Novel protecting group strategies in the synthesis of oligosaccharides

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Chapter 1

Protecting Group Strategies in Carbohydrate Chemistry

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Introduction

Carbohydrates are the most densely functionalized class of biopolymers in Nature. Every monosaccharide features multiple contiguous stereocenters and bears multiple hydroxyl functionalities. These can in turn be decorated with sulfate groups, acyl esters, lactic acid esters and ethers or phosphate moieties. Amine and carboxylate functions can also be present. Most often the amine groups are acetylated, but different amide functions are also found, as well as *N*-sulfates and alkylated amines. The discrimination of the functional groups on a carbohydrate ring has been and continues to be one of the great challenges in synthetic carbohydrate chemistry.[1–3]

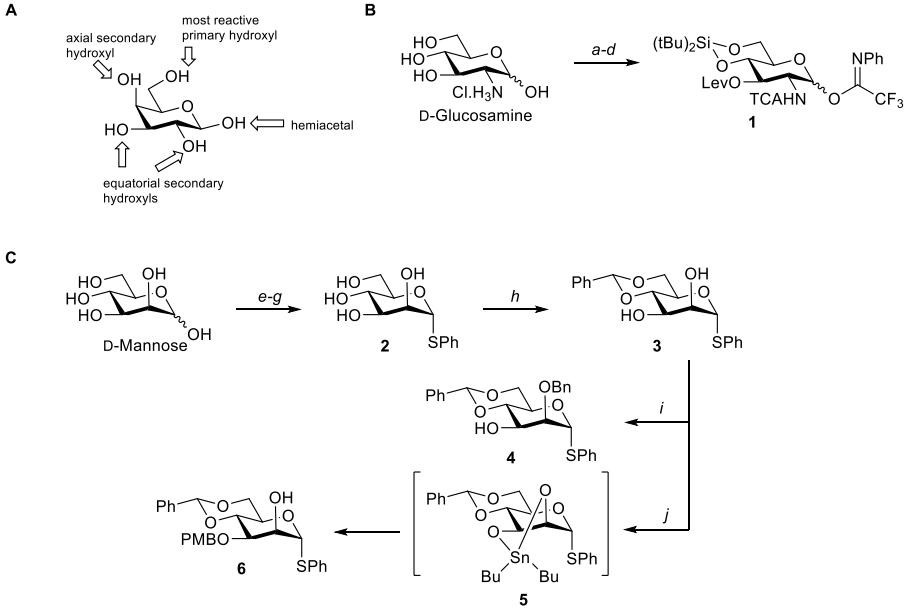
This thesis deals with the development of new protecting group strategies and manipulations in the solution and solid phase assembly of relevant oligosaccharides. This introductory Chapter provides an overview of the difference in reactivity of the various functional groups on a carbohydrate ring and shows how these can be exploited for effective protecting group strategies. The protecting groups on a carbohydrate dictate the reactivity of the (mono)saccharide and this Chapter will describe how protecting group effects can be used to control stereoselective transformations (most importantly glycosylation reactions) and reactivity controlled one-pot synthesis strategies. Applications and strategies in automated synthesis are also highlighted.

Discriminating different functionalities on a carbohydrate ring

The main challenge in the functionalization of a carbohydrate (mono)saccharide is the discrimination of the different hydroxyl functionalities. The - often subtle - differences in reactivity can be capitalized upon to formulate effective protecting group strategies (See Scheme 1A). The primary alcohol functionality is generally the most reactive of the hydroxyl groups because of steric reasons. It can be site selectively addressed using bulky protecting groups such as silyl or trityl ethers. The anomeric hydroxyl group discerns itself from the other secondary hydroxyl groups in that it is part of a hemiacetal functionality. It can therefore be selectively modified using acetal chemistry, and acid catalyzed acetal and mixed thioacetal formations are amongst the most used methods to start a protecting group manipulation sequence. Because it is part of a hemiacetal functionality the anomeric hydroxyl group is also the most acidic alcohol on a carbohydrate ring and it can be chemoselectively modified under basic conditions. Conversely, it is less reactive than the other secondary alcohol groups under acidic conditions. Axial secondary alcohols are generally somewhat less reactive than the equatorial ones on a carbohydrate ring and these reactivity differences can often be exploited in designing an efficient protecting group scheme. Finally, the position of a hydroxyl group on the carbohydrate ring and the nature of its neighboring substituents affect its reactivity. In this regard the use of cyclic protecting groups that engage two hydroxyl groups in a cyclic context has proven to be a very powerful tool.[4] Benzylidene acetals and silylidene ketals can be used to mask C-4 C-6 diols, where isopropylidene groups and orthoesters are commonly employed to protect *cis*-hydroxyl groups in a five membered ring constellation. Butane 2,3-bisacetals and the recently introduced *o*-xylylene groups can be used to protect vicinal diequatorial diols.[5] To illustrate how the reactivity of various

alcohol groups can be exploited two examples are given in Scheme 1B and 1C. The first example shows a four-step reaction sequence that has been used to site selectively mask all groups of a glucosamine synthon **1**. Thus, the nitrogen functionality in D-glucosamine can be chemoselectively protected with a trichloroacetyl group, by virtue of its higher nucleophilicity with respect to the alcohols present. Next the primary alcohol at C-6 and the hydroxyl group at C-4 can be masked with a di-*tert*-butyl silylidene ketal. The selectivity of this transformation originates from the bulky nature of the protecting group and the fact that a stable *trans*-decalin system can be formed. Next the anomeric hydroxyl group can be selectively addressed using basic conditions to install an imidate group. Finally the remaining alcohol can be masked with a levulinoyl ester.[6] In the second example the different hydroxyls of D-mannose are discriminated using the following steps (Scheme 1C). First all hydroxyl groups are acetylated, concomitantly locking the mannose monosaccharide in a pyranoside ring. Next the anomeric thioacetal is installed under Lewis acidic conditions. After saponification of the four remaining acetyl groups (**2**), the alcohol groups are diversified through the installation of a benzylidene acetal[7,8] (**3**) and

Scheme 1. A) Relative reactivity of carbohydrate alcohols; B) Four step reaction sequence to mask all functional groups in glucosamine; C) Site selective modification of mannosyl hydroxyl groups.

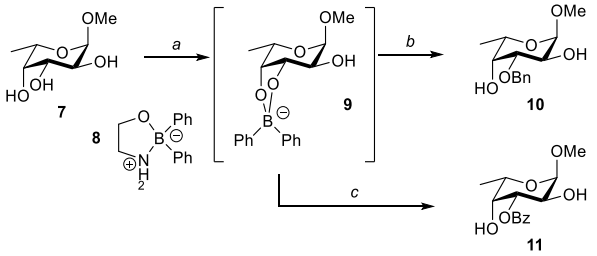


Reagents and conditions: a) Cl_3CCOCl, Et_3N, MeOH; b) $(tBu)_2Si(OTf)_2$, pyridine, DMF, -40°C (86% over two steps); c) $CF_3C(=NPh)Cl$, Cs_2CO_3, acetone (98%); d) LevOH, DIC, DMAP, DCM (82%). C) Site selective modification of mannosyl hydroxyl groups; e) Ac_2O, pyridine; f) PhSH, BF_3•OEt_2, DCM (75% over two steps); g) NaOMe, MeOH (100%); h) HBF_4•OEt_2, $PhCH(OMe)_2$, DMF (60%); i) Bu_4NHSO_4, BnBr, NaOH, DCM (75%); j) *i*. Bu_2SnO, toluene, reflux; *ii*. CsF, Bu_4NBr, PMBCl, toluene, reflux (94%).

selective benzylation of the C2-OH using phase transfer conditions (**4**).[9] The selectivity in the latter transformation can be explained by taking into account the relative mild basic

conditions (as opposed to the use of NaH in DMF) and the slightly higher acidity of the C2-OH because of its closer proximity to the anomeric center. Alternatively, the C3-OH can selectively be protected by exploiting the slightly higher nucleophilicity of this alcohol. Selective acylation is possible as well as regio selective alkylation. To further enhance the reactivity difference between neighboring axial and equatorial hydroxyl groups the use of stannylidene ketals presents a very effective approach.[10] Thus, diol **3** can be transformed into a dibutylstannylidene ketal (**5**) using dibutyltin oxide, after which the tin ketal can react with an appropriate electrophile, such as *para*-methoxybenzyl chloride under the *aegis* of cesium fluoride and tetrabutyl ammonium bromide (**6**).

