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# Bromonium ion-promoted glycosidic bond formation and simultaneous bromination of an activated aryl aglycon

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**Abstract**

*N*-Bromosuccinimide (NBS) together with a catalytic amount of $Me_3SiOTf$ was found to be effective for the activation of thioglycosides. Concurrently with formation of the glycosidic bond, bromination took place on the activated aromatic ring of a 4-methoxyphenyl aglycon. © 2002 Elsevier Science Ltd. All rights reserved.

*Keywords:* *N*-Bromosuccinimide; Thioglycoside; Bromination

## 1. Introduction

Thioglycosides are very frequently used as glycosyl donors in the synthesis of oligosaccharides with a variety of promoters, such as iodonium dicollidine perchlorate (IDCP),[1] *N*-iodosuccinimide–triflic acid (NIS–TfOH)[2a,2b] and methyl triflate.[3] In addition, Nicolaou et al.[4] and Sasaki et al.[5] used *N*-bromosuccinimide (NBS) alone, or NBS–TfOH, to activate phenyl thioglycosides. As compared with NIS, NBS is more stable and is more practical in large-scale synthesis because of its much lower price. However, in contrast with other activation reagents, NBS has seldom been reported as a promoter for thioglycosides.

In our program for synthesizing glycoconjugates, we have employed NBS–$Me_3SiOTf$ to activate phenyl and ethyl thioglycosides to introduce spacer arms with good yields. However, in the course of synthesis of two disaccharides under the same conditions, using a 4-methoxyphenyl glycoside as the glycosyl acceptor, bromination on the aromatic ring of the methoxyphenyl group was observed. The positions of bromination were determined by NMR spectroscopy. In contrast, no iodination occurred when formation of the same disaccharides was promoted by the NIS–TfOH method.

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## 2. Results and discussion

2-Bromoethyl[6] and 2-azidoethyl[7] glycosides are useful intermediates for the preparation of neoglyco conjugates. As shown in Table 1, in entries I–III, we utilized NBS–$Me_3SiOTf$ as a promoter to introduce a $C_2$ spacer arm to glycosyl donors in good yields. For the phenyl thioglycoside **1**, the reactivity of its 3-OH group is dramatically decreased by the neighboring tetrachlorophthalimido (TCP)[8] group, and therefore, it could directly couple with 2-bromo- or 2-azido-ethanol (entries I–II) without further protection of the free hydroxy group. Entry III shows that ethyl thioglycosides can also be activated by the NBS–$Me_3SiOTf$ method.

Entry IV, attempting to synthesize disaccharide **12** under the conditions used in entries I–III, two main products (**8** and **9**) were separated in approximately 2:1 proportion. In the $^{13}C$ NMR spectra of compounds **8** and **9**, resonances for C-1′ were observed at 97.99 and 98.40 ppm, respectively. In their $^1H$ NMR spectra, the coupling between H-1′ and H-2′ was ~8.5 Hz in both cases, clearly indicative of the β-D configuration for the newly introduced glucosamine moiety. The most significant differences in their $^1H$ NMR spectra were in the aromatic proton range of 6.8–7.0 ppm. For compound **8**, there was a one-proton doublet at 6.82 ppm ($J_o$ 9.00 Hz) and a one-proton doubled doublet at 6.96 ppm ($J_o$ 9.00, $J_m$ 2.90 Hz), whereas for compound **9**, only a

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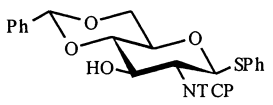
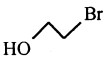
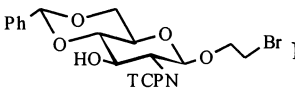
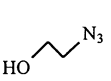
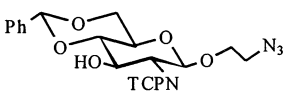
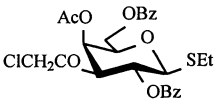
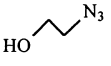
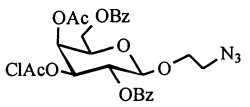
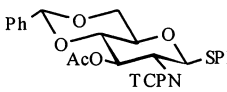
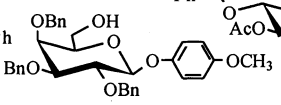
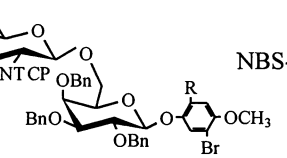
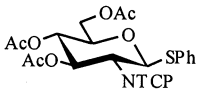
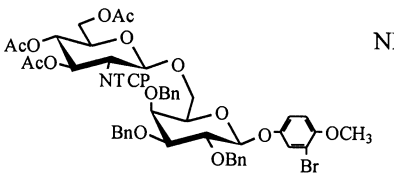
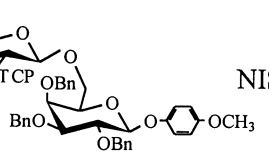
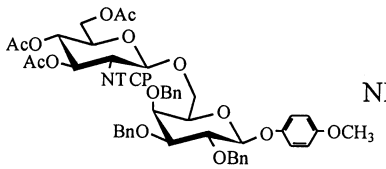
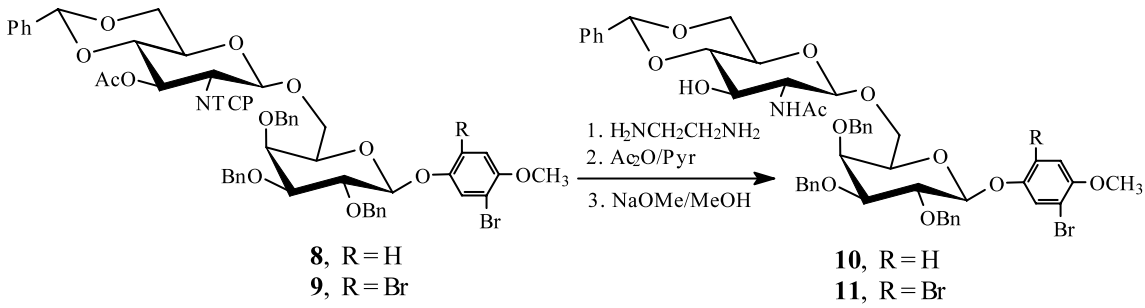
one-proton singlet was observed at 7.03 ppm. These data suggested that substitution had occurred in the 4-methoxyphenyl group. The mass spectra indicated that compound **8** was a monobrominated product and compound **9** was a dibrominated one. Obviously, the brominations were caused by the bromonium ion generated from NBS and $Me_3SiOTf$ in a pattern very similar to that described by Van Boom et al.[2a]

