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MMTr as an efficient anomeric S-protecting group for the synthesis of glycosyl thiols

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Abstract—The 4-monomethoxytrityl (MMTr) group was introduced in high yields to anomeric sulfhydryl functions using commercially available MMTrCl. Significantly, it is stable to a variety of reaction conditions, including acids and bases, and is removable under very mild acidic conditions, which are compatible with the presence of a number of other acid-labile hydroxyl protecting groups. The successful preparation of seven glycosyl thiols indicates that MMTr has potential application for the synthesis of complex 1-thiosugars.

The rapid development of glycobiology has created a great demand for structurally defined carbohydrates and their mimetics as biological probes. Among them, thioglycosides have attracted considerable attention due to their resistance to chemical and enzymatic hydrolysis and their similar solution conformation and biological activities compared to native counterparts.[1] As a consequence, efforts have been devoted to synthesize thioglycosides, including thiosaccharides and S-glycoconjugates, in order to provide valuable compounds for biological studies.[2] For instance, a series of 6-β-thiosaccharide analogues of morphine-6-glucuronide (M6G) have been synthesized and evaluated with the objective of preparing an analogue of M6G with improved biological activity.[3] Also, carbohydrate epitopes of conjugate vaccines have been modified to contain S-linked residues and the resulting S-linked immunogens generated an antigen-specific immune response that even exceeded the response to the native oligosaccharides.[4]

Currently, glycosyl thiols or their precursors, such as anomeric thioacetates, which can be S-deacetylated in situ to generate the desired glycosyl thiols, are the key building blocks for the construction of thioglycosides,[2] although thioglycosides can also be synthesized conventionally from normal glycosyl donors and the corresponding sulfur-containing acceptors.[5] The advantage of the glycosyl thiol-based approach is the ready availability and chemical stability of glycosyl thiols. The preparation of glycosyl thiol dates from nearly half a century ago[6] and new preparative procedures are still emerging.[7] On the other hand, both α- and β-glycosyl thiols are quite stable, and do not mutarotate even under basic conditions,[3] hence the anomeric stereochemistry is maintained during the glycosylation process. Therefore, by utilizing glycosyl thiols, various thioglycosides have been synthesized as stable glycoside analogues and as potential agents for therapeutic intervention.[2,8] S-Glycopeptides have been synthesized recently by two independent groups, in which glycosyl thiols were utilized as sugar building blocks.[8a,b]

In addition to their wide application in thioglycoside synthesis, glycosyl thiols are also useful in the synthesis of many other carbohydrate contexts, such as C-glycoside synthesis,[9] glycosyl sulfenamide and glycosyl sulfonamide synthesis,[10] and glycosyl disulfide synthesis.[11] Glycosyl thiols have been employed to prepare carbohydrate thionolactones[12] which could be useful in the construction of spiro-C/O-glycoside-containing natural products. Moreover, novel sugar species have been developed from glycosyl thiols, such as GTM-Cl,[13] which could be applied in the synthesis of various neoglycoconjugates. Very recently, glycosyl thiol was used to generate the transient species, glycosylsulfenic acid.[14]

Although glycosyl thiol has exhibited great utility and potential in contemporary carbohydrate chemistry, to

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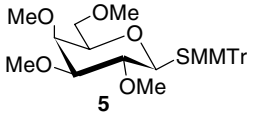
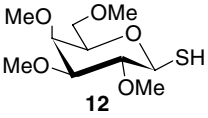
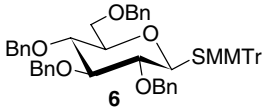
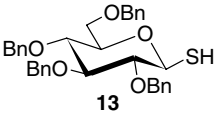
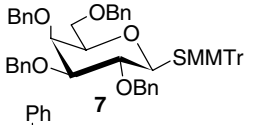
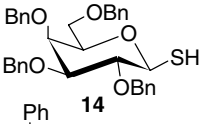
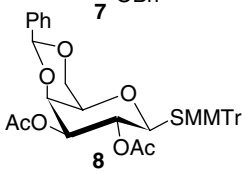
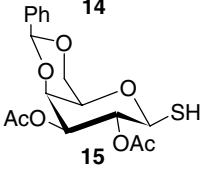
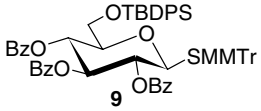
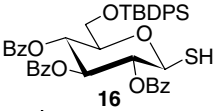
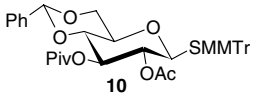
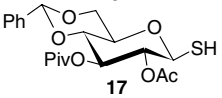
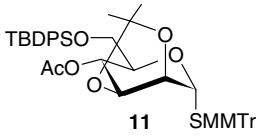
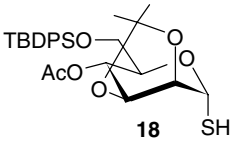
Table 1. Deprotection of thioglycosides **5**–**11** with TFA/TESH[a]

