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PhD IN CHEMICAL SCIENCES XXIII CYCLE

SYNTHESIS AND ELABORATION OF MONO- AND OLIGO-SACCHARIDES

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Portions of this work have been adapted from the following articles that were co-written by the author:

* Pastore, A.; Adinolfi, M.; Iadonisi A. *Eur. J. Org. Chem.* **2008**, 6206-6212.

** Iadonisi A.; Adinolfi, M.; Pastore, A. *Tetrahedron Letters* **2009**, *50*, 7051-7054.

*** Valerio S.; Pastore, A.; Adinolfi, M.; Iadonisi A. *J. Org. Chem.* **2008**, *73*, 4496-4503.

**** Pastore, A.; Adinolfi, M.; Iadonisi A.; Valerio S. *Eur. J. Org. Chem.* **2010**, *4*, 711-718.

**** Pastore, A.; Adinolfi, M.; Iadonisi A.; Valerio S. *Carbohydr. Res.* **2010**, *345*,1316-1323.

Chapter A

Introduction

General Introduction

Carbohydrates represent the third class of bio-informative macromolecules, together with nucleic acids and proteins. This concept has strongly emerged only recently, although sugars have already been considered for very long time as one of the most important class of bio-molecules, because of their essential role in metabolism and as important structural components of biological systems.[1]

The idea of carbohydrates, one of the most abundant macromolecules in nature, "just" as energy source or building block for cell walls, is pretty limiting.

Abundant and diverse glycans cover all the cells of all living organisms. Carbohydrate chains are prominent components at the surfaces of mammalian cells, occurring as *N*- and *O*-glycans on glycoproteins, glycosaminoglycan chains on proteoglycans, and oligosaccharides of glycolipids. Carbohydrate chains also occur on many secreted and extra cellular glycoproteins. Some carbohydrate sequences are widely distributed in different cell types, while others, such as the blood group antigens,[2] are genetically determined. Still others have a regulated expression at different stages of embryonic development and cellular differentiation.[3]

A very different portrait of sugars has been emerging due to new rising fields of research gathered under the very general name of glycoscience. The study of the structure-function relation of carbohydrates and of oligosaccharide chains of carbohydrate-decorated molecules (also known as glycoconjugates) evidenced that the saccharidic moieties are very often involved in cell communication, signaling and trafficking processes, playing key roles in immune response, viral replication, cell-cell adhesion, fertilisation, parasitic infection, cell growth and differentiation, and inflammation.[4] Cancer is another area where carbohydrates turn out to play a pivotal role, helping to transmit the signals that trigger unchecked cell growth.[5] Obviously the involvement of carbohydrates in so many crucial biological processes suggested their use in medicinal chemistry. Several carbohydrate-based drugs have been developed in several different fields.[6]

The multiplicity of signal trasduction processes involving specific oligosaccharide sequences put strongly in evidence the bio-informative nature of carbohydrates. But, in contrast to the two major classes of bio-informative macromolecules, in the case of sugars, scientists haven't cracked the code yet. The pivotal, but still not well understood, role of sugars in so many and

different cellular processes has been driving the scientific community to investigate the glycome -all the glycan molecules synthesized by an organism- in the same systematic way as for DNA and proteins. A new field of research has been opened named glycomics, in analogy with genomics and proteomics, with the aim of creating a cell-by-cell catalogue of glycan structures and glycosyltransferases involved in their bio-synthesis.

In 1958 F. Crick referred to the "central dogma" as a universally accepted rule for the direction of genetic information (DNA to mRNA, and mRNA to protein). Almost fifty years ago the central dogma ended with proteins, nowadays we should reconsider it, including the post-translational modifications of the proteins, terminating the cascade of the genetic information with glycans. Post-translational glycosylation of proteins is a non-template-driven synthesis, a glycan structure does not mimic the sequences of the proteins that produced it, this means that at the sugars point nature gives a new challenge to scientists: a code-break. The task of the glycoscientists is to decipher the "sweet-code". From this point of view, glycomics is far behind genomics and proteomics, not only because the youngest subject, but also for the great structural complexity carbohydrates exhibit. While DNA and proteins have essentially linear sequences, sugars branch; DNA has just four basic building blocks and proteins have 20, but sugars have more than 30. The number of all linear and branched isomers of an hexasaccharide is calculated to be over $1x10^{12}$. Because of this great structural diversity between carbohydrates and the others bioinformative molecules glyco-scientists have to face a completely different scenario, "the languages of both nucleic acids and proteins can be compared to the Western phonogram (alphabet); and that of glycans, to the Eastern ideogram (kanji)".[7]

Clearly, for unravelling the mysteries of sugars, elucidating their biological functions, pure oligosaccharides of defined structure are required in sufficient amounts for biophysical and biochemical studies. But these biomolecules are often found in nature in low concentrations and in microheterogeneous forms. Most glycoproteins are not uniform, but consist of various "glycoforms" differing in type, length, branching and terminal decoration of oligosaccharides, and number or site of glycosylation. The isolation of oligosaccharides in a pure form from natural sources is therefore extremely challenging, when at all possible.

Access to pure carbohydrates for biological studies relies on chemical or enzymatic synthesis. No amplification methods analogous to the polymerase chain reaction (PCR) for DNA are available for carbohydrates, nor a fully developed automated synthesis technology as in the case of oligopeptides and oligonucleotides. Recently automated[8] and computer-assisted[9] synthetic approaches have been developed to boost the raising field of glycomics. To date

these technologies are not yet diffused and the synthesis of target molecules is still mainly practised by chemical synthesis. Enzymatic or chemoenzymatic approaches are certainly promising, but of the vast array of glycosyltranferases involved in biosynthetic pathways of carbohydrates, only a small fraction has been overexpressed and few of these are commercially available.[10] Additionally, glycosyltranferases have narrow substrate specificities, being able to catalyse the formation of single types of glycosidic linkages. The extreme specificity exhibited by enzymes is the dream of every synthetic chemist, guaranteeing the desired glycosylation outcomes in terms of regio- and stereo-selectivity, without any previous chemical modification of the substrates. But, since every type of linkage requires a specific enzyme, the synthesis of target oligosaccharides *via* enzymatic catalysis is still expensive.

In conclusion, although lots of promising approaches for the synthesis of oligosaccharide have been emerging as the future, unfortunately we are still in the present and the chemical approach is still more reliable and cheap.

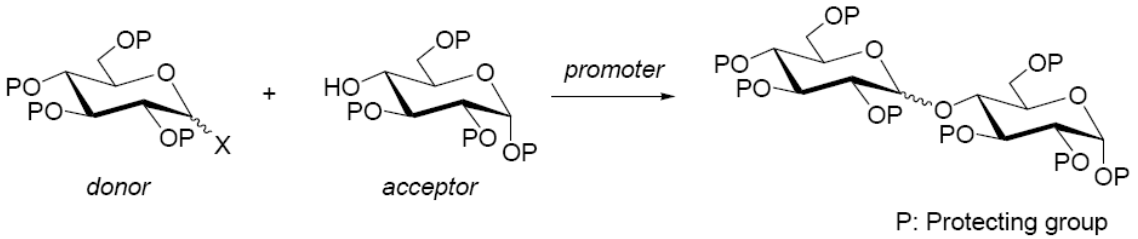
Glycosylation Reaction

The key step in oligosaccharide synthesis is the glycosylation reaction. The majority of glycosylations are performed by nucleophilic substitution reaction at the anomeric carbon (**Scheme 1**).

Scheme 1 Glycoside Synthesis by Nucleophilic Substitution at the Anomeric Carbon.

The glycosylating agent is called *glycosyl donor*. Generally it carries a leaving group at the anomeric position, that can be activated by an appropriate promoter. Several different glycosylation methods exist whose classification relies on the nature of the leaving groups. Every class of leaving groups requires specific promoting systems. Since a universal glycosylation method – generally applicable - hasn't been developed yet, several different methods are used and the choice depends on the specific reaction to be performed and on the planned synthetic strategy.

The nucleophile species is generally called *glycosyl acceptor* (**Scheme 2**).



Scheme 2 Glycosylation Reaction.

An ideal glycosylation reaction should be fast, high yielding, experimentally simple and completely regio- and stereo-selective.

The regioselectivity of glycosidation is generally controlled by the use of protection strategies. Both *glycosyl donor* and *acceptor* have several nuclephilic functionalities (mostly hydroxyl and amino groups) that are able to compete each other in the reaction with the glycosylating agent. The regioselective protection of all the potentially reactive moieties, but the one desired, allows the regiochemical outcome to be perfectly controlled.

Stereoselectivity is one of the major challenge in glycosylation reactions. The anomeric carbon on the glycosyl donor is a chiral centre, thus the nucleophilic attack on it generates two diasteroisomers that are referred to as anomers, designated α or β (**Figure 1**) according to the configurational relationship between the anomeric centre and a specified anomeric reference atom. The anomeric reference atom is the configurational atom of the parent. In the α anomer, the exocyclic oxygen atom at the anomeric centre is formally *cis*, in the Fischer projection, to the oxygen attached to the anomeric reference atom; in the β anomer these oxygen atoms are formally *trans*.

Figure 1 Anomeric Configurations of D-Glucopyranose.

Several approaches are used to achieve the desired stereoselectivity. The most effective method involves the use of neighboring group participation. Installation of an acyl protecting group at the donor *O*-2 generally results in excellent stereoselectivities for 1,2-*trans*-glycoside syntheses. When formation of 1,2-*cis*-glycosides is required, different strategies have to be used. Very common is the use of solvent effect: coordinating solvents such as ethers or

nitriles influence the stereochemical outcome of the reaction via the formation of intermediate carbocation-solvent adducts.

Further aspects have to be considered when approaching to the synthesis of structures longer than a disaccharide. The synthesis of oligosaccharides requires a careful planning of the protection strategy and differentiation between permanent and temporary protecting groups is crucial. Thus, the building blocks synthesis becomes more complicate and time consuming. Also the synthetic strategy is a matter of choice, often driven by the intrinsic nature of the target molecules. The oligosaccharide chain can be elongated following stepwise or convergent approaches, or more straightforwardly in one-pot fashion.

Insights in all these aspects of the glycosylation reactions are the object of next paragraphs and represent the topic of several excellent works.[11]

Glycosylation Methods

As anticipated in the previous paragraph, glycosylations are mostly carried out by nucleophilic substitution at the anomeric carbon of the glycosyl donor. Other approaches are used such as the nucleophilic substitution at the aglycone carbon or addition reactions to 1,2-unsaturated sugars.

Most of the methods belong to the first class, they are classified on the nature of the leaving group on the *glycosyl donor* and can be grouped according to the heteroatom attached to the anomeric center (**Figure 2**).

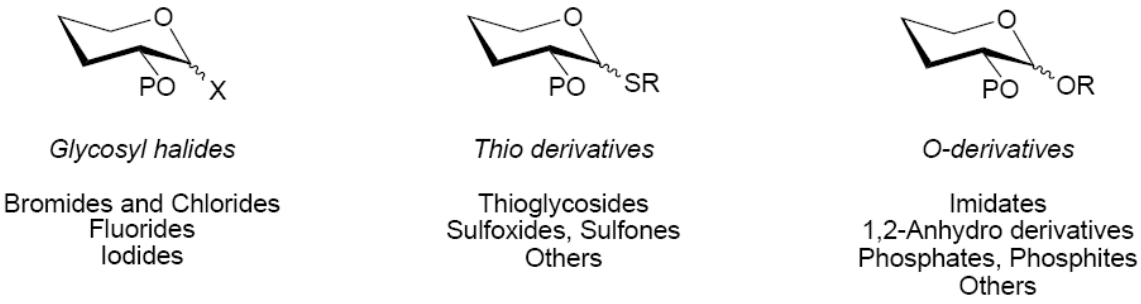


Figure 2 Types of Glycosyl Donors.

The departure of the leaving group is generally activated by the use of specific promoters. The choice of the glycosylation method implies the use of a specific promoter, which means that also the synthetic strategy has to be planned considering the compatibility of all protecting groups to the glycosylation conditions.

