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Trityl ethers in Oligosaccharide Synthesis: A Novel Strategy for the Convergent Assembly of Oligosaccharides

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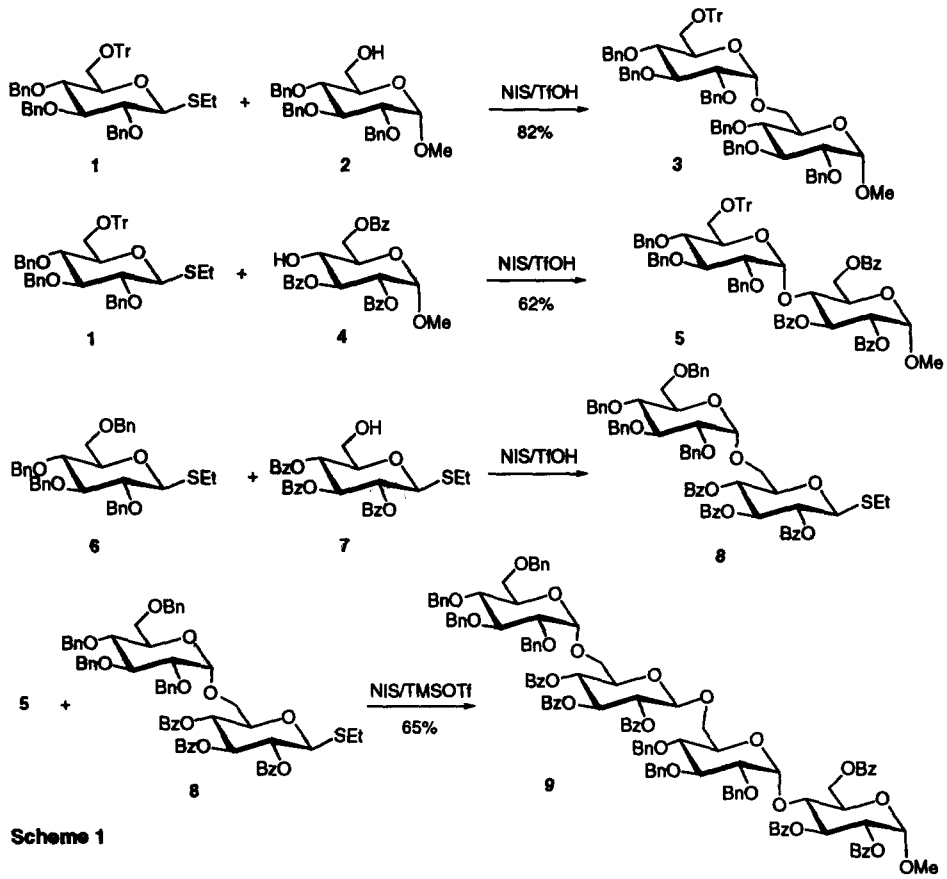
Abstract: We have developed a novel glycosylation strategy in which a tritylated thioglycoside can act as a glycosyl donor and acceptor. In combination with previously reported chemoselective glycosylations, this feature enables highly convergent assembly of oligosaccharides

Traditionally, the most widely used glycosylation methods utilised anomeric halide derivatives of carbohydrates as glycosyl donors.[1] However, these compounds often suffer from instability and require relatively drastic conditions for their preparation. The introduction of the ortho-ester[2] and imidate[3] procedures were the first attempts to find alternatives to the glycosyl halide methodologies. Many other leaving groups for the anomeric centre have been reported[4] and nowadays the anomeric fluorides, trichloroacetimidates, and thioglycosides are the most widely applied glycosyl donors. These compounds can be prepared under mild conditions, are sufficiently stable to be purified and stored for a considerable period of time and undergo glycosylations under mild conditions. These versatile glycosyl donors have paved avenues for the synthesis of complex oligosaccharides of biological relevance. However, such synthesis are only successful if manipulations of complex oligosaccharides are kept at a minimum.[5] Thus, most of the synthetic effort should be directed towards the preparation of the (oligo)saccharide building blocks which are assembled into complex structures involving a minimal number of synthetic steps.

