Pergamon

Tetrahedron Letters 39 (1998) 2187–2190

TETRAHEDRON LETTERS

A Two Directional Glycosylation Strategy for the Convergent Assembly of Oligosaccharides

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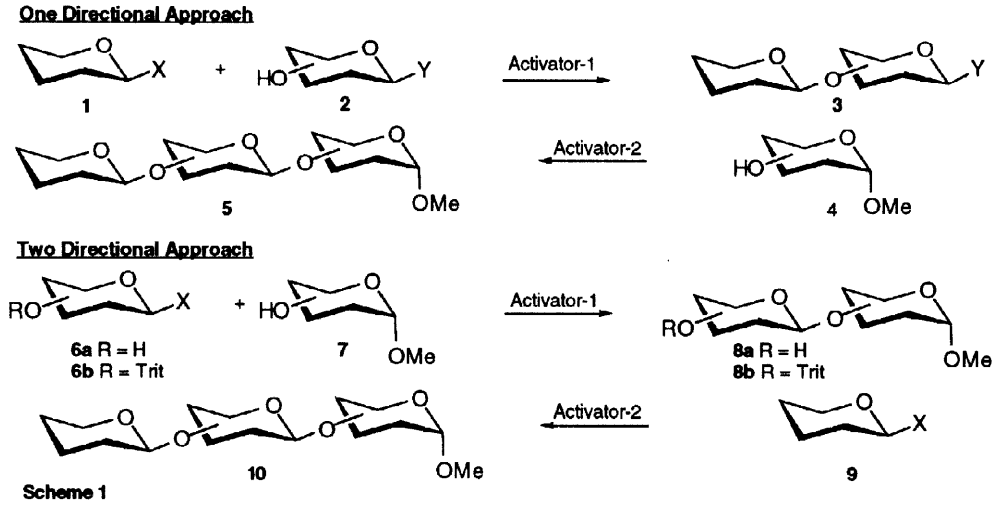
Received 10 December 1997; revised 13 January 1998; accepted 16 January 1998

Abstract: A novel glycosylation strategy has been developed whereby a silyl protected thioglycoside can act as both glycosyl donor and acceptor. Taking advantage of a two directional approach in combination with previously reported orthogonal glycosylations, enables highly convergent and versatile assembly of oligosaccharides.

During the last decade, efficient strategies for the synthesis of complex oligosaccharides have been developed in which most of the synthetic effort is directed towards the preparation of (oligo)saccharide building blocks that can be assembled into complex structures using a minimal number of synthetic steps.[1] In a linear chemoselective glycosylation strategy, a glycosylation product (**3**, Scheme 1) is immediately used as a glycosyl donor in a subsequent coupling. Such a sequential assembly of monosaccharides can use donors (**1**) and acceptors (**2**) that have the same type of anomeric group (X = Y = SR, pentenyl, F) but with different anomeric reactivities.[1] In these cases, the anomeric reactivity is primarily controlled by the nature of the protecting groups. Sequential glycosylations have also been conducted by using donors and acceptors that have different anomeric groups (*e.g.* X = F and Y = SR) and consequently can be activated by different promoters.[1] These types of synthetic approaches are particularly attractive since none or very few protecting group manipulations are involved during the assembly of a complex oligosaccharide. It also enables to perform one-pot multi-step glycosylations which provide an attractive alternative to solid phase methods. Undeniably however, the overall efficiency of such a process can be compromised by the linear nature of the glycosylation sequence and by the fact that the growing oligosaccharide chain acts in all glycosylations as the glycosyl donor.