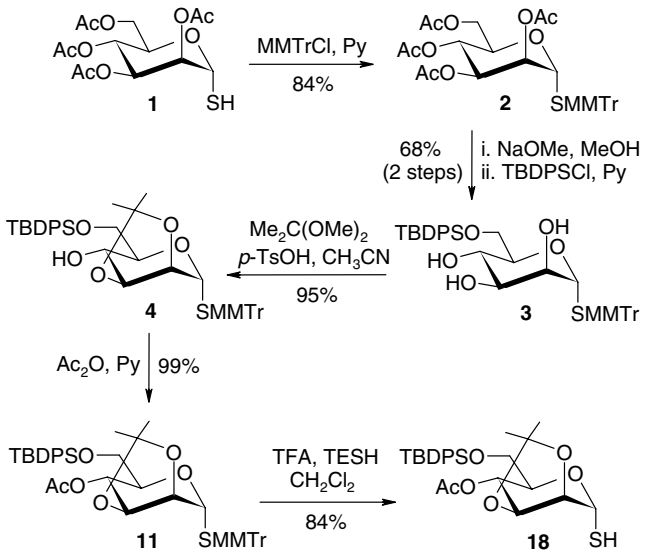
Entry	Substrate	Product	Yield[b] (%)
1	 **5**	 **12**	96
2	 **6**	 **13**	86
3	 **7**	 **14**	83
4	 **8**	 **15**	83
5	 **9**	 **16**	88
6	 **10**	 **17**	93
7	 **11**	 **18**	84

[a] All reactions were conducted with 0.8% TFA in CH_2Cl_2 containing 1% TESH at 0 °C; see Ref. 21 for details.
[b] Yield of pure, isolated product with correct analytical and spectral data.

the best of our knowledge, only a few papers describe the development of sulfhydryl protecting groups, which could allow access to glycosyl thiols with enhanced structural diversity and complexity. The xanthenyl (Xan) group has been reported as a S-protecting group,[15] however, its application in thioglycoside synthesis is limited due to the harsh protection and deprotection conditions. Reactions to introduce the triphenylmethyl (Tr) group onto an anomeric sulfhydryl group were troublesome and low yielding, besides, the strong acidic conditions required for its removal would also cleave other acid-sensitive protecting groups on the sugar ring.[16] The triisopropylsilyl (TIPS) group has also been used to protect glycosyl thiols,[8b] however, its application is limited in view of the fact that the silyl group is one of the most popular O-protecting groups in carbohydrate chemistry.

Under these circumstances, the development of a new and efficient protecting group for the synthesis of glycosyl thiols is of great interest. As part of our ongoing interest in S-glycoconjugates,[8a] we report here the 4-monomethoxytrityl (MMTr) group as a practical protecting group for glycosyl thiols, which can be easily introduced and selectively removed under very mild conditions.

Although the MMTr protecting group has been well studied in both nucleoside and peptide chemistry,[17] little is known about this group in carbohydrate chemistry. MMTr was reported to be cleaved under very mild acidic conditions in peptide synthesis, however, its compatibility with common acid-labile hydroxyl protecting groups on a sugar ring remains to be tested. To clarify this issue, we prepared a range of monomethoxyltrityl thioglycosides **5**–**11**, as depicted in Table 1, which bear typical acid-labile carbohydrate protecting groups, such as benzyl, benzylidene, *tert*-butyldiphenylsilyl and isopropylidene. In practice, the corresponding *per*-acetyl glycosyl thiols, such as mannosyl thiol **1**[18] (Scheme 1), were prepared as starting materials and then treated with commercially available MMTrCl in pyridine at room temperature to give the desired *per*-acetyl thioglycoside intermediates,[19] such as compound **2**, in very high yields. Subsequently, deacetylation of these intermediates with NaOMe in MeOH followed by protecting group manipulations, such as methylation with MeI under the action of NaH; benzylation with BnBr in the presence of NaH; benzylidenation with $PhCH(OMe)_2$ catalyzed by *p*-TsOH; silylation with TBDPSCl in pyridine and isopropylidenation with $Me_2C(OMe)_2$ catalyzed by *p*-TsOH, furnished substrates **5**–**11** in generally very good yields.



Scheme 1. An example of MMTr as an S-protecting group for the synthesis of glycosyl thiols. Synthesis of mannosyl thiol **18**.

Next, we examined the deprotection of the MMTr group on the above compounds **5**–**11**. It is well known that the removal of trityl-type protecting groups, such as Tr, MMTr, and DMTr, from sulfur is reversible due to the high stability of the trityl cation and the strongly nucleophilic nature of the sulfhydryl group. As a result, a cation scavenger is usually necessary to drive the detritylation to completion. After screening several conditions,[20] 0.8% trifluoroacetic acid (TFA) in CH_2Cl_2 containing 1% triethylsilane (TESH) was chosen to effect all the deprotections shown in Table 1. All the reactions were performed at 0 °C. Under these conditions,[21] glycosyl thiols **12**–**18** were obtained in very high to excellent yields. It is important to note that all the acid-labile protecting groups present, including benzyl, benzylidene, silyl, and isopropylidene, which are frequently used in carbohydrate chemistry, were unaffected. Most notably, the benzylidene protecting group survived the present conditions as indicated by the good to excellent yields of thiols **15** and **17**.

