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Application of novel, *N*-DTPM protected D-glucosamine building blocks in oligosaccharide synthesis

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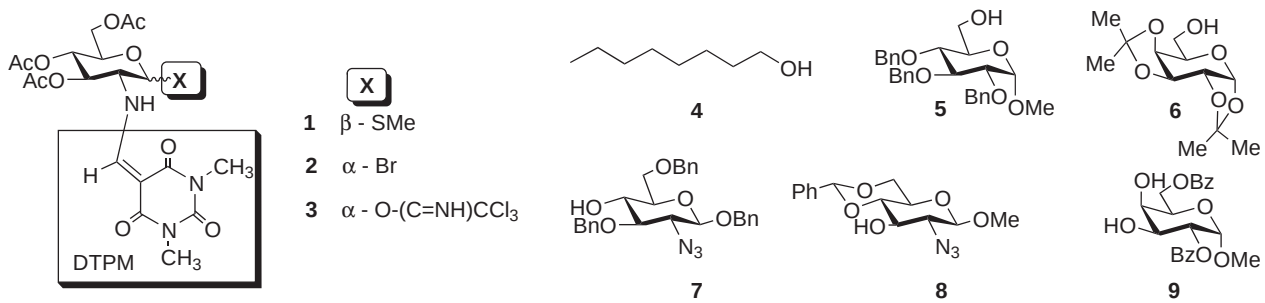
Abstract—A study of glycosylation reactions was performed, using novel *N*-DTPM protected glucosamine donors **1**–**3** and acceptors **4**–**9** ranging from achiral primary alcohols to various alcohols within the D-GlcNAc-, D-Gal- and D-Glu-series. The results show high yielding reactions with good β-selectivities. © 2001 Elsevier Science Ltd. All rights reserved.

2-Amino-2-deoxy-glycopyranosides are ubiquitous and important constituents of glycoproteins, glycolipids and proteoglycans. The carbohydrate moieties therein are involved in important biological processes including cancer metastasis, inflammation and other cellular recognition phenomena.[1] The syntheses of these biologically active structures requires orthogonal protecting groups which are both efficient and cost effective. Within the framework of a project on the syntheses of complex oligosaccharides, the novel (1,3-dimethyl-2,4,6 (1*H*,3*H*,5*H*)-trioxopyrimidin-5-ylidene) methyl protecting group ('DTPM' group, Scheme 1) was developed. This amino protecting group was designed as a cheap and efficient amino protecting group orthogonal to the most common reaction conditions encountered in carbohydrate chemistry (i.e. acylation/deacylation, alkylation, silylation/desilylation, hydrogenolysis, reductive arylidene cleavage, oxidative aryl ether cleavage and Lewis acid promoted reactions).[2]

Herein we present a systematic study exploring the stereochemical course in *N*-DTPM assisted glycosylations using the glucosamine building blocks **1**–**3** as glycosyl donors[3] and compounds **4**–**9** as acceptors[4] of varying reactivities (Scheme 1). The products obtained from glycosylations of the acceptors **4**–**8** with the donors **1**–**3** are shown in Scheme 2 and the results are shown in Table 1 (vide infra).

From our studies, a general pattern of reactivities and selectivities emerges. Thiomethyl glycoside **1** and trichloroacetimidate **3** are the donors of choice for high yielding reactions with *N*-DTPM protected building blocks. Even though the *N*-DTPM is apparently non-



Scheme 1. *N*-DTPM protected D-glucosamine building blocks **1**–**3**[3] served as glycosyl donors during the glycosylation studies; the alcohols **4**–**9**[4] were used, representing glycosyl acceptors of various reactivities.

Keywords: amino sugars; glycosidation; vinylogous amide.

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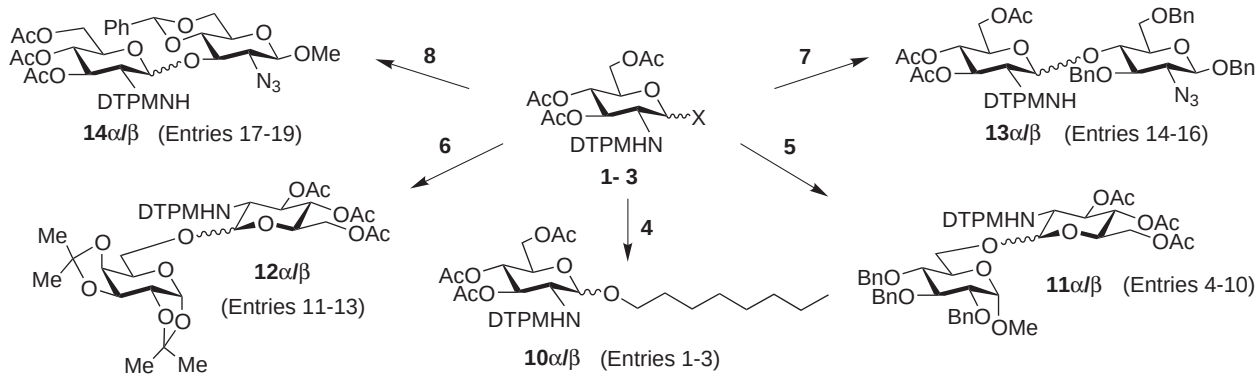


