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Protective group strategies in carbohydrate and peptide chemistry

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**General Introduction: Novel
protecting groups in
carbohydrate chemistry**

CHAPTER
1

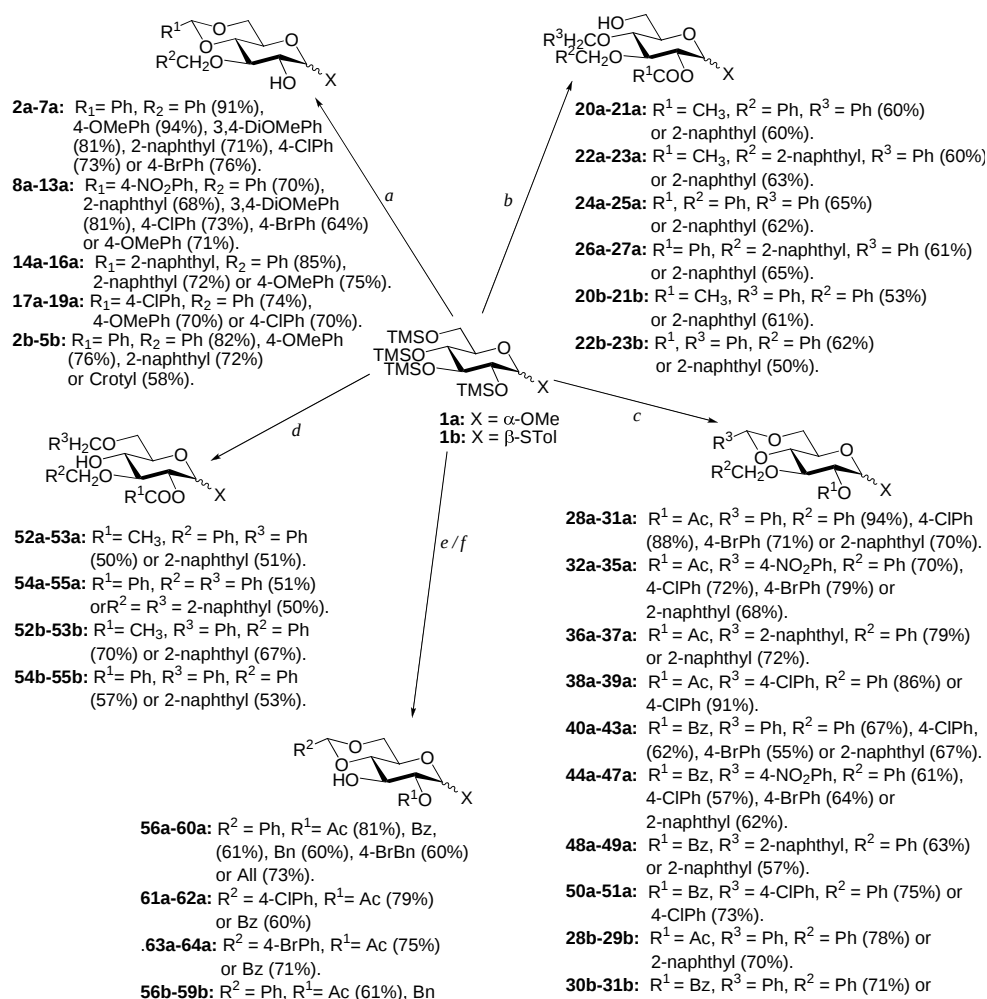
Protecting groups play a key role in the synthesis of complex natural products.¹ This holds especially true for the synthesis of oligosaccharides,² of which the monomeric carbohydrate building blocks usually contain up to five different hydroxyl functions. The discrimination of these hydroxyl functions requires a careful protecting group strategy and typically involves multistep protocols. Although protecting groups primarily function to mask a given functionality on the carbohydrate core, they also have a profound effect on the overall reactivity of a carbohydrate building block³ and can control the stereochemical outcome of a glycosylation reaction.⁴ Furthermore protecting groups can be used to introduce extra functionality on the carbohydrate core, such as visualization and/or

purification handles.⁵ This chapter describes selected examples of novel protecting groups and protection strategies in carbohydrate chemistry from the beginning of the 21st century and highlights how protecting group chemistry has evolved from a necessary time consuming burden to a sophisticated synthetic tool for the efficient and stereoselective assembly of oligosaccharides.⁶

Advances in the regioselective protection of carbohydrates:

The regioselective manipulation of the different hydroxyl groups on a carbohydrate monomer is key to any protecting group strategy. Although all hydroxyl groups are of comparable reactivity they can be discriminated by exploiting their subtle reactivity differences and their relative orientation. The nucleophilicity of the different hydroxyls under neutral or acidic conditions increases from the anomeric to the secondary to the primary alcohol function. The anomeric hydroxyl group is most acidic and therefore selective protection of the hemiacetal -OH can be achieved in the presence of other secondary hydroxyls using basic reaction conditions. The general reactivity difference between an axially and an equatorially oriented hydroxyl group can often be exploited to attain a regioselective protection step. Commonly, the use of cyclic protecting groups presents a more robust way to discriminate between the different functionalities on a carbohydrate ring. For example, benzylidene type acetals are widely used to selectively mask the C-4 and C-6 alcohols,⁷ whereas isopropylidene ketals are used to block two neighboring *cis* hydroxyls,⁸ and butane 2,3-bisacetals to protect vicinal diequatorial diols.⁹

Recently several sequential procedures have been developed to streamline the regioselective protection of carbohydrates. Hung and co-workers disclosed that anomERICALLY protected per-silylated carbohydrate monomers can be transformed into a wide array of differentially protected building blocks using a one-pot protocol, which combines up to five reaction steps (Scheme 1).¹⁰ Because all steps are consecutively executed in the same reaction vessel the intermediate work-up and purification steps are omitted making this process highly efficient. The strategy builds on the trimethylsilyltriflate (TMSOTf) catalyzed installment of a O-4, O-6 arylidene function, which is followed by the

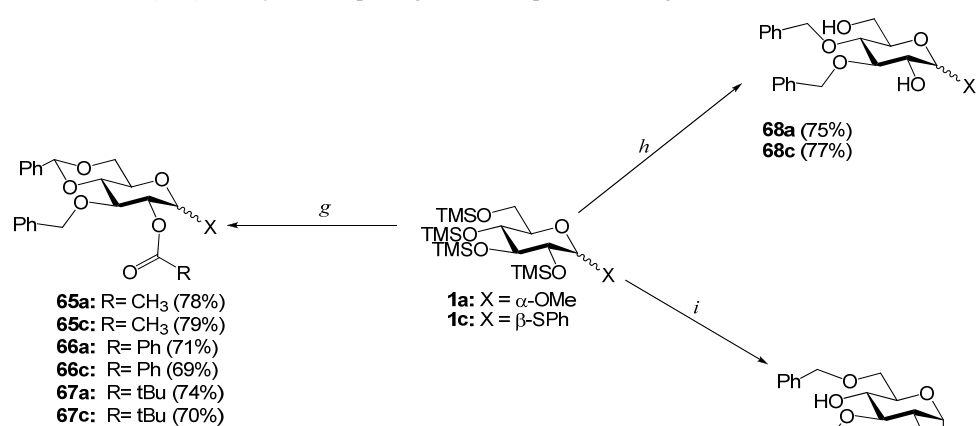
Scheme 1: One-pot regioselective protection of glucosides.

Reagents and conditions: a) i- TMSOTf (*cat*), $R^1\text{CHO}$, DCM, 3 Å MS, -86 °C; ii- $R^2\text{CHO}$, Et_3SiH , -86 °C; iii- TBAF (1 M); b) i- TMSOTf (*cat*), $R^3\text{CHO}$, DCM, 3 Å MS, -86 °C; ii- $R^2\text{CHO}$, Et_3SiH , -86 °C; iii- $(R^1\text{CO})_2\text{O}$; iv- BH_3/THF c) i- TMSOTf (*cat*), $R^3\text{CHO}$, DCM, 3 Å MS, -86 °C; ii- $R^2\text{CHO}$, Et_3SiH , -86 °C; iii- TBAF (1 M); iv- base, electrophile; d) i- TMSOTf (*cat*), $R^3\text{CHO}$, DCM, 3 Å MS, -86 °C; ii- $R^2\text{CHO}$, Et_3SiH , -86 °C; iii- $(R^1\text{CO})_2\text{O}$; iv- $\text{HCl}_{(g)}$, NaCNBH_3 ; e) i- TMSOTf (*cat*), $R^2\text{CHO}$, DCM, 3 Å MS, -86 °C; ii- 4-OMePhCHO, Et_3SiH , -86 °C; iii- TBAF; iv- electrophile; v- DDQ; f) i- TMSOTf (*cat*), $R^2\text{CHO}$, DCM, 3 Å MS, -86 °C; ii- 2- $\text{C}_{10}\text{H}_7\text{CHO}$, Et_3SiH , -86 °C; iii- Acid anhydride; iv- DDQ.

regioselective formation of a benzyl type ether at O-3. Next, the C-2-OH can be acylated and the arylidene opened to liberate either the C-4-OH or C-6-OH. Alternatively the C-3-benzyl ether is removed to expose the C-3-alcohol. Instead of the introduction of a O-2 acyl functionality also the incorporation of various ethers was described. Using the one-pot protocol, Hung and co-workers reported the synthesis of a large panel of differentially protected glucosides, two galactosides, a mannoside and one glucosamine building block.

Simultaneously, Beau and co-workers reported a closely related procedure in which per-silylated glucosides were functionalized with a O-4, O-6 benzylidene acetal and a O-3 benzyl ether using benzaldehyde using $\text{Cu}(\text{OTf})_2$ catalysis (Scheme 2).¹¹ They also demonstrated the possibility to extend the one-pot reaction sequence with an acylation step or a reductive opening of the benzylidene acetal.

