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Minireview

Thioglycosides as Glycosylating Agents in Oligosaccharide Synthesis

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A review is given of the use of thioglycosides as glycosyl donors in oligosaccharide synthesis. Both indirect use, by conversion of the thioglycoside into a glycosyl halide and direct use, by electrophilic activation of the thioglycoside, are discussed.

Introduction

In the stepwise approach to the synthesis of oligosaccharides, in which one monosaccharide unit at a time is added to the growing chain, it will eventually become necessary to perform protecting group manipulations on large molecules. One of the advantages of a convergent block synthesis approach is that these manipulations can be kept to a minimum since they are instead performed on smaller fragments. The latter approach, however, raises the problem of activation of the anomeric position in oligosaccharide blocks into efficient glycosyl donors.

The classical donors in glycosylation are glycosyl halides. Problems may arise in the conversion of many oligosaccharide derivatives (such as e.g. glycosides or glycosyl esters) into glycosyl halides, resulting in low-yielding steps quite far into the synthetic sequence [1, 2]. For this reason thioglycosides have attracted considerable attention.

Abbreviations: DMTST, dimethyl(methylthio)sulfonium trifluoromethanesulfonate; Bz, benzoyl; Bn, benzyl; pNBz, *p*-nitrobenzoyl; Phth, phthallyl; Ph, phenyl.

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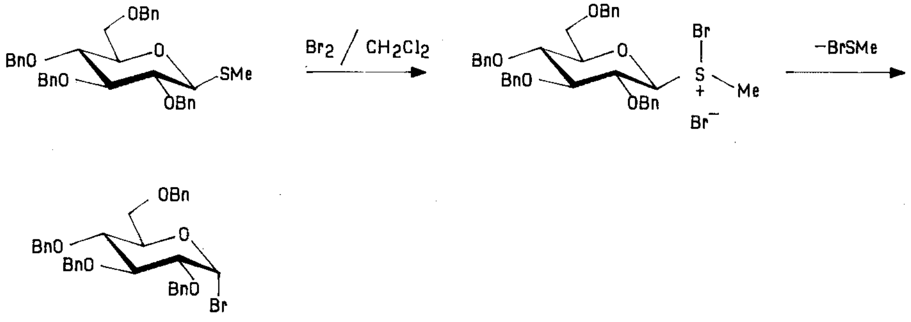

Figure 1. Reaction of a benzylated thioglycoside with bromine.

Thioalkyl or -aryl groups appear to offer efficient temporary protection of the anomeric centre, and at the same time, several possibilities for regioselective activation into glycosyl donors exist. Early attempts to use 1-thioglycosides as glycosyl donors include activation by mercury(II) sulfate [3], mercury(II) chloride [4, 5], phenylmercury trifluoromethanesulfonate [6], mercury(II) benzoate [7], mercury(II) nitrate [8], copper(II) trifluoromethanesulfonate [9], lead(II) perchlorate [10, 11] and *N*-bromosuccinimide [8, 12]. These various promoters did not yield results that led to their subsequent widespread use in oligosaccharide synthesis. Heavy metal salts apparently are not reactive enough to be of general application. This problem was circumvented by using heterocyclic thioglycosides which are more reactive [8, 9]. Heavy metal salt promoters also found some application in the field of 2-deoxy sugar synthesis, where work with glycosyl halides is especially problematical and the reactivity of the thioglycoside is higher than usual. Thus, thioglycosides and heavy metal salt promotion was used in the synthesis of erythromycin [10], avermectin [11] and digitoxin [4, 5].

Recent work has shown that thioglycosides can be conveniently and reproducibly activated in at least two other different ways. The first of these is "two-step" activation, which involves first forming a glycosyl halide, and then further activating this with a halophilic reagent. The second way involves one-step activation with a thiophilic reagent such as methyl trifluoromethanesulfonate (methyl triflate) or dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST). These two different activation methods are treated separately below.