Scheme 2. Glycosylation reactions of *N*-DTPM protected D-glucosamine derivatives **1**–**3** with several glycosyl acceptors ranging from achiral primary alcohols to various alcohols within the D-GlcNAc-, D-Gal- and D-Glu-series.

Table 1. Glycosylation reactions of ***N*-DTPM** protected D-glucosamine derivatives **1**–**3** with alcohols **4**–**8**

Entry	Donor	Acceptor	Promotor[a]	Solvent (temperature, °C)	Product (yield, %)	α/β-Ratio[b]
1	**1**	**4**	DMTST	CH_2Cl_2 (0)	**10** (95)	1/5
2	**2**	**4**	AgOTf	CH_3CN (0)	**10** (95)	1.2/1
3	**3**	**4**	TMSOTf	CH_2Cl_2 (0)	**10** (98)	1/5
4	**1**	**5**	DMTST	CH_2Cl_2 (0)	**11** (90)	1/8.2
5	**1**	**5**	DMTST	CH_3CN (0)	**11** (82)	1/4.2
6	**1**	**5**	NIS/TfOH	CH_3CN (0)	**11** (94)	1/4.7
7	**2**	**5**	AgOTf	CH_3CN (0)	**11** (80)	1/4.2
8	**3**	**5**	TMSOTf	CH_2Cl_2 (0)	**11** (88)	1/2.3
9	**3**	**5**	TMSOTf	Et_2O (0)	**11** (79)	1/1
10	**3**	**5**	TMSOTf	Et_2O (−78)	**11** (77)	1.3/1
11	**1**	**6**	DMTST	CH_2Cl_2 (0)	**12** (95)	1/8
12	**2**	**6**	AgOTf	CH_3CN (0)	**12** (37)	1/6
13	**3**	**6**	TMSOTf	CH_2Cl_2 (0)	**12** (97)	1/2
14	**1**	**7**	DMTST	CH_2Cl_2 (0)	**13** (84)	1/3.5
15	**2**	**7**	AgOTf	CH_3CN (0)	**13** (54)	1/1.2
16	**3**	**7**	TMSOTf	CH_2Cl_2 (0)	**13** (53)	1/1
17	**1**	**8**	DMTST	CH_2Cl_2 (0)	**14** (86)	1/1.3
18	**2**	**8**	AgOTf	CH_3CN (0)	**14** (83)	1/2.1
19	**3**	**8**	TMSOTf	CH_2Cl_2 (0)	**14** (80)	1/4.2

[a] The following equivalents of activating reagents were added: (i) DMTST[5] (5 equiv.); (ii) NIS (1.7 equiv.)/TfOH[7] (0.17 equiv.); (iii) AgOTf [8] (1.5 equiv.); (iv) TMSOTf [9] (0.2 equiv.).

[b] Selected ^{1}H NMR data is shown in Ref. 10.

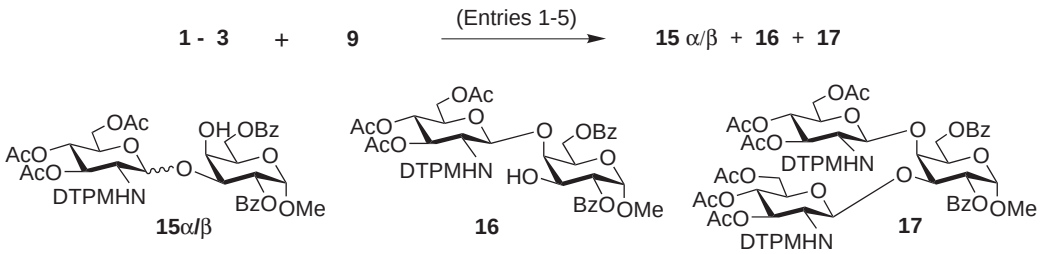
neighbouring group participating in origin, good β-selectivities were obtained with the thioglycoside **1** and DMTST[5] as promoter, especially with primary alcohol acceptors (entries 1, 4 and 11). Despite recent reports in the literature,[6] NIS/TfOH[7] as promoter for **1** was much less efficient than DMTST and only the entries in Tables 1 and 2 gave satisfactory results.