Glycosyl halides (especially bromides and chlorides) were the first type of glycosyl donors used for the synthesis of complex oligosaccharides. Glycosylations with glycosyl **bromides**

and chlorides in the presence of stoichiometric amounts of silver salts (Ag_2O, Ag_2CO_3), known as the Koenigs-Knorr reaction,[12] is one of the oldest glycosylation methods. Over the years a wide variety of promoters to activate glycosyl halides in glycosylation reactions have been developed. The heavy metal salts frequently used as promoters include silver salts of hydroxyl carboxylic acids, such as silver salicylate,[12b] silver imidazolate,[13] $Hg(CN)_2$ and $HgBr_2$,[14] HgO and $HgBr_2$,[15] HgI_2[16] and $CdCO_3$.[17] $AgClO_4$[18] and AgOTf [19] are the most efficient among the heavy metal promoters, and the latter is the most frequently used. Heterogeneous catalysts such as silver silicate,[20] silver zeolite[21] and silver silica-alumina[22] were developed particularly for the synthesis of otherwise hard to synthesize β-mannosidic and β-rhamnosidic linkages. Besides heavy metal salts, Lewis acids such as $SnCl_4$, $BF_3{\cdot}Et_2O$, [23] or $ZnCl_2$[24] have also been introduced as promoters.

The use of acid scavengers and drying agents in the reaction mixture in combination with the promoters is advantageous, and often necessary. Metal carbonates and oxides (Ag_2O, Ag_2CO_3, HgO, $CdCO_3$) not only do serve as promoters, but they also neutralize the acid released in the reaction.

It should be noted that glycosylation reactions of glycosyl halides bearing participating groups at *O*-2 in the presence of excess base lead to 1,2-orthoesters instead of glycosides. Therefore the amount of base in the reaction mixture should be limited.

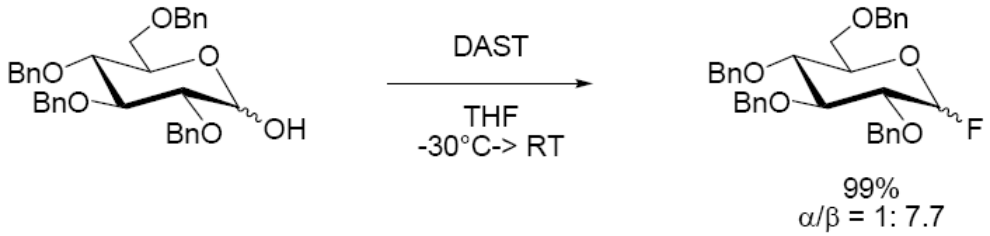
A different type of activation was introduced by Lemieux converting α-glycosyl bromides into glycosides *via* their highly reactive β-anomers.[25] In these cases, promoters such as Bu_4NBr or Et_4NBr in combination with DIPEA (Hünig's base) are used. These halide ion-catalyzed glycosylations give 1,2-*cis*-glycosides in excellent stereoselectivity. Unfortunately, the scope of the method is limited to reactive glycosyl halides and acceptors.

Glycosyl halides, for a long time pratically the only type of glycosyl donors, have now lost their predominant role in glycosylations. This is due to attempts to avoid the use of stoichiometric amounts of toxic, expensive and often light- and moisture-sensitive heavy metal salts for their activation. Additionally, glycosyl halides are moderately stable. In the synthesis of glycosyl halides with non trivial protecting group patterns, the introduction of the halide is usually the last step of the synthetic pathway. The chemical elaboration of the non-anomeric carbinols can be hardly performed without damaging the highly reactive halide at the anomeric position. Furthermore, purification of the halides from these reactions is often problematic.

Installation of the halogen at the anomeric centers is generally performed by treatment of 1-*O*-Ac-sugars with the desired hydrogen halide in acetic acid. Of course, this procedure is not

compatible with acid-labile protecting groups and several different approaches have been developed; however for the synthesis of peracetylated glycosyl halides this still represents one of the easiest and most reliable procedures.

Glycosyl fluorides are more stable than glycosyl bromides and chlorides, but this has an effect also on their reactivity. Infact they are too unreactive to be activated under standard Koenigs-Knorr conditions, and, for this reason, their use as glycosyl donors was explored relatively late. Their use was introduced in 1981 by Mukaiyama and coworkers,[26] and glycosyl fluorides are currently among the most frequently used glycosyl donors. Several methods for the preparation of glycosyl fluorides are known.[27] They are commonly synthesized by the reaction of a protected sugar with a free anomeric hydroxyl group with diethylaminosulfur trifluoride (DAST) (**Scheme 3**).[28]

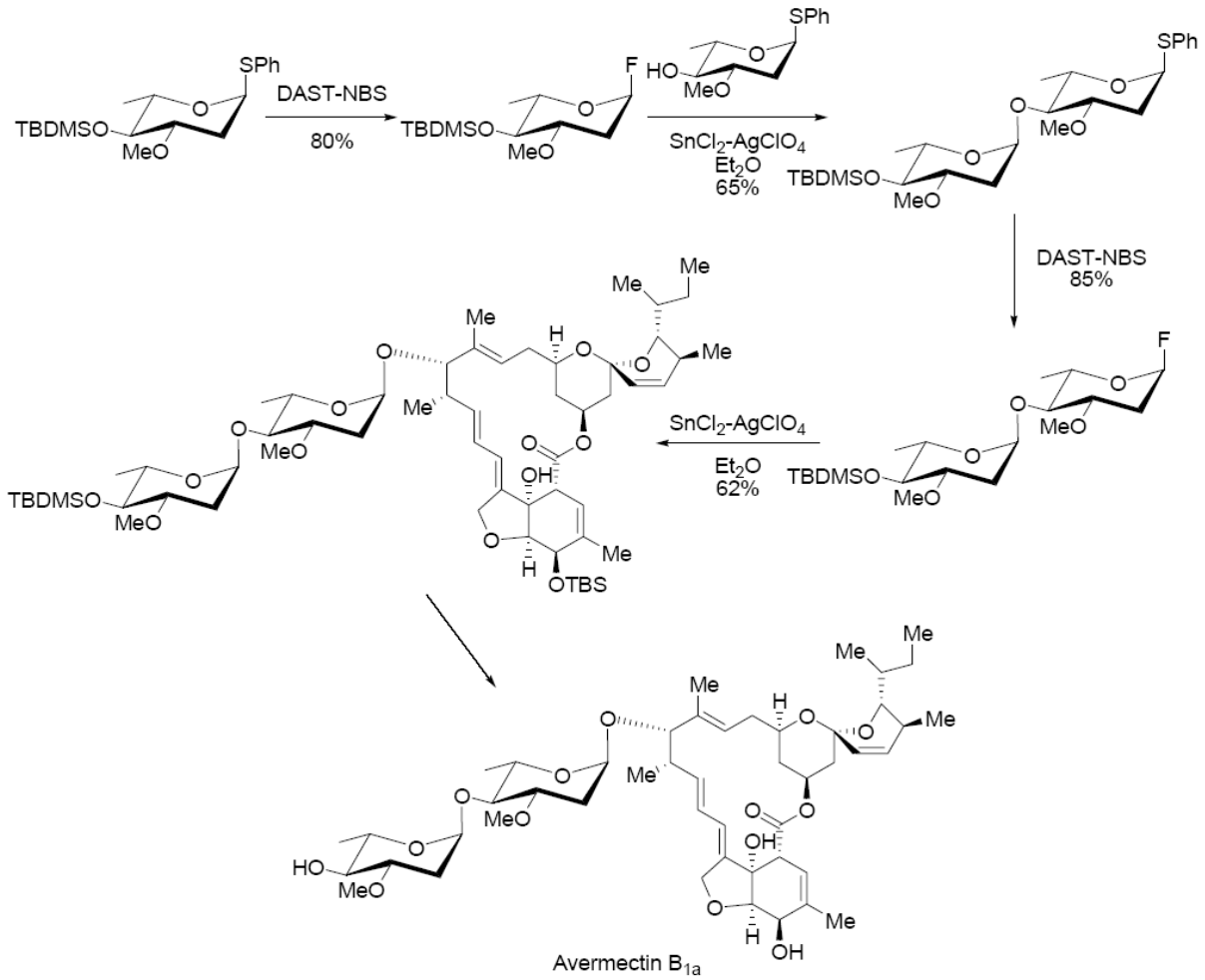


Scheme 3 Synthesis of Glycosyl Fluorides.

Most importantly, glycosyl fluorides can be activated under specific conditions compatible with the stability of most protecting groups. The first useful activation of glycosyl fluorides for glycosylation was introduced by Mukaiyama[27] using a combination of $SnCl_2$ with $AgClO_4$ (often replaced by AgOTf).[29] Noyori and coworkers introduced the use of SiF_4 and TMSOTf,[30] whereas $BF_3{\cdot}Et_2O$ was introduced independently by Nicolau and Kunz.[31] Additionally, Wessel et al. introduced Tf_2O as a powerful glycosylaton promoter for glycosyl fluoride donors.[32] The sequence TMSOTf < $SnCl_2$-AgOTf <Tf_2O was suggested for the relative reactivity of different promoters, all used in stoichiometric amounts. Catalytic amounts of the protic acid TfOH were recently used by Mukaiyama and coworkers.[33]

Glycosyl fluorides have found use in the synthesis of a wide range of complex natural products. In **Scheme 4** is reported the Nicolaou's synthesis of avermectin B_{1a}, where glycosyl fluorides are prepared from thioglycosides by reaction with NBS and DAST.[34] Although emphasis is placed on the donor properties of glycosyl fluorides, it should be mentioned that, in contrast to glycosyl bromides, partially unprotected glycosyl fluorides could also serve as glycosyl acceptors in oligosaccharides synthesis, acting as latent glycosylating agents. They

can be glycosylated by a variety of methods including thioglycoside and trichloroacetimidate donors.[35]



Scheme 4 Synthesis of Avermectin B_{1a}.

Glycosyl iodides have been known for a long time.[36] However, because of their instability, they have been used only occasionally as glycosyl donors. Since the introduction of the halide ion-catalysed glycosylation method,[25] a number of glycosylations actually proceeded through *in situ* generated glycosyl iodides intermediates by activating glycosyl bromides with tetraalkylammonium iodides. Recently improved methods for the preparation of glycosyl iodides have been developed, and several glycosyl iodides were prepared and isolated. Although benzylated glycosyl iodides are very unstable and should be used directly, acyl protected derivatives are considerably less labile, and stable crystalline glycosyl iodides can be prepared.[37]

Thioglycosides are the most used class of donors in oligosaccharide synthesis. The first thioglycoside was synthesized in 1909,[38] but it is only recently that their excellent glycosyl donor qualities have been recognized. The strength of thioglycosides as glycosylating agents

lies in their easy synthesis combined with their stability, and, at the same time, their effective activation using chemoselective thiophilic promoters.

Thioglycosides show remarkable stability: not only they do have long shelf lives, but they also tolerate very diverse chemical manipulations leaving the thioglycoside function intact. Importantly, most of the common carbohydrate protecting group manipulations can be performed on thioglycosides, a feature making the preparation of highly functionalized thioglycoside donors possible. Moreover, they are inert under several glycosylation conditions, so thioglycosides can serve as glycosyl acceptor in the assembly of oligosaccharide blocks. In addition, thioglycosides can also be directly converted into other types of donors, making them a very versatile class of compounds (**Figure 3***)*.