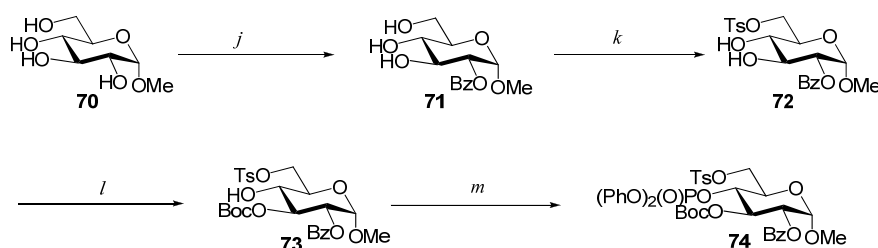
Scheme 2: $\text{Cu}(\text{OTf})_2$ catalyzed one-pot regioselective protection of glucosides.



Reagents and conditions; g) i- PhCHO, Et₃SiH, Cu(OTf)₂, DCM/ACN (4:1), RT (X = α -OMe) or 0 °C (X = β -SPh), 10 min; ii- Ac₂O, DCM, RT, 1 h or Bz₂O, DCM, reflux, 24 h or Piv₂O, DCM, reflux, 24 h; h) i- PhCHO, Et₃SiH, Cu(OTf)₂, DCM/ACN (4:1), RT (X = α -OMe) or 0 °C (X = β -SPh), 10 min; ii- BH₃, THF, Cu(OTf)₂, RT, 3 h; i) i- PhCHO, Et₃SiH, Cu(OTf)₂ (10 mol%), DCM/ACN (4:1), RT (X = α -OMe) or 0 °C (X = β -SPh), 10 min; ii- Et₃SiH, Cu(OTf)₂ (5 mol%), RT, 2 h, 58%.

Stannyl ethers and dialkylstannylene acetals have found wide application in the regioselective protection of carbohydrates ever since their introduction in 1974. Onomura and co-workers recently described the use of a catalytic amount of dimethyltin dichloride (Me_2SnCl_2) for the regioselective protection of various monosaccharides.¹² The regioselectivity in the Me_2SnCl_2 benzylation was shown to depend on the relative stereochemistry of the hydroxyl functions present. A fully protected α -O-methyl glucopyranose was obtained as depicted in Scheme 3. Thus, benzylation of glucoside **70** provided the C-2 acylated compound **71** in 82% yield. The subsequent tosylation occurred selectively at the C-6 hydroxyl to give diol **72** in 88%. Next a *tert*-butyl carbonate was introduced at the C3-OH and phosphorylation of the remaining alcohol provided the fully functionalized glucoside **74**.

Scheme 3: Dimethyltin dichloride catalyzed regioselective protection of glucose.



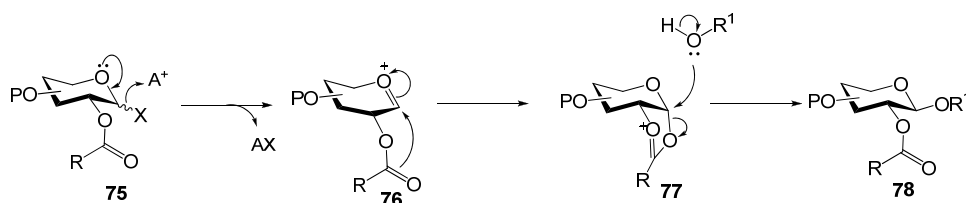
Reagents and conditions: j) Me_2SnCl_2 , BzCl , DIPEA, THF, RT, 82%; k) Me_2SnCl_2 , TsCl , DIPEA, THF, RT, 88%; l) Me_2SnCl_2 , Boc_2O , DIPEA, DMAP, THF, RT, 93%; m) CIP(O)(OPh)_2 , pyr, DMAP, DCM, RT, 95%.

Protecting groups in the stereoselective construction of glycosidic bonds:

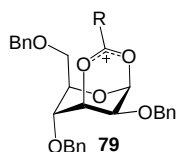
Although the primary purpose of a protecting group is to prevent a given hydroxyl from reacting, it is now well established that the nature of the protecting group has a major effect on the reactivity of glycosyl building blocks and the stereoselectivity and yield of a glycosylation reaction. This is of course best demonstrated considering a C-2 acyl protecting group in a donor glycoside, which not only deactivates this donor species as compared to its C-2 ether counterpart, but also reliably provides anchimeric assistance in the glycosylation process to provide 1,2-*trans* glycosidic bonds (see Scheme 4a). It is now

Scheme 4: Protecting groups providing anchimeric assistance during glycosylation.

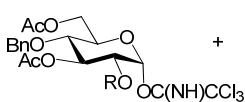
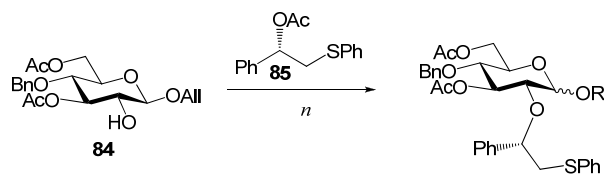
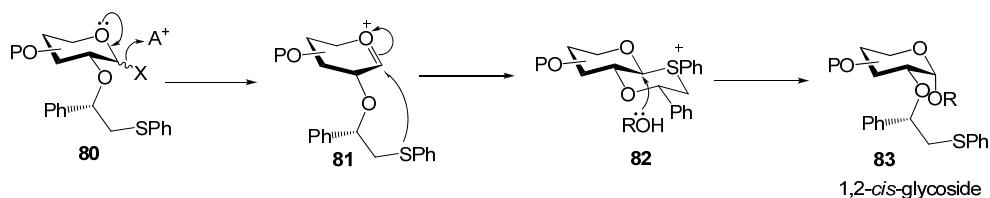
a- Acyl at C-2: Classical neighboring group participation by C-2 ester leading to 1,2-trans glycosides.



b- Acyl at C-3 in mannosides: participation from (C-3).



c- Boons auxiliary



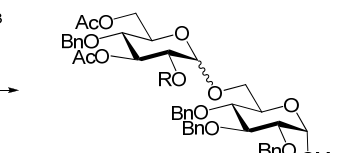
89: R = Bn

90: R = (CH₂)₂SPh

91: R = (R)-CH(Ph)CH₂SPh

92: R = (S)-CH(Ph)CH₂SPh

93



94: R = Bn: a. *q*, 94%, α:β = 3:1;

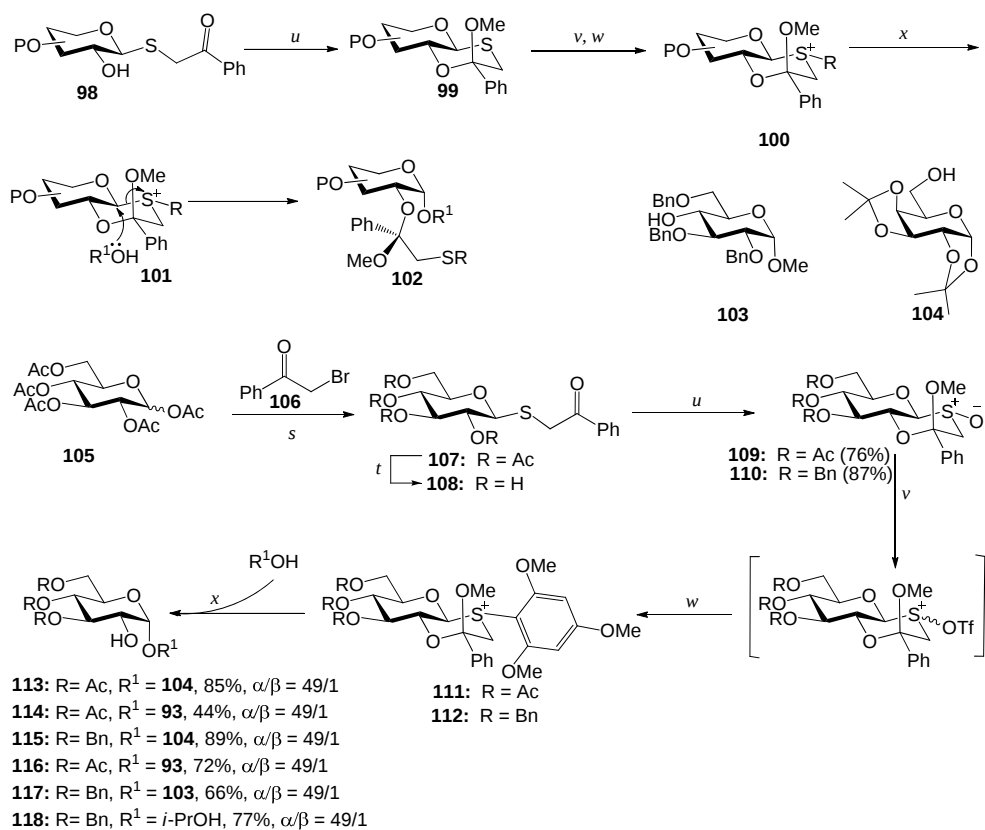
b. *r*, 92%, α:β = 6:1

95: R = (CH₂)₂SPh, *q*, α:β = 8:1

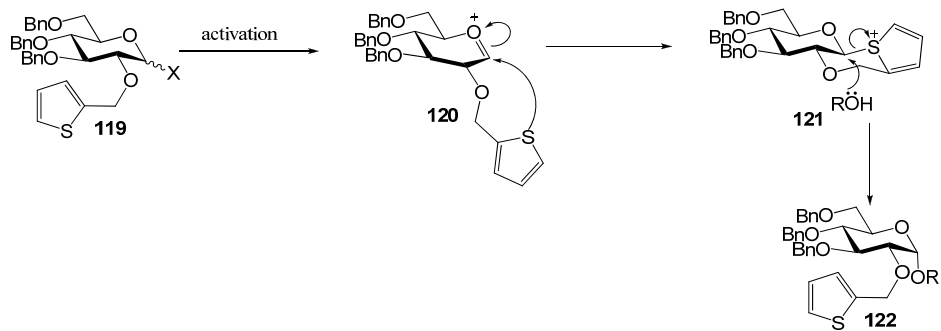
96: R = (R)-CH(Ph)CH₂SPh, *q*, α:β = 1:1

