7 Hz, $OCH_2CH_2SiMe_3$), 3.09 (s, 1 H, OH), 2.40 (d, 1 H, *J* 4.2 Hz, OH), 0.77 (m, 2 H, $OCH_2CH_2SiMe_3$), −0.19 (s, 9 H, $SiMe_3$). HRMS: Calcd for $C_{26}H_{33}NO_7Si$ (M + 1): *m/z* 500.2105. Found: *m/z* 500.2115.

*2-(Trimethylsilyl)ethyl 6-O-benzyl-2-deoxy-2-phthalimido-4-O-[3,4,6-tri-O-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-*D*-glucopyranosyl]-β-*D*-glucopyranoside* (**18**).—Compounds **5** [5] (76 mg, 0.15 mmol) and **17** (50 mg, 0.10 mmol) were dissolved in dry CH_2Cl_2 (1 mL) and cooled to −60 °C under Ar. A solution of silver trifluoromethanesulfonate (77 mg, 0.30 mmol) in dry acetonitrile was added, followed by a solution of methylsulfenyl bromide in 1,2-dichloroethane (4 M) during 20 min. The mixture was stirred for 2 h at −45 °C and quenched by addition of isopropylamine (0.200 mL). The stirring was continued for 1 h, the mixture was concentrated, and the residue was chromatographed (SiO_2, 3:1 heptane–EtOAc) to give **18** (80 mg, 83%); $[\alpha]_D^{20}$ −17.7° (*c* 0.8 $CHCl_3$); ^{1}H-NMR data ($CDCl_3$): δ 7.70–7.85 (m, 4 H, NPhth), 7.45–7.55 (m, 5 H, Ph), 5.21 (d, 1 H, *J* 8.5 Hz, H-1), 4.83 (t, 1 H, *J* 10.0 Hz, H-3′), 4.75, 4.66 (ABq, 1 H each, *J* 12.0 Hz, OCH_2Ph), 4.86–4.92 (m, 2 H, Cl_3CH_2, H-4′), 4.42 (d, 1 H, *J* 12.3 Hz, Cl_3CH_2), 4.33 (t, 1 H, *J* 10.0 Hz, H-3), 4.25 (d, 1 H, *J* 8.9 Hz, H-1′), 4.14–4.20 (m, 1 H, H-2), 4.11 (d, 2 H, *J* 4.7 Hz, H-6′), 3.96 (dt, 1 H, *J* 10.0, 5.5 Hz, $OCH_2CH_2SiMe_3$), 3.87 (d, 1 H, *J* 1.0 Hz, 3-OH), 3.60–3.80 (m, 5 H,

H-2',4,5',6), 3.58 (d, 1 H, *J* 8.7 Hz, H-5), 3.51 (dt, 1 H, *J* 9.7, 6.7 Hz, $OCH_2CH_2SiMe_3$), 2.02, 1.98, 1.97 (3 s, 3 H each, 3 × Ac), 0.70–0.90 (m, 2 H, $OCH_2CH_2SiMe_3$), −0.14 (s, 9 H, $SiMe_3$). HRMS: Calcd for $C_{41}H_{51}Cl_3N_2O_{16}Si$ (M + Na): *m/z* 983.1971. Found: *m/z* 983.1982. Anal. Calcd for $C_{41}H_{51}Cl_3N_2O_{16}Si$: C, 51.2; H, 5.3; N, 2.9. Found C, 51.2; H, 5.3; N, 2.8.

A sample of **18** was conventionally acetylated; the product gave a ^{1}H-NMR signal at δ 5.65 (dd, 1 H, *J* 10.8, 8.8 Hz, H-3).

2-(Trimethylsilyl)ethyl 6-O-benzyl-2-deoxy-2-phthalimido-4-O-[3,4,6-tri-O-acetyl-2-deoxy-2-(2,2,2-trichloroethoxycarbonylamino)-β-D-galactopyranosyl]-β-D-glucopyranoside (**19**).—Compound **6** (76 mg, 0.15 mmol) and **17** (50 mg, 0.10 mmol) were treated as above (**5** + **17** → **18**) to give **19** (71 mg, 74%); $[\alpha]_D^{20}$ −19.5° (*c* 0.9, $CHCl_3$); ^{1}H-NMR data ($CDCl_3$): δ 7.65–7.80 (m, 4 H, NPhth), 7.30–7.50 (m, 5 H, Ph), 5.27 (d, 1 H, *J* 2.5 Hz, H-4'), 5.23 (d, 1 H, *J* 8.5 Hz, H-1), 4.92, 4.43 (ABq, 1 H each, *J* 12.2, 12.4 Hz, Cl_3CH_2), 4.77, 4.68 (ABq, 1 H each, *J* 12.0 Hz, OCH_2Ph), 4.65 (dd, 1 H, *J* 11.2, 3.3 Hz, H-3'), 4.39 (dd, 1 H, *J* 11.3, 10.3 Hz, H-3), 4.21 (dd, 1 H, *J* 10.7, 8.5 Hz, H-2), 4.18 (d, 1 H, *J* 8.3 Hz, H-1'), 3.95 (dt, 1 H, *J* 8.5, 6.0 Hz, $OCH_2CH_2SiMe_3$), 3.75–4.10 (m, 6 H, H-2',5',6,6'), 3.72 (d, 1 H, *J* 11.1 Hz, H-4), 3.61 (d, 1 H, *J* 9.4 Hz, H-5), 3.53 (dt, 1 H, *J* 9.7, 6.7 Hz, $OCH_2CH_2SiMe_3$), 2.10, 1.99, 1.97 (3 s, 3 H each, 3 × Ac), 0.70–0.90 (m, 2 H, $OCH_2CH_2SiMe_3$), −0.14 (s, 9 H, $SiMe_3$). HRMS: Calcd for $C_{41}H_{51}Cl_3N_2O_{16}Si$ (M + Na): *m/z* 983.1971. Found: *m/z* 983.1943.