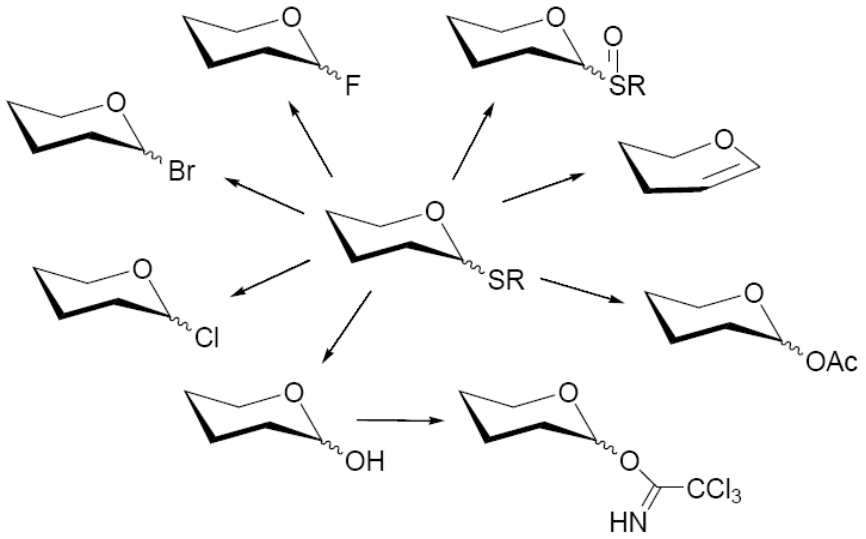
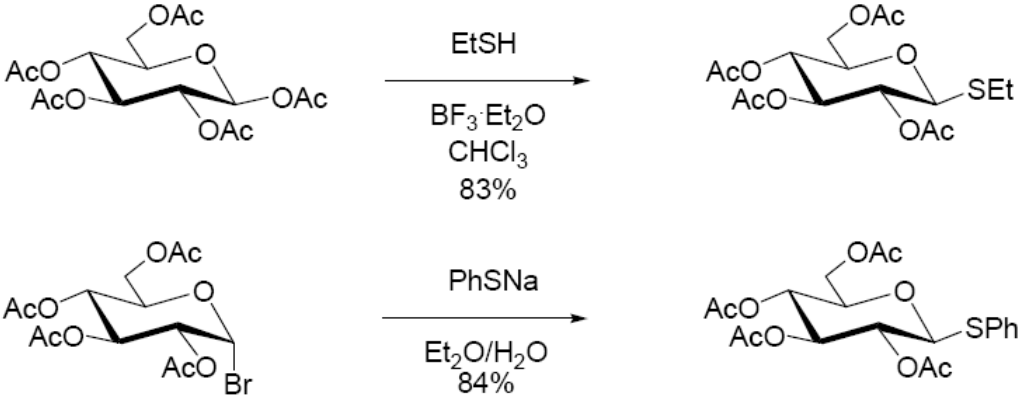


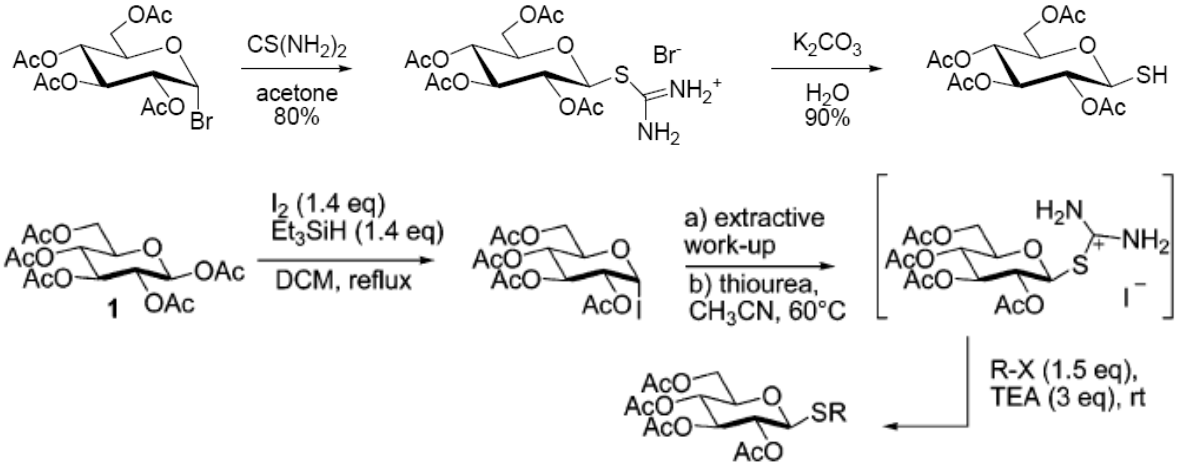
Figure 3 Conversion of Thioglycosides into Other Types of Donors.

The synthesis of the most used types of thioglycoside donors, mainly simple alkyl and aryl glycosides, is straightforward and can be performed on a large scale using cheap chemicals. Often the product is crystalline and can be purified without chromatography. Numerous ways to prepare thioglycosides have been described,[39] but for the easy production of thioglycosides mainly two synthetic methods are commonly employed, namely the reaction of peracetylated glycosides with a thiol in the presence of a Lewis acid[40] and the reaction of an acylated glycosyl halide with a thiolate (**Scheme 5***)*.[38]



Scheme 5 Synthesis of Thioglycosides.

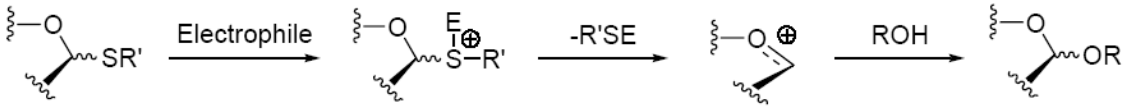
Indirect formation of thioglycosides can also be performed from glycosyl halides. Reaction with thiourea yields a pseudothiouronium salt, which can be hydrolyzed under mild, selective conditions to give the anomeric thiol, which then can be alkylated in an efficient, non-smelling procedure to produce thioglycosides (**Scheme 6**).[41]



Scheme 6 Alternative non-Smelling Procedure for Thioglycosides Generation.

All common protecting groups such as esters, ethers, acetals and orthoesters can effectively be introduced, manipulated and removed. Problems encountered are the removal of benzyl groups using catalytic hydrogenolysis, since the sulfur generally contaminates the catalyst.

Despite their stability, thioglycosides can be easily activated with thiophilic reagents, typically soft electrophilic reagents, under mild conditions (**Scheme 7**). Treatment of a thioglycoside with a thiophilic electrophile leads to the formation of a sulfonium ion species, that, with the assistance of the ring oxygen or a neighbouring group, evolves to the common intermediate of glycosylation reactions, the oxycarbenium ion depicted in the scheme, which then reacts with the nucleophile to afford the desired glycoside.



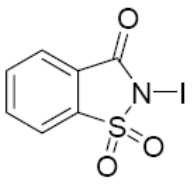
Scheme 7 Activation of Thioglycosides for Glycosylations by Electrophilic Reagents.

The first efforts to use thioglycosides directly as donors were performed mainly with mercury (II) salts as promoters. It was early recognised that mercury had high affinity for the sulfur functionality. In the first successful attempt $HgSO_4$ was employed.[42] Other mercury salts, such as $Hg(OAc)_2$, $HgCl_2$, $Hg(OBz)_2$, and PhHgOTf, were tried later.[43] These activations gave moderate yields, and were not powerful enough to be of general use.

Starting from the mid-1980s, however, a series of highly powerful activation methods of thioglicosides was developed. Starting with NBS,[44] and especially with MeOTf[45] and dimethyl(methylthio)sulfonium triflate (DMTST)[46] a seemingly never-ending spectrum of new promoters has been reported, but also electrochemical and radical activation have been described.[47]

Iodine-containing compounds are also used as promoters. Iodonium dicollidine perchlorate (IDCP) was introduced first as iodonium source,[48] later on the corresponding triflate (IDCT) started to be effectively used.[49] A very efficient promoter system, *N*-iodosuccinimide in the presence of a catalytic amount of triflic acid, was introduced independently by van Boom[50] and Fraser-Reid.[51] Glycosylations promoted by NIS-TfOH are frequently used as they proceed at low temperatures within a short time, and are capable of activating a wide variety of glycosyl donors with various acceptors. Triflic acid is frequently replaced by different Lewis acids such as TMSOTf, TESOTf, AgOTf or $BF_3 \cdot Et_2O$.

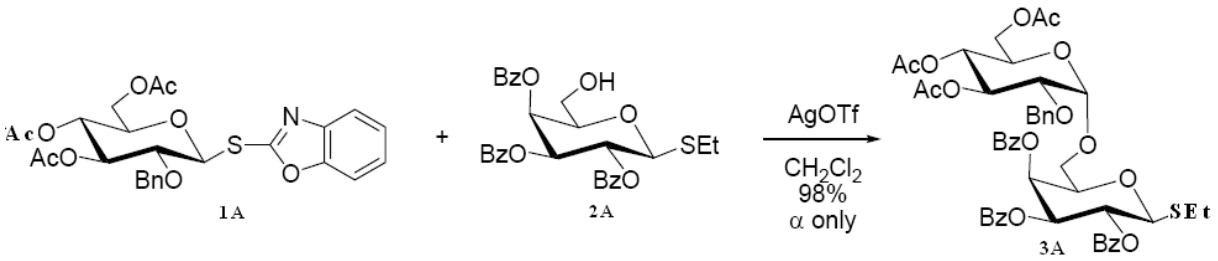
N-iodosaccharin (NISac) (**Figure 4**) was recently proposed as a replacement of NIS to reduce occasional by-products caused by the nucleophilicity of succinimide generally obtained as by-product in NIS promoted reactions.[52]



NISac

Figure 4 *N*-iodosaccharin.

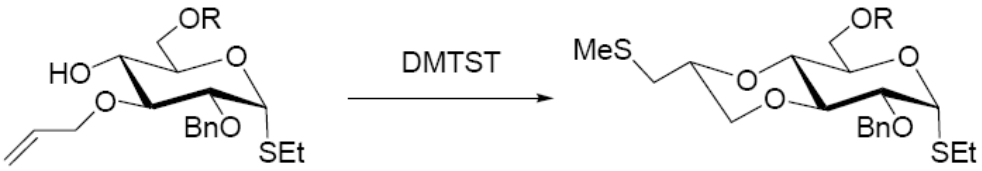
Numerous highly complex structures have been synthesized using the here cited promoting systems, verifying the impressive utility of the method. These promoters also nicely complement each other regarding reactivity, from the least reactive IDCP and MeOTf through the intermediate DMTST up to the most reactive NIS/TfOH. This promoter reactivity difference, in combination with the different reactivity of donors and acceptors, allows many practical orthogonal couplings between thioglycosides. Furthermore, thioglycosides reactivity can also be tuned by the choice of the aglycone.[53] Bulky or electron withdrawing groups on the sulphur decrease the reactivity of thioglycoside donors. Furthermore, several heterocyclic aglycones, such as benzothiazol-2-yl,[54] pyridine-2-yl,[44a] pyrimidin-2-yl[44a] and, most recently, benzoxazol-2-yl[55] derivatives, have been installed on the sulfur atom. These heterocyclic thioglycosides can be activated by the remote activation concept by reagents, which do not necessarily activate common alkyl- and aryl-thioglycosides. Thus, pyrimidinyl thioglycosides, for example, were activated by TMSOTf, which does not activate alkyl-/aryl-thioglycosides, to give glycosides in good yields.[56] AgOTf or $ZrCl_4$-Ag_2CO_3 proved to be effective promoters for the recently introduced benzoxazolyl thioglycosides (SBox glycosides).[55b] As shown in **Scheme 8**, the thioglycoside acceptor **2A** could be glycosylated by SBox glycoside **1A** in excellent yield as the promoter does not activate the ethylthio-function of the acceptor **2A**.[55b]



Scheme 8 Glycosylation with SBox Thioglycoside.