Ideally, a saccharide building block should have the ability to act as a glycosyl donor as well as an acceptor which will enable an oligosaccharides to be assembled in a very flexible and highly convergent manner. Such a strategy requires that an anomeric functionality can serve as a protecting group as well as a leaving group after activation with a suitable reagent. In addition, a hydroxyl should be functionalised in such a manner that it can act as a protecting group but also can function as glycosyl acceptor.

Thioglycosides have attracted considerable attention; they are stable under a variety of chemical transformations but can be activated by thiophilic reagents.[6] Trityl ethers of saccharides provide efficient protection for hydroxyls but can also serve as glycosyl acceptors with 1,2-cyanoethylidine glycosides.[7] We report here that by using appropriate reaction conditions, tritylated thioglycosides can act as glycosyl donors as well as glycosyl acceptors. These features enabled the development of a novel chemoselective glycosylation strategy in which oligosaccharides can be assembled in a convergent building block approach avoiding protecting group manipulations at the oligosaccharide stage.

We anticipated that the trityl ether of compound **1** is sufficiently stable to withstand glycosylation with *N*-iodosuccinimide and a catalytic amount of triflic acid (NIS/TfOH) in a suitable solvent. Indeed, NIS/TfOH mediated coupling of **1** with glycosyl acceptor **2** gave disaccharide **3** in an excellent yield of 82%. Mass spectroscopic analysis of the coupling products revealed that self-condensation or oligomerisation had not occurred. Furthermore, the NMR spectra of **3** showed that mainly the α-anomer was formed. Interestingly, a modest anomeric selectivity was obtained when ethyl 2,3,4,6-tetra-*O*-benzyl-thioglucopyranoside was coupled with **2**. Thus, the bulky trityl ether at C-6 of 2,3,4-tri-*O*-benzyl-6-O-trityl-thioglucopyranoside (**1**) directs the stereochemical outcome of the glycosylation.[8]



