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The 2-*N,N*-Dibenzylamino Group as a Participating Group in the Synthesis of β-Glycosides**

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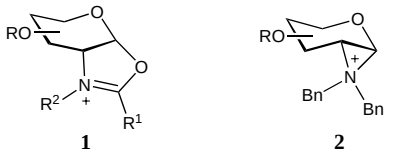
2-Amino-2-deoxyglycopyranosides are important constituents of proteoglycans, glycoproteins, peptidoglycans, and glycolipids, which are widely distributed in living organisms or plants.[1, 2] Most are N-acetylated and are present in 1,2-*trans*-glycosidic linkages. Numerous synthetic approaches to this class of glycosidic linkage have been developed. Because of its nucleophilicity, the amino functionality is always protected during the glycosylation reaction to avoid N-glycosylation, and the choice of protecting group can provide control of stereoselectivity. The most commonly used method for the construction of 1,2-*trans*-glycosidic linkages employs 2-amino sugar donors that contain a participating group as the amino-protecting functionality. The ideal amino protecting group should be stable and impart sufficient reactivity, stereoselectivity, and high yield in glycosylation reactions. Moreover, the protecting group should be readily removed under mild conditions and in high yield.

Many amino protecting groups have been developed for the 1,2-*trans*-glycosylation of 2-amino sugars. The *N*-phthalimido (NPhth)[3] group is most widely used for this purpose. The *N*-acetamido (NHAc) group has also been used,[2] but the oxazolinium intermediate **1** (Figure 1), which is presumed to be formed in the glycosylation reaction, is rather stable and makes this donor unreactive. Generation of a free amine from either NPhth or NHAc requires strongly basic conditions that often cause partial decomposition of the product.[4] A number of alternative amino protecting groups have therefore been developed. These include *N*-4,5-dichlorophthaloyl (NDCPhth),[5a] *N*-tetrachlorophthaloyl (NTCPhth),[5b, c] *N*-2,2,2-trichloroethoxycarbonyl (NTroc),[5d] *N*-trichloroacetyl ($NCOCl_3$),[5e] *N*-dichloroacetyl ($NCOCHCl_2$),[5f] *N*-monochloroacetyl ($NCOCH_2Cl$),[5g] *N*-trifluoroacetyl ($NCOCF_3$),[5h] *N*-sulfonyl (NSO_2-Ph),[5i] *N,N*-diacetyl (NAc_2),[5j] *N*-acetyl-*N*-2,2,2-trichloroethoxycarbonyl (NAcTroc),[5k] and *N*-*p*-nitrobenzyloxycarbonyl (PNZ).[5l] These protecting groups have proven very useful.



1 **2**

Figure 1. Postulated intermediates in glycosylation reactions. R = Bn, R^1 = Me, R^2 = Ph; Bn = benzyl.

In the course of a program on the preparation of N-linked oligosaccharide analogues, we found that attempted synthesis of the β-GalNPhth(1→2)α-Man linkage resulted in an unusually high proportion of α-linked disaccharide, despite the expected participation of the NPhth group. A similar situation had been previously encountered.[6] A β:α mixture (3:1, 75% yield) was formed on glycosylation of acceptor **7** with the tri-*O*-benzyl-NPhth-thioglycoside donor **8** (see Scheme 1). This was presumably due to a "mismatch"[7] in the donor–acceptor pair, and we therefore sought out an alternative donor that would not result in an intermediate similar to the oxazolinium ion **1**. In the search for such a donor, we also recognized that the final deprotection step in almost all synthetic schemes for oligosaccharides involves the removal of persistent O-benzyl ether groups by hydrogenolysis. We therefore elected to examine the *N,N*-dibenzylthioglycoside donor **6** as a potential glycosylation agent. 2-Amino sugars bearing N-alkyl groups have not previously been used as glycosylation donors, presumably because of the expected problematic N-glycosylation.

The donors **6** and **8** were prepared as shown in Scheme 1. Removal of the phthalimido group in **4** followed by O- and N-benzylation with BnBr and NaH in DMF provided **6** in 85% overall yield. Treatment of **4**, which is obtained from **3**,[8] with BnBr and NaH in the presence of Bu_4NI in DMF gave **8** in high yield (88%).