In order to simplify the $^{13}C$ NMR spectra, the TCP groups of compounds **8** and **9** were removed to yield compounds **10** and **11**, whose positions of bromination were determined by NMR data (Scheme 1).

Table 1
Bromonium ion-promoted glycosidic bond formation and its simultaneous bromination effect

| Entry | Glycosyl donor | Acceptor | Product | Promoter | Yield |
|---|---|---|---|---|---|
| I |  **1** |  |  **2** | $NBS–Me_3SiOTf$ | 70% |
| II | **1** |  |  **3** | $NBS–Me_3SiOTf$ | 78% |
| III |  **4** |  |  **5** | $NBS–Me_3SiOTf$ | 73% |
| IV |  **6** |  **7** |  **8**, R = H; **9**, R = Br | $NBS–Me_3SiOTf$ | 59% |
| V |  **13** | **7** |  **14** | $NIS-Me_3SiOTf$ | 71% |
| VI | **6** | **7** |  **12** | NIS-TfOH | 54% |
| VII | **13** | **7** |  **15** | NIS-TfOH | 76% |




Scheme 1.

For compound **10**, the DEPT 135 spectrum further confirmed it was a monobrominated product because of the disappearance of the resonance at 111.7 ppm. Its structure was finally determined from the NOE between the aromatic proton (6.82 ppm, 1 H, d, $J_o$ 9.00 Hz) and the methoxy proton (Scheme 2), indicating that bromination occurred ortho to the methoxy group.

Similarly, the DEPT 135 spectrum of compound **11** showed it to be a dibrominated product because of disappearance of the resonances at 110.3 and 111.8 ppm. The HMQC spectrum of this compound displayed one-proton singlet at $\delta$ 7.09 correlated with the $^{13}C$ resonance at 116.69 ppm, through which we could assign the proton at 7.09 ppm to one of aromatic protons of the brominated OMp ring. Among the four possible structures (**A**–**D**) for dibrominated products, only structure **B** was consistent with the NMR data for compound **11** (Fig. 1).

In entry V, the coupling reaction between the donor **13** and the acceptor **7** was also mediated by NBS–$Me_3SiOTf$, and monobrominated **14** was separated as the only main product. In entry VI, the same donor **6** and acceptor **7** were coupled in the presence of NIS–TfOH to afford disaccharide **12** in a yield similar to that in entry IV, but no iodination occurred. As expected, iodination was not observed in entry VII either.

In summary, NBS–$Me_3SiOTf$ can activate phenyl and ethyl thioglycosides for the synthesis of *O*-glycosides and disaccharides in high yields. However, concurrently with introduction of the glycosidic bond, bromination occurred on an activated aromatic ring in the acceptor. Therefore, if there are no activated aromatic structures in either glycosyl donor and acceptor, NBS–(cat.) $Me_3SiOTf$ is an effective and practical promoter for thioglycosides. NBS, together with a catalytic amount of $Me_3SiOTf$ is also useful as a very mild and convenient brominating reagent in organic synthesis.

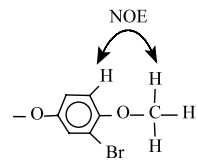
## 3. Experimental

*General methods.*—All reactions were monitored by TLC on Silica Gel $GF_{254}$. Column chromatography was performed using Silica Gel $H_{60}$. All solvents were dried and/or distilled before use. Optical rotations were measured at rt with an AA-10R (Optical Activity Co. Ltd) polarimeter. NMR spectra were recorded (internal standard $Me_4Si$) with a Bruker ARX-400 or JEOL-300 type spectrometer using $CDCl_3$ as the solvent. Elemental analyses were performed on a Perkin–Elmer 240C instrument. MALDI-TOF were taken on a LDI 1700 instrument. Melting points were determined on a X4 melting-point apparatus and are uncorrected.