Thioglycoside Activation by Conversion to Glycosyl Halide

It is well known that thioglycosides react with chlorine or bromine to give glycosyl chlorides [13] or bromides [14, 15]. The reaction is fast (1-10 min) at room temperature in dichloromethane solution and the conditions are mild enough to leave sensitive pro-

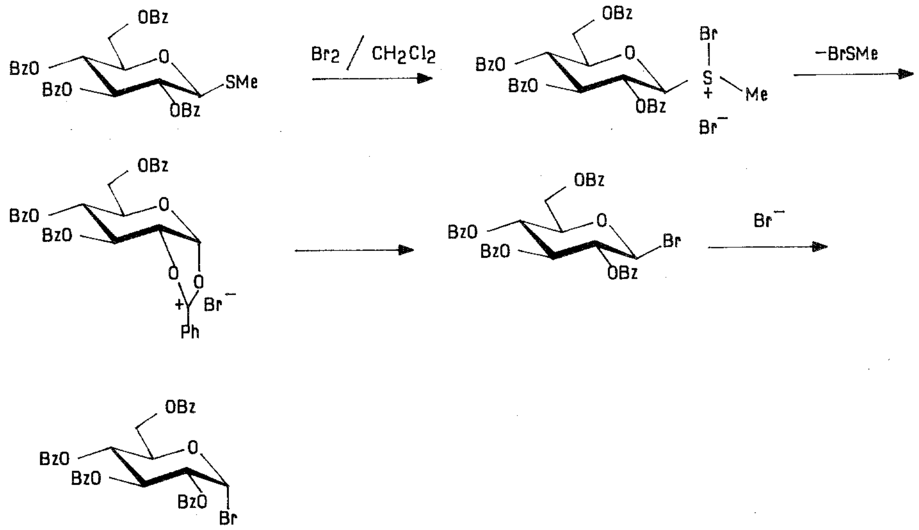

Figure 2. Reaction of an acylated thioglycoside with bromine.

tecting groups such as benzylidene acetals unaffected. When the thioglycoside carries a non-participating group in the 2-position (Fig. 1), the reaction with halogens first gives inversion of configuration at the anomeric carbon [15]. If the glycosyl halide formed is the most stable anomer (e.g. α for the *gluco* or *galacto* configurations), this will be the final product of the reaction. When the unstable halide anomer is formed, it will subsequently anomerise to the stable one. If the thioglycoside carries a 2-acyl protecting group (Fig. 2), the 1,2-*trans* halide is first formed, presumably via an acyloxonium type intermediate. If this 1,2-*trans* halide is the unstable anomer, prolonged reaction time will give anomerisation to the stable anomer.

Bromine or chlorine treatment of a mono- or oligosaccharide thioglycoside can be used in oligosaccharide synthesis to activate the anomeric centre. The halide formed can be further activated for glycosidation with any of the many existing "halophilic" reagents [16], e.g. silver or mercury salts or tetraethylammonium bromide [17]. Koto *et al.*, in 1973, first reported [18] the use of thioglycosides in this context. Isomalto-oligosaccharides were synthesised (Fig. 3) from the monosaccharide precursor **2**. Activation at the anomeric centre of **2** by bromine treatment gave the bromide **3**, which was used for glycosidation of **1** (the precursor of **2**). The disaccharide thioglycoside **4** obtained was then converted to the bromide **5**, and reacted with **6** (deacylated **4**) to form the tetrasaccharide thioglycoside derivative **7**. Repeating the procedure once more gave an octasaccharide thioglycoside, which was subseqently deprotected to give isomalto-octaose. The above approach has also been used [19-22] for the synthesis of more complex oligosaccharides. The advantage of this strategy is twofold: Firstly, stable mono- or oligosaccharide thioglycoside blocks, having the desired protecting group arrangement, can be assembled and activated for glycosidation when desired. This is the general advantage of using thioglycoside protection of the anomeric centre, regardless of activation method. Secondly, when a thioglycoside is activated by conversion to a