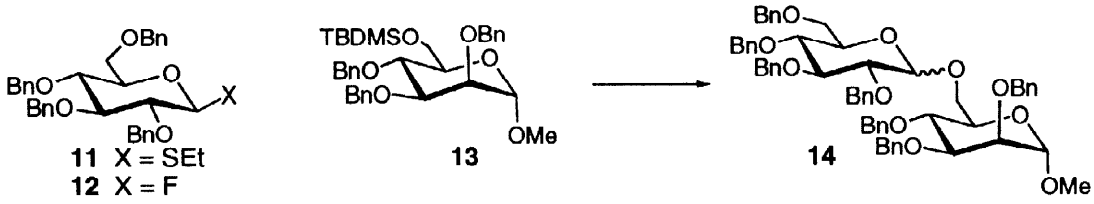
Scheme 1

PII: S0040-4039(98)00171-3

To address the above mentioned problems, we have developed a two directional glycosylation strategy (Scheme 1) in which a partly protected glycosyl donor (**6a**) is coupled with a glycosyl acceptor (**7**), the product bearing free hydroxyl (**8a**) can be used in subsequent glycosylations.[2] In combination with previously reported chemoselective glycosylation approaches (*e.g.* **9** = **3**), this methodology makes it possible to prepare a range of tri- and tetrasaccharides without protecting group manipulations between glycosylation steps. An important requirement of this strategy is that the hydroxyl of the acceptor is sufficiently more reactive than the hydroxyl of the glycosyl donor. The latter requirement imposes some limitations which in part were addressed by the application of tritylated thioglycosides.[3] Tritylated thioglycosides are sufficiently stable to act as glycosyl donors (**6b**, Scheme 1) but function efficiently as glycosyl acceptors (**8b**) under a different set of reaction conditions. However, this methodology is restricted in appliction to primary trityl ethers since secondary trityl ethers enhance the nucleophilicity of hydroxyls in a glycosylation[4] whilst being too labile to be part of a glycosyl donor. Ideally, a particular primary or secondary protected hydroxyl should be sufficiently stable under particular glycosylation conditions but be able to act as an acceptor under a different set of glycosylation conditions.

We report here that particular primary and secondary silyl ethers of thioglycosides are sufficiently stable under NIS/TMSOTf or IDCP mediated glycosylations, but the products of such glycosylations are very appropriate acceptors when glycosylated with glycosyl fluorides in the presence of $Cp_2ZrCl_2/AgOTf$[5] as the promoter.