Scheme 2. Borinic acid catalysis to regioselectively protect alcohol functionalities.

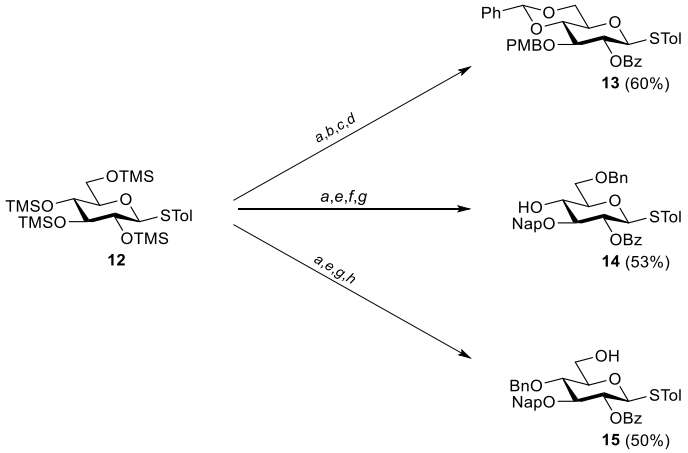


Reagents and conditions: a) **8**; b) BnBr, Ag_2O, MeCN, 40°C, 48h (94%); c) BzCl, $i Pr_2NEt$, MeCN (92%).

Although the use of tin ketals, in stoichiometric and catalytic amounts, represents a very powerful means to discriminate alcohol functionalities, it requires the use of toxic tin species. To circumvent this drawback Taylor and co-workers have introduced borinic acid catalysis to regioselectively protect glycosyl polyols.[11,12] α-*O*-methyl-fucopyranoside **7** can be regioselective alkylated or acylated using a catalytic amount of diphenylborinic ethylamine ester **8** and benzylbromide or benzoylchloride (Scheme 2). The reaction proceeds *via* borinate intermediate **9** that reacts in a highly regioselective manner to protect the equatorial alcohol at C3. (**10** and **11**, respectively)

To streamline the introduction of protecting groups, the groups Hung[13–16] and Beau[17–19] have devised a strategy to provide fully orthogonal protected building blocks in a one-pot fashion. Key to the strategy is the transformation of all hydroxyl groups into trimethylsilyl (TMS) ethers, which renders the carbohydrate **12** well soluble in an organic solvent, such as dichloromethane, even at low temperature. As shown in Scheme 3, the next steps in Hung's strategy involve the selective TMSOTf mediated formation of a C4-C6-acetal, ensuing installation of a C2-C3 acetal and regioselective opening of the most reactive acetal (which is the acetal at C2-C3). This liberates the C2-O-TMS, which can be benzoylated to provide glucoside **13**. Regioselective, reductive opening of the C4-C6-acetal can then give access to either the C4 (**14**) or C6-alcohol (**15**). Using this strategy the one-pot generation of a large variety of building blocks has been reported.[13–16]

Scheme 3. One-pot protection of per-silylated thioglycoside to form different protected building blocks **13**-**15**.



Reagents and conditions: a) TMSOTf, PhCHO, DCM, -86°C; b) 4-MeOPhCHO, Et_3SiH, -86°C; c) TBAF; d) BzCl, Et_3N, 0°C to rt; e) 2-NapCHO, Et_3SiH, -86°C; f) Bz_2O, 0°C; g) 4M HCl/dioxane, $NaCHBH_3$, 0°C; h) BH_3/THF, 0°C.

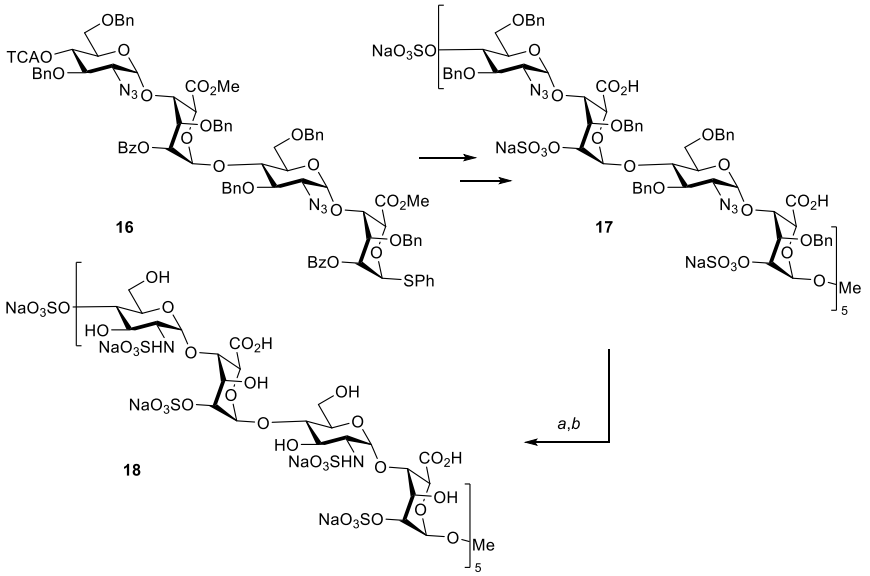
Strategies for an (oligo)saccharide synthesis campaign

During an (oligo)saccharide synthesis campaign different types of protecting groups can be discerned: those that will be removed during the assembly to allow for the manipulation of the unmasked alcohol: the temporary protecting groups; and those that are only to be removed at the very end of the assembly line: the permanent protecting groups. The latter groups should be stable to all reaction conditions used and be cleavable under mild conditions that do not jeopardize the integrity of the (oligo)saccharide target with all its functionalities. Benzyl ethers are by far the most used permanent protecting used to date, because they are stable to both acidic and basic conditions and can be removed using mild catalytic hydrogenation conditions.

An impressive recent example of a synthesis, featuring benzyl groups for permanent protection, is presented in Scheme 4. Protected heparin eicosasaccharide **17** was built up from tetrasaccharide building block **16**. In the penultimate step 40 benzyl ethers and ten azides were removed simultaneously to give the fully deprotected 20-mer **18** in 89% yield. In the final step the ten liberated amino groups were chemoselectively sulfated.[20]

It deserves mentioning that the last step(s) in the assembly of an oligosaccharide may be less trivial than they seem. Most oligosaccharide synthesis campaigns are based on a global deprotection event using a palladium catalyzed hydrogenation as the key step to simultaneously remove a multitude of functional groups (benzyl ethers, benzyloxycarbonyl groups, benzylidene acetals, azides).[21] Because many lipophilic groups are removed from the target compound to expose hydrophilic alcohols or amines, the polarity of the substrates increases tremendously leading to poorly soluble semi-protected intermediates, complicating the full deprotection of the target compounds. The presence of functional

Scheme 4. Block coupling to heparin-like 20-mers.

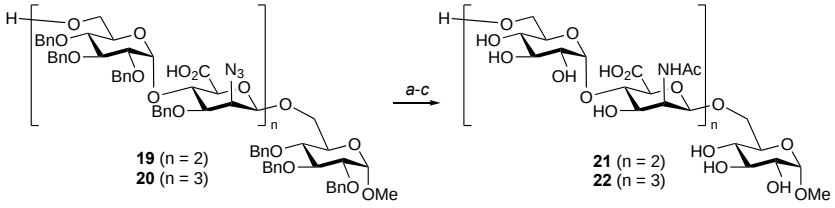


Reagents and conditions: a) $Pd(OH)_2/C$, $EtOH/H_2O$ (89%); b)SO_3•Pyridine, H_2O.

groups such as amines and thiols that can deactivate the palladium catalyst, renders the final deprotection step(s) even more complicated.