97: R = (S)-CH(Ph)CH₂SPh, *q*, α only

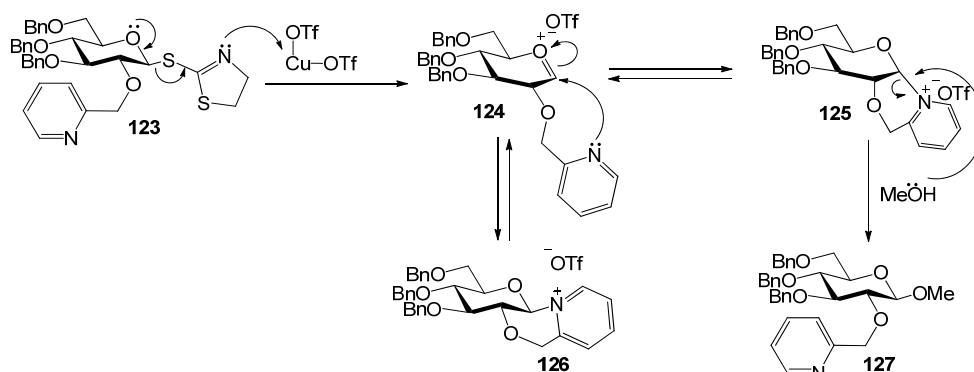
d- Turnbull's strategy.



e- Fairbanks' strategy.



f- Demchenko's picolyl ether protecting group



Reagents and conditions; n) $\text{BF}_3 \cdot \text{OEt}_2$, AcOH, DCM, 0 °C, 10 min, 74%; o) $\text{Pd}(\text{Ph}_3\text{P})_4$, AcOH, RT, 24 h, 90%; p) DBU, trichloroacetonitril, DCM, 0 °C, 1 h, 93%; q) TMSOTf, DCM; ; r) TMSOTf, PhSEt, DCM; s) i- thiourea, $\text{BF}_3 \cdot \text{OEt}_2$, ACN; ii- **92**, Et_3N , 64%; t) NaOMe, MeOH, 99%; u) i- TsOH, MeOH; ii- Ac_2O , pyr or BnBr, NaH, DMF iii- *m*-CPBA; v) Tf_2O ; w) 1,3,5-trimethoxybenzene, DIPEA, -30 °C; x) DIPEA, R^1OH , -10 °C-50 °C, 18h.

becoming more and more clear that protecting groups at other positions than the C2-OH can have a powerful stereodirecting effect. For example, Kim and co-workers recently demonstrated that the installment of an acyl function on the C-3 hydroxyl of a mannosyl donor leads to the stereoselective formation of α -mannosides (Scheme 4b) through neighboring group participation.¹³

The stereoselective formation of 1,2-*cis* glycosidic bonds has been a long standing problem in carbohydrate synthesis. In 2005 the group of Boons developed two C-2 OH protecting groups that were capable of promoting the formation of 1,2-*cis* glycosidic bonds by neighbouring group participation.¹⁴ As depicted in Scheme 4C, the (1S)-phenyl-2-(phenylsulfanyl)ethyl ether can be introduced at the C2 hydroxyl of glucoside **84** with (1S)-phenyl-2-(phenylsulfanyl)ethyl acetate **85** in the presence of $\text{BF}_3 \cdot \text{OEt}_2$. The configuration of the chiral center of the newly introduced ether is retained in this reaction because of the intermediate formation of an episulfonium ion, which is displaced at the benzylic position. Using standard protecting group manipulations, glucoside **86** was transformed into trichloroacetimidate **88**. This donor could be (pre)-activated with TMSOTf to provide a meta-stable sulfonium ion **82**, having a *trans*-decalin structure. In this constellation the

phenyl substituent of the C-2 chiral auxiliary occupies an equatorial position. The alternative *cis*-decalin system is not formed because this would place the phenyl group in an unfavorable axial orientation. Nucleophilic displacement of the intermediate sulfonium ion then provides the 1,2-*cis* products. The influence of the C2-chiral auxiliary was compared to the effects of an external sulfide, a non-chiral internal sulfide and the effect of the same auxiliary of opposite chirality. As can be seen in Scheme 4c, the best stereoselectivity was obtained with the (1*S*)-phenyl-2-(phenylsulfanyl)ethyl donor. Along the same line, the Boons laboratory developed the ethoxycarbonylbenzyl ether for the stereoselective construction of α -glucosyl and α -galactosyl linkages. It should be noted that the best selectivities were obtained with electron withdrawing protecting groups on the C-3 OH.¹⁵

To circumvent the extra synthetic effort that is required to introduce the Boons auxiliary in a suitable donor, Turnbull introduced oxathiane type donors as depicted in Scheme 4d.¹⁶ This type of donor can be activated by transformation into the corresponding sulfoxide which can then be treated with triflic anhydride to provide a glycosylating species. Because the activated leaving group remains attached to the molecule upon glycosylation and thus ends up in the final product, the resulting sulfenyl triflate was transformed into arylsulfonium ion **111** and **112** by treatment with trimethoxybenzene. This species can be displaced with the acceptor alcohol (Scheme 4d). Because of the stability of the intermediate trimethylphenyl sulfonium ion relatively high temperatures are required for this substitution and best results were obtained with primary alcohols. Notably the stereoselectivity of the glycosylations did not depend on the nature of the other protecting groups on the donor glycoside.

The 2-*O*-(thiophen-2-yl)methyl group was introduced by Fairbanks to provide a similar kind of anchimeric assistance as Boons' phenyl-2-(phenylsulfanyl)ethyl ether.¹⁷ Good to excellent α -selectivities were reported for otherwise benzylated donors. No conditions were reported for the removal of the 2-*O*-(thiophen-2-yl)methyl group (Scheme 4e).

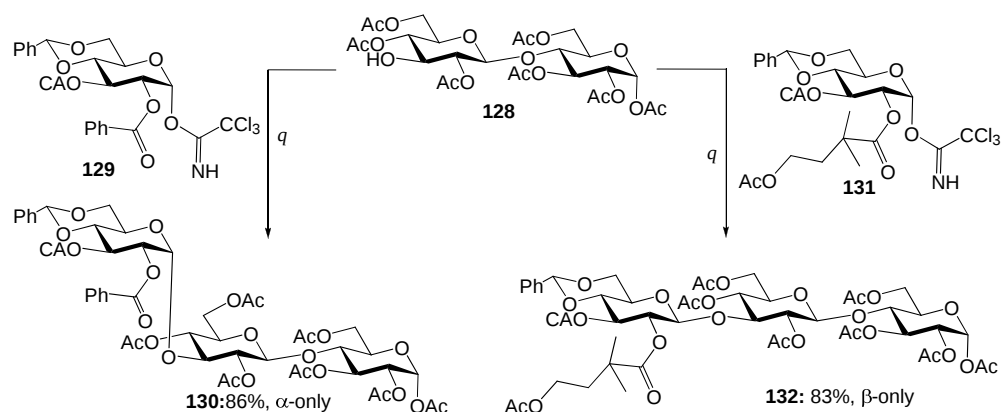
The *trans*-directing effect of the 2-picolyl ether described by Demchenko and co-workers stands in contrast to the α -directing effect of the sulfur-based participating groups (scheme 4f).^{18,19} The C-2 picolyl ether was introduced as a “non-disarming” alternative for the participating C-2 acyl function. It was demonstrated that C-2 picolyl *S*-thiazoliny donor **123** was transformed into a mixture of two bicyclic products, in which the α -oriented pyridinium ion **125** prevailed (20 : 1 at room temperature, 5 : 1 at 50 °C). The predominant formation of the 1,2-*cis* bicycle obviously differs from the generation of the β -sulfonium ions described above. Possibly, active participation of the picolyl ether in the expulsion of the *S*-thiazolyl under the mild activation conditions ($\text{Cu}(\text{OTf})_2$) is at the basis of this contrasting behavior. The α -pyridinium intermediate could be displaced by a glycosyl nucleophile at elevated temperature (50 °C) to provide the 1,2-*trans* products. The β -pyridinium ion proved to be inert under these conditions and was isolated after the reaction.

Besides the conceptually novel participating groups described above, several new acyl type protecting functions have recently been reported. For example, the 4-acetoxy-2,2-dimethylbutanoate was introduced as a pivaloyl analogue, which can be removed under relatively mild conditions (Scheme 5a).²⁰ The 3-(2'-benzyloxyphenyl)-3,3-dimethylpropanoate ester has been developed as a participating group that can be removed by catalytic hydrogenolysis in concert with regularly used benzyl ethers (Scheme 5b).²¹ Iadonisi and co-workers introduced alkoxycarbonates as participating functionalities to circumvent orthoester formation, which is a common side reaction when C-2-*O*-acyl protected donors are used in combination with mild activating conditions (Scheme 5c).²²

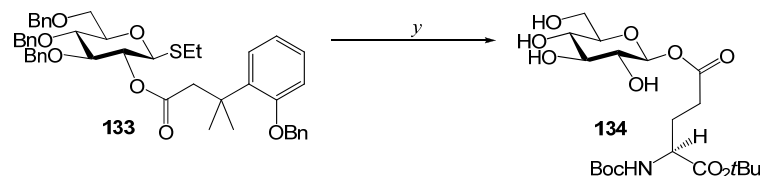
Chapter 2 of this thesis describes that the methylsulfonylethoxycarbonyl group is an orthogonal protecting group for hydroxyl functions in oligosaccharide synthesis that provides anchimeric assistance and excludes orthoester formation, when placed on the C2-OH of a glycosyl donors.²³ The group of Yamago showed that dialkylphosphate esters at the C-2-OH position are stereodirecting protecting groups for the synthesis of 1,2-*trans*-glycosides.