To evaluate **6** as a glycosyl donor for the synthesis of the 2-amino-2-deoxy-β-D-galactopyranosyl-(1→2)-α-D-mannopyranoside sequence, we condensed it with octyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (**7**)[9] in the presence of the neutral promoter dimethyl(methylthio)sulfonium tetrafluoroborate ($DMTSBF_4$)[10] (Scheme 1). The glycosylation with **6** resulted in excellent β-selectivity (β:$\alpha \geq 13$:1) and high yield (86%). One-step deprotection of **10** by hydrogenolysis gave the free amine **11** in 94% yield.

We then investigated the behavior of **6** with the partially protected galactopyranosides **12**–**15**,[9] which represent a

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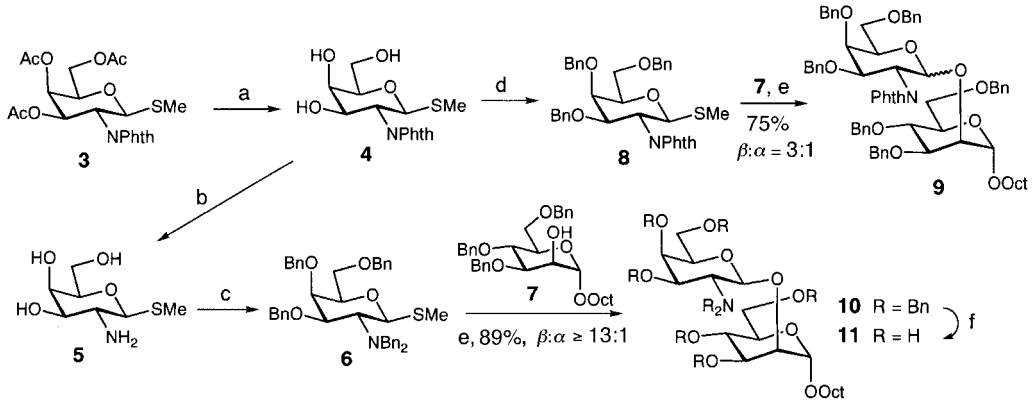


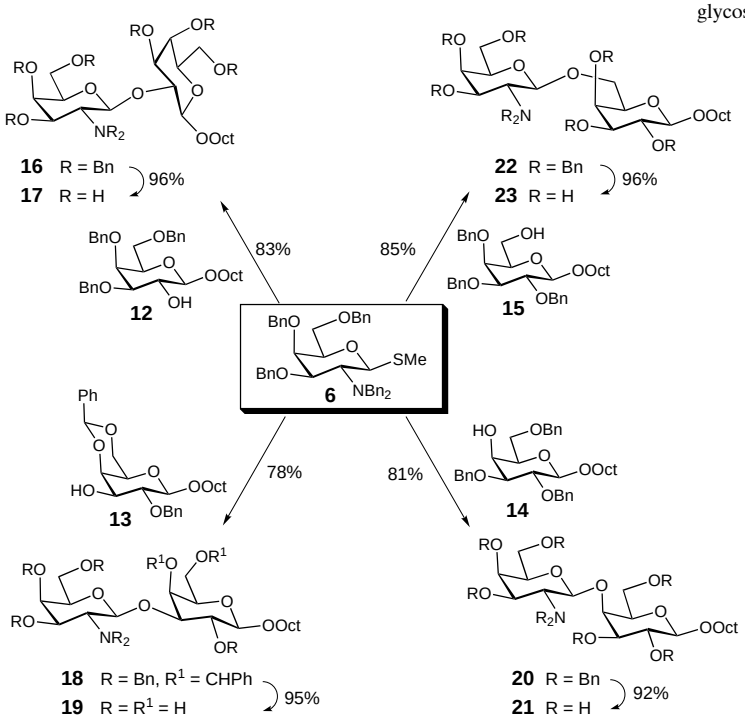
Scheme 1. Synthesis of donors **6** and **8**. a) NaOMe (0.02 M), MeOH, room temperature (RT), 1 h; b) NH_2NH_2/EtOH (1/10), reflux; c) BnBr (7.5 equiv), NaH (10 equiv), DMF, 0 °C → RT, overnight, 85 % (over three steps a – c); d) BnBr (4.5 equiv), NaH (9 equiv), Bu_4NI (9 equiv), DMF, 0 °C → RT, 4 h, 88 %; e) **6** or **8** (2 equiv), $DMTSBF_4$ (4 equiv), 4-Å molecular sieves, CH_2Cl_2, −30 → 0 °C, 2 h; f) $Pd(OH)_2$/C, H_2, HCl (0.2 %), EtOH, 3 h, 94 %.