As an alternative to a catalytic hydrogenation, a dissolving metal (Birch) reduction can be employed. For these reductions it also holds that the changing polarity of the substrate during the reaction can be a complication. Although impressive global deprotection events have been described using a Birch reduction, unexpected side reaction may occur. For example, in the final deprotection of *Micrococcus luteus* teicuronic acid stretches, composed of alternating *N*-acetyl mannosaminuronic acid and glucose residues, the unexpected cleavage of glycosidic linkages was encounterd leading to fragmentation of the oligosaccharides (see Scheme 5).[22] The cleavage occurred chemoselectively at the anomeric center of the mannosaminuronic acid residues, indicating that the cleavage was not the result of a β-elimination caused by the basic conditions of the Birch reduction.

Scheme 5. Birch reduction of teicuronic acid oligosaccharides in which cleavage of the mannosaminuronic acid linkages was encoutered.

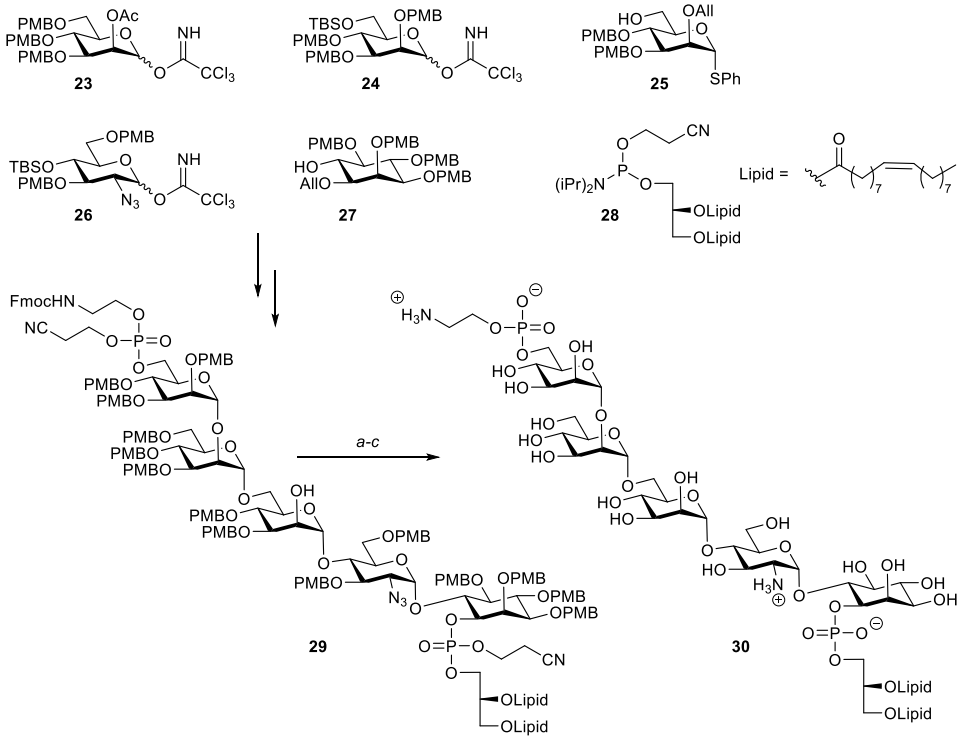


Reagents and conditions: a) Na (s), liquid NH_3, THF, -60°C; b) HPLC-purification; c) Ac_2O, $NaHCO_3$, THF/H_2O (**21**:35% over 2 steps; **22**: 14% over 2 steps)

Many types of protecting groups have been employed as temporary groups, including silyl ethers, (substituted) acetyl esters, such as the levulinoyl, and chloroacetyl esters, carbamates, carbonates, allyl and substituted benzyl ethers.

The presence of double bonds precludes the use of catalytic hydrogenation for global deprotection of a target compound and therefore represents a synthetic challenge. Guo and co-workers have reported on the synthesis of a complex glycosyl phosphatidyl inositol (GPI) anchor, bearing unsaturated lipids.[23] They selected PMB ethers to mask the hydroxyl functions throughout the synthesis (scheme 6). With monosaccharides **23**, **24** and **25**, a trisaccharide was assembled, which was coupled to a disaccharide (constructed from **26**, **27** and **28**), to form pentasaccharide **29**. Although PMB groups can be labile under Lewis acidic glycosyation conditions, no side reactions due to PMB cleavage occurred during the glycosylations. Deprotection commences with the reduction of the azide with zinc in acetic acid, followed by base catalyzed removal of the Fmoc and cyanoethyl groups. The last step is the removal of all PMB groups using trifluoacetic acid. All PMB groups are removed without affecting the glycosidic linkages or the unsaturated lipid bearing phosphatidyl inositol.

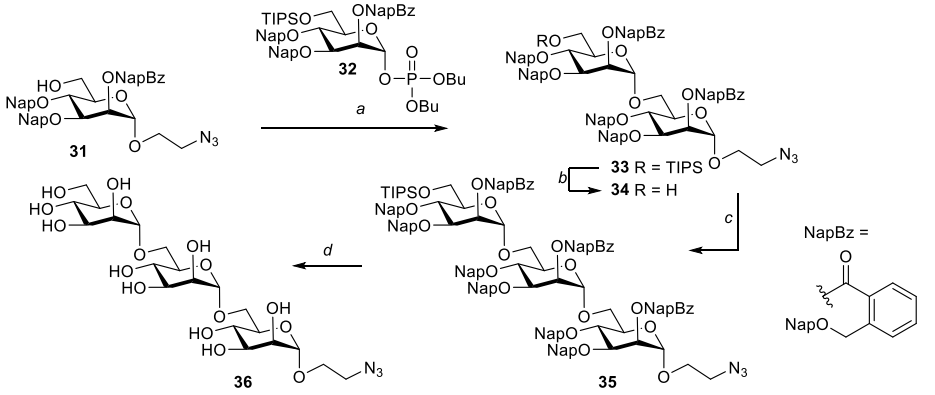
Scheme 6. GPI synthesis using a global deprotection strategy based on PMB protecting groups.



Reagents and conditions: a) Zn, AcOH, CH_2Cl_2, 2h; b) DBU, DCM, 1h; c) DCM-TFA (9:1), 1h, 81% (three steps).

Recently Liu and co-workers described the use of TFA in toluene to remove substituted benzyl ethers for the global deprotection of oligosaccharides. They introduced PMB and 2-naphthylmethyl (Nap)-protected hydroxymethylbenzoates as acid labile ester protecting groups for the same purpose.[24] Elongation of the reducing end terminus mannoside **31** with dibutylphosphate donor **32** using stoichiometric amounts of TMSOTf provided dimer **33** (Scheme 7). Of note, under these Lewis acidic conditions all protecting groups remained unaffected. Removal of the temporary tri-*iso*-propyl silyl ether (**34**) and ensuing coupling with another copy of **32** provided the target trisaccharide **35**. Global deprotection of this molecule by treatment with TFA in toluene gave the deprotected trisaccharide **36** in quantitative yield. Although it remains to be seen how general this methodology is, it can present a powerful alternative to the use of heterogeneous metal catalyzed hydrogenolysis commonly used.

Scheme7. Global deprotection using TFA in toluene.