In summary, the 4-monomethoxytrityl group has been employed as a new S-protecting group for the synthesis of glycosyl thiols, which can be installed conveniently and cleaved selectively in the presence of other acid-labile hydroxyl protecting groups. In view of these attributes, together with the recent use of the more acid-labile dimethoxytrityl protecting group under glycosidation conditions,[22] the monomethoxytrityl group described herein may find valuable and versatile use in thioglycoside chemistry. Its application toward the synthesis of complex oligosaccharidyl thiols is currently underway.

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19. *Typical procedure for the introduction of the MMTr group.* To a solution of the thiol **1** (1.45 g, 3.98 mmol) in dry pyridine (18 mL) was added MMTrCl (1.36 g, 4.34 mmol). The resulting mixture was stirred overnight at room temperature. Pyridine was then removed in vacuo and the residue was purified by flash column chromatography (hexane/EtOAc, 3:1) to give the desired tritylated compound **2** (2.13 g, 84%) as a white foam: TLC $R_f = 0.29$ (hexane/EtOAc, 2:1); $[\alpha]_D$ +83.2 (*c* 0.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 12H, ArH), 6.81 (d, $J = 8.8$ Hz, 2H, ArH), 5.29 (dd, $J = 3.2$, 1.6 Hz, 1H, H-2), 5.26 (m, 2H, H-3, H-4), 4.82 (d, $J = 1.6$ Hz, 1H, H-1), 4.28 (m, 2H, H-5, H-6_a), 3.93 (dt, $J = 10.0$, 3.6 Hz, 1H, H-6_b), 3.78 (s, 3H, OMe), 2.11, 2.03, 2.02, 1.97 (4s, 12H, Ac); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.0, 169.9, 169.7 (4Me*C*O), 158.7, 144.7, 144.6, 136.3, 131.3, 130.03, 130.00,

128.3, 127.4, 113.5 (aromatic carbons), 83.2 (C-1), 72.5 (C-2), 71.2 (C-5), 70.0 (*C*SAr), 69.7, 66.2 (C-3, C-4), 62.6 (C-6), 55.5 (*C*H_3O), 21.0, 20.9, 20.8 (*C*H_3CO); ESI-MS *m*/*z* 659.2 [M+Na^+].

20. Deprotection was unsuccessful using dichloroacetic acid and anisole as the alternative to acid and cation scavengers, respectively.
21. *Typical procedure for cleavage of the MMTr group.* To a stirred solution of the thioglycoside **11** (268 mg, 0.34 mmol) in CH_2Cl_2 (34 mL) at 0 °C was added dropwise TFA (0.27 mL) followed by Et_3SiH (0.34 mL). The mixture was stirred at 0 °C for 80 min, after which time TLC indicated the disappearance of the starting material. The mixture was then concentrated in vacuo at room temperature, and azeotroped with toluene to give a residue, which was purified by flash column chromatography (hexane/EtOAc, 8:1) to give the thiol **18** (148 mg, 84%) as a colorless syrup: TLC $R_f = 0.51$ (hexane/EtOAc, 3:1); $[\alpha]_D$ +31.4 (*c* 0.7, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (m, 4H, Ph), 7.40 (m, 6H, Ph), 5.78 (d, $J = 6.4$ Hz, 1H, H-1), 5.23 (dd, $J = 10.0$, 6.8 Hz, 1H, H-4), 4.26 (m, 2H, H-2, H-3), 4.11 (ddd, $J = 9.8$, 4.8, 2.9 Hz, 1H, H-5), 3.76 (dd, $J = 11.5$, 4.9 Hz, 1H, H-6_a), 3.72 (dd, $J = 11.4$, 2.8 Hz, 1H, H-6_b), 2.13 (d, $J = 6.4$ Hz, 1H, SH), 1.98 (s, 3H, Ac), 1.57 (s, 3H, Me), 1.36 (s, 3H, Me), 1.07 (s, 9H, ^{t}Bu); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7 (Me*C*O), 136.0, 135.9, 133.53, 133.49, 129.91, 129.87, 127.90, 127.85 (aromatic carbons), 110.6 (Me_2C), 78.2 (C-2), 76.3 (C-1), 75.8 (C-3), 71.1 (C-5), 69.7 (C-4), 62.9 (C-6), 27.8 (*Me*$_2$C), 27.0 (*Me*$_3$C), 26.8 (*Me*$_2$C), 21.1 (*Me*CO), 19.5 (Me_3C); ESI-MS *m*/*z* 517.3 [M+H^+], 539.2 [M+Na^+], 555.2 [M+K^+].
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