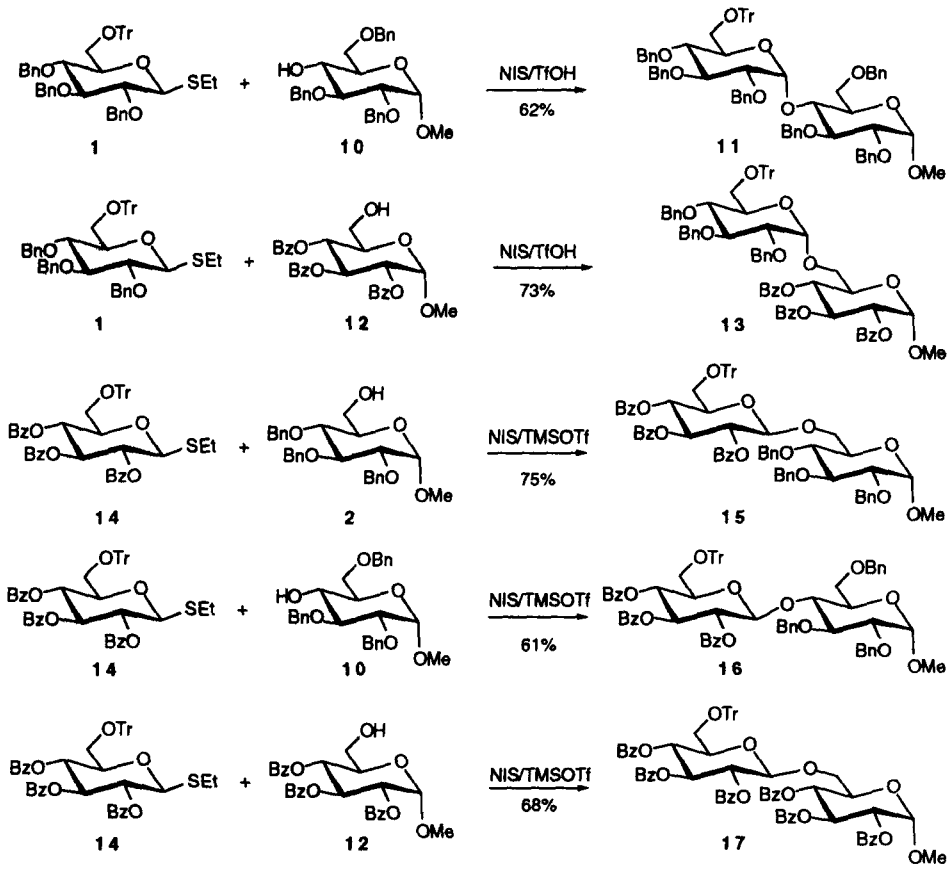
Scheme 1

It was further shown that the tritylated thioglycoside **1** was able to glycosylate the unreactive alcohol of acceptor **4** to produce disaccharide **5** in an acceptable yield of 62%.

The versatility of the approach is illustrated by the preparation of tetrasaccharide **9**. Thus, disaccharide **8**, which was prepared by a chemoselective glycosylation of the armed thioglycoside donor **6** with the disarmed thioglycoside acceptor **7**,[9] was coupled with the tritylated disaccharide **5** using NIS and a stochiometric amount of TMSOTf to give tetrasaccharide **9** in a yield of 65%.[10] Thus, tetrasaccharide **9** can be assembled from the monosaccharides **1**, **4**, **6** and **7** in a highly convergent manner avoiding protecting group manipulations at the oligosaccharide stage.

The choice of the coupling condition used for glycosylation of the trityl ether requires some elaboration. NIS/TfOH mediated glycosylation of alcohols regenerates the acid rendering the reaction catalytic in acid. On the otherhand, glycosylation of a trityl ethers produces a trityl-cation. We have shown that trityl perchlorate can activate NIS but is less efficient than TMSOTf and TfOH. Therefore, glycosylation of a trityl ether requires a stochiometric amount of acid to activate efficiently all the NIS. Furthermore, in another study, we observed that TMSOTf is a more powerful activator of NIS. It is important to note that under the applied reaction conditions, the trityl ether of **5** acts as a glycosyl acceptor and does not hydrolyse prior to glycosylation. This feature was demonstrated by subjecting the trityl ether **5** to the glycosylation conditions which did not induce hydrolysis. However, when thioglycoside **8** was added to this mixture, the coupling was completed within 1 minute.