*General procedure for glycosylation reactions—(a) NBS–$Me_3SiOTf$-mediated glycosylation reaction.*—Thioglycoside donor (1 equiv) and glycosyl acceptor (1.5–2 equiv) were dissolved in dry $CH_2Cl_2$ under argon, and pulverized activated molecular sieves (4 Å) were added. The mixture was stirred for at least 1 h at rt and then cooled to about −50 °C. NBS (2–2.5 equiv) and $Me_3SiOTf$ (0.2 equiv) were added, stirring was continued for 45 min at this temperature. The solution was then diluted with $CH_2Cl_2$, filtered, and washed successively with aq $NaHCO_3$, $NaHSO_3$ and water. The organic layer was dried ($MgSO_4$), concentrated, and purified by column chromatography.

*(b) NIS–TfOH-mediated glycosylation.* Operation was as just described; for work up, the solution was washed successively with aq $NaHCO_3$, $Na_2S_2O_3$, and water. The organic layer was dried ($MgSO_4$), concentrated, and purified by column chromatography.

*2-Bromoethyl 4,6-O-benzylidene-2-deoxy-2-tetrachlorophthalimido-β-D-glucopyranoside* (**2**).—2-Bromoethanol (1 mL ) reacted with the thioglycoside donor **1** (1.50 g, 2.38 mmol) following the general procedure (a). The crude product was purified by column chromatography, eluting with 1:4 acetone–petroleum ether to afford the title compound as a white foam (1.10 g, 70%): mp 180–182 °C, $[\alpha]_D$ −30.8° (*c* 1.7, $CHCl_3$); $R_f$




Scheme 2.

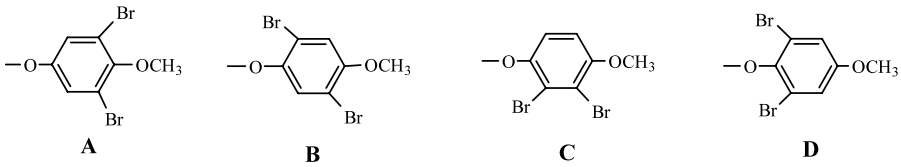



Fig. 1. Four possible structures of dibrominated products.

0.40 (1:3 acetone–petroleum ether); IR ($cm^{-1}$): 1710, 1770 (C=O); $^1H$ NMR (400 MHz, $CDCl_3$): 7.26–7.47 (m, 5 H, ArH), 5.55 (s, 1 H, PhC*H*), 5.27 (d, 1 H, *J* 8.48 Hz, H-1), 4.63 (dd, 1 H, *J* 10.56, 8.56 Hz, H-3), 4.36–4.40 (m, 1 H, H-2), 4.25 (dd, 1 H, *J* 10.50, 8.50 Hz, H-4), 4.11–4.15 (m, 1 H, H-6a), 3.73–3.82 (m, 2 H, H-5, H-6b), 3.60–3.64 (m, 2 H, –OC*H*$_2$CH$_2$Br), 3.34–3.38 (m, 2 H, –OCH$_2$*CH*$_2$Br), 2.04 (br, 1 H, OH); $^{13}C$ NMR (75 MHz, $CDCl_3$): 140.2 (Ar–C, TCP), 136.7, 129.4, 128.3, 128.3, 127.2, 126.1 (Ar–C), 101.8 (Ph*C*H), 98.8 (C-1), 81.9 (C-4), 69.6 (–O*C*H$_2$CH$_2$Br), 68.5 (C-6), 68.1 (C-3), 66.3 (C-5), 56.8 (C-2), 30.4 (OCH$_2$*C*H$_2$Br). Anal. Calcd for $C_{23}H_{18}BrCl_4NO_7$: C, 43.01; H, 2.82; N, 2.18. Found: C, 43.38; H, 2.92; N, 2.37.

*2-Azidoethyl 4,6-*O*-benzylidene-2-deoxy-2-tetrachlorophthalimido-β-*D*-glucopyranoside* (**3**).—2-Azidoethanol (220 μL) reacted with the thioglycoside donor **1** (630 mg, 1 mmol) following the general procedure (a). The crude product was purified by column chromatography, eluting with 1:4 acetone–petroleum ether to afford the title compound as a white foam (480 mg, 78%): mp 114–116 °C, $[\alpha]_D$ −13.9° (*c* 1.44, $CHCl_3$); $R_f$ 0.34 (1:3 acetone–petroleum ether); IR ($cm^{-1}$): 2102 (–$N_3$), 1775, 1715 (C=O); $^1H$ NMR (300 MHz, $CDCl_3$): 7.36–7.47 (m, 5 H, ArH), 5.56 (s, 1 H, PhCH), 5.32 (d, 1 H, *J* 8.40 Hz, H-1), 4.60 (dd, 1 H, *J* 10.30, 8.50 Hz, H-3), 4.36–4.41 (m, 1 H, H-2), 4.26 (dd, 1 H, *J* 10.80, 8.40 Hz, H-4), 3.99–4.06 (m, 1 H, H-6a), 3.80–3.86 (m, 1 H, H-6b), 3.57–3.69 (m, 3 H, OC*H*$_2$CH$_2$N$_3$ and H-5), 3.12–3.47 (m, 2 H, OCH$_2$C*H*$_2$N$_3$), 2.16 (br, 1 H, OH); $^{13}C$ NMR (75 MHz, $CDCl_3$): 163.8 (C=O, TCP), 162.8 (C=O, TCP), 140.2 (Ar–C, TCP), 136.7, 129.4, 128.3, 127.2, 126.1 (Ar–C), 101.8 (Ph*C*H), 98.6 (C-1), 81.9 (C-4), 68.8 (O*C*H$_2$CH$_2$N$_3$), 68.5 (C-6), 68.0 (C-3), 66.2 (C-5), 56.8 (C-2), 50.3 (OCH$_2$*C*H$_2$N$_3$). Anal. Calcd for $C_{23}H_{18}Cl_4N_4O_7$: C, 45.71; H, 3.00; N, 9.27. Found: C, 45.59; H, 2.90; N, 9.07.