Scheme 5: Novel participating acyl groups.

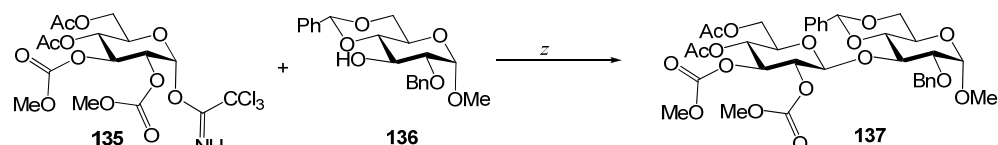
a- 4-acetoxy-2,2-dimethylbutanonyl as 1,2-*trans* directing group.



b- Crich's 3-(2'-benzyloxyphenyl)-3,3-dimethylpropanoate ester.



c- Iadonisi's alkoxycarbonate.



Reagents and conditions; q) TMSOTf, DCM; y) i- BocNH-L-Glu-O-*t*-Bu, NIS, TfOH, DCM, -40 °C, 90%; ii- Pd/C, 3 atm H₂, RT, 86%; z) Yb(OTf)₂, tol., 50 °C, 2h, 82%.

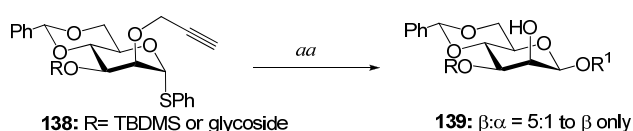
Protecting group size can have a major effect on the stereochemical outcome of a glycosylation reaction. For example, the large C-6 trityl ether has been shown to enhance the α -selectivity of glucosylations, presumably by steric shielding of the β -face. Crich and co-workers have reported on steric buttressing of large protecting groups at the C-3 hydroxyl in 2-*O*-benzyl-4,6-benzylidene mannosyl donors, which typically react in a highly β -selective fashion.²⁴ Placement of a large *tert*-butyldimethylsilyl (TBDMS) group at the C-3 hydroxyl caused erosion of this selectivity because the large silyl group pushes the C-2 substituent towards the anomeric center of the mannosyl donor thereby obstructing the

nucleophilic attack on the β -face of the molecule. To overcome the poor selectivities of mannosyl donors with bulky C-3 substituents, Crich and co-workers introduced various propargyl ethers as minimally intrusive hydroxyl protecting groups. Firstly, the use of an unsubstituted propargyl ether was reported, which efficiently restored the β -selectivity of mannosyl donor **138** as depicted in Scheme 6a.²⁵ Because the removal of the propargyl ether required a two step sequence, namely base induced isomerisation followed by oxidative cleavage of the intermediate allene ether by catalytic OsO₄, substituted propargyl ethers were developed next (Scheme 6b). The 1-naphthylpropargyl can be cleaved in a single step using DDQ in wet DCM, but proved to be incompatible with the commonly used sulfonium activator systems BSP/Tf₂O and Ph₂SO/Tf₂O.²⁶ Furthermore, when placed at the C-2 hydroxyl, it engages in nucleophilic attack of the activated anomeric center. Therefore the 4-trifluoromethylbenzyl propargyl ether group was introduced.²⁷ This ether was shown to be sterically minimally demanding and compatible with electrophilic activators, while it could be cleaved using lithium naphthalenide (Scheme 6c).

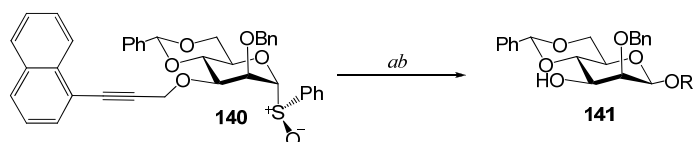
The C-2 propargyl ether was exploited by Fairbanks and co-workers in an intramolecular aglycon delivery (IAD) strategy towards β -mannosides.²⁸ As depicted in Scheme 6d, the propargyl ether in **144** was isomerised to the allenyl ether, which provided the mixed acetal **147** upon treatment with an glycosyl alcohol and iodonium ions. Dimethyldisulfide-Tf₂O mediated intramolecular glycosylation led to the completely stereoselective formation of the disaccharide **148**.

Scheme 6: Propargyl ethers in carbohydrate chemistry.

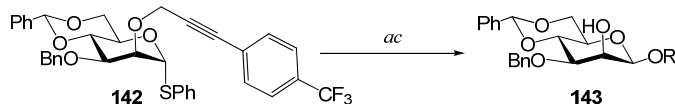
a- unsubstituted propargyl in the synthesis of β -mannosides.



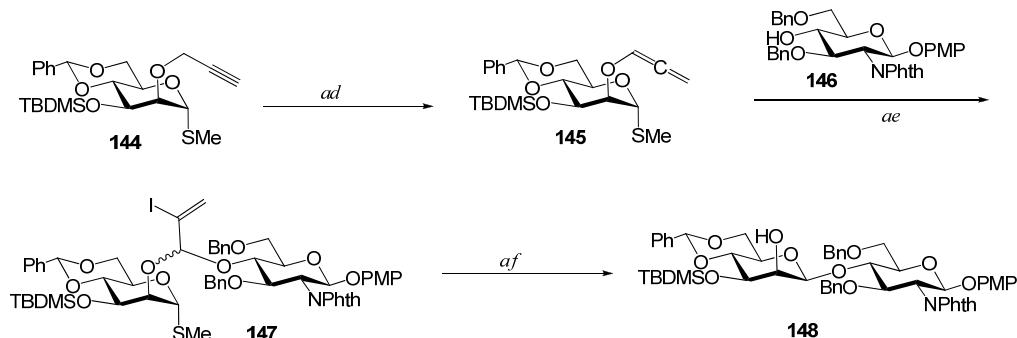
b- 1-Naphthylpropargyl in the synthesis of β -mannosides.



c- 4-Trifluoromethylbenzylpropargyl protective group the synthesis of β -mannosides.



d- Intramolecular aglycon delivery (IAD).



Reagents and conditions; aa) i- BSP, TTBP, Ti_2O , DCM; ii- R^1OH ; iii- $t\text{-BuOK}$, OsO_4 , NMNO; ab) i- 1-octene, TTBP, Ti_2O , DCM; ii- ROH; iii- DDQ, DCM; ac) i- BSP, TTBP, Ti_2O , DCM; ii- ROH; iii- lithium naphthalenide; ad) $t\text{-BuOK}$, Et_2O , 66%; ae) I_2 , AgOTf, DTBMP, DMC, -78°C -RT, 88%; af) Me_2S , Ti_2O , DTBMP, DCM, 0°C -RT, 81%.

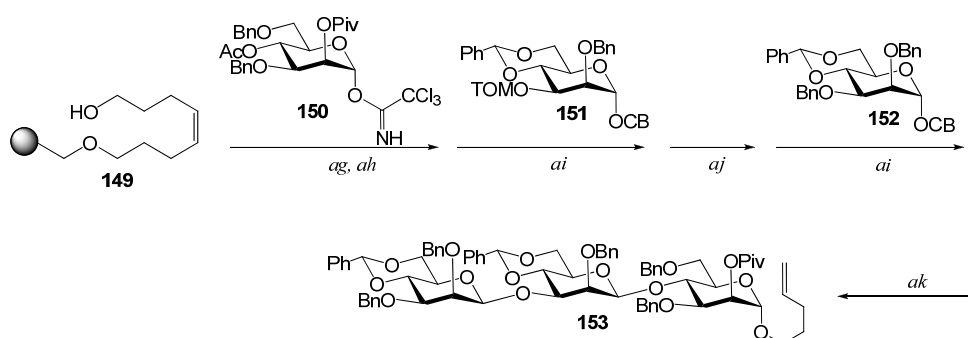
Seeberger and co-workers described another solution to overcome the steric buttressing of the large TBDMS ether described above. They showed that the tri-*iso*-propylsilyloxymethyl (TOM) group, in which the oxymethylene moiety moves the bulk to the silyl group away from the mannosyl core, could be used to install the β -mannosidic linkage.²⁹ The C-3-O-TOM mannosyl donors were used in the automated solid phase synthesis of β -mannosides (Scheme 7a).

Chapter 4 of this thesis describes the methylsulfonylethoxymethyl (Msem) group as a new hydroxyl protecting group in oligosaccharide synthesis.³⁰ The Msem group is sterically unbiased and could be used for the synthesis of an all *cis*-linked 1,3-*O*-mannotrioside.

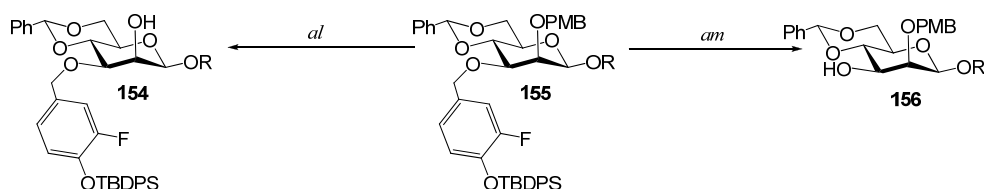
The 4-(*tert*-butyldiphenylsiloxy)-3-fluorobenzyl group was developed as a fluorine labile benzyl ether, attuned to the synthesis of β -mannosides.³¹ The fluorine in this *p*-siloxybenzyl type ether was introduced to enhance its stability under acidic and oxidative conditions. The 4-(*tert*-butyldiphenylsiloxy)-3-fluorobenzyl group was introduced using the corresponding benzyl bromide, which was synthesized in three steps from commercially available 3-fluoro-4-hydroxybenzoic acid, and cleaved with tetrabutyl ammonium fluoride (TBAF) at elevated temperatures under microwave irradiation (Scheme 7b). Lower temperatures only led to removal of the silyl group.