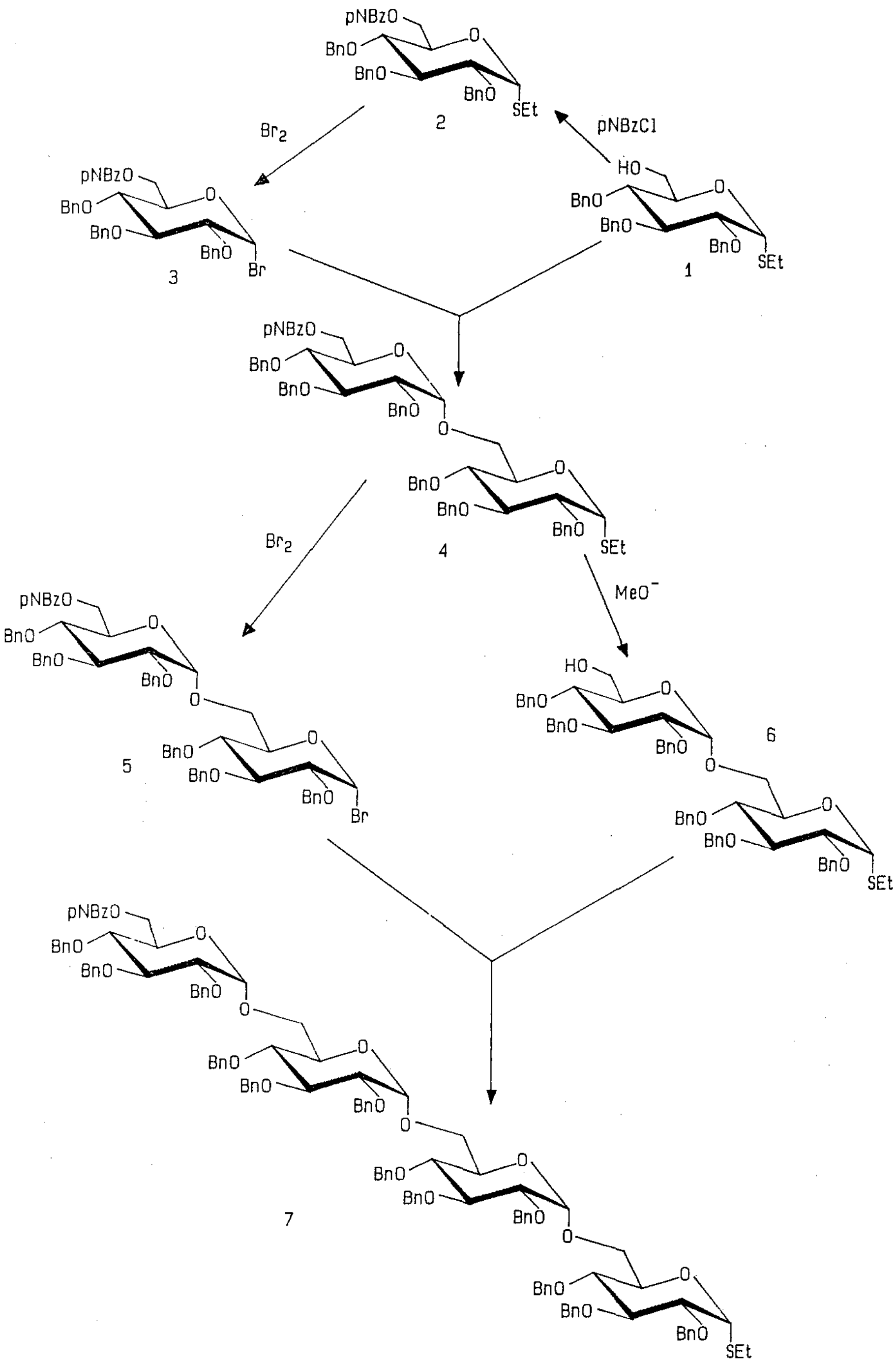

Figure 3. Synthesis of an isomaltotetraose derivative from thioglycoside precursors.