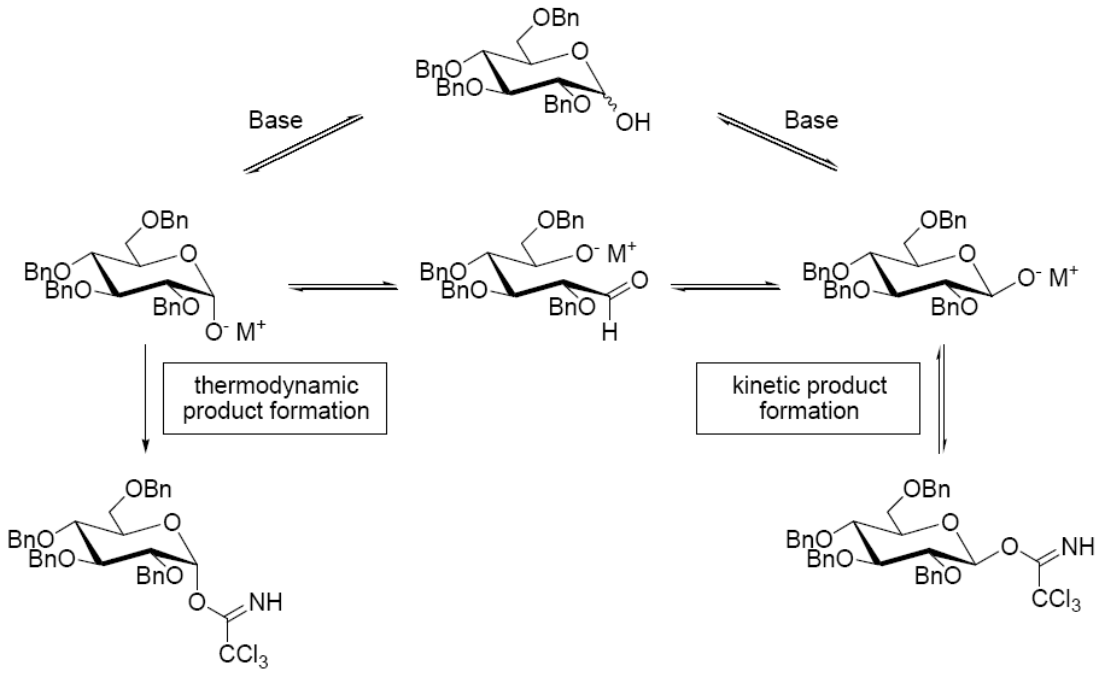
Notwithstanding the efficiency of thioglycosides as donors, problems can, of course, be encountered in various applications. The problems are connected both to the type of thioglycoside used and to the promoter employed. As to the promoter, MeOTf can, if the acceptor is unreactive, give methylation instead of glycosylation of the acceptor hydroxyl group.[57] As previously reported, *N*-succinimide glycosides can be formed as major products in NIS-promoted glycosylations with unreactive acceptors.[58] Soft nucleophilic centers, such as double bonds, could compete with the sulfur in its reaction with the electrophilic promoter, but allyl and pentenyl groups proved to be compatible with thioglycoside method performing glycosidation under controlled conditions.[59] Problems have been encountered when the

acceptor hydroxyl group is adjacent to an allyl protecting group, which have resulted in internal addition to an activated double bond being the major reaction (**Scheme 9**).[48a]



Scheme 9 Side-product of Thioglycosides Activation.

The use of thioglycosides in glycosylations has been reviewed.[60] Thioglycoside method is surely the most exploited in oligosaccharide syntheses, another very versatile and widely used approach is represented by **glycosyl trichloroacetimidate** method. Although the first paper on this method was published as recently as 1980,[61] it has already become a classical approach. This is essentially because only catalytic amounts of promoter are required to provide very high glycosyl donor properties whereas the here so far described methods generally require at least equimolar amounts of promoting system, which is obviously often associated with disadvantages of various sort. Glycosyl trichloroacetimidates are synthesized by reacting the free hydroxyl of lactols with trichloroacetonitrile under basic conditions. This reaction is generally high-yielding and, because of its reversibility, high anomeric control can often be achieved. In the presence of a weak base, such as potassium carbonate, the β-imidate can be isolated as the kinetic product, whereas the use of strong bases, such as sodium hydride or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), results in the formation of the thermodynamically more stable α-trichloroacetimidates (**Scheme 10**).[62]

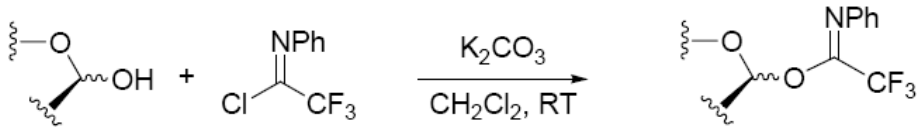


Scheme 10 Anomeric Control in Trichloroacetimidate Synthesis.

Controlling the anomeric configuration of glycosyl trichloroacetimidates isn't only of academic interest. The two diasteromers exhibit different reactivity, α anomers are generally more stable, thus less reactive, and require slightly harsher conditions to be activated. Furthermore, the use of diasteroisomerically pure glycosyl donors is of utmost importance when a S_N2 mechanism in the glycosylation medium is invoked.

Recently, Yu and coworkers introduced a class of fluorinated analogues of the Schmidt's donors: **glycosyl *N*-phenyl trifluoroacetimidates**.[63] Schmidt and co-workers also pioneered the preparation of glycosyl trifluoroacetimidates, whereupon the toxic CF_3CN with low boiling point (-63.9 °C) was used.[64]

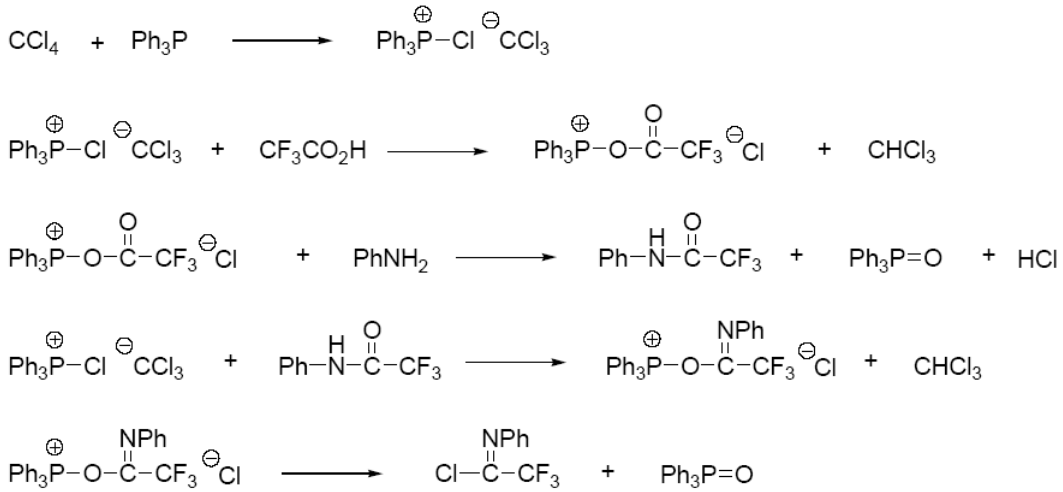
Glycosyl *N*-phenyl trifluoroacetimidates are synthesized in high yield by treatment of the corresponding 1-hydroxyl sugar with *N*-phenyl trifluoroacetimidoyl chloride in the presence of Cs_2CO_3 or K_2CO_3 in lab grade non-anhydrous CH_2Cl_2 or acetone at room temperature (**Scheme 11***)*.



Scheme 11 Synthesis of *N*-Phenyl Trifluoroacetimidates.

It should be mentioned that moisture in the solvent was found to be important, it might increase the solubility of K_2CO_3 and/or result in the presence of HO^- to facilitate the deprotonation of 1-OH sugars, otherwise the reaction was found sluggish.[65] Furthermore, thermodinamically favoured α anomers were produced predominantly due to the anomeric effect of the corresponding 1-*O*-potassium sugars. When DIPEA is used as base in anhydrous dichloromethane almost exclusively β anomers were obtained.[66]

Unlike trichloroacetonitrile, *N*-phenyl trifluoroacetimidoyl chloride is not commercially available and it has to be synthesized by reacting trifluoroacetic acid with aniline in a PPh_3-Et_3N-CCl_4 system (**Scheme 12***)*.[67]



Scheme 12 Synthesis of *N*-phenyl Trifluoroacetimidoyl Chloride.

Aniline can easily be replaced by other nucleophiles, thus variously *N*-substituted trifluoroacetimidate donors might be prepared, providing an additional element for tuning the reactivity of the glycosyl trifluoroacetimidate donors.[68] The presence of electron-withdrawing fluorine atoms on the leaving group greatly influences both reactivity and stability of *N*-phenyl trifluoroacetimidate donors. As a matter of fact, if compared with the chlorinated analogues, they are less prone to undesired degradation reactions during glycosylations and exhibit improved storability properties. Like glycosyl halides, trichloro- and trifluoro-acetimidate moieties are too labile to survive protecting group manipulations. Thus, installation of the imidate leaving group at the anomeric centre is the last step of multistep glycosyl donor syntheses.

Generally in the early steps, a temporary protecting group is installed at the anomeric centre, in order to safely manipulate the other hydroxyl groups on the saccharide backbone. Both glycosyl trichloro- and *N*-phenyl trifluoro-acetimidates are relatively stable under basic or neutral conditions, but react readily in presence of catalytic amounts of Brønsted or Lewis

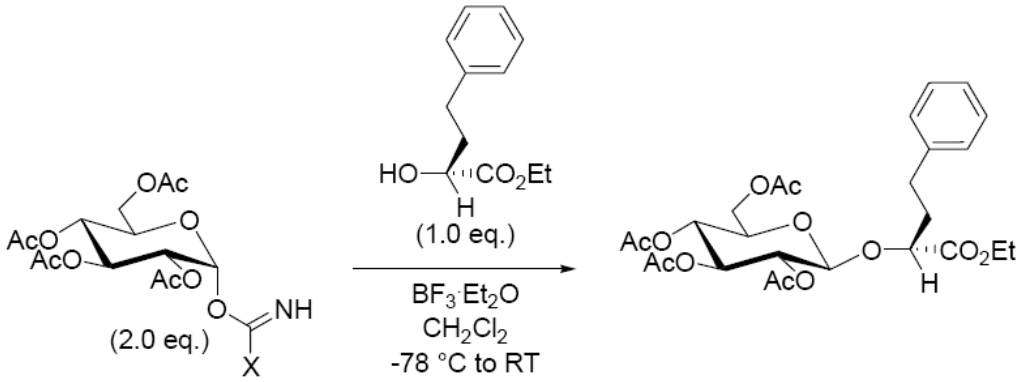
acids. Originally, *p*TsOH and $BF_3 \cdot Et_2O$ were used,[61] while currently the latter and TMSOTf[69] are the most frequently employed promoters. Glycosylations with these promoters take place at low temperatures and in high yields. Besides the activators mentioned thus far, several additional promoters have been introduced, these include strong protic and Lewis acids.

One of the aim of our lab is the development of new mild, moisture-stable, non-corrosive glycosylation promoting systems for the trihaloacetimidate methods. Several mild promoters have been proposed during the last years, such as the system I_2/Et_3SiH, as source of *in situ* generated HI,[70] and lanthanide salts such as $Sm(OTf)_3$[71] or $Yb(OTf)_3$.[72]

More recently, commercially available acid washed molecular sieves (AW 300 MS) proved to effectively activate trihaloacetimidates without any further promoter.[73] The last and very powerful promoting system developed in our lab concerns the use of catalytic amounts of $Bi(OTf)_3$.[74] Especially in the cases of $Yb(OTf)_3$, AW 300 MS and $Bi(OTf)_3$ the glycosylation conditions proved to be extremely mild and compatible with a number of acid sensitive protecting groups. In the case of $Yb(OTf)_3$-catalyzed glycosylations, it has been proved the stability of the extremely labile dimethoxytrityl group (DMT), never used before in glycosylation media.[75]

The higher stability of *N*-phenyl trifluoro- compared with that of trichloro-acetimidates has also an effect on the reactivity. Generally, Schmidt's donors are activated at lower temperatures and by smaller amounts of promoter than those required by the fluorinated-analogues. These observations allowed the development of an effective one-pot procedure in which trichloroacetimidates are initially chemoselectively activated by catalytic amounts of $Yb(OTf)_3$ or $Bi(OTf)_3$ in the presence of partially protected *N*-phenyl trifluoroacetimidates. After completion of this first glycosidation step, conditions are adjusted so to activate the protected *N*-phenyl trifluoroacetimidate for the second glycosidation step.[76] It should be observed that the presence of three fluorine atoms is responsible by itself of the higher amount of promoter required for effectively activating glycosyl trifluoroacetimidates, whereas the presence of a bulky group on the nitrogen might entails the better yields often registered with *N*-phenyl trifluoroacetimidates, if compared with trichloroacetimidate donors.

In **Table 1** is shown a comparative study on $BF_3 \cdot Et_2O$-catalyzed glycosylations with glycosyl trichloro- *vs* trifluoro-acetimidate donors.[77] As evident from the table, best results are achieved with 0.25 equivalents of promoter for trichloroacetimidate donor and with 0.5 equivalents in the case of the fluorinate-analogue, in both cases the desired product was isolated in 73% yield.