Scheme 7: Sterically minimally intrusive silyl based protecting groups in the construction of β -mannosides.

a- TOM protective group.



b- Silyl substituted benzyl ether.

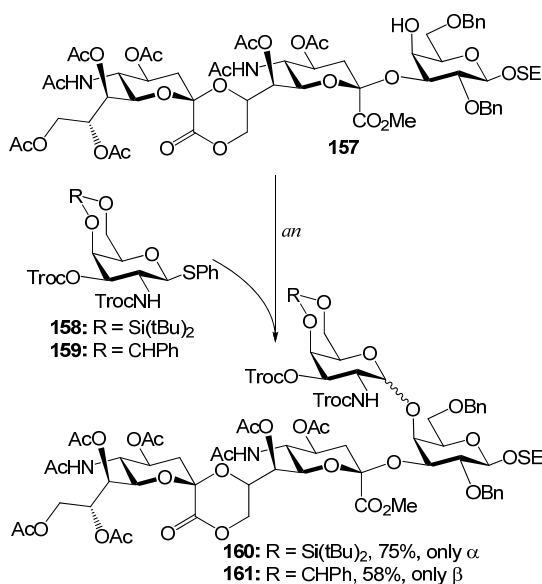


Reagents and conditions; ag) TMSOTf, toluene, DCM, 15 min, repeat; ah) NaOMe, MeOH, DCM, repeat; ai) TiF_4 , DTBMP, DCM, -30°C , 2 h, repeat; aj) TBAF, THF, 20 min, repeat; ak) the Grubbs catalyst 1st generation, DCM, ethylene atmosphere, overnight; al) DDQ, DCM/ H_2O , RT, 80-84%; am) TBAF, THF, 90°C , microwave, 74-78%.

The 4,6-di-*tert*-butylsilylene (DTBS) group was introduced in carbohydrate chemistry by Nishimura as a more acid stable alternative to the commonly used cyclic ketal

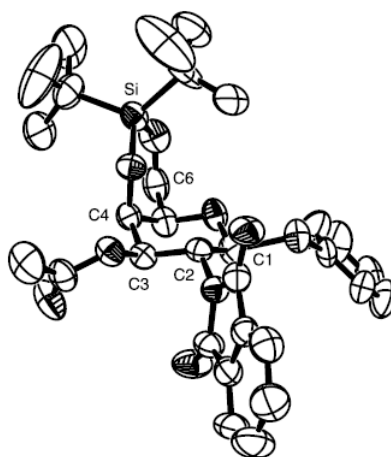
and acetal functions, such as the isopropylidene and benzylidene groups.³² Dinkelaar *et al.* employed this group for the protection of glucosamine synthons in the assembly of a set of hyaluronan oligosaccharides, where the benzylidene group proved to be insufficiently stable towards the slightly acidic coupling conditions used.³³ Besides its acid stability the 4,6-DTBS has attracted considerable attention because of the α -directing effect it has when mounted on a galactosyl donor.³⁴ Although the reasons for this stereodirecting effect are not completely clear yet, it has been hypothesized based on a crystal structure of a DTBS-protected thiogalactoside (Figure 1) that the near half chair conformation of the silylene group places one of the *tert*-butyl groups over the β -face of the galactosyl donor during glycosylation (Scheme 8). Notably the α -directing effect is so strong that it can override neighboring group participation by C-2 acyl functions, such as the C-2-*O*-benzoyl, C-2-*N*-trichloroethylcarbonate (Troc), and C-2-*N*-Phthaloyl (Phth).

Scheme 8: Stereoselective α -galactosylation using 4,6-silylidene galactosides.



Reagents and conditions; an) NIS, TFOH, DCM, MS 4Å, 0 °C.

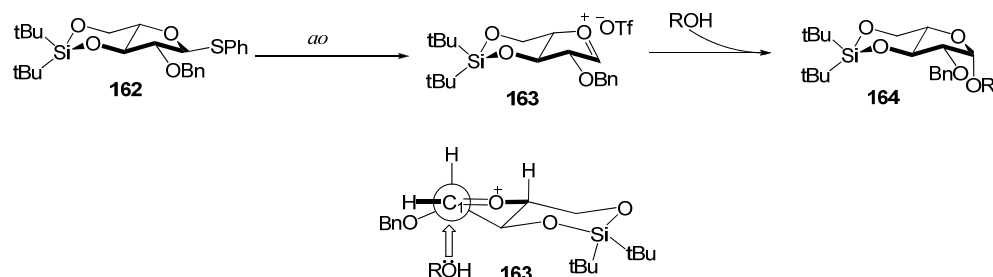
Figure 1: Crystal structure of DTBS protected thioglycoside **158**.



The DTBS has also been applied in the stereoselective synthesis of β -arabinofuranosides.³⁵ As depicted in Scheme 9, it was proposed that the 3,5-DTBS group

locks the arabinosyl oxacarbenium ion in the E_3 conformation, which is attacked from the β -face in order to avoid eclipsing interaction on the α -face, to provide the 1,2-*cis* arabinosides.

Scheme 9: Stereoselective arabinofuranosylation using a 3,5-DTBS group.

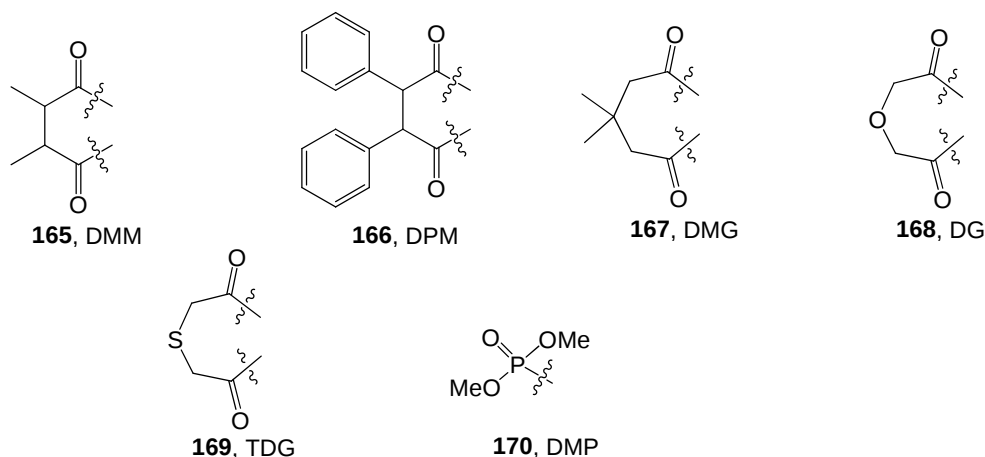


Reagents and conditions; ao) NIS, AgOTf, DCM, -30 °C.

Protecting groups for the amino group in glycosamines:

Several new protecting groups for the glucosamine nitrogen function have also been reported recently. Schmidt and co-workers investigated several C_2 -symmetric *N,N*-diacyl groups, such as the dimethylmaloyl (DMM), diphenylmaloyl (DPM), dimethylglutaryl (DMG), diglycolyl (DG) and thiodiglycolyl (TDG) group (Figure 2).³⁶ Of these the DG group proved to perform best in terms of ease of introduction, removal and compatibility in glycosylation reactions. Yang and Yu introduced the *N*-dimethylphosphoryl (DMP) group for the protection of the glucosamine nitrogen. The DMP-group was used in the synthesis of several β -glucosamines, and shown to be stable to certain basic and acidic reaction conditions and could be readily removed using NaOH or hydrazine. Alternatively the *N*-DMP could be transformed into *N*-acyl derivatives using an acyl chloride in refluxing pyridine.³⁷

Figure 2: The dimethylmaloyl (DMM), diphenylmaloyl (DPM), dimethylglutaryl (DMG), diglycolyl (DG), thiodiglycolyl (TDG) and dimethylphosphoryl (DMP) groups.



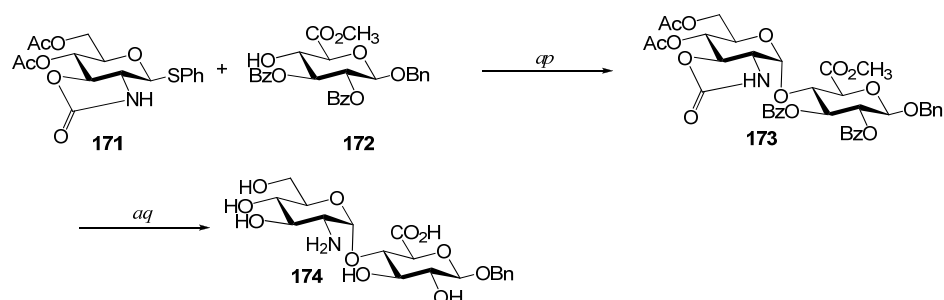
While there is a plethora of *trans*-directing nitrogen protecting groups, very few groups are available to mask the glycosyl amino function with a non-participating group. In fact the azide group has almost exclusively been used for the installation of 1,2-*cis* glycosylamine linkages. In 2001 Kerns and co-workers introduced the oxazolidinone group for the protection of 2-aminoglycosides and it was shown that oxazolidinone protected glucosamine donors stereoselectively provided 1,2-*cis* linked products.³⁸ Mechanistic studies revealed that the stereochemical outcome of condensations of these donors depends strongly on the nature of the activator and acceptor nucleophile used (Scheme 10c and 10e).^{39,40} Kerns and co-workers described that 2,3-oxazolidinone-*N*-acetyl protected glucosamine donor **171** can be activated with benzenesulfonylpiperidine (BSP) and triflic anhydride (Tf₂O) in the presence of tri-*tert*-butylpyrimidine (TTBP), to mainly provide an α -anomeric triflate intermediate. Relatively reactive nucleophiles stereoselectively provided β -linked products, whereas the use of sterically hindered, less reactive nucleophiles led to the predominant formation of the α -products (Scheme 10a). These results were interpreted by assuming that the reactive nucleophiles can displace the α -triflate, but that less reactive nucleophiles can only substitute the more reactive β -triflate, or intermediate oxacarbenium ion. In subsequent studies the groups of Oscarson, Ye and Ito showed that the stereochemical outcome of 2,3-oxazolidinone-*N*-acetyl and 2,3-oxazolidinone-*N*-benzyl protected glucosamine donors could be controlled by tuning the

(Lewis)-acidity of the employed activator systems.⁴⁰ Less acidic conditions mainly led to the isolation of β -linked products, where a more acidic milieu favored the formation of α -isomeric products. Convincing evidence has been forwarded that the glucosamine donors initially provide the β -linked products, which rapidly anomerise to the more stable α -isomers under acidic conditions through an *endo*-cyclic ring opening pathway (Scheme 10b and 10d).