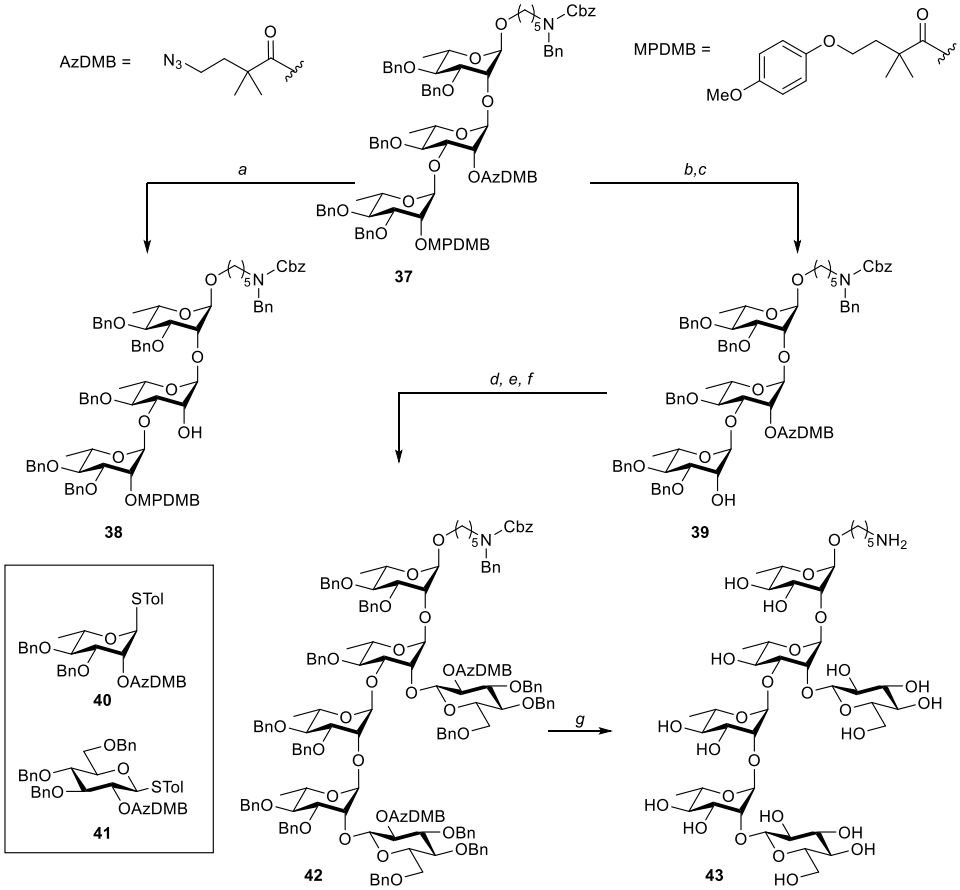
Reagents and conditions: a) TMSOTf, DCM, -20°C (97%); b) HF/Pyridine, pyridine (91%); c) 28, TMSOTf, DCM, -20°C (94%); d) TFA/toluene (10:1, v/v), 0°C to rt (100%).

Permanent acyl protecting groups that are often employed (for example to stereoselectively introduce glycosidic linkages, *vide infra*) are the pivaloyl and benzoyl esters. The former is more stable than the latter, representing an advantage during synthetic manipulations required during the assembly of the target compound. On the other hand its stability necessitates harsh deprotection conditions that may affect other functionalities and linkages in the final product.

In this context, two new pivaloyl-type groups have been introduced, that combine the advantages of the parent pivaloyl ester, *i.e.* stability and suppression of orthoester formation during glycosylation reactions, with ease of cleavage (see Scheme 8).[25] These two pivaloyl-based groups bear a reactive functionality appended to the pivaloyl core. The 2,2-dimethyl-4-(4-methoxy-phenoxy)-butanoate ester (MPDMB) and the 2,2-dimethyl-4-azido butanoate (AzDMB) are pivaloyl analogues that can be removed under either mild oxidative (**39**) or reductive (**38**) conditions, respectively. Glycosylation of AzDMB bearing donor **40** with **39** results in a tetrasaccharide, which, after remomval of the two AzDMB groups, can be decorated with glucose moieties. An added advantage of the latter protecting group is found

in the fact that it can be removed simultaneously with the commonly used permanent benzyl protecting groups using catalytic hydrogenation conditions. Applying hydrogenation conditions on hexasaccharide **42** results in fully deprotected compound **43**.

Scheme 8. Selective deprotection of AzDMB and MPDMB pivaloyl analogues



Reagents and conditions: a) PMe_3, THF/H_2O, then KOH (aq), rt, 24h (78%); b) CAN, 0°C, acetone/H_2O, 40 min; c) DBU, rt, MeOH, 1h (80% over 2 steps); d) **40**, NIS, TMSOTf, -40°C, DCM (88%); e) PMe_3, THF/H_2O, then KOH (aq), rt, 24h (77%); f) **41**, NIS, TMSOTf, 0°C, DCM (69%); g) i. H_2, $Pd(OH)_2/C$, $THF/H_2O/tBuOH$; ii. H_2, $Pd(OH)_2/C$, HCl, H_2O, then Et_3N (excess) (75% 2 steps).

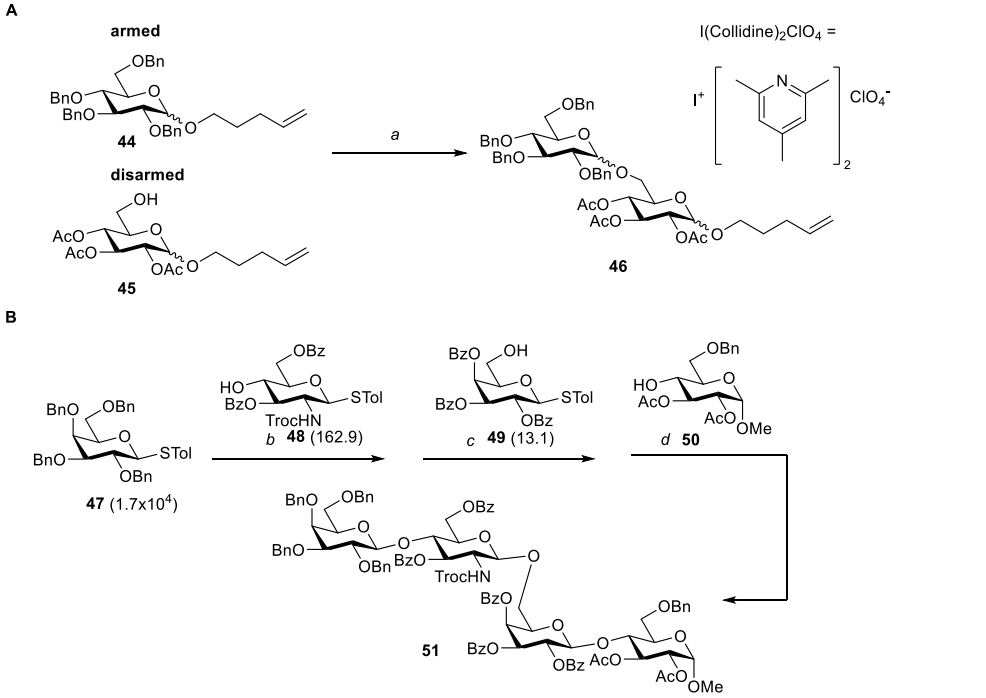
Reactivity and stereochemistry

Protecting groups have a major impact on the reactivity of a carbohydrate synthon. Electron-withdrawing protecting groups, such as acyl groups, deactivate a glycosyl donor, because the electron-withdrawing effect of these groups destabilizes the build up of (partial) positive charge at the anomeric center of the donor upon activation. This effect has been elegantly exploited and conceptualized by Fraser-Reid who introduced the armed-disarmed concept: benzyl ether carrying donors (so-called "armed" donors **44**) can be activated in the presence of acylated ones (termed "disarmed" donors **45**) allowing for the selective condensation of

the armed donor with the disarmed building block (See Scheme 9A).[26] Since the introduction of this seminal concept, insight into glycosyl donor reactivity has tremendously increased and it is now clear that, besides the nature of the protecting groups, the configuration and conformation of the donor glycoside, the orientation of the leaving group and the exact position of the protecting groups, all influence the reactivity of a donor building block.[27] The groups of Ley and Wong have developed reactivity scales, quantifying the relative reactivity of thioglycosides, setting the stage for effective one-pot assembly procedures involving multiple sequential glycosylation steps.[28,29]