*2-Azidoethyl 4-*O*-acetyl-2,6-di-*O*-benzoyl-3-*O*-chloroacetyl-β-*D*-galactopyranoside* (**5**).—2-Azidoethanol (300 μL) reacted with the thioglycoside donor **4** (400 mg, 0.72 mmol) following the general procedure (a). The crude product was purified by column chromatography, eluting with 1:4 acetone–petroleum ether to afford the title compound as a colorless syrup (300 mg, 73%), $[\alpha]_D$ −10.0° (*c* 0.8, $CHCl_3$); IR ($cm^{-1}$): 2104 (–$N_3$), 1721 (C=O); $^1H$ NMR (300 MHz, $CDCl_3$): 7.41–8.01 (m, 10 H, ArH), 5.54–5.59 (m, 2 H), 5.36 (dd, 1 H, *J* 10.50, 2.70 Hz, H-3), 4.79 (d, 1 H, *J* 7.20 Hz, H-1), 4.55–4.61 (m, 1 H), 4.33–4.39 (m, 1 H), 4.16–4.21 (m, 1 H), 3.99–4.06 (m, 1 H), 3.91 (br, 2 H), 3.66–3.73 (m, 1 H), 3.38–3.44 (m, 1 H), 3.26–3.31 (m, 1 H), 2.20 (s, 3 H, OAc); $^{13}C$ NMR (75 MHz, $CDCl_3$): 170.3 (C=O), 166.6 (C=O), 165.8 (C=O), 164.9 (C=O), 133.3, 129.6, 129.6, 129.1, 129.0, 128.4, 128.3 (Ar–C), 101.2 (C-1), 72.5, 70.7, 68.9, 68.3, 66.9, 61.4 (C-2, 3, 4, 5, 6 and O*C*H$_2$CH$_2$N$_3$), 50.4 (OCH$_2$*C*H$_2$N$_3$), 40.2 (Cl*C*H$_2$CO), 20.5 (CO*C*H$_3$). Anal. Calcd for $C_{26}H_{26}ClN_3O_{10}$: C, 54.22; H, 4.55; N, 7.29. Found: C, 54.30; H, 4.76; N, 7.09.

*3-Bromo-4-methoxyphenyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-tetrachlorophthalimido-β-*D*-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-*D*-galactopyranoside* (**8**) *and 3,6-di bromo-4-methoxyphenyl 3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-tetrachlorophthalimido-β-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-*D*-galactopyranoside* (**9**).—The 4-methoxyphenylgalactoside acceptor **7** (1.24 g, 2.23 mmol) was glycosylated with the thioglycoside donor **6** (1.80 g, 2.69 mmol) following the general procedure (a). The crude product was purified and separated by column chromatography, eluting with 1:5 EtOAc–cyclohexane to afford the title compounds in 59% yield (compound **8**, 540 mg, and **9**, 1.10 g), their ratio (**8**:**9**) being ~2:1.

Compound **8** was a foam: mp 114–116 °C, $[\alpha]_D$ −26.3° (*c* 0.76, $CHCl_3$); $R_f$ 0.51 (3:1 cyclohexane–EtOAc); $^1H$ NMR (400 MHz, $CDCl_3$): 7.22–7.44 (m, 21 H, ArH), 6.97 (dd, 1 H, $J_o$ 8.95, $J_m$ 2.86 Hz, OMp), 6.82 (d, 1 H, $J_o$ 9.03 Hz, OMp), 5.71 (t, 1 H, *J* 9.70 Hz, H-3′), 5.49 (s, 1 H, PhC*H*), 5.46 (d, 1 H, *J* 8.40 Hz, H-1′), 4.97, 4.95, 4.64, 4.62 (ABq, 2 H, *J* 11.40 Hz, OBn), 4.89, 4.86, 4.81, 4.78 (ABq, 2 H, *J* 10.90 Hz, OBn), 4.67–4.75 (m, 3 H, OBn, H-1), 4.23–4.28 (m, 2 H, H-2′, H-6a), 4.00 (dd, 1 H, *J* 9.60, 7.8 Hz, H-2), 3.84–3.8 (m, 1 H, H-6a′), 3.82 (s, 3 H, $OCH_3$), 3.68–3.79 (m, 4 H, H-4, H-6b, H-4′, H-6b′), 3.50–3.57 (m, 3 H, H-3, H-5, H-5′), 1.91 (s, 3 H, $H_3$CC=O); $^{13}C$ NMR (100 MHz, $CDCl_3$): 170.7 ($CH_3CO$), 163.5, 162.8 (C=O, TCP), 151.9, 151.4 (C-1, C-4, OMp), 140.7 (TCP), 140.5 (TCP), 138.4, 138.3, 138.2, 136.8, 130.1, 129.8, 129.3, 128.4, 128.4, 128.3, 128.2, 128.0, 127.7, 127.5, 127.1, 126.9, 126.3 (Ar–C), 122.9, 117.2, 112.5, 111.6 (C-2, C-3, C-5, C-6, OMp), 102.9 (C-1), 101.8 (Ph*C*H), 97.9 (C-1′), 81.9 (C-3), 78.9 (C-2), 78.8 (C-4′), 75.4 (O*C*H$_2$Ph), 74.6 (O*C*H$_2$Ph), 73.5 (C-5), 73.4 (C-4), 73.1 (O*C*H$_2$Ph), 70.1 (C-3′), 68.5 (C-6), 68.2 (C-6′), 66.2