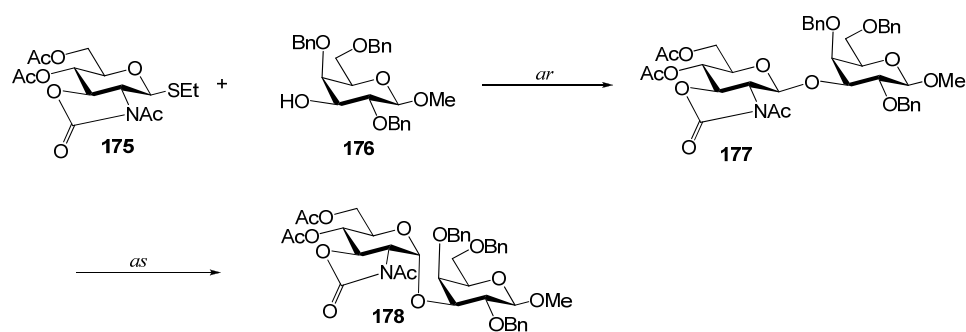
It is also of interest to note the beneficial effect of the 2,3-oxazolidinone-*N* group on the nucleophilicity of the C-4 hydroxyl in *N*-acetyl glucosamines. The reason for this enhanced reactivity probably originates from the tied back nature of the oxazolidinone group.⁴¹

Scheme 10: Stereoselective condensations of 2,3-oxazolidinone protected glucosamine donors.

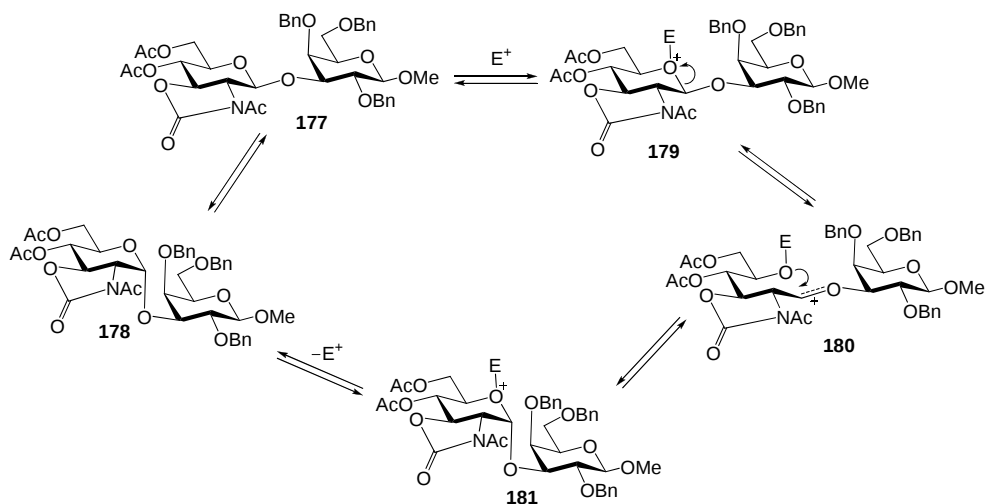
a- Synthesis of a deprotected disaccharide using a 2,3-oxazolidinone protected glucosamine.



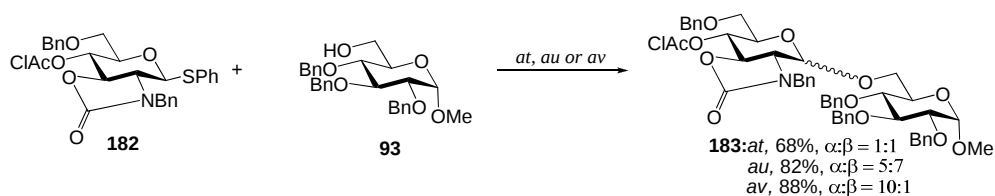
b- Conversion of the stereochemistry under Lewis acid conditions.



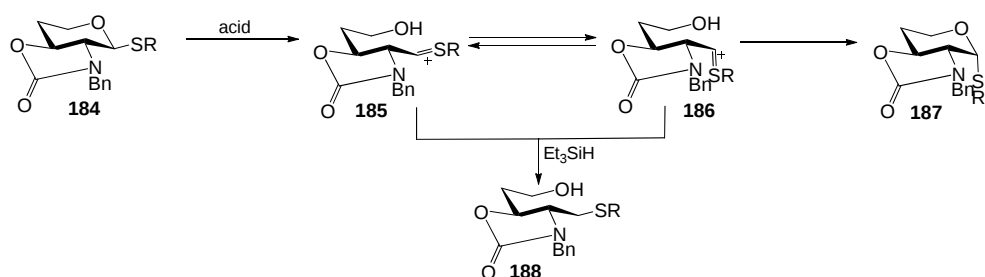
c- Mechanism of the change in stereochemistry.



d- Difference in stereoselectivities with different activator system

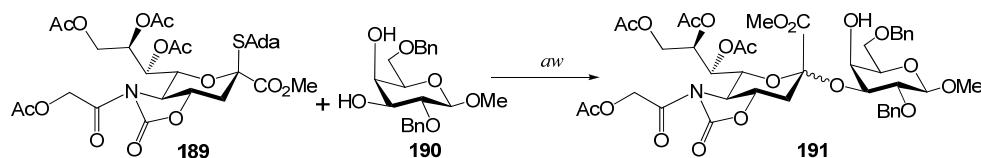


e- Mechanistic explanation of difference is stereoselectivities.



Reagents and conditions; *ap*) PST, DCM, $-78^\circ C$, 75%; *aq*) NaOH, H_2O/THF , 80%; *ar*) NIS, AgOTf (0.1 eq), DCM, RT; *as*) AgOTf (0.4 eq), 82%; *at*) PhSCl, AgOTf, DTBMP, DCM, RT; *au*) *N*-(phenylthio)- ϵ -caprolactam, Tf_2O , DCM, RT; *av*) PhSCl, AgOTf, DTBMP, $tol/1,4$ -dioxane (3:1), $0^\circ C$ - RT.

Finally, the application of the 4,5-oxazolidinone group in the synthesis of α -sialosides deserves mentioning. Various groups have reported on the excellent stereoselectivity achieved with sialic acid donors bearing a 4,5-oxazolidinone group, culminating in various one-pot multi-step glycosylation procedures (Scheme 11).^{41a,42}

Scheme 11: Stereoselective sialylations of 4,5-oxazolidinone protected *N*-acetyl sialic acids.

Reagents and conditions; aw) NIS, TfOH, DCM/ACN (2:1), -78 °C, 64%, α : β = 15:1.

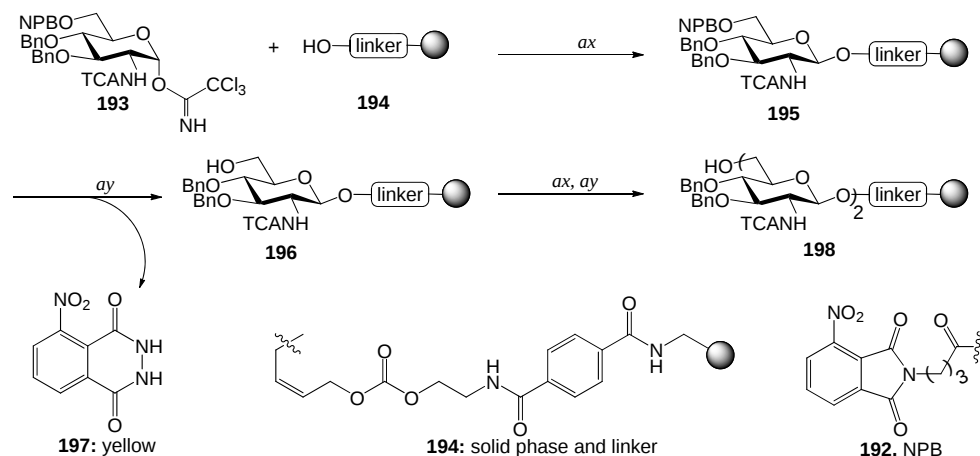
Removal of the oxazolidinone moiety can be accomplished using a variety of nucleophiles (NaOMe in MeOH, LiOH/LiCl in THF/H₂O) but the selective removal of the oxazolidinone in *N*-acyl oxazolidinones has been shown to be difficult in many cases.^{39,41a,42b,43}

Protecting groups as visualization tags:

Besides the primary role of masking a functional group on a carbohydrate, protecting groups can be used to introduce extra functionality in a carbohydrate building block. The UV-active 9-fluorenylmethoxycarbonyl (Fmoc) group has been extensively used as an amine protecting group in automated solid phase peptide chemistry to monitor the efficiency of the coupling steps.⁴⁴ This group has also found application as a hydroxyl protecting group in the automated synthesis of oligosaccharides.⁴⁵ Because the Fmoc is rather base labile when mounted on an alcohol, Pohl and co-workers set out to develop an alternative UV-active hydroxyl protecting group. They introduced the nitrophthalimidobutyric (NPB) ester, which can be introduced on a given hydroxyl function using the corresponding acid.⁴⁶ Cleavage of the NPB ester can be accomplished with hydrazine acetate in DMF at elevated temperature (50 °C) to provide the orange 3-nitrophthalhydrazide **197**, which can be used in the colorimetric monitoring of reaction cycles. To illustrate its applicability Pohl and co-workers described the solid phase synthesis of a resin bound glucosamine dimer **198** as displayed in Scheme 12. Aminomethylated polystyrene, functionalized with an allyl carbonate linker **194**, was glycosylated with trichloroacetimidate donor **193** using a double glycosylation cycle. Cleavage of the NPB ester liberated the primary alcohol for further chain elongation and