spectrum of acceptor reactivities (Scheme 2). The glycosylation was carried out in a range of solvents, and dichloromethane emerged as the preferred solvent (Table 1). Reaction of **6** with the **12** – **15** in the presence of $DMTSBF_4$ and 4-Å molecular sieves in dichloromethane gave the protected disaccharides **16**, **18**, **20**, and **22** in good yields (> 78 %) and high β-selectivities ($\beta:\alpha > 11:1$; Table 1). The glycosylation rates and yields were similar for both primary and secondary sugar alcohols. Hydrogenolysis of disaccharides **16**, **18**, **20**, and **22** over Pearlman's catalyst in ethanol with 0.2 % HCl smoothly removed O- and N-benzyl groups. Subsequent purification by C-18 Sep-Pak adsorption[11] gave the deprotected disaccharides **17**, **19**, **21**, and **23** in yields of over 92 % (Scheme 2).

Table 1. Reaction of glycosyl donors **6** and **8** with glycosyl acceptors **7** and **12** – **15**.

Glycosyl donor	Glycosyl acceptor	Solvent	Reaction time [h]	Yield[a] [%]	$\beta:\alpha$[b]
6	**15**	CCl_4/CH_2Cl_2 (10:1)	10	67	2:1
6	**14**	CCl_4/CH_2Cl_2 (10:1)	10	54	10:1
6	**13**	CCl_4/CH_2Cl_2 (10:1)	10	59	3:1
6	**15**	$MeCN/CH_2Cl_2$ (3:1)	8	85	5:1
6	**14**	$MeCN/CH_2Cl_2$ (3:1)	8	62	11:1
6	**13**	$MeCN/CH_2Cl_2$ (3:1)	8	70	10:1
6	**15**	CH_2Cl_2	2	85	18:1
6	**14**	CH_2Cl_2	2	81	50:1
6	**13**	CH_2Cl_2	2	78	11:1
6	**12**	CH_2Cl_2	2	83	> 50:1
6	**7**	CH_2Cl_2	2	86	13:1
8	**7**	CH_2Cl_2	2	75	3:1

[a] Yield of products purified by column chromatography and based on glycosyl acceptor. [b] Ratio determined by ^1H NMR spectroscopic analysis.



Scheme 2. Reaction of **6** with various partially protected galactopyranosides. Synthesis of **16**, **18**, **20**, and **22**: a) **6** (2 equiv), $DMTSBF_4$ (4 equiv), 4-Å molecular sieves, CH_2Cl_2, −30 → 0 °C, 2 h. Deprotection to **17**, **19**, **21**, and **23**: b) $Pd(OH)_2$/C, H_2, HCl (0.2 %), EtOH, 3 h.

In summary, thioglycoside **6** is a new and mechanistically different glycosyl donor. The glycosidic linkage is formed with high β/α-stereoselectivity and in excellent yield for a range of challenging acceptors. Although we have no direct evidence, the intermediacy of **2** (Figure 1) likely accounts for the net retention of configuration at C1. The N-benzyl groups can be removed very efficiently by hydrogenolysis, which obviates the need for harsh basic or alternative chemical reactions for N-deprotection. We propose that, because of the unique sp^3 hybridization of the nitrogen atom in donor **6**, such donors represent very useful alternatives when the use of N-acylated donors results in low yields or poor stereoselectivities. The behavior of N,N-dibenzyl-protected acceptors in glycosylation reaction is under investigation.