(C-5′), 56.7 ($OCH_3$), 56.2 (C-2′), 20.6 ($CH_3CO$); FAB-MS: 1195 [$M^+$]. Anal. Calcd for $C_{57}H_{50}BrCl_4NO_{14}\cdot H_2O$: C, 56.44; H, 4.29; N, 1.15. Found: C, 56.45; H, 4.22; N, 1.42.

Compound **9** was a foam: mp 116–118 °C, $[\alpha]_D$ −23.7° (*c* 1.18, $CHCl_3$); $R_f$ 0.57 (3:1 cyclohexane–EtOAc); $^1H$ NMR (400 MHz, $CDCl_3$): 7.24–7.44 (m, 21 H, ArH), 7.03 (s, 1 H, OMp), 5.71 (dd, 1 H, *J* 9.96, 9.41 Hz, H-3′), 5.50 (s, 1 H, PhC*H*), 5.49 (d, 1 H, *J* 8.50 Hz, H-1′), 4.62–5.10 (m, 7 H, 3 × OBn, H-1), 4.23–4.31 (m, 2 H, H-2′, H-6a), 4.08 (dd, 1 H, *J* 9.70, *J* 7.68 Hz, H-2), 3.89–3.91 (m, 1 H, H-6a′), 3.82 (s, 3 H, $OCH_3$), 3.69–3.79 (m, 4 H, H-4, H-6b, H-4′, H-6b′), 3.53–3.64 (m, 3 H, H-3, H-5, H-5′), 1.91 (s, 3 H, $CH_3CO$); $^{13}C$ NMR (100 MHz, $CDCl_3$): 170.8 ($CH_3CO$), 163.5, 162.8 (C=O, TCP), 151.8, 148.2 (C-1, C-4, OMp), 140.7 (TCP), 140.4 (TCP), 138.4, 138.4, 138.2, 136.8, 130.1, 129.8, 129.3, 128.4, 128.3, 127.9, 127.7, 127.5, 127.1, 126.9, 126.3 (Ar–C), 121.7, 116.5, 111.7, 110.5 (C-2, C-3, C-5, C-6, OMp), 102.5 (C-1), 101.8 (Ph*C*H), 98.4 (C-1′), 81.9 (C-3′), 78.8 (C-2), 78.6 (C-4′), 75.5 ($OCH_2Ph$), 74.7 ($OCH_2Ph$), 73.4 (C-5), 73.3 (C-4), 73.2 ($OCH_2Ph$), 70.2 (C-3′), 68.5 (C-6), 68.2 (C-6′), 66.3 (C-5′), 56.9 ($OCH_3$), 56.2 (C-2′), 20.6 ($CH_3CO$); MALDI-TOF: 1296.1 $[M+Na]^+$, 1312.2 $[M+K]^+$. Anal. Calcd for $C_{57}H_{49}Br_2Cl_4NO_{14}$: C, 53.75; H, 3.88; N, 1.10. Found: C, 53.70; H, 3.84; N, 0.76.