With the trichloroacetimidate **3**, reactions were fast and generally not as β selective. Because α-linked D-GlcNAc moieties are constituents of biologically relevant proteoglycans (i.e. heparan sulfate, heparin), we tried to achieve α-selectivity in these glycosylation reactions. The reduced β-selectivity of **3** encouraged us to change the reaction conditions towards α-selectivity. Unfortu-

Table 2. Glycosylations on diol **9** using the *N*-DTPM protected D-glucosamine derivatives **1**–**3**

Entry	Donor	Promoter[a]	Solvent (temperature, °C)	Products[a] (yield, %)			
				15α	**15β**	**16**	**17**
1	**1**	DMTST	CH_2Cl_2 (0)	14	51	33	nd
2	**1**	DMTST	CH_2Cl_2 (−40)	15	25	11	nd
3	**1**	NIS/TfOH	CH_2Cl_2/CH_3CN 1/1 (−40)	21	25	19	24
4	**2**	AgOTf	Et_2O (−40)	13	60	10	10
5	**3**	TMSOTf	CH_2Cl_2(40)	16	72	8	nd

[a] See footnote a, Table 1, nd = not determined.



Scheme 3. Reaction of diol **9** with glycosyl donors **1**–**3**; other stereoisomers as shown were not isolated.

nately, the shift to lower temperatures and ether as the solvent (entries 9 and 10) gave only moderate α-selectivities.

In contrast to building blocks **1** and **3**, the reactivity and selectivity of bromide **2** in glycosylation reactions does not follow a general pattern and is strongly dependent on the acceptor substrate. Broadly, it is less stereoselective than the DMTST promotion of thioglycoside **1** and more β-selective than the trichloroacetimidate **3**.

Entries 14–19 show glycosylation reactions of the secondary 3-OH and 4-OH groups of acceptors within the D-glucosamine series. Despite the large steric bulk of the *N*-DTPM protecting group, glycosylations of the 3-OH group of compound **8** (entries 17–19) proceeded rapidly and in high yields. In contrast to other results, trichloroacetimidate **3** displayed the best β-selectivity in glycosylation reactions with **8**.[4d] Next, attention focussed on glycosylations with glycosyl acceptor **7**,[4c] leading to chitobiose derivatives **13α/β**, representing a partial structure of *N*-glycans (entries 14–16). Unlike the reactions on acceptor **8**, the chitobiose formation was slower and required prolonged reaction times. Only the DMTST promoted reaction of thioglycoside **1** (entry 14) furnished compound **13α/β** in high yield and β-selectivity. The best result of chitobiose formation was achieved with the *N*-acetyl analogue of **7**. Its reaction with thioglycoside **1** under NIS/TfOH promotion gave β-selectively the corresponding chitobiose derivative in 72% yield. Analogues of acceptors **7** and **8** bearing the *N*-phthaloyl group as amino protection were also studied. Due to the large steric demand of both *N*-protecting groups, these reactions proceeded very slowly and in low yields. Therefore, we believe that *N*-phthaloyl protected D-glucosamine acceptors are mismatched substrates for *N*-DTPM protected D-glucosamine donors **1**–**3**.

After examining selectively deblocked alcohols as acceptors, we next investigated whether regioselective glycosylations could be achieved with *N*-DTPM protected D-glucosamine donors **1**–**3**. For this purpose, the D-galacto configured diol **9**[4e] was chosen. The products obtained from the glycosylations are shown in Scheme 3 and the results are compiled in Table 2. Compound **9** was expected to be glycosylated at the more reactive equatorial 3-hydroxy group. Glycosylations at 0°C resulted in significantly more (1→4) glycosylation product **16** than at −40°C. At this lower temperature, the regioselectivity could be improved and trichloroacetimidate **3** furnished the 3-*O*-glycosylated disaccharides **15α/β** in excellent yield and regioselectivity (entry 5, 88%, **15α/β**:**16** ~ 11:1). Surprisingly, thioglycoside **1** was inferior to the bromide **2** under these conditions. Furthermore, when **1** was activated by NIS/TfOH (entry 3), no regio- and stereoselective preference was achieved and nearly statistical product distribution was obtained, including overglycosylation to trisaccharide **17**.

In summary we have shown that the novel *N*-DTPM group can be used efficiently in carbohydrate chemistry. The best results were obtained with thioglycoside **1** and trichloroacetimidate **3** of *N*-DTPM protected D-glucosamine. Furthermore, thioglycoside **1** exhibits good β-selectivities when activated by DMTST. Currently we are investigating the utility of *N*-DTPM protection in oligosaccharide synthesis including α-stereoselective linkage of D-galactosamine with serine/threonine, which represents a common motif of biologically important *O*-glycan structures.