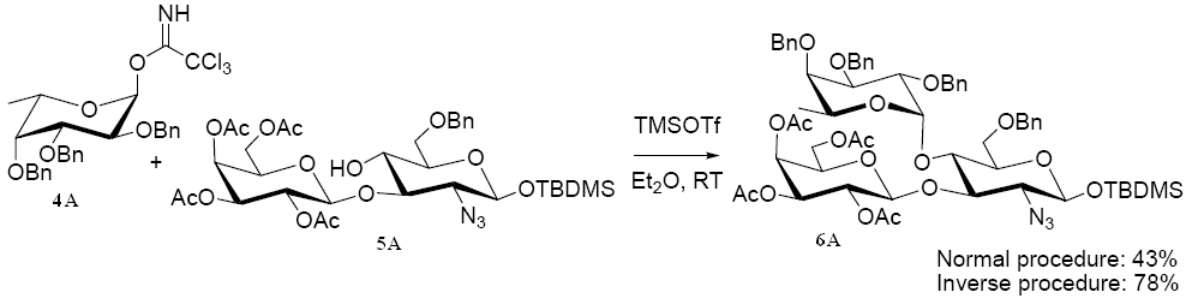


X	*$BF_3 \cdot Et_2O$ (equiv.)*	*Yield (%)*
CCl_3	0.25	73
CCl_3	0.5	67
CF_3	0.25	65
CF_3	0.5	73

Table 1 $BF_3 \cdot Et_2O$-catalyzed Glycosylation: Glycosyl Trichloroacetimidates *vs* Trifluoroacetimidates.

The effect of the phenyl group in *N*-phenyl trifluoroacetimidate donors is generally related to the prevention of undesired side-reactions, that often take place with Schmidt's donors, such as β-elimination[78] or rearrangement to unreactive glycosyl trichloroacetamides.[79] *N*-phenyl trifluoroacetimidate donors proved to be very effective glycosylating agents in several different syntheses sometimes furnishing better results than the Schimidt's donors, but are not yet as diffused as the trichloro-analogues.

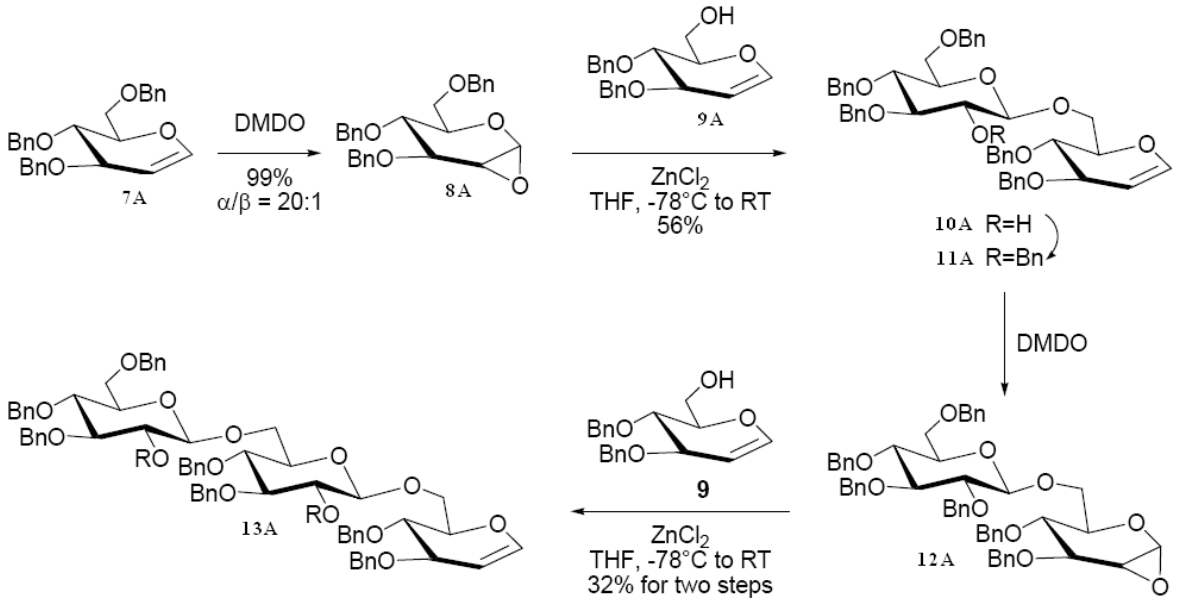
Besides the introduction of new promoters, another technical development related to glycosyl trichloroacetimidates as glycosyl donors was the introduction of the *inverse procedure*.[80] In the original procedure, the promoter is added to a mixture of glycosyl donor and acceptor. It was assumed that highly reactive glycosyl trichloroacetimidates might partially decompose prior to being exposed to the glycosyl acceptor. Consistently with this hypothesis, adding the glycosyl donor to a mixture of the acceptor and promoter resulted in increased yields (**Scheme 13***)*.



Scheme 13 The Normal and the Inverse Procedure.

Glycosylation of the disaccharide acceptor **5A** with the reactive fucosyl imidate **4A** gave trisaccharide **6A** in a 43% yield by the normal procedure and in a 78% yield by the inverse procedure.

A completely different glycosyl donor's family is represented by **1,2-anhydro sugars**. Glycals recently came into the limelight because of the work of Danishefsky and coworkers, who developed a highly efficient procedure for their oxidation to 1,2-anhydro sugars with dimethyldioxirane (DMDO).[81] Reaction of the epoxides **8A** and **12A**, promoted by $ZnCl_2$ in tetrahydrofuran or dichloromethane, produced 1,2-*trans*-glycosides (**Scheme 14**).



Scheme 14 Iterative Glycosylation with Glycals.

Glycosylation of glycals by this method gives a reiterative glycosylation strategy for the synthesis of oligosaccharides. Unfortunately, it was established that the glycosylation reaction is not always stereospecific.[82] A potentially useful feature of the glycosides formed in glycosylations with 1,2-anhydro sugars is that they possess a free 2-OH ready for further transformations, for example, into 2-deoxy glycosides,[83] or for configurational inversion as in the synthesis of β-mannosides from β-glucosides.[84] 1,2-anhydro sugars are very versatile because they can also be readily converted into other types of glycosyl donors, such as thioglycosides, glycosyl fluorides and phosphates.

Glycosyl phosphate triesters can be considered the nature's glycosyl donors. Nucleotide 5'-diphospho sugars (NDPs) (**Figure 5**) are the natural substrates of glycosyl trasferases, that are the enzymes responsible for the biosynthesis of oligosaccharides in living systems.[85]

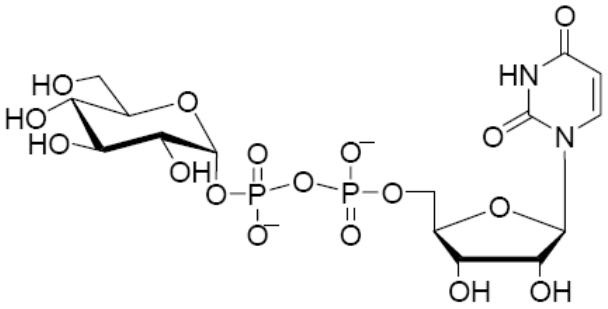


Figure 5 Nucleotide 5'-Diphospho Sugar.

Despite this strong suggestion from nature, glycosyl phosphate triesters were introduced as glycosyl donors in the scenario of oligosaccharide synthesis only relatively recently by Ikegami and co-workers.[86] Stoichiometric amounts of TMSOTf proved to efficiently activate glycosyl phosphates at low temperatures. A variety of other Lewis acids, such as $SnCl_2$, ZnI_2, $Zn(OTf)_2$ and $BF_3{\cdot}Et_2O$, was screened achieving in all cases moderate results.[87]
Most frequently, diphenyl and di-*n*-butyl phosphates are used. Recently, Singh and coworkers introduced the cyclic propane-1,3-diyl phosphates (**Figure 6**).[88]

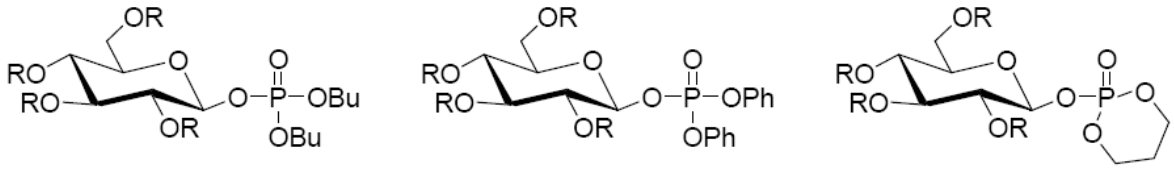
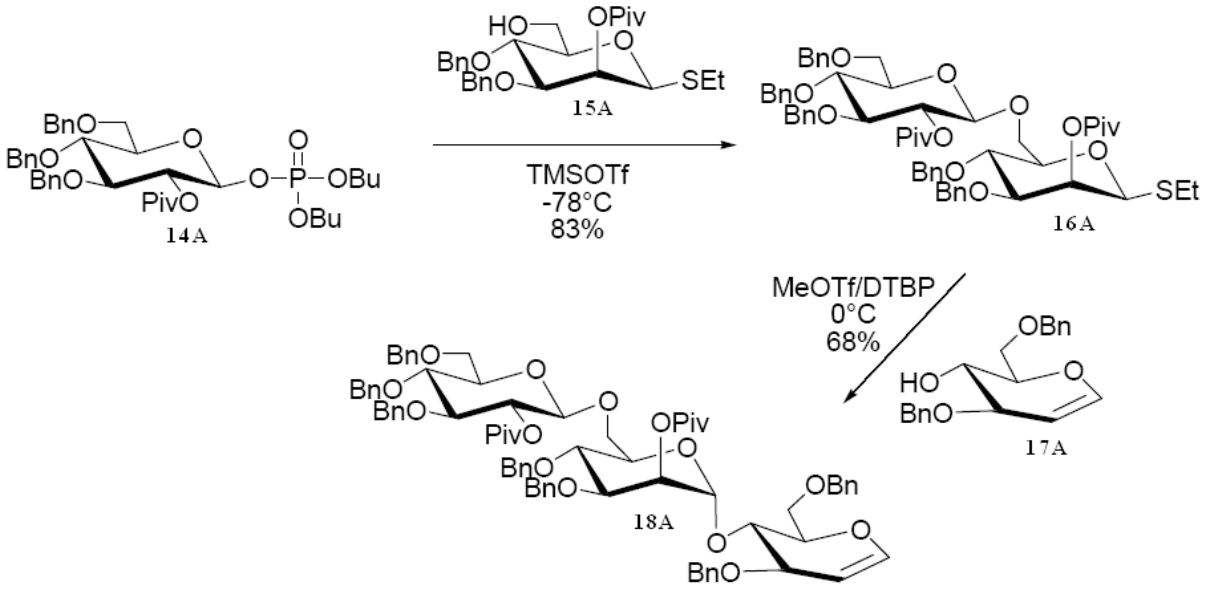


Figure 6 Most Commonly Used Glycosyl Phosphates.

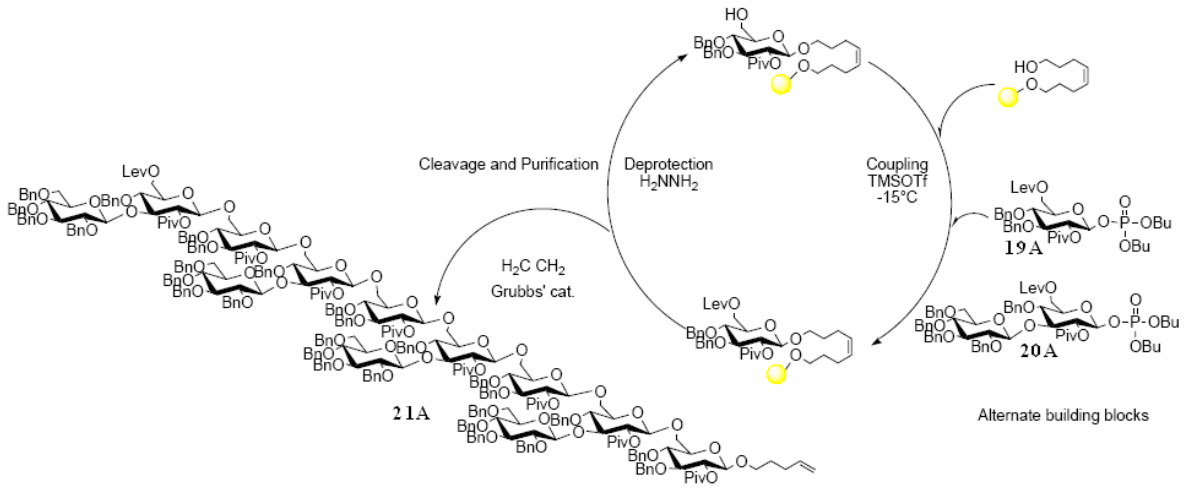
Glycosyl phosphates proved to be very effective glycosylating agents in the syntheses of various biologically relevant oligosaccharides both in solution and on solid-support.[89] Furthermore, their versatility was demonstrated in orthogonal and regioselective glycosylation strategies.[87] Glycosyl phosphate **14A** could be activated in the presence of thioglycoside-acceptor **15A** at very low temperature to furnish the desired disaccharide **16A** in good yield (**Scheme 15**). The disaccharide donor thus obtained was further activated by the use of MeOTf/DTBP system for the coupling with the glycal **17A**, affording the trisaccharide **18A** in 68% yield.