The one-pot synthesis of tetrasaccharide **51** illustrates the use of relative reactivity values (RRVs) in oligosaccharide synthesis (Scheme 9B). The RRV values as determined by Wong and co-workers have been established with respect to the reactivity of tolyl 2,3,4,6-tetra-*O*-acetyl-1-thio-α-mannopyranoside (RRV = 1). The high RRV of thioglycoside **47** compared to thioglycoside **48** allows for the selective coupling of **47** to acceptor **48** in an NIS/TfOH mediated glycosylation reaction. The obtained disaccharide donor is then treated with thioglycoside **49** and an additional amount of NIS to form a trisaccharide. Tetrasaccharide **51** is obtained after addition of acceptor **50** and a third batch of NIS to the reaction mixture. The synthesis of this tetrasaccharide demonstrates the sophistication of the reactivity scales and their usefulness in the one-pot synthesis of oligosaccharides.

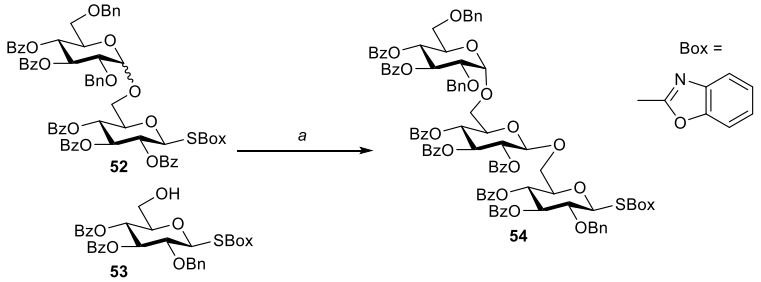
Scheme 9. A) The armed-disarmed concept using n-pentenyl glycosides as conceptualized by Fraser-Reid. B) Exploiting donor reactivity in a one-pot reaction sequence.



Reagents and conditions: a) $I(Collidine)_2ClO_4$, DCM (62%); a) TfOH, NIS, -25°C, DCM; b) NIS, 0°C, DCM; c) NIS, DCM (40%).

The impact of protecting groups on the stereochemical outcome of a glycosylation reaction is best illustrated by the anchimeric assistance that neighboring groups can provide during a glycosylation reaction. Glycosyl donors equipped with a C2-*O* or *N*-acyl group in general provide 1,2-*trans* products with great fidelity (exceptions occur due to stereochemical mismatch situations, or overruling steric requirements).[30] This can be explained by the formation of an intermediate dioxolenium ion that is formed by attack of the C2-acyl group on the (developing) oxocarbenium ion. The dioxolenium ion bridge effectively shields one side of the carbohydrate ring, allowing the nucleophile only to approach from the opposite direction. Even though acyl groups are inherently more electronwithdrawing than for example benzyl ethers, their presence can make a glycosyl donor more reactive because it can provide 'active' anchimeric assistance (scheme 10). For example, disaccharide **52**, bearing three 'disarming' benzoyl groups at C2, C3 and C4 could be selectively activated over building block **53**, carrying an arming benzyl group at C2, next to two disarming benzoates at C3 and C4, with the mild activator $Cu(OTf)_2$.[31] Because of the limited reactivity of the activator, expulsion of the S-box aglycons only occurred when anchimeric assistance was provided by the neighboring C2-benzoate.[32]

Scheme 10. Neighboring group participation assisted selective activation.



Reagents and conditions: a) $Cu(OTf)_2$, TfOH, DCM (70%).

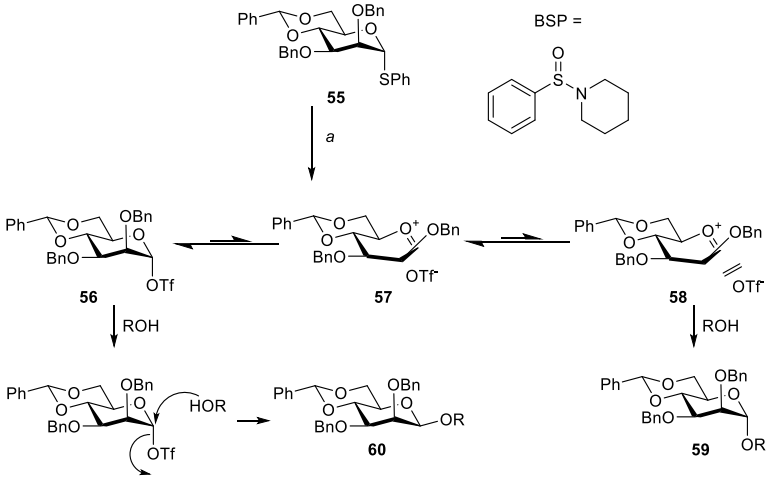
It has been proposed that acyl groups at positions other than C2 can also provide neighboring group participation thereby influencing the stereochemical outcome of a glycosylation reaction.[33,34] There are various examples describing the beneficial effect of C-6-acyl groups for the stereoselective synthesis of glucosyl, galactosyl and mannosyl donors. Similarly, empirical evidence points to possible participation of ester groups at C4 of galactosyl and fucosyl donors. At the same time, studies with model compounds failed to convincingly demonstrate long-range participation leaving the subject open to further debate and showing that more sophisiticated models and deeper insights into the effect of functional groups in glycosylation reactions are needed.

The stereoselective synthesis of 1,2-*cis*- and 2-deoxy glycosidic linkages is considerably more challenging than the construction of 1,2-*trans* bonds, but much progress has been made over the years in the stereoselective syntheses of these difficult linkages.[35–38] In all these syntheses protecting groups play a key role in determining the overall shape and reactivity of the coupling partners. The overall reactivity of a glycosyl donor is decisive for the

stereochemical outcome of a glycosylation reaction as it determines the stability of reactive intermediates that are formed upon activation. These include both covalent species[39,40], such as anomeric triflates, as well as oxocarbenium ion intermediates, be it solvent separated or as part of a contact (or close) ion pair.[41–43] The equilibrium between these species, their stability and the ease with which these are attached by an incoming nucleophile determine the overall stereochemical outcome of a glycosylation reaction. Because it is beyond the scope of this introductory Chapter to provide an all-encompassing overview of these stereodirecting protecting group effects, only one -possibly the most prominent, but for sure the best studied one- example will be described here. Mannosyl donors, equipped with a benzylidene acetal spanning C4 and C6 can be used to effectively provide 1,2-*cis* mannosides. Crich and co-workers, who pioneered the method[44], have rationalized this stereochemical outcome through the intermediacy of the covalent α-triflate as main product forming intermediate (Scheme 11).[45] The benzylidene acetal serves to limit the conformational freedom of the mannosyl ring, making it more difficult to adopt a flattened structure, which is required to accommodate the positive charge in an oxocarbenium ion intermediate. S_N2-type substitution on the anomeric triflate leads to the observed β-selectivity. This methodology has been applied in many different syntheses of complex (bacterial) oligosaccharides and glycoconjugates, including the assembly of β-rhamnoside[36] and *cis*-linked heptose containing oligomers[35]. To further investigate the origin of the striking selectivity, Crich and co-workers have conducted a number of seminal studies, including the determination of primary[46] and secondary[45] kinetic isotope effects and the development of "cation clock" methodology[47,48] to discriminate between associative and dissociative product forming pathways. Primary kinetic isotope effects indicated that the β-linked products are formed through an associative pathway, where the α-products in these reactions resulted from an attack of an oxocarbenium ion intermediate.[49] Secondary isotope effects measured in the glycosylation of between a benzylidene mannose donor and a methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside acceptor revealed that substantial oxocarbenium ion character developed in the transition state leading to the β-linked disaccharide, indicative of an S_N2-reaction with an exploded transition state. In contrast, *C*-glycosylation reactions of benzylidene mannose donors proceed through a dissociative pathway presumably via a $B_{2,5}$-oxocarbenium ion like intermediate.[50] Overall the benzylidene mannose system has not only developed to become the most direct and effective way to construct 1,2-*cis*-mannosidic linkages, it has also proven to be a rich breeding ground for the development of physical organic chemistry methods to investigate the principles underlying glycosylation stereochemistry.