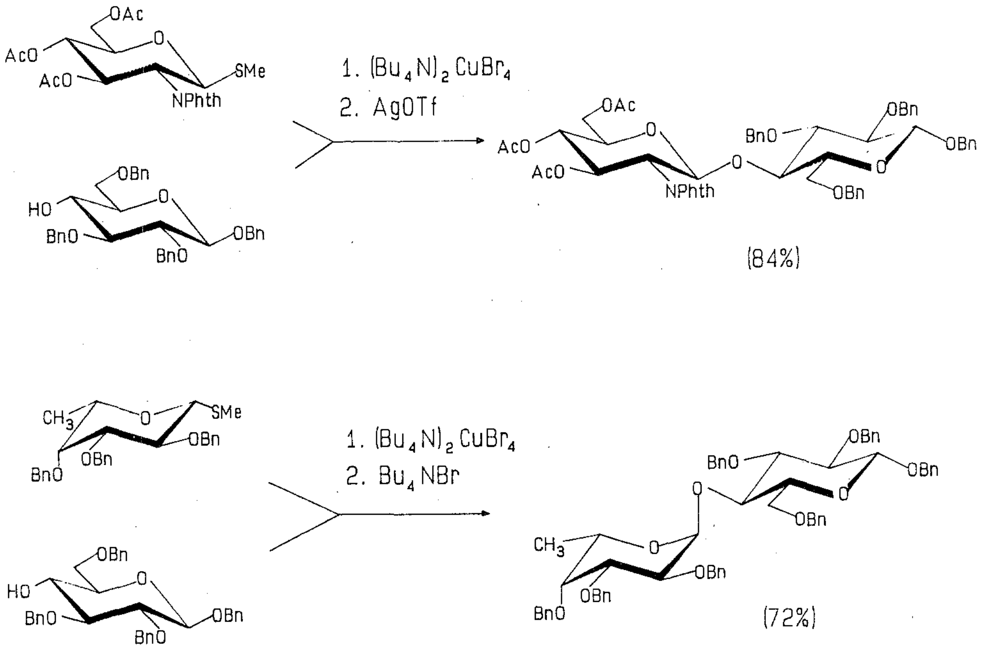

Figure 4. Use of copper(II) bromide-tetrabutylammonium bromide complex for conversion of thioglycosides into glycosyl bromides and subsequent *in situ* glycosidation with halophilic promoters.

glycosyl halide, this halide can then be used in glycosylation of thioglycoside acceptors. Such acceptors cannot be used if "one-step" activation (with e.g. methyl triflate or DMTST) is used, since the acceptor thioglycoside function would also be affected by the activating reagent. The disadvantage is that with some oligosaccharide thioglycosides, difficulties can be encountered in preparing halides in good yields without side-reactions.

A variation of the above strategy is the transformation of methyl thioglycosides into bromides using a copper(II) bromide/tetrabutylammonium bromide complex [23], followed by *in situ* glycosidation using suitable promoters. For example, if the glycosyl donor has a non-participating group in the 2-position, and tetrabutylammonium halide is used as promoter, 1,2-*cis*-glycosides are produced in the resulting slow, but stereoselective reaction. Silver zeolite as promoter gives faster reactions but lower stereoselectivity. If the donor has a participating group in the 2-position and promotion by either silver triflate or mercury(II) bromide is used, 1,2-*trans*-glycosides are produced. Examples are shown in Fig. 4. This variant, however, precludes the use of thioglycosides as glycosyl acceptors.

Although most work on the reaction of thioglycosides to form glycosyl halides has focused on the use of bromides and chlorides, recent reports show [24] that thioglycosides can also be converted into glycosyl fluorides under relatively mild conditions (*N*-bromosuccinimide/diethylaminosulfur trifluoride or *N*-bromosuccinimide/hydrogen fluoride-pyridine-complex). The fluorides can then be further activated for

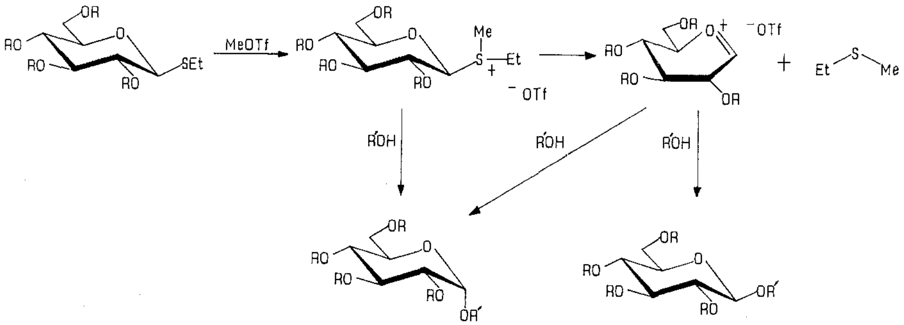

Figure 5. Reaction of a thioglycoside with methyl triflate in the presence of a glycosyl acceptor.