A sample of **19** was conventionally acetylated; the product gave a ^{1}H-NMR signal at δ 5.67 (dd, 1 H, *J* 10.3, 8.9 Hz, H-3).

2-(Trimethylsilyl)ethyl 6-O-benzyl-2-deoxy-2-phthalimido-4-O-[3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl]-β-D-glucopyranoside (**20**).—Compound **9** [10] (62 mg, 0.13 mmol) and **17** (50 mg, 0.10 mmol) were treated as above (**5** + **17** → **18**) to give **20** (63 mg, 69%); $[\alpha]_D^{20}$ +22.4° (*c* 0.8 $CHCl_3$); ^{1}H-NMR data ($CDCl_3$): δ 7.65–7.95 (m, 8 H, NPhth), 7.00–7.30 (m, 5 H, Ph), 5.84 (dd, 1 H, *J* 10.5, 9.1 Hz, H-3'), 5.52 (d, 1 H, *J* 8.5 Hz, H-1'), 5.14 (d, 1 H, *J* 8.6 Hz, H-1), 5.06 (d, 1 H, *J* 10.0 Hz, H-4'), 4.34 (dd, 1 H, *J* 10.7, 8.5 Hz, H-2'), 3.90–4.25 (m, 7 H, H-2,5,5',6', OCH_2Ph), 3.85 (dt, 1 H, *J* 8.5, 6.0 Hz, $OCH_2CH_2SiMe_3$), 3.70 (t, 1 H, *J* 8.1 Hz, H-3), 3.39–3.53 (m, 2 H, H-4, $OCH_2CH_2SiMe_3$), 3.28 (d, 2 H, *J* 2.7 Hz, H-6), 2.02, 1.88, 1.85 (3 s, 3 H each, 3 × Ac), 0.65–0.90 (m, 2 H, $OCH_2CH_2SiMe_3$), −0.17 (s, 9 H, $SiMe_3$). HRMS: Calcd for $C_{46}H_{52}N_2O_{16}Si$ (M + 1): *m/z* 917.3164. Found: *m/z* 917.3180. Anal. Calcd for $C_{46}H_{52}N_2O_{16}Si$: C, 60.2; H, 5.7; N, 3.1. Found: C, 60.2; H, 5.6; N, 3.0.

A sample of **20** was conventionally acetylated; the product gave a ^{1}H-NMR signal at δ 5.67 (t, 1 H, *J* 11.0 Hz, H-3).

2-(Trimethylsilyl)ethyl 6-O-benzyl-2-deoxy-2-phthalimido-4-O-[3,4,6-tri-O-acetyl-2-deoxy-2-phthalimido-β-D-galactopyranosyl]-β-D-glucopyranoside (**21**).—Compound **10** (62 mg, 0.13 mmol) and **17** (50 mg, 0.10 mmol) were treated as above (**5** + **17** → **18**) to give **21** (67 mg, 73%); $[\alpha]_D^{20}$ +7.1 (*c* 0.9, $CHCl_3$); ^{1}H-NMR ($CDCl_3$): δ 7.70–7.95 (m, 8 H, NPhth), 7.00–7.30 (m, 5 H, Ph), 5.84 (dd, 1 H, *J* 11.4, 3.4 Hz, H-3'), 5.48 (d, 1 H, *J* 8.5 Hz, H-1'), 5.44 (d, 1 H, *J* 3.6 Hz, H-4'), 5.15 (d, 1 H, *J* 8.5 Hz, H-1), 4.58 (dd, 1 H, *J* 11.5, 8.5 Hz, H-2'), 4.37 (q, 1 H, *J* 10.0 Hz, H-2), 4.33 (m, 1 H, H-5'), 4.00–4.20 (m, 5 H, H-5,6', OCH_2Ph), 3.84 (dt, 1 H, *J* 10.0, 6.3 Hz, $OCH_2CH_2SiMe_3$),

3.70 (t, 1 H, *J* 9.6 Hz, H-3), 3.51 (d, 1 H, *J* 9.6 Hz, H-4), 3.46 (dt, 1 H, *J* 9.8, 6.8 Hz, $OCH_2CH_2SiMe_3$), 3.26 (d, 2 H, *J* 3.1 Hz, H-6), 2.18, 1.85, 1.84 (3 s, 3 H each, 3 × Ac), 0.70–0.95 (m, 2 H, $OCH_2CH_2SiMe_3$), −0.16 (s, 9 H, $SiMe_3$). HRMS: Calcd for $C_{46}H_{52}N_2O_{16}Si$ (M + 1): *m/z* 917.3164. Found: *m/z* 917.3165.

A sample of **21** was conventionally acetylated; the product gave a ^{1}H-NMR signal at δ 5.72 (dd, 1 H, *J* 10.6, 8.9 Hz, H-3).

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