Acknowledgements

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3. (a) For thiomethylglycoside **1** see Ref. 2; (b) Glycosyl bromide **2** was prepared from D-glucosamine in three steps: (i) DTPM–NMe_2,[2] MeOH (80%); (ii) Ac_2O/pyridine (97%); (iii) HBr/HOAc, CH_2Cl_2, 0°C (91%); (c) Trichloroacetimidate **3** was prepared from D-glucosamine in four steps: (i) DTPM–NMe_2,[2] MeOH (80%); (ii) Ac_2O/

pyridine (97%); (iii) piperidine, THF, 0°C (91%); (iv) Cl_3CCN, K_2CO_3, CH_2Cl_2, 0°C (92%).

4. (a) Compounds **4** and **6** were purchased from Sigma/Aldrich; (b) Compound **5**: Liptak, A.; Jodal, J.; Nanasi, P. *Carbohydr. Res.* **1975**, *44*, 1–11; (c) Compound **7** was prepared from ethyl-4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside[4f] in three steps: (i) BnOH, NIS, TfOH, CH_3CN, −40°C (85%); (ii) $H_2NCH_2CH_2NH_2$, *n*-BuOH, 100°C; Tf–N_3, DMAP, CH_3CN (85%, two steps); (d) Compound **8** was prepared from ethyl-3-*O*-acetyl-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-β-D-glucopyranoside[4f] in three steps: (i) MeOH, NIS, TfOH, CH_3CN, −40°C (85%); (ii) $H_2NCH_2CH_2NH_2$, *n*-BuOH, 100°C; Tf–N_3, DMAP, CH_3CN (83%, two steps); (e) Compound **9**: Buskas, Th.; Konradsson, P. *J. Carbohydr. Chem.* **2000**, *19*, 25–51; (f) Guenther, W.; Kunz, H. *Carbohydr. Res.* **1992**, *228*, 217–241.
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10. For selected ^1H NMR data (500 MHz, $CDCl_3$), see Table 3.

Table 3.

Compound	δ [NH ($J_{NH,2}$)]	δ [H-C=($J_{NH,H-C=}$)]	δ [H-1^1 ($J_{1,2}$)]	δ [H-1^2 ($J_{1,2}$)]	δ (NMe)
10α	10.13 (9.7 Hz)	8.04 (13.4 Hz)	5.02 (3.6 Hz)		3.23, 3.21
10β	10.11 (9.3 Hz)	8.09 (13.2 Hz)	4.41 (8.0 Hz)		3.22, 3.19
11α	10.35 (9.6 Hz)	8.07 (13.9 Hz)	4.59 (3.3 Hz)	5.13 (3.6 Hz)	3.20, 3.14
11β	10.17 (9.3 Hz)	8.16 (13.3 Hz)	4.57 (3.3 Hz)	4.18 (8.0 Hz)	3.20, 3.13
12α	10.22 (9.8 Hz)	8.10 (13.1 Hz)	5.51 (5.0 Hz)	5.05 (3.7 Hz)	3.31, 3.27
12β	10.22 (9.8 Hz)	8.10 (13.1 Hz)	5.37 (5.0 Hz)	4.62 (8.1 Hz)	3.30, 3.26
13α	10.04 (9.9 Hz)	8.10 (13.7 Hz)	4.43 (8.0 Hz)	5.78 (3.9 Hz)	3.25, 3.23
13β	10.02 (9.4 Hz)	7.99 (13.2 Hz)	4.26 (8.2 Hz)	4.28 (8.5 Hz)	3.32
14α	10.20 (10.0 Hz)	7.90 (13.7 Hz)	4.33 (8.0 Hz)	5.34 (3.7 Hz)	3.21, 3.18
14β	10.35 (9.3 Hz)	8.21 (13.4 Hz)	4.42 (7.8 Hz)	4.73 (8.3 Hz)	3.32, 3.27
15α	10.18 (9.9 Hz)	8.31 (13.7 Hz)	5.11 (3.6 Hz)	5.19 (3.6 Hz)	3.17, 3.02
15β	10.05 (8.5 Hz)	8.02 (13.7 Hz)	5.04 (3.7 Hz)	4.80 (8.0 Hz)	3.16, 3.01
16	10.25 (8.9 Hz)	8.10 (14.0 Hz)	5.04 (3.7 Hz)	4.96 (8.2 Hz)	3.31, 3.19
17	10.37 (9.6 Hz), 9.98 (7.6 Hz)	8.29 (13.5 Hz), 7.79 (13.5 Hz)	5.03 (3.7 Hz)	5.10 (7.5 Hz), 4.70 (8.1 Hz)	3.21, 3.11, 3.05, 2.90