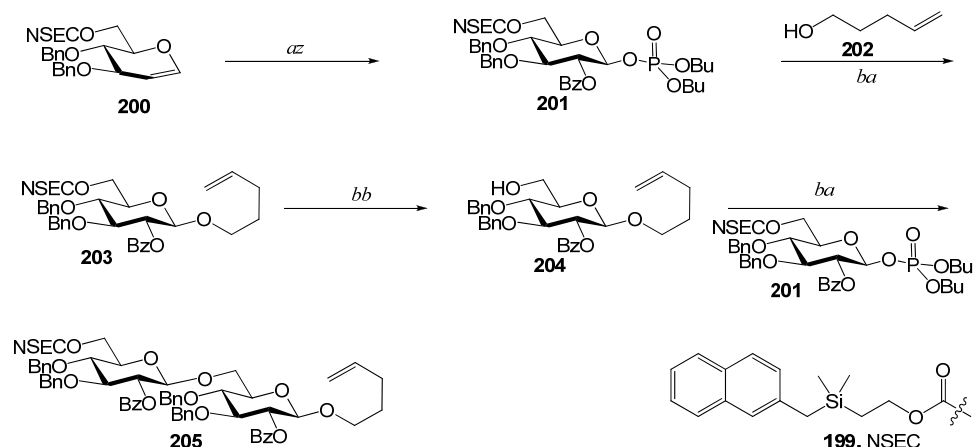
simultaneously allowed the colorimetric monitoring of the coupling efficiency, which was determined to be 98%. The second coupling/deprotection cycle proceeded in 96% yield. The dimer was not cleaved from the resin.

Scheme 12: The NPB ester in the synthesis of resin-bound dimer **198**.



Reagents and conditions; ax) i- TMSOTf, DCM, 15 min; ii- rinse; iii- repeat i and ii; ay) i- $\text{H}_2\text{NNH}_2 \cdot \text{AcOH}$, DMF, 15 min; ii- rinse.

The Seeberger laboratory introduced the UV-active 2-[dimethyl(2-naphthylmethyl)silyl]ethoxycarbonyl (NSEC) as a novel group to mask carbohydrate hydroxyl functions.⁴⁷ The NSEC group was shown to be compatible with various reactions commonly employed in carbohydrate synthesis and could be selectively cleaved with tetrabutylammonium fluoride (TBAF) (Scheme 13). The NSEC group was developed to allow UV-monitoring of glycosylation efficiency during automated synthesis but no such application has been reported yet.

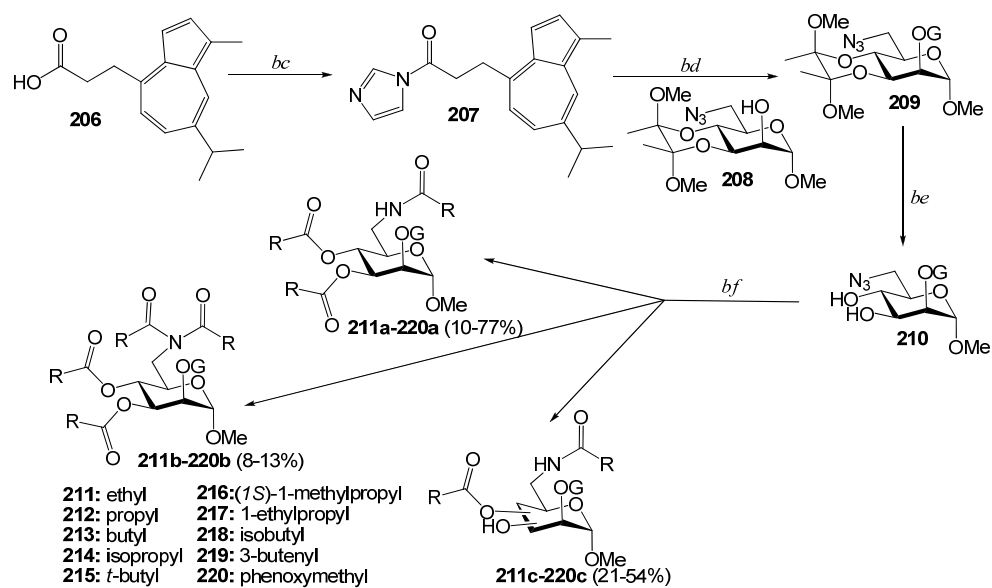
Scheme 13: The NSEC group.

Reagents and conditions; az) i- DMDO, DCM, 30 min; ii- HOP(O)(OBu)₂, DCM, -78 °C, 30 min; iii- BzCl, DMAP, 0 °C, 3h, 47%; ba) TMSOTf, DCM, -78 °C to -30 °C, 3h ; bb) TBAF, THF, 0 °C, 50 min, 96%.

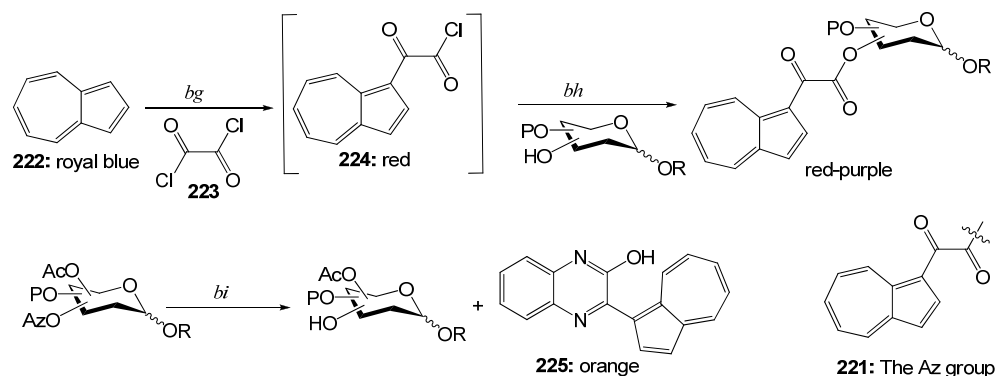
Several recent reports have described the use of azulene derived protecting groups. Azulene is a bicyclic hydrocarbon having a fused 7- and 5-membered ring and a 10-electron π -system, and an intense blue color. Lindhorst and Aumüller used guajazulene derived acid **206** for the protection of mannosyl alcohol **208**.⁴⁸ After deprotection of the BDA-acetal, the mannoside was used in the synthesis of mixtures of acylated products. The blue color of the products allowed the visualization of the products during silica gel column chromatography (Scheme 14a). Timmer *et al.* introduced the azulen-1-yl-dicarbonyl (Az) group **221**, which was used to protect a variety of carbohydrate alcohols.⁴⁹ It was introduced from the corresponding acid chloride, and could be removed using catalytic NaOMe in methanol or diaminobenzene and acetic acid in refluxing ethanol. The latter deprotection conditions allowed the selective removal of the Az-ester in the presence of acetyl groups, providing the colored benzopyrazine **225** as a side product (Scheme 14b). The Az-group was shown to be compatible with glycosylation conditions involving trichloroacetimidate donors (catalytic TMSOTf), but NIS-TfOH mediated activation of an Az-protected thiophenyl galactoside led to thiophenylation of the Az-group. The color of the Az-group aided in the monitoring of reactions by TLC analysis and purification via column chromatography.

Scheme 14: Azulene based protecting groups in carbohydrate chemistry.

a- The gaujazulene (G) protective group.



b- The Az protective group.



Reagents and conditions; bc) CDI, DMF, RT, 1h; bd) DBU, DMF, 0 °C, overnight, 46% over two steps; be) DMP, H[BF₄], DCM, RT, 2 h, 78%; bf) PMe₃, (RCO)₂O, THF, RT, overnight; bg) toluene; bh) DCM, pyr., 89-99%; bi) diaminobenzene, AcOH, EtOH, reflux, 94-98%.