*3-Bromo-4-methoxyphenyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-*D*-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-*D*-galactopyranoside* (**10**).—Compound **8** (190 mg, 0.17 mmol) was dissolved in the mixture of 2 mL dry THF and 10 mL dry EtOH, and 1,2-diaminoethane (70 μL, 1.05 mmol) was added. The mixture was heated at 60 °C for 5 h and concentrated. The residue was filtered through a short column, and the eluate (20:1 $CHCl_3$–MeOH) was concentrated. The residue was dissolved in 6 mL of pyridine, and $Ac_2O$ (4 mL) was added. The mixture was stirred at rt overnight and then cooled in an ice bath. A few drops of water and 5 mL of MeOH were added, and the mixture was concentrated. The residue was dissolved in 30 mL of $CHCl_3$, and washed successively with water and brine. The organic layer was dried and concentrated. The residue was dissolved in 2 mL of $CH_2Cl_2$ and 2.5 mL of dry MeOH. To the solution was added 0.15 mL of 1 M NaOMe–MeOH and the mixture was stirred for 3 h. After neutralization with $H^+$ cation-exchange resin, the solution was filtered and concentrated. The crude product was purified by column chromatography, eluting with 1:3 EtOAc–$CHCl_3$ to afford the title compound as a white solid mass, yield 85 mg (52%), mp 240–242 °C (dec), $[\alpha]_D$ −63.2° (*c* 0.57, $CHCl_3$); $R_f$ 0.22 (1:1 $CHCl_3$–EtOAc); $^1H$ NMR (400 MHz, $CDCl_3$): 7.25–7.49 (m, 21 H, ArH), 6.99 (dd, 1 H, $J_o$ 9.00, $J_m$ 2.90 Hz, OMp), 6.82 (d, 1 H, $J_o$ 9.00 Hz, OMp), 5.65 (d, 1 H, *J* 5.60 Hz, –NH–), 5.52 (s, 1 H, PhCH), 4.54–5.00 (m, 8 H, 3 × OBn, H-1, H-1′), 4.25 (dd, 1 H, *J* 10.30, 5.00 Hz, H-6a′), 4.05 (dd, 1 H, *J* 9.60, 7.70 Hz, H-2), 3.97 (t, 1 H, *J* 9.30 Hz, H-3′), 3.83 (s, 3 H, $OCH_3$), 3.63–3.79 (m, 5 H, H-4, H-5, H-6a, H-6b, H-6b′), 3.59 (dd, 1 H, *J* 9.70, 2.80 Hz, H-3), 3.52 (t, 1 H, *J* 9.20 Hz, H-4′), 3.38–3.48 (m, 2 H, H-5′, H-2′), 1.69 (s, 3 H, $NHCOCH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$): 171.9 (–NH*C*O–), 152.0, 151.5 (C-1, C-4, OMp), 138.3, 138.1, 138.1, 137.0, 129.2, 128.5, 128.4, 128.4, 128.4, 128.3, 128.2, 127.9, 127.9, 127.8, 127.7, 126.4 (Ar–C), 122.6, 117.6, 112.6, 111.7 (C-2, C-3, C-5, C-6, OMp), 103.0 (C-1), 101.9 (PhCH), 101.0 (C-1′), 81.8 (C-3), 81.5 (C-4′), 78.9 (C-2), 75.5 ($OCH_2Ph$), 74.5 ($OCH_2Ph$), 74.4 (C-5), 73.6 (C-4), 73.5 ($OCH_2Ph$), 71.5 (C-3′), 69.3 (C-6), 68.5 (C-6′), 66.2 (C-5′), 59.0 (C-2′), 56.7 ($OCH_3$); MALDI-TOF: 949.0 $[M+Na]^+$, 964.6 $[M+K]^+$. Anal. Calcd for $C_{49}H_{52}BrNO_{12}$: C, 63.49; H, 5.65; Br, 8.62; N, 1.51. Found: C, 63.41; H, 5.70; Br, 8.27; N, 1.32.

*3,6-Di-bromo-4-methoxyphenyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-β-*D*-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-*D*-galactopyranoside* (**11**).—Compound **9** (210 mg, 0.16 mmol) was converted to compound **11** (a white solid, 90 mg, 55.0%) as described for compound **10**; $[\alpha]_D$ −75.0° (*c* 0.32, $CHCl_3$); $R_f$ 0.33 (1:1 $CHCl_3$–EtOAc); $^1H$ NMR (400 MHz, $CDCl_3$): 7.25–7.49 (m, 21 H, ArH), 7.09 (s, 1 H, OMp), 5.67 (d, 1 H, *J* 5.80 Hz, –NH–), 5.52 (s, 1 H, PhC*H*), 4.62–5.17 (m, 8 H, 3 × OBn, H-1, H-1′), 4.27 (dd, 1 H, *J* 10.30, 4.80 Hz, H-6a′), 4.10–4.16 (m, 2 H, H-2, H-3′), 3.83 (s, 3 H, $OCH_3$), 3.67–3.79 (m, 5 H, H-4, H-5, H-6a, H-6b, H-6b′), 3.35–3.44 (m, 2 H, H-5′, H-2′), 1.69 (s, 3 H, $NHCOCH_3$); $^{13}C$ NMR (100 MHz, $CDCl_3$): 171.8 ($NHCOCH_3$), 151.9, 148.3 (C-1, C-4, OMp), 138.3, 138.1, 138.0, 137.0, 129.2, 128.5, 128.4, 128.4, 128.4, 128.3, 128.3, 127.9, 127.9, 127.8, 127.7, 126.4 (Ar–C), 121.5, 116.7, 111.8, 110.3 (C-2, C-3, C-5, C-6, OMp), 102.5 (C-1), 101.9 (PhCH), 100.9 (C-1′), 81.7 (C-3), 81.6 (C-4′), 78.6 (C-2), 75.6 ($OCH_2Ph$), 74.6 ($OCH_2Ph$), 74.6 (C-5), 73.6 (C-4), 73.6 ($OCH_2Ph$), 70.9 (C-3′), 69.4 (C-6), 68.5 (C-6′), 66.2 (C-5′), 59.6 (C-2′), 56.9 ($OCH_3$), 23.2 ($NHCOCH_3$); MALDI-TOF: 1028.6 $[M+Na]^+$, 1044.9 $[M+K]^+$. Anal. Calcd for $C_{49}H_{51}Br_2NO_{12}$: C, 58.51; H, 5.11; Br, 15.89; N, 1.39. Found: C, 58.47; H, 5.17; Br, 15.29; N, 1.29.