Scheme 15 Orthogonal Glycosylation with Glycosyl Phosphates and Thioglycosides.

Orthogonal glycosylation strategies, similar to that described above, had previously been established for glycosyl donors other than glycosyl phosphates.

One of the reason for the growing interest toward glycosyl phosphates is their compatibility with the automated solid-phase approach. Recently, Seeberger and coworkers developed the first automated solid-phase oligosaccharide synthesizer.[8] A peptide synthesizer was adapted to carbohydrate synthesis. Specific coupling cycles were designed for glycosyl trichloroacetimidate and phosphate methods. The success of the approach was demonstrated by the assembly of the phytoalexin elicitor (PE) dodecasaccharide in automated fashion (**Scheme 16**). Two different glycosyl phosphate donors, **19A** and **20A**, were synthesized. Levulinoyl esters were employed as 6-*O* temporary protecting groups and the 2-*O*-pivaloyl group was used to control the stereochemical outcome of the glycosylation reaction *via* neighbouring participation effect. Each cycle incorporated double glycosylations (at -15 °C) and double deprotections to ensure high yielding steps (**Table 2**). A branched hexasaccharide was constructed in ten hours in over 80% yield, whereas dodecasaccharide **21A** was prepared in 17 hours and in 50% yield using the same cycle.



Scheme 16 Automated Solid Phase Synthesis of Protected Phytoalexin Elicitor β-Glucan.

Step	*Function*	*Reagent*	*Time (min)*
1	Couple	5 equiv. building block and 5 equiv. TMSOTf	30
2	Wash	Dichloromethane	6
3	Couple	5 equiv. building block and 5 equiv. TMSOTf	30
4	Wash	1:9 Methanol:Dichloromethane	4
5	Wash	Tetrahydrofuran	4
6	Wash	3:2 Pyridine:Acetic Acid	3
7	Deprotection	2 x 20 equiv. Hydrazine (3:2 Pyridine:Acetic Acid)	30
8	Wash	3:2 Pyridine:Acetic Acid	3
9	Wash	1:9 Methanol:Dichloromethane	4
10	Wash	0.2 M Acetic Acid in Tetrahydrofuran	4
11	Wash	Tetrahydrofuran	4
12	Wash	Dichloromethane	6

Table 2 General Cycle Used with Glycosyl Phosphate Donors.

Despite the efficiency and versatility of glycosyl phosphate donors, their use isn't widely spread. This can be attributed to different reasons. First of all, their synthesis often requires the use of moisture-sensitive, expensive, or non-commercially available reagents.[90] Furthermore glycosyl phosphates are unstable toward prolonged time purifications on silica gel. Synthetic procedures requiring only fast filtration of the reaction crude are generally preferable. Once in pure form, α- and β-glycosyl phosphates were found to be completely stable to storage for several months at 0 °C. The use of stoichiometric amounts of promoter implies strong acidic condition in the glycosylation medium. This limits the number of protecting groups compatible with the method. Acid-labile protecting groups have to be

avoided, but an efficient protection strategy has been developed, using base-labile and UV-detectable 9-fluorenylmethylcarbonate (Fmoc) as temporary group.[91]

Besides glycosyl phosphates, a variety of other phosphorus containing leaving groups have been designed and proposed. **Glycosyl phosphites** were introduced by Schmidt,[92] Wong[93] and Watanabe.[94] They react with alcohols at low temperatures in the presence of catalytic amounts of Lewis acid promoters such as TMSOTf, $BF_3{\cdot}Et_2O$ and $Sn(OTf)_2$, thus creating glycosides. The typical activators are $ZnCl_2$, $ZnCl_2$-$AgClO_4$ and $BiCl_3$.[87, 95]

Glycosyl thio compounds with phosphorus in the leaving group, such as **dithiophosphates**[96,87] or **phosphorodiamidimidothioates**,[97] have also been studied (**Figure 7**).

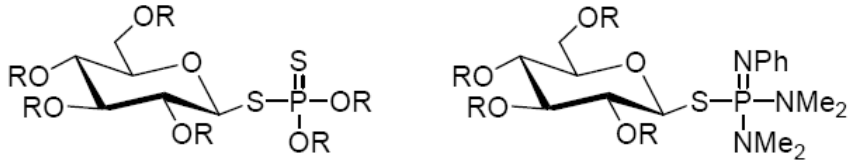
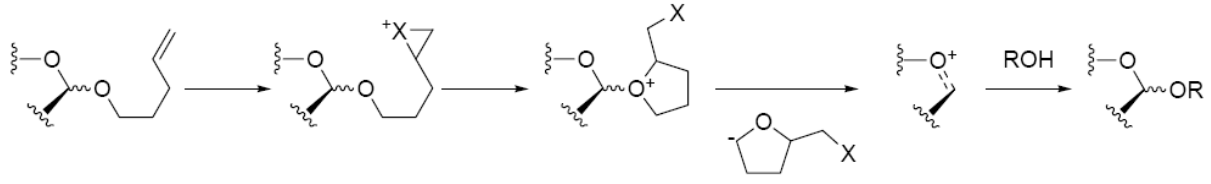


Figure 7 Glycosyl Dithiophosphate and Phosphorodiamidimidothioate Donors.

Despite their efficiency, none of the glycosylation methods described so far is generally applicable. The choice of the suitable glycosylation method for a given glycosidation depends on several parameters, among the others the specific linkage to be formed and the nature of the coupling partners. Generally the best results cannot be predicted in advance and come after several experimental attempts. Often a complementarity is found among the methods and for this reason many new glycosylation methods are being developed. Although we are still far to it, very efficient methodologies have been described and, besides the ones already illustrated, some others are worth mentioning.

***n*-Pentenyl glycosides**, introduced by Fraser-Reid,[98] provide excellent stability under a variety of protecting group manipulations. These glycosyl donors are activated by electrophilic halogenation of the double bond, which results in cyclization and the release of the aglycone, thus providing active glycosylating carbocation (**Scheme 17**).



Scheme 17 Glycosylation with *n*-Pentenyl Glycosides.

These glycosylation reactions are promoted by NBS, iodonium dicollidine perchlorate (IDCP) or the corresponding triflate (IDCT). NIS in combination with catalytic amounts of protic or Lewis acids such as TfOH[99] or TESOTf,[100] was introduced as a more active catalyst. The *n*-pentenyl glycosylation was used in the synthesis of biologically important molecules.[101]

Glycosyl sulfoxides as glycosyl donors were introduced by Kahne.[102] When activated by triflic anhydride or catalytic amounts of triflic acid, glycosyl sulfoxides react with unreactive substrates giving glycosides in good yields. The reaction is reported to procede through the glycosyl α-triflate, which forms the basis of a very useful method for the synthesis of β-mannopyranosides.[103] Compared with glycosyl sulfoxides, **glycosyl sulfones** are far less reactive. Neverthless, activation of sulfones of some 2-deoxy sugars has been successfully used in glycosylations using $MgBr_2 \cdot Et_2O$.[104]

Stereoselectivity of Glycosidation Reactions

The effectiveness of a glycosylation doesn't only rely on the coupling yield. The stereoselectivity is a crucial issue in glycosylation reactions. Problems of stereocontrol arise as result of difficulties in accomplishing clean S_N2 reactions at the anomeric center. The ready assistance of the endocyclic oxygen in the glycosyl donor's leaving group diparture and subsequent stabilisation of the carbocation gives a considerable S_N1 component to these reactions rendering stereocontrol difficult. Depending on the spatial orientation of the substituent on the anomeric center, the newly formed glycosidic linkage can either be α or β, but it can also referred to as 1,2-*trans* or 1,2-*cis*, highlighting the relation with the substituent at the neighbouring carbon (**Figure 8**).

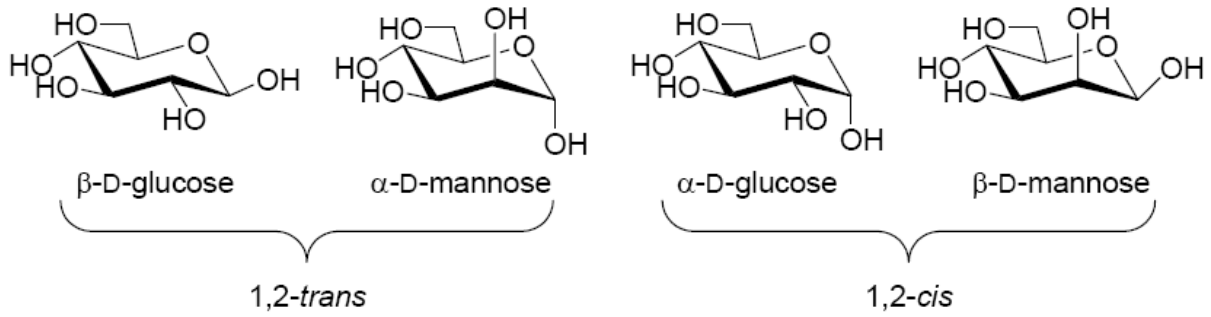
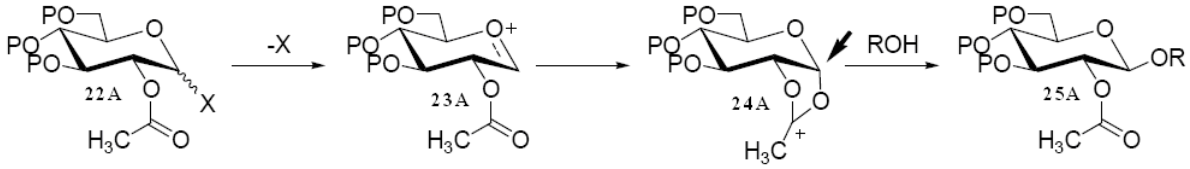


Figure 8 Anomeric Configurations of D-Glucose and D-Mannose.

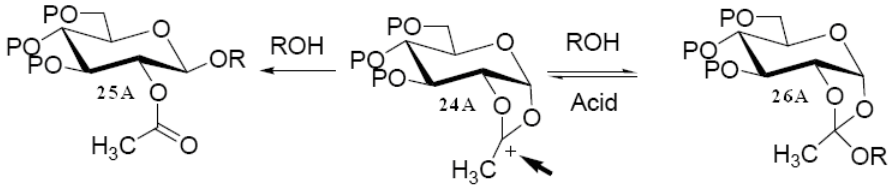
The latter description is rather diffused, because it furnishes an easy way of understanding the difficulty of making a determinate glycosidic bond. 1,2-*trans*-Glycosides can be easily synthesized exploiting **neighbouring group participation**. When a glycosyl donor is equipped at *O*-2 position with an acyl group, the departure of the leaving group on the

anomeric position is anchimerically assisted by the carbonyl moiety and the acyloxonium ion **24A** is readily formed (**Scheme 18**).



Scheme 18 Neighbouring Group Participation.