Many different covalent reactive species have been reported and characterized by spectroscopic techniques such as NMR.[40] However, in the majority of cases, the stereochemical outcome of glycosylation reactions involving these species, can not be simply traced back to the covalent reactive intermediates. Clearly other reactive intermediates have to be taken into account and more insight is needed how protecting and functional groups control the stability and reactivity of the different reactive intermediates.

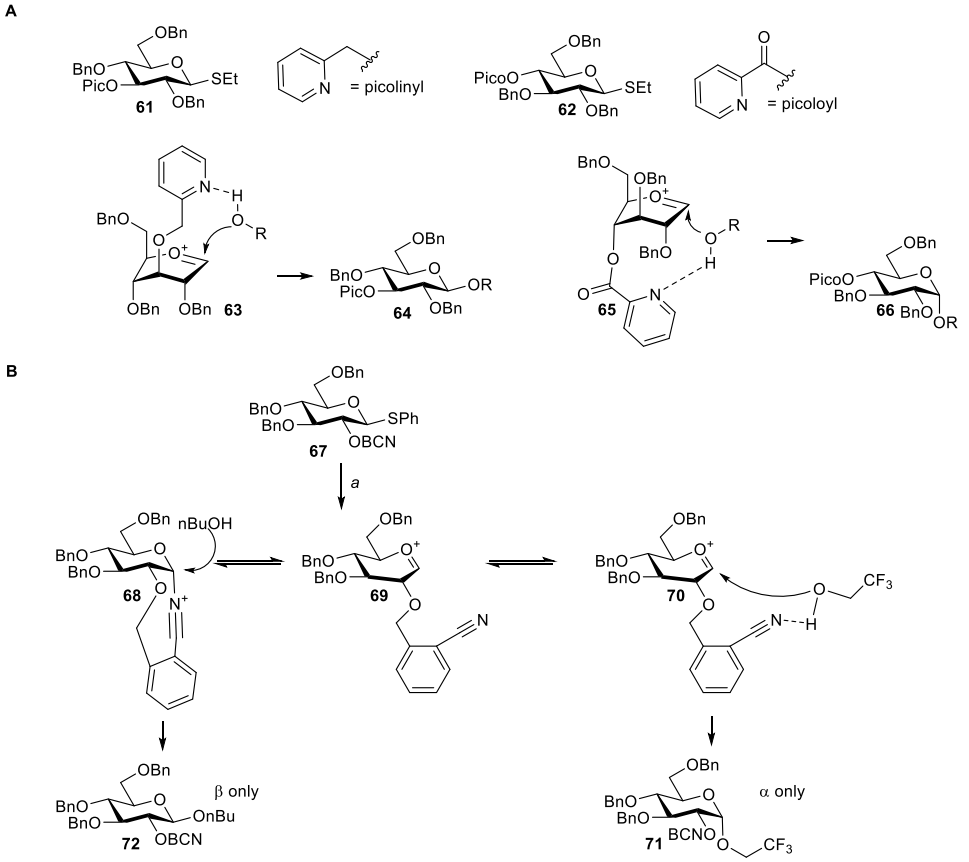
Scheme 11. Reaction mechanism manifold to account for the stereoselectivity in glycosylation reactions of benzylidene mannose donors.



Reagents and conditions: a) BSP, Tf_2O, -80°C, DCM.

Recently several reports have appeared that make use of hydrogen bonding between donor and acceptor to direct glycosylation stereochemistry (Scheme 12). Demchenko and co-workers have used picolinyl ethers (**61**) and picolinoyl esters (**62**) to direct the incoming nucleophile to the activated donor species with excellent facial selectivity.[51,52] Hoang and Liu have described that glucosyl (**67**) and galactosyl donors bearing an *O*-cyanobenzyl ether at C2 can provide either α- or β-linked products, depending on the reactivity of the acceptor and the solvent system used.[53] Reactive acceptors and the use of toluene lead to β-products, where unreactive alcohols and diethyl ether provide the opposite anomers. To account for the latter stereochemistry the authors speculated that a hydrogen bond between the cyano group and the incoming acceptor could guide the nucleophile to the α-face of the donor molecule. How these new hydrogen bonding protecting groups behave in the context of complex oligosaccharide synthesis will have to be shown in the near future.

Scheme 12. A) Hydrogen bonding accepter delivery by picolinyl ether and picoloyl ester; B) Hydrogen bonding acceptor delivery by cyanobenzyl ethers.



Reagents and conditions: a) Ph_2SO, Tf_2O, -80°C, DCM.

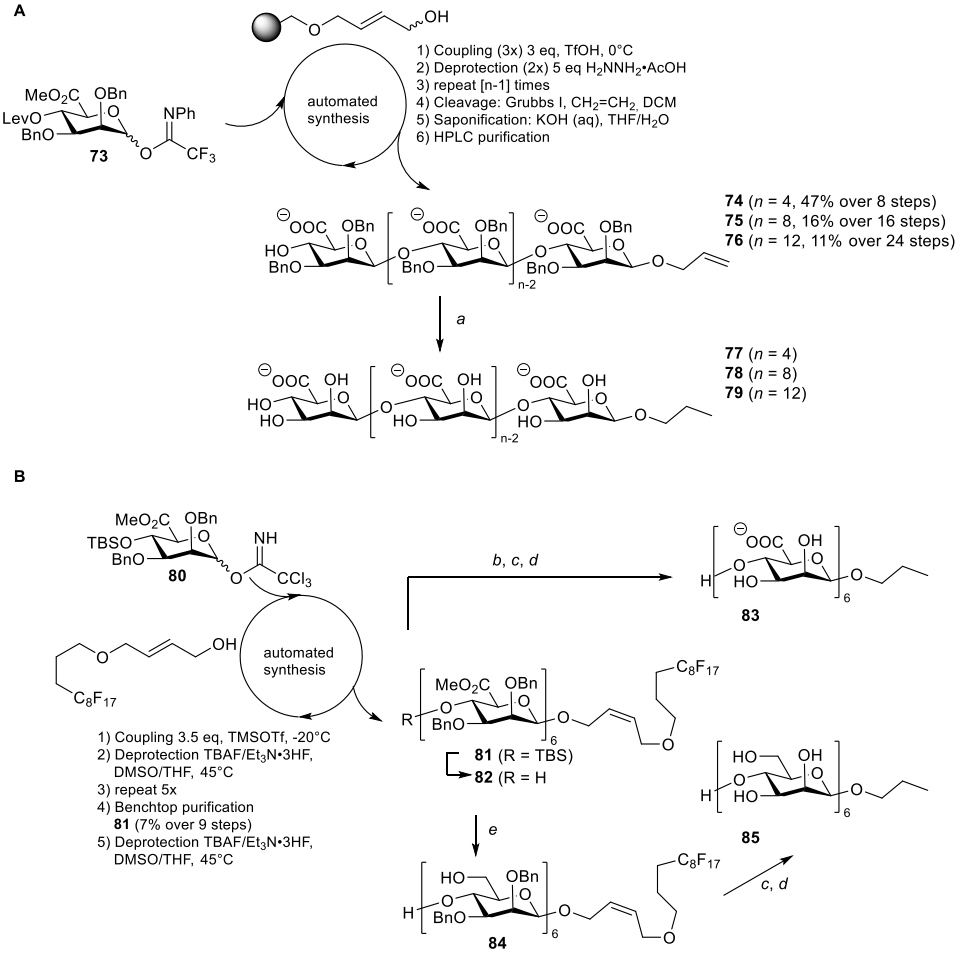
Protecting groups in automated synthesis