*4-Methoxyphenyl 3-acetyl-4,6-*O*-benzylidene-2-deoxy-2-tetrachlorophthalimido-β-*D*-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-*D*-galactopyranoside* (**12**).—The 4-methoxyphenylgalactoside acceptor **7** (110 mg, 0.19 mmol) was glycosylated with the thioglycoside donor **6** (170 mg, 0.25 mmol) following the general procedure (b). The crude product was purified by column chromatography eluting with 5:1 cyclohexane–EtOAc to afford title the compound as a syrup (120 mg, 54%), $[\alpha]_D$ −32.7° (*c* 0.49, $CHCl_3$); $R_f$ 0.53 (3:1 cyclohexane–EtOAc); $^1H$ NMR (400 MHz, $CDCl_3$): 7.25–7.43 (m,

20 H, ArH), 6.77–6.96 (AA′BB, 4 H, OPMP), 5.70 (t, 1 H, *J* 9.70 Hz, H-3′), 5.50 (s, 1 H, PhCH), 5.45 (d, 1 H, *J* 8.40 Hz, H-1′), 4.61–4.97 (m, 7 H, 3 × $OCH_2Ph$ and H-1), 4.22–4.27 (m, 2 H, H-2′, H-6a), 4.00 (dd, 1 H, *J* 9.70, 7.40 Hz, H-2), 3.80–3.84 (m, 1 H, H-6a′), 3.74 (s, 3 H, $OCH_3$), 3.68–3.77 (m, 4 H, H-4, H-6b, H-4′, H-6b′), 3.50–3.55 (m, 3 H, H-3, H-5, H-5′), 1.92 (s, 3 H, OAc); $^{13}C$ NMR (100 MHz, $CDCl_3$): 170.7 ($CH_3CO$), 163.5 (C=O, TCP), 162.8 (C=O, TCP), 155.2, 151.4 (Ar–C, C-1, C-4, OMp), 140.6 (Ar–C, TCP), 138.5, 138.4, 138.3, 136.8, 132.4, 129.7, 129.3, 129.0, 128.5, 128.4, 128.4, 128.3, 128.3, 128.2, 128.2, 128.1, 127.9, 127.6, 127.5, 126.3 (Ar–C), 118.5 (2 C, OMp), 114.5 (2 C, OMp), 103.0 (C-1), 101.8 (PhCH), 97.9 (C-1′), 81.9 (C-3), 78.9 (C-2), 78.8 (C-4′), 75.3 ($OCH_2Ph$), 74.5 ($OCH_2Ph$), 73.6 (C-5), 73.41 (C-4), 73.2 ($OCH_2Ph$), 70.1 (C-3′), 68.5 (C-6), 68.3 (C-6′), 68.1 (C-5′), 56.2 ($OCH_3$), 55.6 (C-2′), 20.6 ($COCH_3$); MALDI-TOF: 1138.5 $[M + Na]^+$, 1153.8 $[M + K]^+$. Anal. Calcd for $C_{57}H_{51}Cl_4NO_{14}$: C, 61.35; H, 4.61; N, 1.25. Found: C, 61.27; H, 4.60; N, 1.61.

*3-Bromo-4-methoxyphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-tetrachlorophthalimido-β-*D*-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-*D*-galactopyranoside* (**14**).—The 4-methoxyphenylgalactoside acceptor **7** (550 mg, 1 mmol) was glycosylated with the thioglycoside donor **13** (870 mg, 1.30 mmol) following the general procedure (a). The crude product was purified by column chromatography, eluting with 4:1 cyclohexane–EtOAc to afford the title compound as a syrup (120 mg, 71%), $[\alpha]_D$ +5.5° (*c* 0.73, $CHCl_3$); $R_f$ 0.25 (3:1 cyclohexane–EtOAc); $^1H$ NMR (400 MHz, $CDCl_3$): 7.24–7.34 (m, 15 H, ArH), 7.239 (d, 1 H, $J_m$ 2.88 Hz, OMp), 7.02 (dd, 1 H, $J_o$ 8.90, $J_m$ 2.82 Hz, OMp), 6.85 (d, 1 H, $J_o$ 9.06 Hz, OMp), 5.57 (dd, 1 H, *J* 10.50, 9.0 Hz, H-3′), 5.41 (d, 1 H, *J* 8.47 Hz, H-1′), 5.16 (dd, 1 H, *J* 10.10, 9.10 Hz, H-4′), 4.64–4.95 (m, 7 H, 3 × OBn, H-1), 4.23–4.29 (m, 2 H, H-2′, H-6a′), 3.98–4.05 (m, 2 H, H-2, H-6b′), 3.85 (s, 3 H, $OCH_3$), 3.76–3.83 (m, 3 H, H-4, H-6a, H-6b), 3.51–3.54 (m, 3 H, H-3, H-5, H-5′), 2.03 ($CH_3CO$), 2.02 ($CH_3CO$), 1.88 ($CH_3CO$); $^{13}C$ NMR (100 MHz, $CDCl_3$): 170.6 ($CH_3CO$), 170.5 ($CH_3CO$), 169.4 ($CH_3CO$), 151.8, 151.3 (C-1, C-4, OMp), 140.6 (TCP), 138.3, 138.3, 138.2, 129.9, 128.4, 128.3, 128.3, 128.3, 128.2, 128.2, 128.0, 127.7, 127.7, 127.5, 126.9 (Ar–C), 123.0, 116.8, 112.5, 111.6 (C-2, C-3, C-5, C-6, OMp), 102.4 (C-1), 97.2 (C-1′), 81.9 (C-3), 78.8 (C-2), 75.4 ($OCH_2Ph$), 74.5 ($OCH_2Ph$), 73.9 (C-5), 73.4 (C-4), 73.2 ($OCH_2Ph$), 72.0 (C-5′), 71.0 (C-3′), 68.4 (C-4′), 68.1 (C-6), 61.7 (C-6′), 56.0 ($OCH_3$), 55.4 (C-2′), 20.7 ($CH_3CO$), 20.6 ($CH_3CO$), 20.5 ($CH_3CO$); MALDI-TOF: 1214.1 $[M + Na]^+$, 1229.7 $[M + K]^+$. Anal. Calcd for $C_{54}H_{50}BrCl_4NO_{16}$: C, 54.46; H, 4.23; N, 1.18. Found: C, 54.01; H, 4.30; N: 0.82.