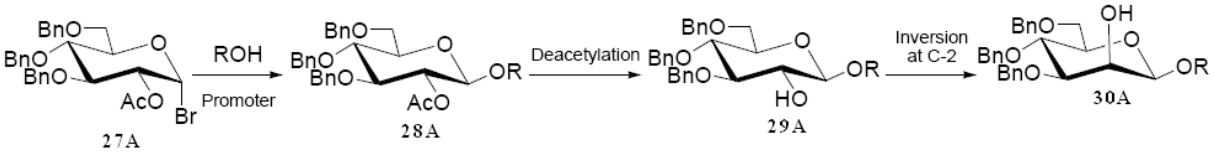
Reaction of the nucleophile with the acyloxonium ion **24A** takes place from the upper face of the ring and therefore results in the formation of 1,2-*trans*-glicoside **25A** with regeneration of the acyloxy group. The nucleophile might also react with the other electrophile carbon, thus forming the undesired orthoester **26A** (**Scheme 19**).



Scheme 19 1,2-Orthoester Formation.

In the most commonly used glycosylation methods, strong Lewis and Brønsted acids are used as promoters and the orthoester formation is a reversible process. When mild promoters are used, such as lanthanide salts for the trihaloacetimidate methods,[71,72] glycosyl orthoesters become non-reactive side-products that negatively affect the glycosylation yield. Electrophilicity of the carbonyl carbon can be decreased in order to avoid this side-reaction. Sterically hindered pivaloyl groups are often used, but their cleavage require harsher conditions than those used for the common acetyl and benzoyl groups. Recently, methoxycarbonyl group was introduced as neighbouring participating group.[105] The use of this protecting group guarantees complete 1,2-*trans*-stereoselectivity, orthocarbonate side-products being not detected even in glycosylations assisted by very mild promoters. Furthermore, cleavage of methoxycarbonyl moieties requires the same conditions as for acetyl and benzoyl groups. Neighbouring group participation represents the most reliable tool to control the stereoselectivity of glycosylation reactions with various glycosyl donors. However the neighbouring group participation is limited to the synthesis of 1,2-*trans*-glycosides, but, since its effectiveness, it is sometimes used for the indirect synthesis of 1,2-*cis*-mannosides (**Scheme 20**). In this approach, the first step takes the advantage of the ready formation of 1,2-*trans*-glucoside **28A** by neighbouring group participation from glucosyl donor **27A**, which

possesses orthogonally removable acetyl at *O*-2. After selective removal of this protecting group, the *C*-2 configuration of the resulting **29A** is inverted by nucleophilic displacement or oxidation-reduction type reactions, thus creating the 1,2-*cis*-mannoside **30A**.



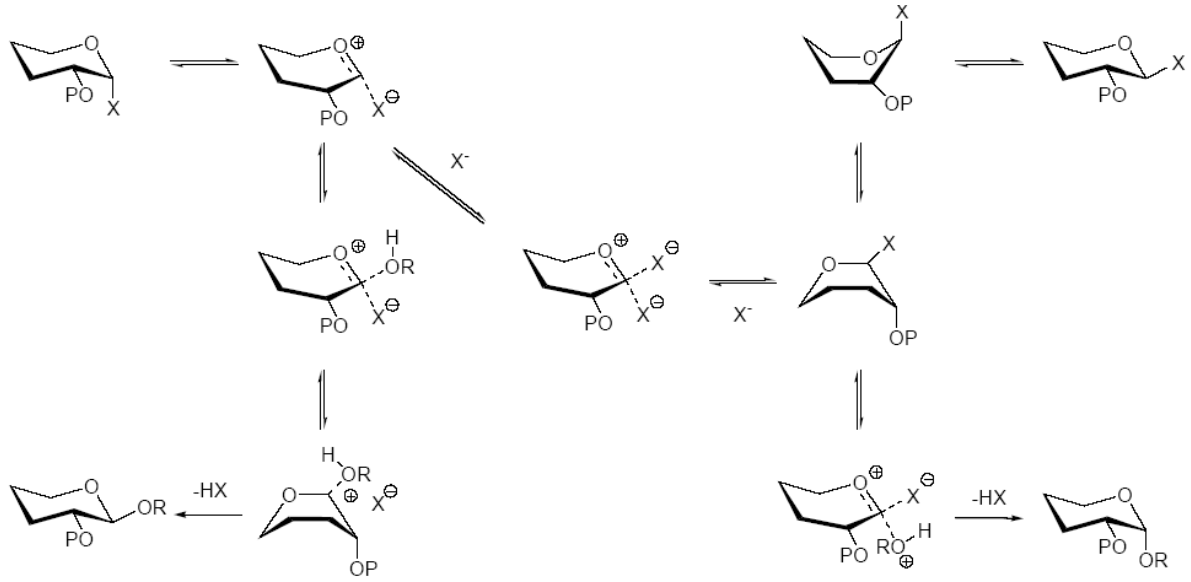
SCHEME 20 Synthesis of β-D-Mannopyranosides by Configurational Inversion at *C*-2.

Other approaches to achieving stereoselective glycosylations have been developed. Obviously, the major challenge is represented by formation of 1,2-*cis*-glycosides, but it's useful when not necessary to rely on alternative methods for the control of the stereochemistry of glycosylations also for 1,2-*trans*-linkage formation. Participating groups are generally carbonyl based functionalities. These groups don't only influence the stereochemical outcome of the reactions but also the reactivity of glycosyl donors. Their electron-withdrawing nature has a destabilizing effect on the carbocation intermediate that is formed after the departure of the glycosyl donor leaving group. Glycosyl donors equipped with electron-withdrawing protecting groups are called *disarmed* and exhibit decreased reactivity.[106] Depending on specific synthetic demands, this effect might be undesired and also 1,2-*trans*-selectivity has to be achieved in a different fashion.

The **solvent effect** is widely used for controlling the stereoselectivity of glycosylation reactions. A prerequisite for the use of the solvent effect is the avoidance of participating groups at glycosyl donors *O*-2. Ether-type protecting groups have a low participation tendency and are therefore commonly used for this purpose. In these cases, benzyl ethers are the most frequently used derivatives for hydroxyl groups, whereas for amino sugars, the azido function serves as an excellent non-participating masked form of the amino group. In non-coordinating solvents, such as toluene and CH_2Cl_2, glycosylation reactions procede through a tight ion pair, favouring an S_N2-like mechanism with inversion of configuration at the anomeric carbon (**Scheme 21**).[107]

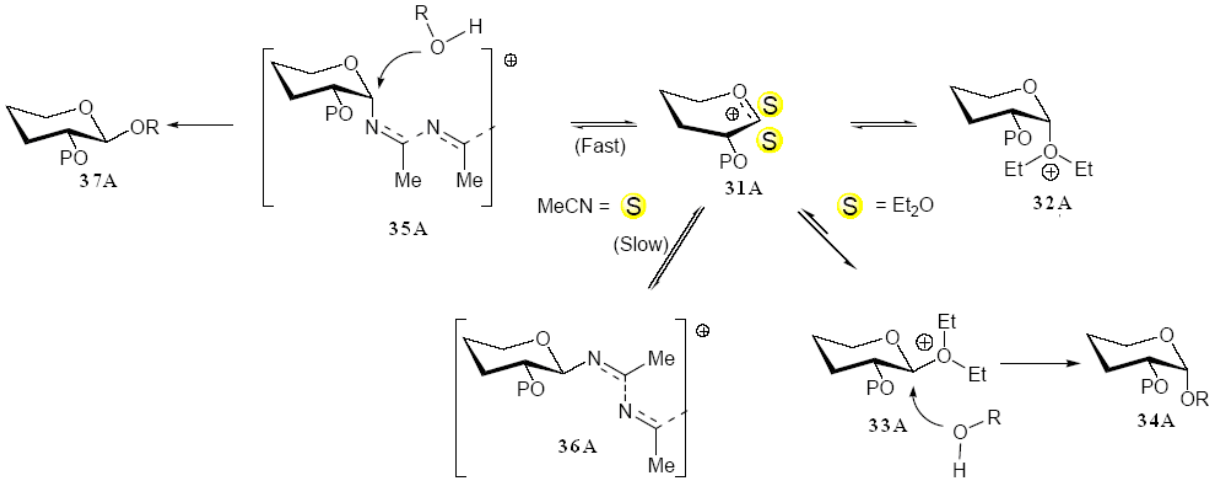
The accomplishment of a pure S_N2 reaction is very difficult. The ready participation of the endocyclic oxygen in leaving group displacement gives a considerable S_N1 component and, generally, anomeric mixtures, enriched in the inversion product, are obtained. When glycosylation reactions are conducted in coordinating solvents, the stereoselectivity is altered by the direct involvement of the solvent in the reaction mechanism. Experimental evidence

has shown that ether-type solvents favour formation of α-glycosides, whereas the use of nitrile-type solvents shifts the selectivity toward the preferential formation of β-anomers.



Scheme 21 Halide Ion-Catalized Glycosylation.

This effect on the stereoselectivity was rationalized invoking an S_N1-type reaction mechanism in which a sugar-solvent adduct is formed as intermediate.[108] After the departure of the leaving group from the glycosyl donor, the oxocarbenium ion **31A** is solvated by the coordinating solvent (**Scheme 22**).



Scheme 22 Solvent Participation in Glycosylations.

In the case of ether-type solvents, the kinetic formation of the α-adduct **32A** is rapidly followed by its conversion into the thermodinamically favoured β-oxonium intermediate **33A**. The β-adduct **33A** is more stable than the axial oxonium **32A** because of the reverse anomeric

effect. The presence of a positive charge on the exocyclic heteroatom, favours the equatorial displacement of the aglycone because of dipolar effects (**Figure 9**).

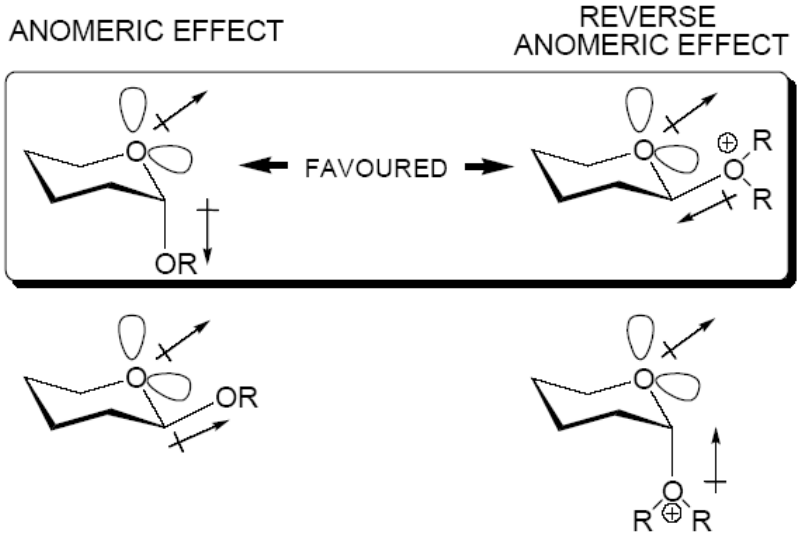
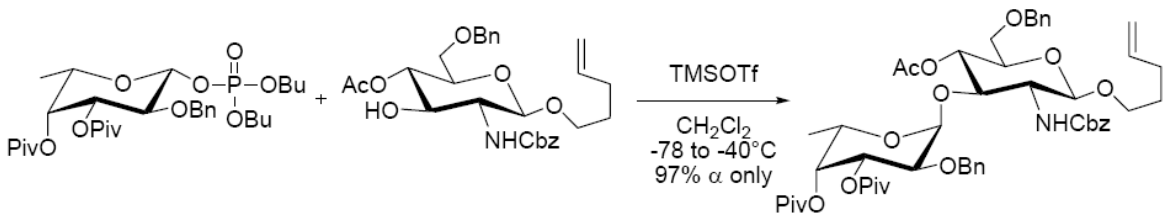


Figure 9 Dipole-Dipole Interaction in Direct and Reverse Anomeric Effects.