To streamline oligosaccharide assembly much effort has been devoted to the development of automated synthesis techniques.[54–56] The automated solid phase synthesis of peptides and nucleic acids is one of the major contributions of synthetic organic chemistry to the life sciences. However, solid phase automated carbohydrate chemistry is significantly more challenging than the assembly of the other two biopolymers, because one has to deal with all the different functionalities present on the carbohydrate ring and the union of two carbohydrate building blocks involves the creation of a new stereocenter. Different strategies have been developed to automate oligosaccharide assembly based on either solution phase synthesis or solid phase techniques and automated solid phase synthesizers are now commercially available. Both techniques are based on the attachment of the growing oligosaccharide to a support. For the solution phase approach a light fluorous tag is used[57], where the solid phase methodology commonly employs a polystyrene type resin.[58] The support makes it possible to separate the target compound from the reagents used by filtration

or a relatively simple fluorous solid phase extraction step, thus allowing the use of excess reagents to drive reactions to completion. Other intermediate purification steps are not performed. Overall this makes the process very efficient, but it also puts stringent constraints on the protecting groups used in the assembly. The use of excess reagent makes the reaction conditions employed harsher than the conditions that would be used in an equivalent solution phase step. At the same time cleavage of the temporary protecting groups has to proceed effectively because the build up of deletion sequences leads to complex product mixtures necessitating a difficult, if not impossible, purification at the end of the assembly. Scheme 13 depicts the assembly of two oligomannuronic acid sequences through automated solid phase[59] and automated fluorous phase synthesis[60]. Both approaches rely on the use of mannuronic acid donor synthons, because these enable the stereoselective formation of the 1,2-*cis* mannosidic linkage with great fidelity.[61–63] Obviously the generation of epimeric mixtures is highly undesirable because it will generate very complex mixtures at the end of the assembly. Parallels between both approaches are the use of a double bond based linker system (cleavable by cross metathesis) and the use of imidate donors. Using the solid phase approach, mannuronic acid tetramer **74**, octamer **75** and dodecamer **76** were assembled (in 47%, 16% and 11% over 8, 16 and 24 steps, respectively), where the latter approach was used to create hexasaccharide **81** (7% over 9 steps).

Two relevant protecting group related issues deserve mentioning here. Firstly, the methyl ester moieties can be used as precursors for the corresponding alcohol functionalities. It was shown that hexamannuronate **82** could be transformed into protected hexamannoside **84** through DIBAL reduction of the methyl esters in 82% yield. The second issue to note is that during the solid phase assembly of the oligomers deletion sequences were generated because of incomplete glycosylation steps (efficiency ~92% per step, no capping step was included). Saponification of the methyl esters allowed for the easy HPLC separation of the target stretches from their shorter counterparts. In designing automated oligosaccharide

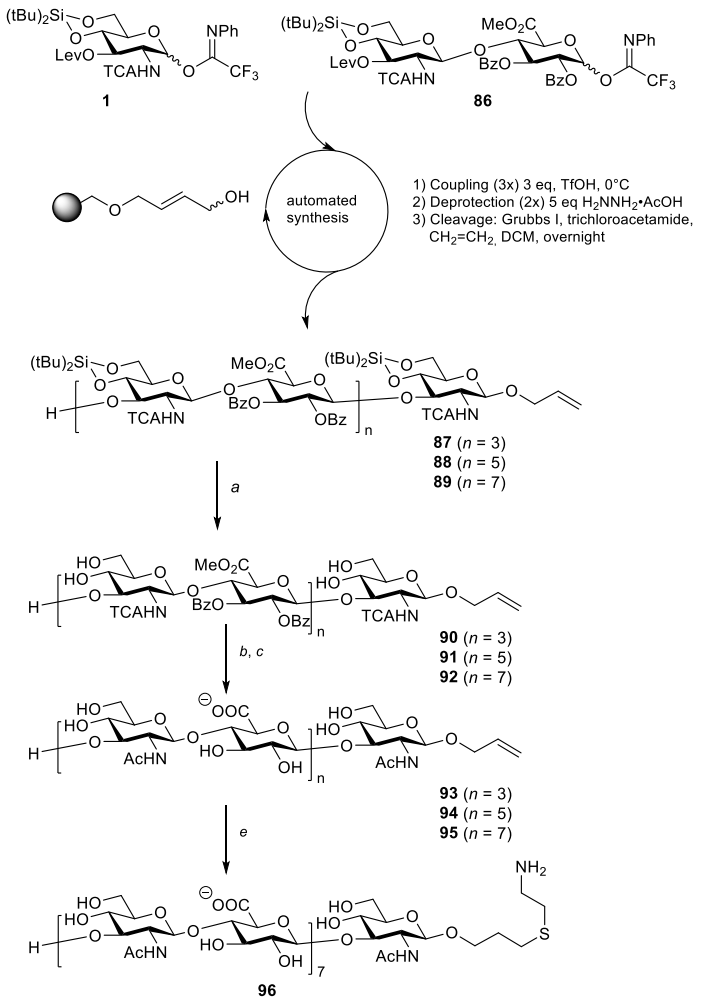
Scheme 13. Automated synthesis of oligomannuronic acids. A) Solid phase approach. B) Fluorous phase approach.



Reagents and conditions: a) Pd/C, Pd black, H_2, THF/H_2O/tBuOH (**77**: 99%, **78**: 99%, **79**: 95%); b) Grubbs II, CH_2=CH_2, DCM; c) KOH (aq), THF/H_2O; d) Pd/C, Pd black, H_2, MeOH/AcOH (**83**: 61% over 3 steps, **85**: 73% over 2 steps); e) DIBAL-H, 0°C, DCM/toluene (83%).

assemblies it can be worthwhile to implement the possibility to purify semi-protected intermediates before the ultimate deprotection event, because compounds featuring both hydrophilic and lipophilic groups allow for effective HPLC procedures, where fully protected compound can be too lipophilic and fully deprotected compound too hydrophilic to efficiently purify. The latter strategy has also been applied in the automated solid phase assembly of a set of hyaluronic acid (HA) oligomers (Scheme 14).[64]

Scheme 14. Automated solid phase assembly of hyaluronic acid oligosaccharides.



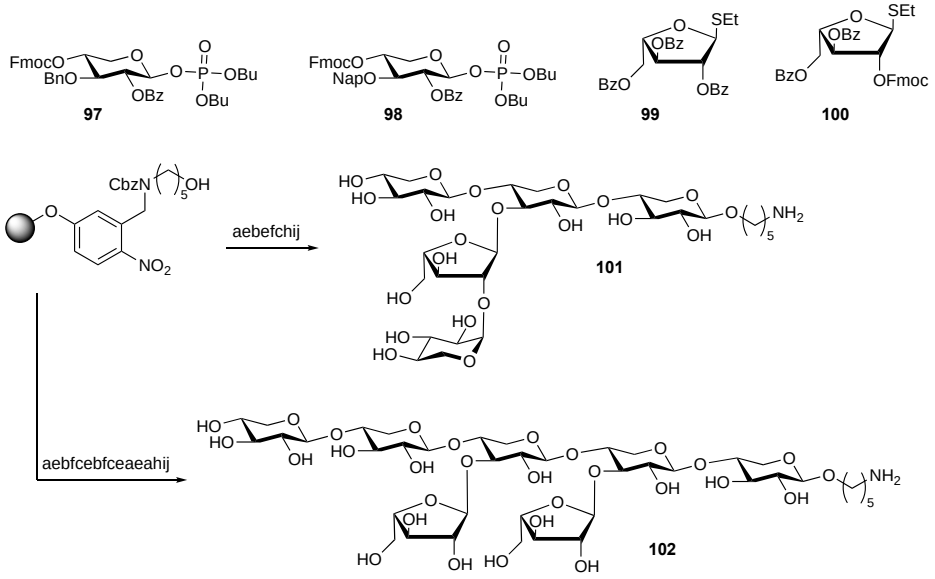
Reagents and conditions: a) Et_3N•3HF, THF (**90** 26% over 10 steps, **91**: 32% over 14 steps, **92**: 18% over 18 steps); b) KOH (aq), THF/H_2O; c) Ac_2O, $NaHCO_3$, H_2O (**93**: 90% over 2 steps, **94**: 70% over 2 steps, **95**: 69% over 2 steps); e) Cysteamine•HCl, *hv*, H_2O, (92%).