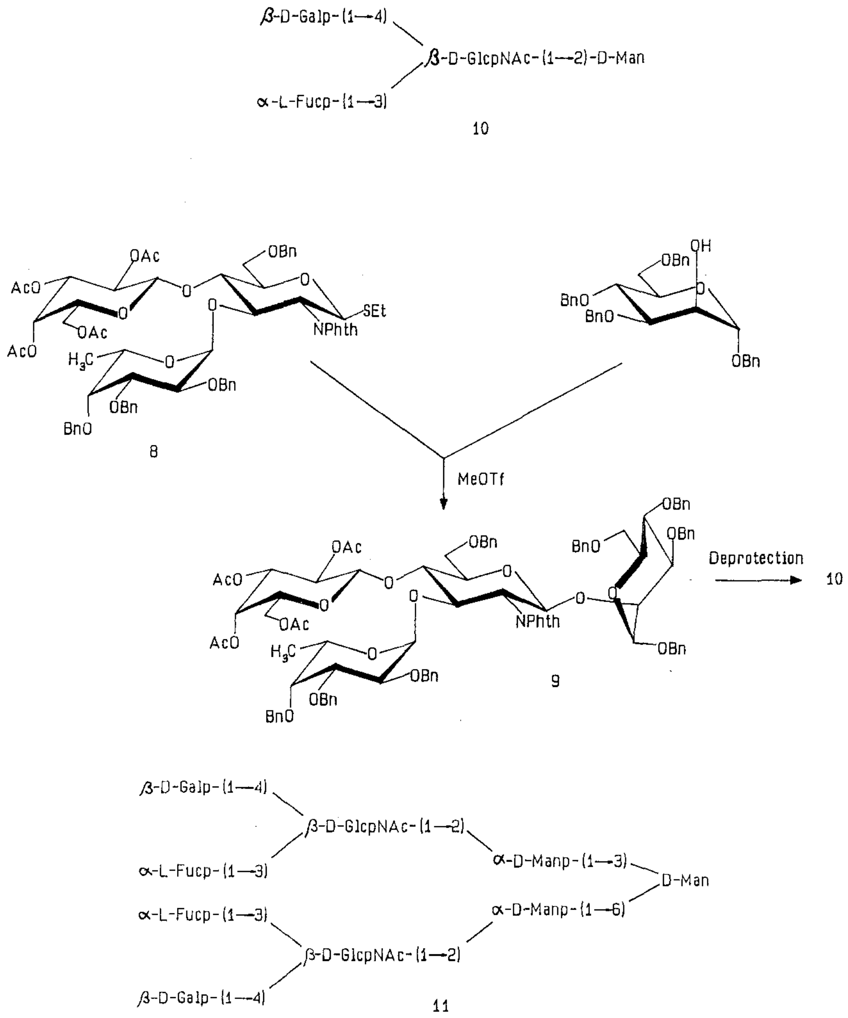

Figure 6. Use of methyl triflate in the synthesis of oligosaccharides related to *N*-linked glycoprotein glycans.

glycosidation by, e.g. tin(II) chloride/silver perchlorate [25], boron trifluoride etherate [26] or other Lewis acids [27, 28]. Complex oligosaccharides have been synthesised by this method by the Nicolaou group [12, 23, 26]. The generality of this approach, with respect to the stability of common protecting groups to the reaction conditions used, however, still has to be demonstrated.

According to a recent report [29] a phenylthioglycoside unprotected in the 2-position can be stereospecifically converted into a 2-phenylthioglycosyl fluoride. Such derivatives could be useful in stereocontrolled 2-deoxyglycoside synthesis.

Direct Activation by the Use of Thiophilic Reagents

A. Methyl Trifluoromethanesulfonate (Methyl Triflate)

The use of methyl triflate offers an efficient and more direct alternative to the use of halogen for activation of thioglycosides. Methyl triflate preferentially *S*-methylates thioglycosides producing sulfonium ions, even in the presence of a glycosyl acceptor hydroxyl group [30-33] (Fig. 5). The glycosyl sulfonium ions (or ions derived from them) are good glycosylating agents. Several oligosaccharides typical for glycoproteins have been synthesised in high yields using this approach. Thus, the tetrasaccharide **9** (Fig. 6) was prepared [31] from the trisaccharide thioglycoside block **8** in 67% yield. The nonasaccharide **11** was similarly prepared [32]. The heptasaccharide **12**, having phytoalexin elicitor activity was synthesised [34] in high yield using methyl triflate as promoter and thioglycosides as glycosyl donors (Fig. 7). Methyl triflate-promoted glycosidations with thioglycosides have also been successfully used in other work [19, 35, 36]. Moreover, 1,2-*cis*-glycosides have been prepared in good yield from thioglycosides with a non-participating group in the 2-position. In a model study [33] (Fig. 8), the highest yields and best stereoselectivity were obtained using diethyl ether as solvent. A disadvantage with the use of methyl triflate for activation is the suspected health hazard involved in the use of this reagent. However, in work on the small scale and with careful handling this problem is surmountable. For large scale synthesis, a less toxic activating agent is needed.