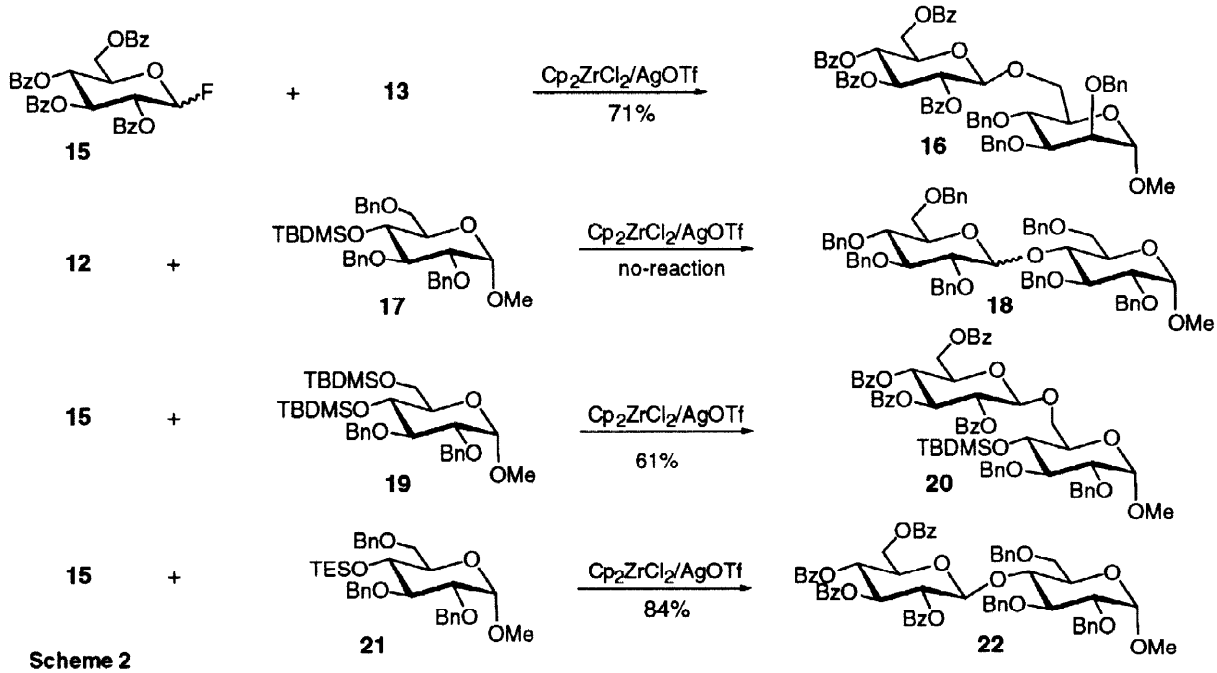
In first instance, the glycosyl accepting properties of primary and secondary silyl ethers were examined. Thus, coupling of thioglycoside **11** with TBDMS protected mannoside **13** under a variety of different reaction conditions gave disappointing results and the best yield obtained was by employing NIS and a stochiometric amount of HBF_4 (Entry 1, Table 1). Ziegler and co-workers reported[6] that 1,1,3,3-tetraisopropyldisiloxane-1,3-diyl protected glycosides are appropriate glycosyl acceptors for regioselective glycosylation using $BF_3.Et_2O$[7] as the promoter. Therefore, the glycosylation of TBDMS protected acceptor **13** with glycosyl fluoride **12** using a range of reaction conditions was attempted. As shown in Table 1, the best results were obtained when $Cp_2ZrCl_2/AgOTf$ was used as the activator and disaccharide **14** was isolated in a yield of 85%.[9] (Entry 5) A good anomeric selectivity was obtained when toluene/dioxane[10] was used as the solvent mixture but in this case the yield was somewhat compromised by trehalose formation. When the benzoylated glycosyl donor **15** was used as the glycosyl donor, the β-linked disaccharide **16** was obtained exclusively in a yield of 71%. (**Scheme 2**).



Donor	Acceptor	Entry	Promoters	Solvent	Yield	α/β
11	13	1	NIS / HBF_4	DCM/Ether (1/1)	54%	1.4/1
12	13	2	$BF_3.Et_2O$	Benzene	52%	1/1
12	13	3	Tf_2O[8]	Diethyl ether	68%	3/1
12	13	4	$Cp_2ZrCl_2/AgBF_4$	Benzene	74%	1/1
12	13	5	$Cp_2ZrCl_2/AgOTf$	Benzene	85%	1/1
12	13	6	$Cp_2ZrCl_2/AgOTf$	Toluene/1,4-dioxane (1/3)	70%	6/1