HA-7-mer, 11-mer and 15-mer were generated on a butanediol functionalized polystyrene resin using monomeric building block **1** (Scheme 1) and disaccharide **86** (Scheme 14). After cleavage of the resin by cross metathesis the fully protected oligomers **87-89** proved to be too lipophilic for purification, but removal of the silylidene ketals liberated two free alcohol groups per dimer repeat providing compounds **90-92** that were readily purified by HPLC. Of note, the silylidene group was employed in these syntheses, because the corresponding benzylidene acetal proved to be too labile to withstand the acidic glycosylation conditions.[6] Global deprotection of the HA fragments was achieved by the saponification of all methyl and benzoyl esters and the trichloroacetyl amides. Selective *N*-acetylation gave the final

compounds **93-95**. Because the protecting group strategy did not require the use of hydrogenation conditions, the reducing end anomeric allyl functionality could be retained. This in turn allowed the installment of a ligation handle through thiol-ene chemistry to give compound **96**.[65]

Scheme 15 depicts the assembly of two plant arabinoxylans.[66] These syntheses nicely illustrate the use of the 9-fluorenylmethoxycarbonyl (Fmoc)-Nap couple as a set of orthogonal temporary protecting groups and the use of an UV-cleavable linker system. The former protecting group was used as a base labile protecting group to mask the hydroxyl groups used for the elongation of the xylose backbone. Of note, cleavage of the Fmoc group generates a fulvene, the concentration of which can be measured spectroscopically providing an effective method to monitor the efficiency of the coupling events on-line.

Scheme 15. Automated solid phase assembly of plant cell wall arabinoxylan fragments



Reagents and conditions: a) donor **97**, TMSOTf, DCM, -35°C to -15°C; b) donor **98**, TMSOTf, DCM, -35°C to -15°C; c) donor **99**, NIS/TfOH, DCM/dioxane, -40°C to -20°C; d) donor **100**, NIS/TfOH, DCM/dioxane, -40°C to -20°C; e) 20% Et_3N in DMF, 25°C; f) 0.1M DDQ in DCE/MeOH/H_2O (64:16:1); g) Ac_2O, pyridine, 25°C; h) *hv* (305 nm); i) NaOMe, THF/MeOH; j) H_2, Pd/C, EtOAc/MeOH/H_2O/AcOH (**101**: 42%, **102**: 21%).

The Nap-ether was used at positions on the xylose building blocks where arabinofuranosyl branches were to be introduced. Cleavage of the Nap ethers was affected under oxidative conditions (DDQ) using a DCE/MeOH/H_2O solvent system. Although it is notable that aqueous solvent systems can be employed in combination with the polystyrene resin, the fact that the cleavage of the Nap ethers required seven repetitive reaction cycles illustrates the room for possible improvement. Cleavage of the arabinoxylan fragments from the solid support was affected by exposing the oligosaccharide-bearing resin to 305 nm UV light in a tailor made continuous flow reactor.[67]

Summary and Outlook

Protecting group chemistry can make or break any (oligo)saccharide synthesis effort. Much progress has been made over the years to understand and exploit reactivity differences between the functional groups on a carbohydrate and many efficient protecting group strategies and schemes are now available. Even though these schemes may present multistep synthesis routes, they often involve optimized chemistry, assuring reliable synthetic outcomes. Nonetheless there is a demand for ever-shorter synthetic routes and the development of one-pot operations to introduce multiple protecting groups is therefore of high importance.

The demand for more efficiency can also be met by the development of better and more effective protecting groups. For instance, novel protecting groups and/or cleavage conditions are required to mask amines on carbohydrate rings, especially functionalities that do not provide anchimeric assistance in glycosylation reactions. The only group that is now available for this purpose is the azide and in cases where different orthogonally functionalized amine groups are required the availability of more non-participating amine functionalities would be a valuable asset.[68–71] In general, protecting groups that are more robust during a solution and/or solid phase synthesis campaign and/or can be removed more easily at the end of these syntheses are needed.

Another important issue is represented by the limited number of possible optimizations for deprotection procedures by the minimal amount of the fully protected target oligosaccharide that is usually available. Insight into why some global deprotection events proceed uneventfully, where others are accompanied by side reactions leading to complex reaction mixtures and difficult purifications would be very valuable indeed. Innovative chromatography procedures to purify the highly polar target compounds, often lacking (UV)-chromophores for detection, would also represent a great addition to the oligosaccharide synthesis toolbox.

Outline of the thesis

This **Chapter** has provided a brief overview of recent developments in the area of protecting group manipulations in carbohydrate chemistry. **Chapter** 2 describes a new method to cleave substituted benzyl ethers (PMB and Nap) using catalytic amounts of HCl in DCM/hexafluoro-*iso*-propanol (HFIP).[72] These conditions were found to effectively cleave both PMB and Nap ethers while leaving other acid labile functionalities (primary TBDPS ethers, glycosidic linkages) intact. In addition, the homogeneous conditions are amendable to a solid phase setting[73,74] and can therefore provide a more effective use of Nap ethers in solid phase oligosaccharide synthesis. The method described in Chapter 2 was successfully applied in the building block synthesis in Chapter 3. In **Chapter** 3, the new cyanopivaloyl (PivCN) group is introduced, which, in combination with other Piv-type groups should open possibilities in the synthesis of carbohydrate fragments. The PivCN group, bearing a cyano group on one of the methyl groups, possesses all the characteristics of the conventional Piv group, with the additional advantage that it can be removed by hydrogenation. The newly

developed group was used in the synthesis of two bacterial rhamnan structures. The usefulness of the PivCN group was demonstrated by the one step deprotecting leading to the target molecules. The value of the PivCN group is shown in **Chapter** 4, where it is incorporated in a disaccharide donor for automated carbohydrate synthesis. Two donors are synthesized and used on a new automated system. The donor with the PivCN group is applied in the synthesis of a library of rhamnose fragments, corresponding to the Group A *Streptococcus* bacterial backbone. An additional advantage was found, as a catalytic amount of base was sufficient to deprotect all PivCN groups. The automated synthesis method resulted in multimilligram quantities of biologically relevant rhamnose fragments, up to 16 monosaccharides. The first part of **Chapter** 5 describes the building block synthesis towards a set of disaccharides leading to a well-defined sulfated mannuronic acid molecule. The deprotection of the fragments was optimized, applying the method developed in Chapter 2, resulting in a selectively sulfated, deprotected mannuronic acid disaccharide. In the second part of Chapter 5, modified donors were synthesized and used in the construction of the target fragments. It was found that the designed molecules show great difference in reactivity depending on their conformation. This leads towards the synthesis of a tetrasaccharide donor to construct a sulfated mannuronic acid tetrasaccharide. **Chapter** 6 summarizes the findings of this Thesis and future plans and outlines strategies.

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