B. Dimethyl(methylthio)sulfonium Trifluoromethanesulfonate (DMTST)

By contrast to methyl triflate, which may cause a certain amount of *O*-alkylation (Fügedi P, Garegg PJ; unpublished results), especially in reactions with slow-reacting thioglycoside glycosyl donors, DMTST [37] is uniquely thiophilic and gives rise to faster glycosylations than does methyl triflate [38]. Using glycosyl donors with a participating group in the 2-position, 1,2-*trans*-linked glycosides are formed. In model experiments [38] in which (1-2)-, (1-3)-, (1-4)-, and (1-6)-linked disaccharides were made, excellent yields and virtually complete stereospecificity were observed (Fig. 9). If the glycosyl donor has a non-participating group in the 2-position, the total yields are also high, but the stereoselectivity is poor. The presence of tetrabutylammonium bromide in these reaction mixtures gives an *in situ* conversion of the thioglycoside into the corresponding bromide which then, as in the method of Sato *et al.* [23], gives slow, but highly

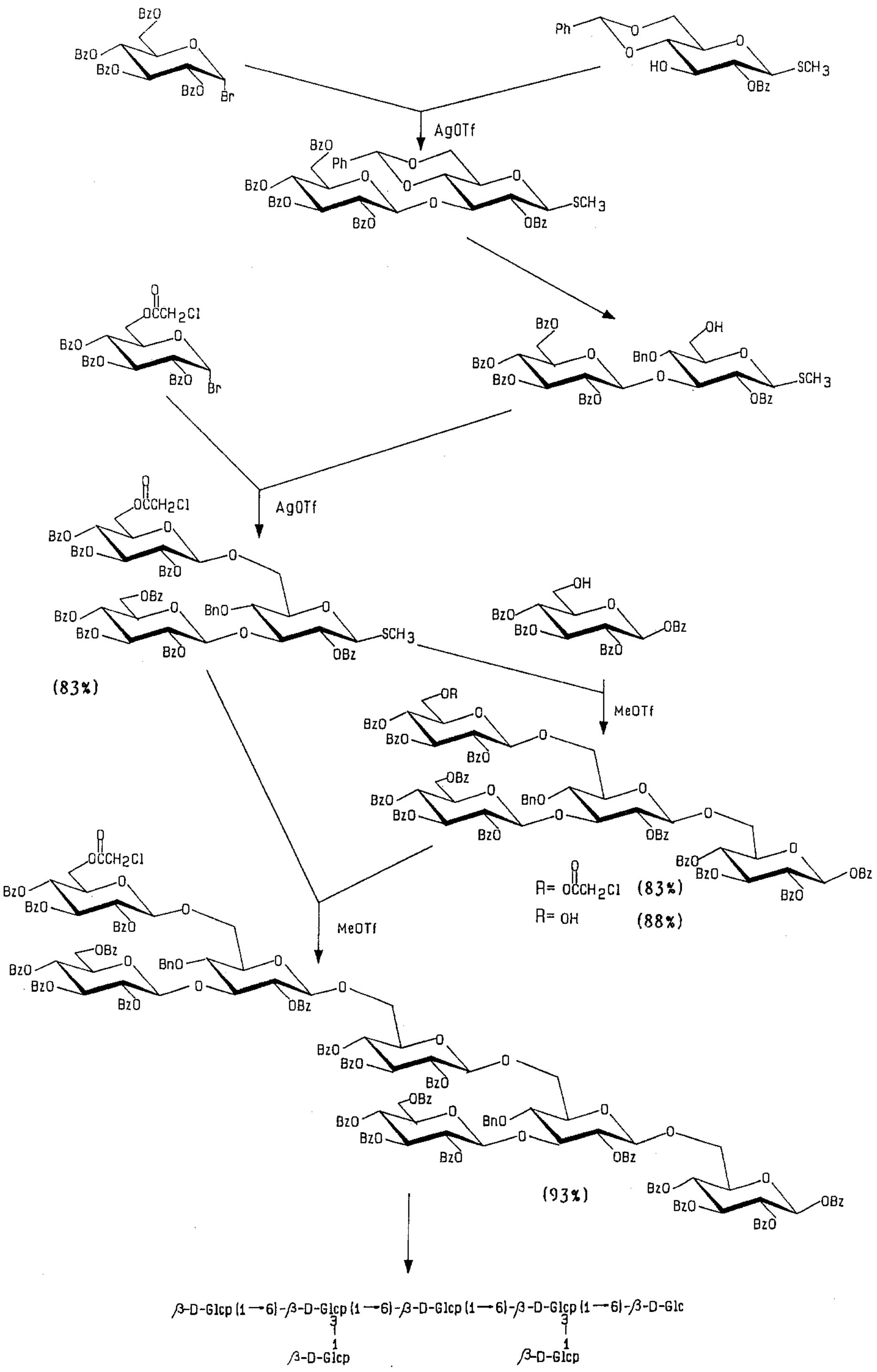

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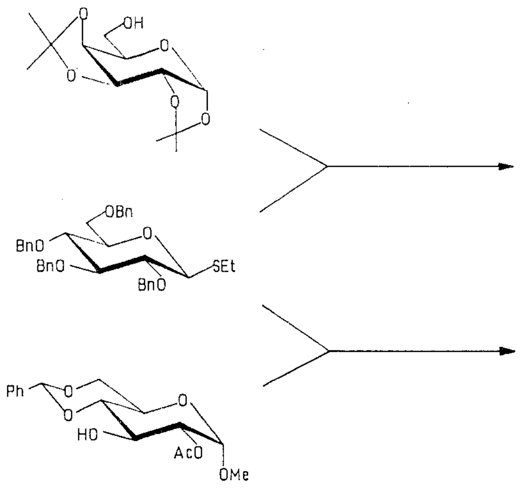
Figure 7. Use of methyl triflate in the synthesis of a heptasaccharide with phytoalexin elicitor activity.



solvent	α/β	disaccharide yield, (%)
diethyl ether	3,5:1	87
dichloromethane	0,9:1	80
acetonitrile	1:5	75
diethyl ether	6,7:1	96
dichloromethane	3,6:1	85
acetonitrile	0,9:1	72

Figure 8. Use of methyl triflate for synthesis of 1,2-*cis* glycosides.