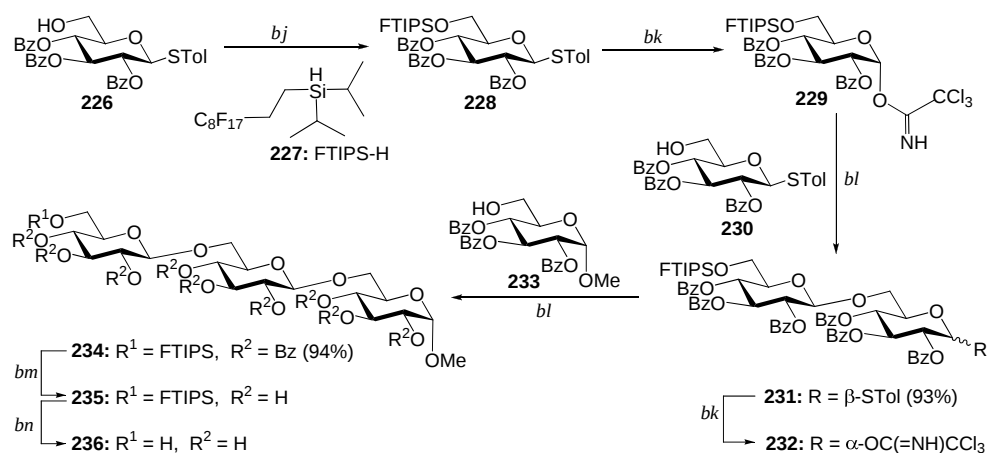
Protecting groups as purification handles:

Fluorous chemistry has been applied in various chemistry areas,⁵⁰ including catalysis,⁵¹ combinatorial and parallel synthesis,⁵² and selective tagging of biomolecules.⁵³ The properties of fluorous tags, being both hydrophobic and lipophobic, have been widely used in protecting group chemistry. Both “heavy” and “light” fluorous tags have been introduced as purification handles and their use has been extensively reviewed. “Heavy” fluorous groups are characterized by the presence of many fluorine atoms (39 or more) on multiple alkyl chains, often described as ponytails.⁵⁴ The high fluorine content of these groups renders the molecules to which it is attached soluble in a fluorous solvent but insoluble in both organic and aqueous solvents. “Heavy” fluorous compounds can therefore be purified from non-fluorous compounds by simple liquid-liquid extractions. “Light” fluorous groups contain significantly less fluorine atoms, typically between 9 and 17. Because of the lower fluorine content these molecules are often cheaper, easier available and much more soluble in organic solvents.⁵⁵ Purification of “light” fluorous compounds can be effected by fluorous solid phase extraction (FSPE) techniques.⁵⁶ Light fluorous versions of the most commonly used carbohydrate protecting groups have been described, including fluorous benzyl,⁵⁷ trityl,⁵⁸ allyl,⁵⁹ and pentenyl ethers,⁶⁰ the fluorous benzylidene acetal,⁶¹ and various fluorous acyl^{62,59d} and silyl based⁶³ groups.

In analogy to oligosaccharide synthesis on solid or soluble polymeric supports, two strategies can be followed in the fluorous supported assembly of oligosaccharides. In a “donor-bound” strategy, the growing oligosaccharide chain is build up from the non-reducing end, with a donor glycoside bearing a fluorous protecting group/tag. The “acceptor-bound” strategy on the other hand starts with a fluorous acceptor building block. Both strategies have been employed, but the latter has found most applications, because most side reactions in a glycosylation reaction take place on the donor glycosides. Liu and co-workers described the synthesis and application of fluorous glycosyl donor, in which the light fluorous tag was attached to the C-6 hydroxyl *via* a di-*iso*-propylsilyl ether.^{63c} As depicted in Scheme 15, *S*-tolyl glucoside **226** was silylated with fluorous di-*iso*-

propylsilane under the agency of triflic acid (TfOH) and subsequently converted into trichloroacetimidate **229**. This donor was glycosidated with an excess of primary acceptor **230** to provide the disaccharide **231** in 93% yield. The S-tolyl disaccharide was transformed into a trichloroacetimidate to be coupled to reducing end glucoside **233** in the next step. After both glycosylation steps, FSPE was used to purify the products and recover the excess acceptor. Purification by silicagel chromatography was required in the transformation of the thioglycosides into the corresponding trichloroacetimidates. The fluoros di-*iso*-propylsilyl ether was cleaved at the end of the synthesis using 0.02 M HCl in MeOH/H₂O.

Scheme 15: Donor-bound fluoros synthesis of a trisaccharide using a fluoros di-*iso*-propylsilyl ether (FTIPS).

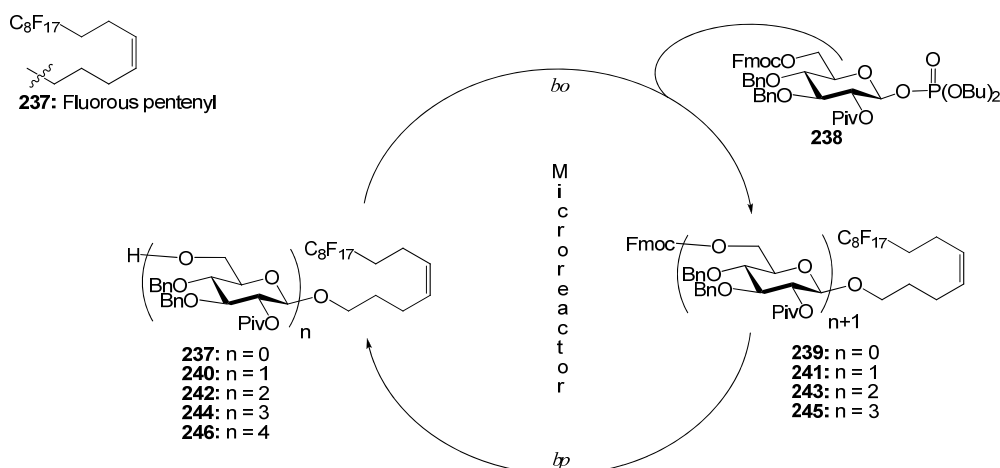


Reagents and conditions; bj i- TfOH, 0 °C; ii- 2,6-lutidine, DCM, RT, 99%; *bk* i- NBS, TMSOTf, DCM/H₂O, 0 °C-RT; ii- Cl₃CCN, DBU, DCM, RT, 76%; *bl* i- TMSOTf, DCM, MS 4 Å, -40 °C; ii- FSPE; *bm* i- NaOMe, MeOH/DCM, RT; ii- FSPE, 94%; *bn* i- HCl_(aq), MeOH, RT; ii- FSPE, 84%.

An example of an “acceptor-bound” oligosaccharide assembly strategy is depicted in Scheme 16. In 2007, Seeberger and co-workers introduced the fluoros version of the *n*-pentenyl group **237**, which was employed in the assembly of a tetrasaccharide.⁶⁰ A silicon-glass microreactor was used for the optimization of the glycosylation reactions. It was described that β -glycosyl phosphate donor **238** could be employed at room temperature using reaction times ranging from 20 to 60 seconds (Scheme 16). The first glycosylation had to be executed in a mixture of dichloromethane and trifluorotoluene (TFT) to keep the

fluorous pentenyl alcohol in solution. The lipophilic O-6 Fmoc protecting group was removed in the quenching step to facilitate purification by FSPE (Scheme 16). After oligosaccharide assembly, the fluorous *n*-pentenyl group could be cleaved using *N*-bromosuccinimide or transformed into different functional groups.

Scheme 16: Acceptor-bound fluorous synthesis of an oligosaccharide using the fluorous pentenyl group.

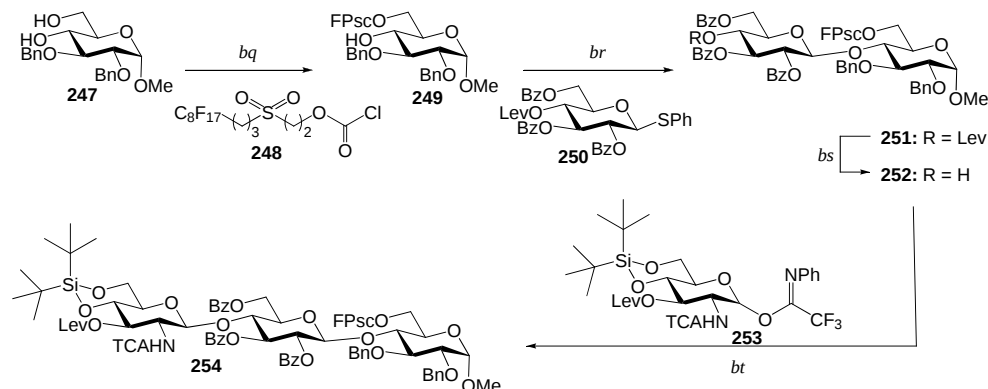


Reagents and conditions; *bo*) TMSOTf, DCM or TFT, 0 °C or 20 °C; *bp*) *i*-piperidine/DMF (1:4), TBAF; ii- FSPE.

In chapter 3, the fluorous version of the Msc-group is introduced.^{50e} It was found that an ethylene insulator, which is commonly used to spacer a fluorous tail from a functional group in a fluorous protecting group, made the FMsc very base labile. Therefore the C₈F₁₇-moiety was removed from the sulfonyl group by a C3 spacer to provide the fluorous propylsulfonylethoxycarbonyl (FPsc) group.²³ This sulfonyl carbonate was successfully employed in the synthesis of a trisaccharide as depicted in Scheme 17. First the FPsc was regioselectively introduced at the primary alcohol of glucoside **247**. The resulting acceptor was coupled with levulinoyl protected thioglucoside **250** to provide the fluorous dimer **251** in 93% yield after FSPE. Deprotection of the Lev-ester then gave disaccharide

252 (81% after FSPE), which was elongated with glucosamine **253** to yield the trisaccharide **254** in 78% after FSPE.

Scheme 17: Oligosaccharide synthesis using the FPsc group.



Reagents and conditions; bq) pyr., DCM, -40 °C-RT, 4 h, 94%; br) i- NIS, TMSOTf, DCM, 0 °C-RT, 1h; ii- FSPE, 93%; bs) i- H₂NNH₂.H₂O, pyr./HOAc, 5 min; ii- FSPE, 94%; bt) i- TFOH, DCM, -20 °C-RT, 15 min; ii- FSPE, 78%.

Besides fluoruous supports, large lipophilic moieties and ionic liquids have also been recently introduced for the construction of oligosaccharides.

Conclusion:

Protecting groups take up a central role in carbohydrate chemistry and hold a key position in controlling the stereoselectivity of glycosylation reactions. Over the years several new and ingenious protecting groups have been added to the broad palette of carbohydrate protecting groups to allow the stereoselective construction of both 1,2-*cis* and 1,2-*trans* linkages. New protecting groups, with tailor-made properties in terms of chemical stability and lability, allow ever more sophisticated glycosylation schemes to be developed, while colored or UV-active groups and purification tags continue to increase the efficiency of oligosaccharide assembly. Given the growing demand for ever more and complex, pure and well-defined oligosaccharides in all fields of glycoscience, it is anticipated that the

development of new protecting groups and protection/deprotection schemes will continue to be a major theme in carbohydrate chemistry.

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