*4-Methoxyphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-tetrachlorophthalimido-β-*D*-glucopyranosyl-(1→6)-2,3,4-tri-*O*-benzyl-β-*D*-galactopyranoside* (**15**).—The 4-methoxyphenylgalactoside acceptor **7** (100 mg, 0.18 mmol) was glycosylated with the thioglycoside donor **13** (160 mg, 0.24 mmol) following the general procedure (b). The crude product was purified by column chromatography, eluting with 4:1 cyclohexane–EtOAc to afford the title compound as a foam (170 mg, 76%), $[\alpha]_D$ +6.5° (*c* 1.86, $CHCl_3$); $R_f$ 0.26 (3:1 cyclohexane–EtOAc); $^1H$ NHR (400 MHz, $CDCl_3$): 7.25–7.34 (m, 15 H, ArH), 6.77–6.97 (AA′BB′, 4 H, OPMP), 5.59 (dd, 1 H, *J* 10.50, 9.10 Hz, H-3′), 5.41 (d, 1 H, *J* 8.48 Hz, H-1′), 5.16 (t, 1 H, *J* 9.60 Hz, H-4′), 4.64–4.96 (m, 7 H, 3 × $OCH_2Ph$ and H-1), 4.22–4.29 (m, 2 H, H-2′, H-6a′), 3.99–4.05 (m, 2 H, H-2, H-6b′), 3.77–3.83 (m, 3 H, H-4, H-6a, H-6b), 3.76 (s, 3 H, $OCH_3$), 3.50–3.56 (m, 3 H, H-3, H-5, H-5′), 2.04 (s, 3 H, OAc), 2.03 (s, 3 H, OAc), 1.88 (s, 3 H, OAc); $^{13}C$ NMR (100 MHz, $CDCl_3$): 170.5 (C=O, OAc), 170.5 (C=O, OAc), 169.3 (C=O, OAc), 163.3 (C=O, TCP), 162.5 (C=O, TCP), 155.1, 151.2 (Ar–C, C-1, C-4, OMp), 140.5 (Ar–C, TCP), 138.4, 138.3, 138.2, 132.3, 129.9, 129.3, 128.3, 128.2, 128.2, 128.1, 127.6, 127.4, 126.7 (Ar–C), 118.2 (2 C, OMp), 114.4 (2 C, OMp), 102.5 (C-1), 97.2 (C-1′), 81.9 (C-3), 78.8 (C-2), 75.2 ($OCH_2Ph$), 74.4 ($OCH_2Ph$), 73.6 (C-5), 73.5 (C-4), 73.1 ($OCH_2Ph$), 71.9 (C-5′), 70.9 (C-3′), 68.4 (C-4′), 68.2 (C-6), 61.6 (C-6′), 55.5 ($OCH_3$), 55.4 (C-2′), 20.6 (OAc), 20.5 (OAc), 20.4 (OAc); MALDI-TOF: 1135.3 $[M + Na]^+$, 1151.4 $[M + K]^+$. Anal. Calcd for $C_{54}H_{51}Cl_4NO_{16}\cdot 2\ H_2O$: C, 56.50; H, 4.79; N, 1.22. Found: C, 56.36; H, 4.50; N, 1.49.

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## References

1. Veeneman, G. H.; Van Boom, J. H. *Tetrahedron Lett*. **1990**, *31*, 275–278.
2. (a) Veeneman, G. H.; Van Leeuwen, S. H.; Van Boom, J. H. *Tetrahedron Lett*. **1990**, *31*, 1331–1334;
   (b) Konradsson, P.; Udodong, U. E.; Fraser-Reid, B. *Tetrahedron Lett*. **1990**, *31*, 4313–4316.
3. Lonn, H. *Carbohydr. Res*. **1985**, *139*, 115–121.
4. Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc*. **1983**, *105*, 2430–2434.
5. Sasaki, M.; Tachibana, K. *Tetrahedron Lett*. **1991**, *32*, 6873–6876.
6. Dahmen, J.; Frejd, T.; Gronberg, G.; Lave, T.; Magnusson, G.; Noori, G. *Carbohydr. Res*. **1983**, *116*, 303–307.
7. Chernyak, A. Y.; Sharma, G. V. M.; Kononov, L. O.; Krishna, P. R.; Levinsky, A. B.; Kochetkov, N. K. *Carbohydr. Res*. **1992**, *223*, 303–309.
8. (a) Debenham, J. S.; Madsen, R.; Fraser-Reid, B. *J. Am. Chem. Soc*. **1995**, *117*, 3302–3303;
   (b) Castro-Palomino, J. C.; Schmidt, R. R. *Tetrahedron Lett*. **1995**, *36*, 5343–5346.