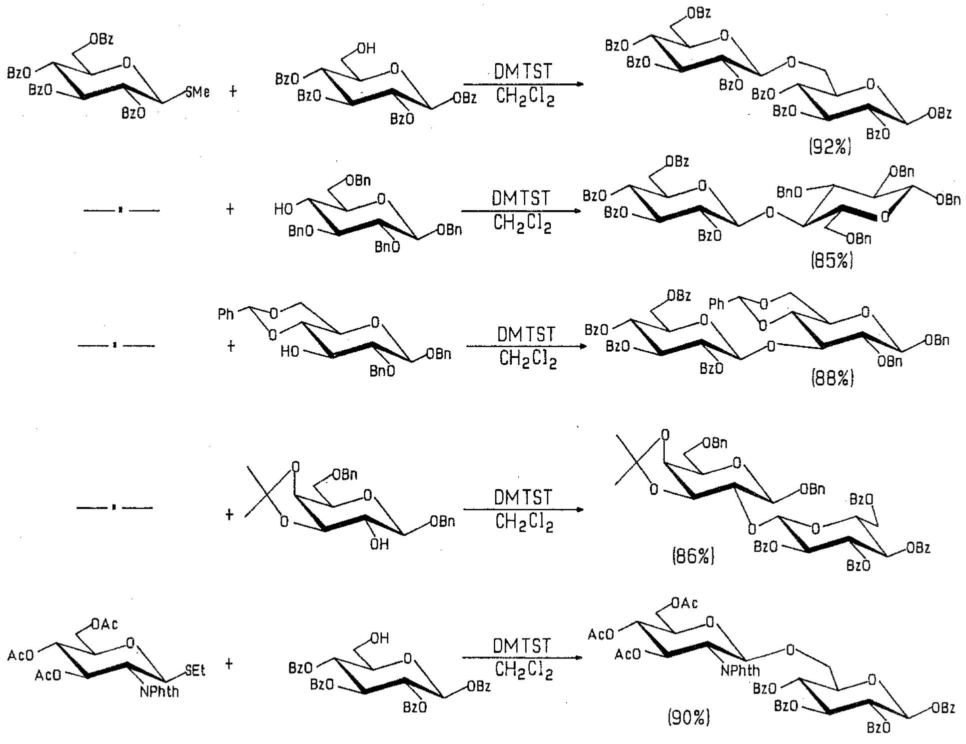


Figure 9. Use of DMTST for synthesis of 1,2-*trans* glycosides.

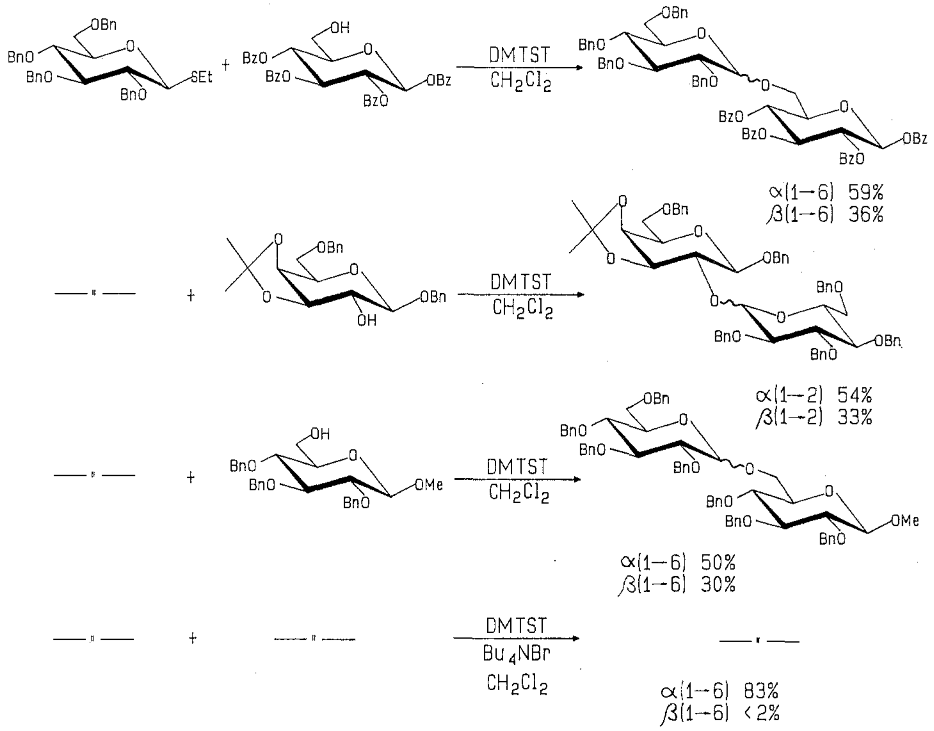


Figure 10. Use of DMTST for synthesis of 1,2-*cis* glycosides.

stereoselective halide-ion promoted formation of a *cis*-1,2-glycoside [39] (Fig. 10). 2-Azidodeoxy-α-glycosides have also been prepared in good yields from the corresponding thioglycosides using DMTST as promoter [36].

Conclusions

Several methods are now available for the use of thioglycosides as glycosyl donors in oligosaccharide synthesis. These include: activation by conversion into a glycosyl halide, either *in situ* or by isolation before proceeding to glycosylation, or direct activation by the use of methyl triflate or the highly thiophilic dimethyl(methylthio)sulfonium triflate. Of these various possibilities, conversion of the thioglycoside into a glycosyl halide (fluoride, bromide, chloride) is the only one at present which allows the use of a thioglycoside *acceptor* carrying a thioalkyl or thioaryl group at the anomeric centre, which then, when desired, can be turned into a glycosyl *donor* unit. The disadvantage of this approach is that it necessitates the making and isolation of oligosaccharide glycosyl halides, which may turn out to be difficult. With regard to glycosylation efficiency, this will vary from situation to situation, in a manner that is not always predictable. However, several examples of exceptionally high yields have now accumulated using methyl triflate and dimethyl(methylthio)-sulfonium triflate.

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