Experimental Section

6: To a solution of **5** (300 mg, 1.4 mmol) in DMF (25 mL) at 0 °C was added NaH (430 mg, 80 %, 14.4 mmol). The mixture was stirred for 30 min at room temperature, and then BnBr (1.3 mL, 10.8 mmol) was added. After 10 h the mixture was worked up and subjected to column chromatography to give **6** (850 mg,

90%). ^{1}H NMR ($CDCl_3$): $\delta = 4.85$ (d, 2H, $J = 11.5$ Hz, 2 × OC*H*Ph), 4.61 (d, 1H, $J = 11.5$ Hz, OC*H*Ph), 4.55 (d, 1H, $J = 11.5$ Hz, OC*H*Ph), 4.48, 4.43 (2d, 2H, $J = 11.5$ Hz, OCH_2Ph), 4.32 (d, 1H, $J = 10.0$ Hz, H1), 4.15 (d, 1H, $J = 2.5$ Hz, H4), 3.86 (dd, 1H, $J = 10.5$, 2.5 Hz, H3), 3.79 (br, 4H, N(CH_2Ph)$_2$), 3.65–3.58 (m, 2H, 2 × H6), 3.47 (m, 1H, H5), 3.45 (t, 1H, $J = 10.0$ Hz, H2), 1.90 (s, 3H, SMe); selected ^{13}C NMR data ($CDCl_3$): $\delta =$ 85.39, 82.22, 76.64, 74.27, 73.68, 72.21, 70.58, 68.87, 58.15, 12.15; HR-MS (ES): m/z: 660.3146 $[M+H]^+$.

8: Compound **4** (190 mg, 0.56 mmol), NaH (85 mg, 95%, 3.36 mmol), and Bu_4NI (1.24 g, 3.36 mmol) in DMF (20 mL) were stirred for 30 min at room temperature, and then BnBr (0.4 mL, 3.36 mmol) was added. After 4 h the mixture was worked up and purified by column chromatography to give **8** (300 mg, 88%). ^{1}H NMR ($CDCl_3$): $\delta = 5.14$ (d, 1H, $J = 10.5$ Hz, H1), 4.98 (d, 1H, $J = 11.5$ Hz, OC*H*Ph), 4.85 (t, 1H, $J = 10.5$ Hz, H2), 4.60 (d, 2H, $J =$ 12.0 Hz, 2 × OC*H*Ph), 4.51, 4.46 (2d, 2H, $J = 11.5$ Hz, OCH_2Ph), 4.39 (dd, 1H, $J = 11.0$, 2.8 Hz, H3), 4.32 (d, 1H, $J = 12.0$ Hz, OC*H*Ph), 4.10 (d, 1H, $J = 2.8$ Hz, H4), 3.83 (t, 1H, $J = 6.5$ Hz, H5), 3.66 (m, 2H, 2 × H6), 2.15 (s, 3H, SMe); selected ^{13}C NMR data ($CDCl_3$): $\delta = 80.76$, 77.53, 77.39, 74.53, 73.55, 72.37, 71.51, 68.50, 51.04, 11.05; HR-MS (ES): m/z: 610.2188 $[M+H]^+$.

General procedure for glycosylation and deprotection: A mixture of glycosyl donor (2 equiv), alcohol acceptor (1 equiv), and 4-Å molecular sieves in dichloromethane was stirred for 1 h at room temperature, cooled to −30 °C, and treated with $DMTSBF_4$ (4 equiv). The temperature was increased to 0 °C over 2 h. Thin-layer chromatography (TLC) showed complete disappearance of starting alcohol. After workup and chromatographic purification, disaccharides **9**, **10**, **16**, **18**, **20**, and **22** were obtained. The yields and β:α ratios are shown in Table 1. Protected disaccharides **10**, **16**, **18**, **20**, and **22** were subjected to hydrogenolysis over $Pd(OH)_2$/C (10%) in EtOH with HCl (0.2%) for 3 h. The mixture was then filtered through a Millex-GV filter unit. The residue was purified with a C-18 Sep-Pak cartridge to give **11**, **17**, **19**, **21**, and **23**, respectively. The yields are shown in Scheme 2. Selected physical data are given in the following:

9: ^{1}H NMR ($CDCl_3$): $\delta = 5.14$ (d, 1H, $J = 3.5$ Hz, H1), 5.23 (d, 1H, $J =$ 8.5 Hz, H1′).

10: ^{1}H NMR ($CDCl_3$): $\delta = 5.03$ (d, 1H, $J = 2.0$ Hz, H1), 4.36 (d, 1H, $J =$ 7.8 Hz, H1′); ^{13}C NMR ($CDCl_3$): $\delta = 101.40$ (C1′), 97.13 (C1), 59.05 (C2′).