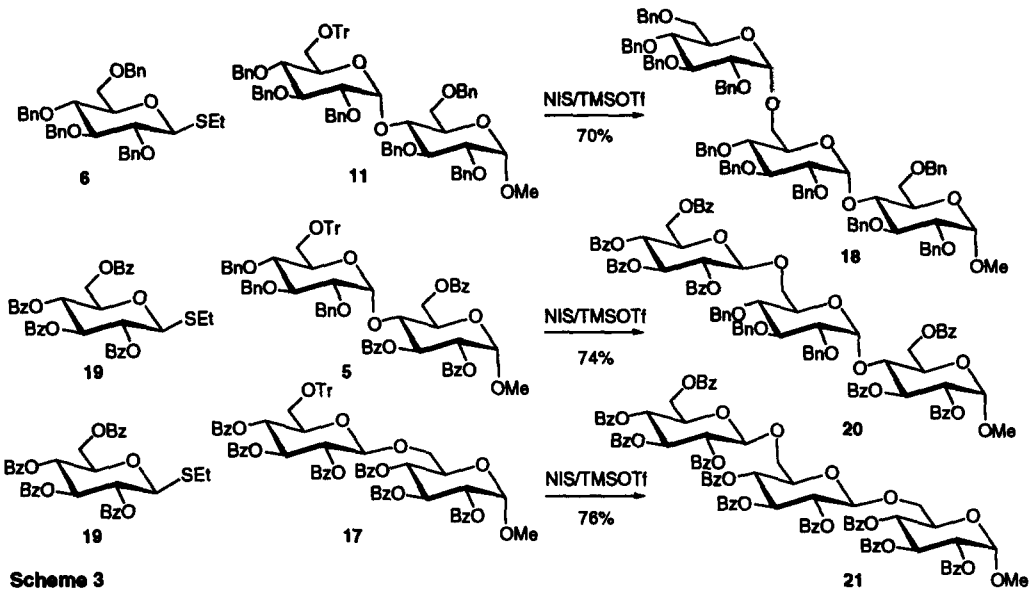
A series of di- and trisaccharides were synthesised to demonstrate the generality of the new methodology (**Scheme 2**). As expected, the coupling of tritylated glycosyl donor **1** with acceptor **10** having an unreactive 4-hydroxyl afforded disaccharide **11** in a yield of 62% (α/β = 6/1). Coupling of glycosyl donor **1** with the benzoyl protected acceptors **12**, using standard conditions, gave the corresponding disaccharide **13** in good yield of 73%. Neighbouring group participation can be employed for the preparation of β-linked glucosides. Thus, tritylated glycosyl donor **14** was coupled under standard conditions with the acceptors **2**, **10** and **12** and the β-linked disaccharides were **15**, **16** and **17**, respectively were isolated in good yield.



Scheme 2

Having successfully prepared a range of tritylated disaccharides, we turned our attention to the use of trityl ethers as glycosyl acceptors. As can be seen in **Scheme 3**, coupling of benzylated thioglycosyl donor **6** with the tritylated acceptor **11**, using NIS and a stochiometric amount of TMSOTf as the activator, gave the trisaccharide **18** in excellent yields as a mixtures of anomers (α/β 3/1). When the benzoylated glycosyl donor **19** was coupled with the tritylated acceptors **5** and **17** equally good results were obtained and only the β-linked glycosides **20** and **21** were formed.

In conclusion, we have demonstrated that tritylated thioglycosides can act as efficient glycosyl donors and acceptors. In combination with earlier described[9,11] chemoselective glycosylations of thioglycosides, the new approach enables the assembly of oligosaccharides in a convergent manner avoiding protecting group manipulations. The latter feature, was illustrated by the preparation of tetrasaccharide **9** which was assembled in three reaction steps from the monosaccharides **1**, **4**, **6** and **7**.



Scheme 3

Acknowledgement

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10. To a mixture of **5** (80 mg, 0.076 mmol) and **8** (72 mg, 0.060 mmol) and molecular sieves (0.2 g) in dichloromethane/ether (2.0 ml, 1/1, v/v) was subsequently added a solution of NIS (25 mg, 0.11 mmol) and TMSOTf (2.8 µL, 0.014 mmol) in dichloromethane/ether (1.5 ml, 1/1, v/v) and TMSOTf (16.4 µL, 0.084 mmol). After stirring for 15 minutes, the reaction mixture was quenched by the addition of triethylamine, diluted with dichloromethane (10 mL), then washed with aqueous $Na_2S_2O_3$ (5 ml, 20%) and aqueous $NaHCO_3$ (5 ml, 10%), dried ($MgSO_4$) and concentrated under reduced pressure. The residual oil was purified by silica gel column chromatography. Concentration of the appropriate fraction gave tetrasaccharide **9** as a clear oil in a yield of 65% (76 mg). Selected data: ^1H NMR ($CDCl_3$): 5.13 (d, 1H, H-1, J1,2 =3.37 Hz), 4.96 (d, 1H, H-1', J1',2' = 3.17 Hz), 484 (d, 1H, H-1''', J1''',2''' = 3,46 Hz), 4.65 (d, 1H, H-1", J1", 2" = 8.02 Hz).
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