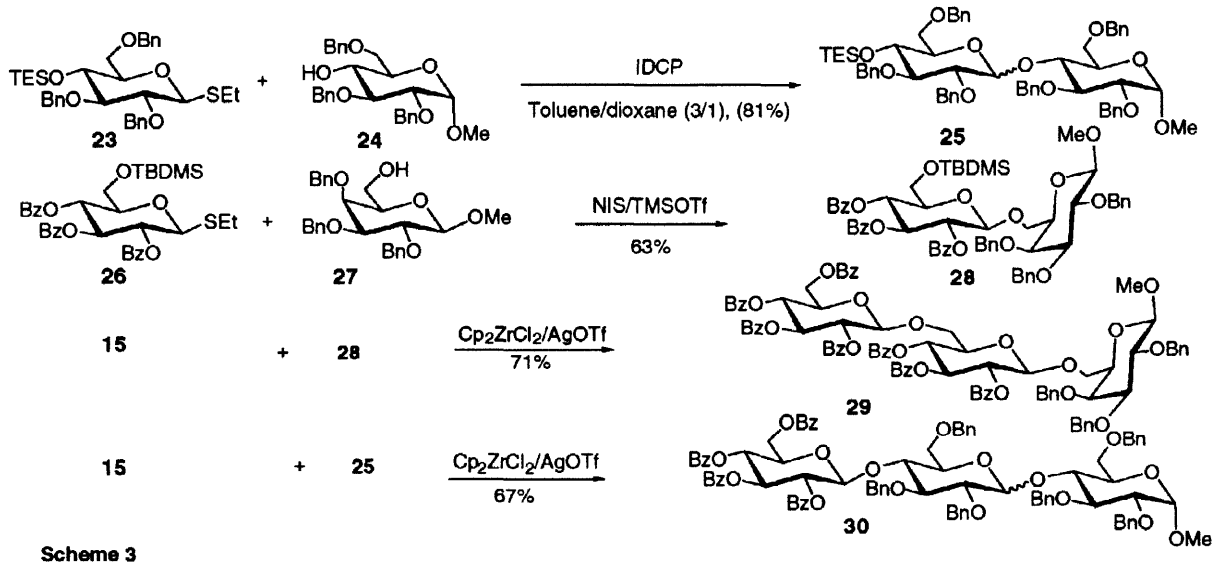
Table 1

Encouraged by these results, secondary silyl ethers were used as glycosyl acceptors. Unfortunately, only a trace amount of **18** was formed in Cp_2ZrCl_2/AgOTf mediated coupling between **12** and **17** and this can be reasoned by different reactivities of primary and secondary silylated positions. Indeed, when the disilylated saccharide **19** was glycosylated with **15**, the reaction took place only at the primary position to give disaccharide **20**[11] in a yield of 61%. Interestingly, glycosylation of a similar ditritylated glycosyl acceptor gives mainly reaction at the secondary position.[4] In this case, the C-O bond of the secondary trityl ether is probably lengthened by steric hindrance making it more polarised and therefore more reactive towards glycosylation. A Si-O bond is considerably longer and probably a secondary TBDMS ether does not experience significant additional steric hindrance. In addition, it has been reported that under carefully controlled conditions TBDMS ether can selectively be cleaved without affecting less accessible TBDMS ethers.[12] The stability of silyl ethers can also be tuned by the nature of the alkyl/phenyl moiety of the silicon group and for example a triethylsilyl ether (TES) is approximately hundred times more sensitive towards acidic cleavage than TBDMS analogues.[13] Indeed, glycosylation of the TES ether **21** with glycosyl fluoride **15** gave the expected disaccharide **22** in an excellent yield of 84%.



Scheme 2

Having successfully used silylated glycosides as glycosyl acceptors, we turned our attention to the use of silyl ethers as glycosyl donors. As can be seen in **Scheme 3**, coupling of thioglycosyl donor **23** having a TES protecting group at C-4 with the acceptors **24**, using IDCP as the activator, gave the disaccharide **25** in excellent yield (α/β = 3/1). When the benzoylated TBDMS protected glycosyl donor **26** was coupled with the acceptor **27** only the β-linked glycoside **28** was formed. Both disaccharides **25** and **28** proved to be convenient glycosyl acceptors and coupling with **15** in the presence of Cp_2ZrCl_2/AgOTf gave the trisaccharides **30** and **29**, respectively in good yields. The preparation of the trisaccharides **29** and **30** illustrates the versatility of the approach and these compounds can be assembled from readily available monosaccharide building blocks avoiding protecting group manipulations at the oligosaccharide stage.



Scheme 3

In conclusion, we have demonstrated that primary TBDMS ethers and secondary TES ether of thioglycosides are gratifyingly stable under NIS/TMSOTf or IDCP mediated glycosylation conditions and the products of such glycosylations are very appropriate acceptors when glycosylated with glycosyl fluorides in the presence of Cp_2ZrCl_2/AgOTf as the promoter. In combination with chemoselective glycosylations (armed-disarmed) or orthogonal glycosylations[1] even complex saccharide building blocks can be synthesized in a highly convergent manner avoiding protecting group manipulations at the oligosaccharide stage.

References and Notes

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