11: ^{1}H NMR (D_2O): $\delta = 4.98$ (d, 1H, $J = 1.7$ Hz, H1), 4.38 (d, 1H, $J =$ 8.3 Hz, H1′), 2.90 (dd, 1H, H2′); ^{13}C NMR (D_2O): $\delta = 102.80$ (J(C1′,H1′) = 160.6 Hz, C1′), 98.20 (J(C1,H1) = 170.7 Hz, C1); HR-MS (ES): m/z: 454.6257 $[M+H]^+$.

16: ^{1}H NMR ($CDCl_3$): $\delta = 5.01$ (d, 1H, $J = 8.0$ Hz, H1′), 4.51 (d, 1H, $J =$ 7.8 Hz, H1); ^{13}C NMR ($CDCl_3$): $\delta = 102.60$, 97.95 (C-1′, C1).

17: ^{1}H NMR (D_2O): $\delta = 4.51$ (d, 1H, $J = 7.9$ Hz, H1′), 3.0 (dd, 1H, H2′); HR-MS (ES): m/z: 454.2695 $[M+H]^+$.

18: ^{1}H NMR ($CDCl_3$): $\delta = 5.06$ (d, 1H, $J = 8.0$ Hz, H1′), 4.58 (d, 1H, $J =$ 8.0 Hz, H1); ^{13}C NMR ($CDCl_3$): $\delta = 103.00$, 101.00 (C1′, C1).

19: ^{1}H NMR (D_2O): $\delta = 4.53$ (d, 1H, $J = 8.1$ Hz, H1′), 4.43 (d, 1H, $J =$ 8.1 Hz, H1), 2.93 (dd, 1H, H2′); ^{13}C NMR (D_2O): $\delta = 103.10$ (J(C1,H1) = 160.2 Hz, C1), 105.90 (J(C1′,H1′) = 160.3 Hz, C1′); HR-MS (ES): m/z: 454.2652 $[M+H]^+$.

20: ^{1}H NMR ($CDCl_3$): $\delta = 5.08$ (d, 1H, $J = 7.8$ Hz, H1′), 4.36 (d, 1H, $J =$ 8.0 Hz, H1); ^{13}C NMR ($CDCl_3$): $\delta = 103.86$, 100.88 (C1′, C1).

21: ^{1}H NMR (D_2O): $\delta = 4.52$ (d, 1H, $J = 8.2$ Hz, H1′), 4.41 (d, 1H, $J =$ 7.9 Hz, H1), 2.90 (dd, 1H, H2′); ^{13}C NMR (D_2O): $\delta = 103.50$ (J(C1,H1) = 160.4 Hz, C1), 105.50 (J(C1′,H1′) = 161.7 Hz, C1′); HR-MS (ES): m/z: 454.2654 $[M+H]^+$.**22**: ^{1}H NMR ($CDCl_3$): $\delta = 4.76$ (d, 1H, $J = 8.0$ Hz, H1′), 4.42 (d, 1H, $J = 7.7$ Hz, H1); ^{13}C NMR ($CDCl_3$): $\delta = 104.10$, 102.49 (C1′, C1).

23: ^{1}H NMR (D_2O): $\delta = 4.72$ (d, 1H, $J = 8.6$ Hz, H1′), 4.42 (d, 1H, $J =$ 8.1 Hz, H1), 3.22 (dd, 1H, H2′); HR-MS (ES): m/z: 454.2652 $[M+H]^+$.

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Supramolecular Catalysis of Ester and Amide Cleavage by a Dinuclear Barium(II) Complex**

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A most exciting development in supramolecular chemistry has been the design, synthesis, and evaluation of abiotic catalysts that share with natural enzymes a number of features related to efficient catalysis.[1] Our research efforts are aimed at the development of prototype supramolecular catalysts by means of a modular approach in which an efficient catalytic unit for a given reaction and a receptor unit that is complementary to a nonreacting part of the substrate are covalently connected by means of a suitable spacer.

We have now considered the bis-barium(II) complex $\mathbf{1}\cdot(Ba^{2+})_2$ of the homoditopic ligand **1**, in which two aza[18]-

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