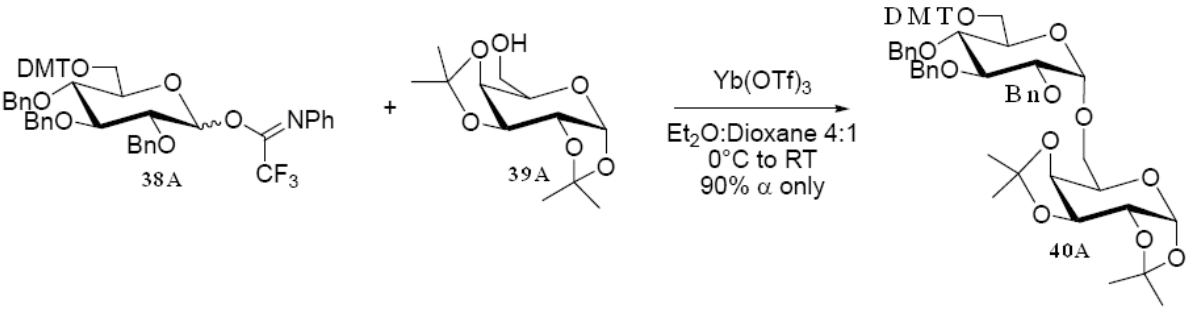
Intermediate **33A** then reacts with the nucleophile to form the axial glycoside **34A**, thus achieving the desired α-stereoselectivity. When nitrile-type solvents are used, the same model can be applied. In this case, the conversion of the α-adduct **35A** into the termodinamically more stable β-nitrilium ion **36A** is slower than in the case of ether-type solvents. This is due to the formation of nitrilium-nitrile-conjugate species that, stabilized by polydispersion of the positive charge, evolves to the corresponding β-adduct very slowly. The nucleophile, in this case, attaks the α-adduct with an equatorial approach leading to the formation of the desired β-glycoside **37A**. This model is well established and the solvent effect is widely recognized. It had been supported by several experimental evidences, collected in the course of the years. Reaction at different temperatures and rates were conducted and the nitrilium ion was also trapped.[109]

Although the solvent and the neighbouring participation effect are the most used methods, other approaches have been developed in order to control the sereoselectivity of glycosylation reactions. Protecting groups on position other than *O*-2 can influence the stereochemistry of glycosylations exploiting long range participation or sterical and torsional effects. The use of an acyl protection on *O*-4 of galactose and fucose donors proved to improve the α-selectivity of glycosylation reactions via **long range participation effect** (**Scheme 23**).[87]



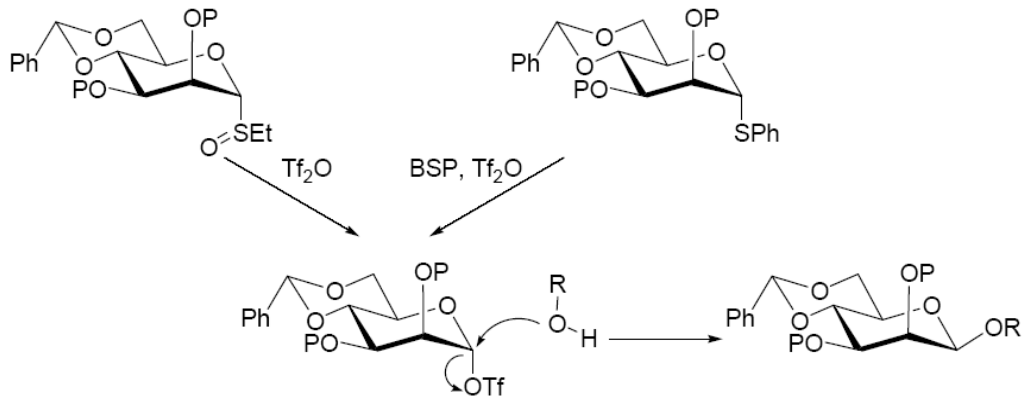
Scheme 23 Long-Range Participation Effect.

Furthermore, α-selectivity can also be enhanced by the use of **bulky protecting groups** on the primary hydroxyl of glycosyl donors. As shown in **Scheme 24**, the presence of the bulky dimethoxytrityl group on the *O*-6 of glucosyl *N*-phenyl trifluoroacetimidate **38A** guaranteed the exclusive formation of the desired α-glycoside **40A** in high yield (**Scheme 24**).[75]



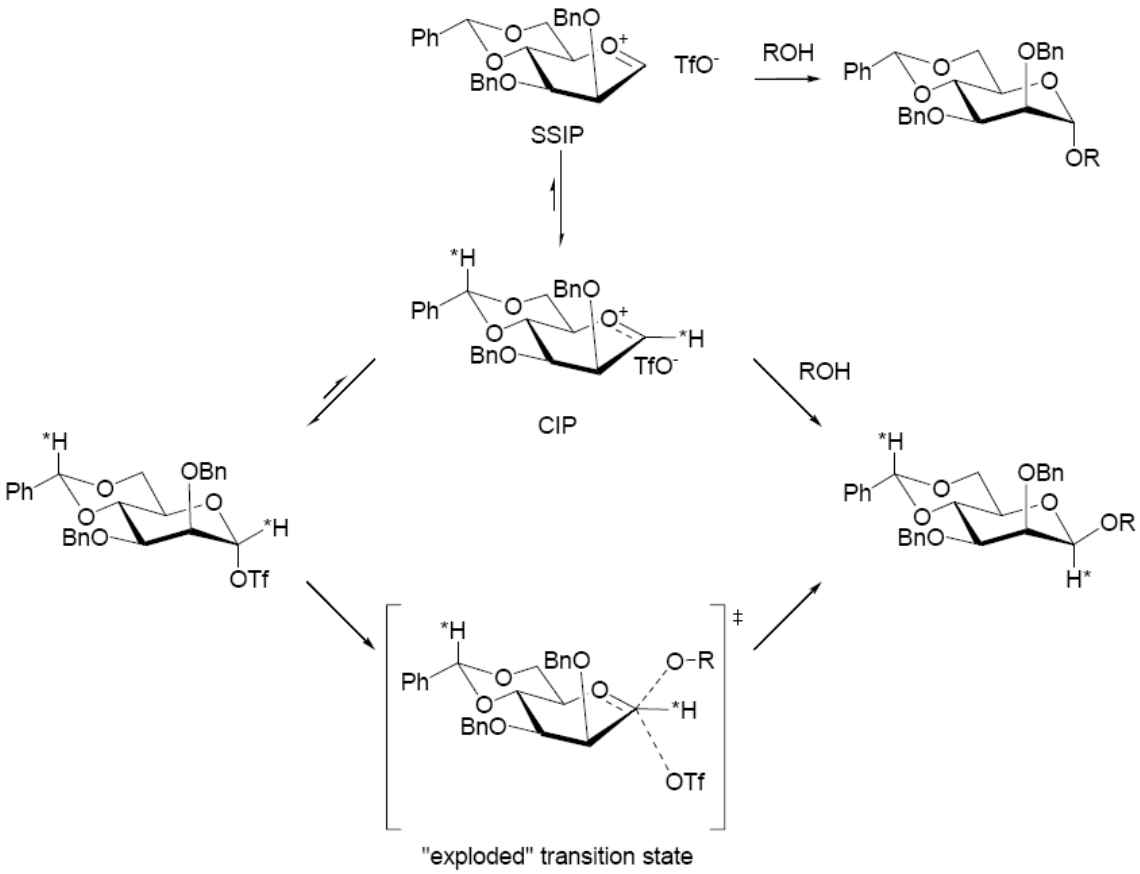
Scheme 24 Effect of the donor 6-*O*-substituents on α-selectivity of glycosylations.

The use of **4,6-*O*-benzylidene protection** on mannosyl donors is one of the keys to the efficient 1,2-*cis*-selectivity reported by Crich and coworkers in their work.[110] 4,6-*O*-Benzylidene-protected mannosyl sulfoxides are first activated with triflic anhydride to give a covalent triflate, that is then displaced by the acceptor to give the β-mannoside with excellent yield and selectivity. In a more recent version, the α-mannosyl triflate is generated from a mannosyl thioglycoside by the combination of triflic anhydride and 1-benzenesulfinyl piperidine (BSP) before addition of the acceptor (**Scheme 25**).[111]



Scheme 25 Synthesis of β-Mannosides via α-Triflate Formation.

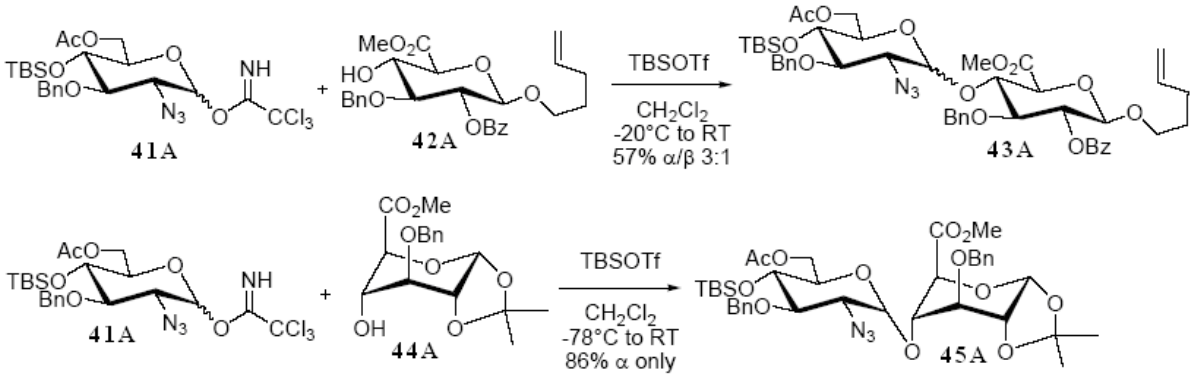
The mechanism proposed and verified by Kinetic Isotope Effect invokes the formation of a transient contact ion pair (CIP) or a functionally equivalent "exploded" transition state (**Scheme 26**).[112] In the CIP mechanism the triflate anion is necessarily closely associated with the face of the oxacarbenium ion from which it has just departed and shields that face against attack by the incoming alcohol. In the alternative mechanism there is a loose association of the nucleophile with the anomeric center as the leaving group departs. The minor amount of α-mannosides formed in these reactions most likely arise through the intermediacy of a looser, perhaps solvent-separated, ion pair (SSIP), which is in equilibrium with an initial CIP. The benzylidene group plays an important role in this equilibrium. It opposes to rehybridisation at anomeric carbon because of torsional effect and, so, shifts the complete set of equilibria toward the covalent triflate and away from the SSIP, thereby minimizing α-glycoside formation.



Scheme 26 Proposed Glycosylation Mechanism for Crich Method.

In most of the approaches described so far, the steric and electronical nature of the glycosyl donor is tuned to direct the stereochemistry of glycosylation reactions. Manipulation of the protection pattern of the glycosyl acceptor to control the stereochemical outcome of coupling reactions has received less attention. Two features of the acceptor are known to influence the

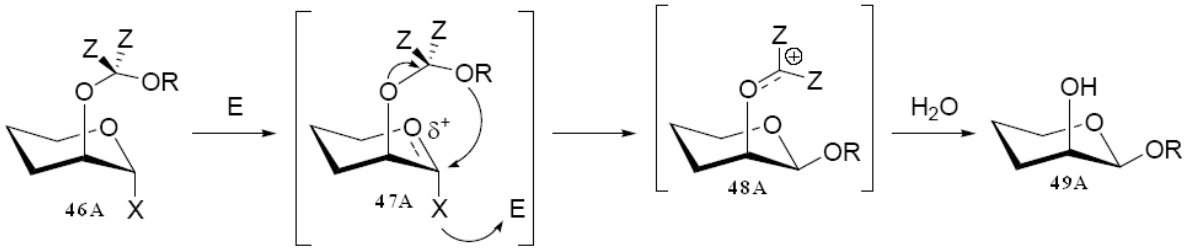
streochemical course of the reaction: the intrinsic reactivity of the hydoxy groups that function as nucleophile (axial hydroxyl groups are generally less reactive than equatorial hydroxyl groups)[113] and steric factors, which result in matched/mismatched pairs of glycosyl dononors and acceptors.[114] Recently, a new concept for stereochemical control of glycosylation reaction has been developed by **locking the conformation of the monosaccharide acceptor**.[115] In the synthesis of key disaccharide building blocks for the assembly of the heparin backbone, the reaction of *C*-2-azido glucose trichloroacetimidate **41A** with glucuronic acid acceptor **42A** yielded anomeric mixture of disaccharide **43A** (**Scheme 27**).



Scheme 27 Improvement of α-Selectivity by Conformational Locking of Glycosyl Acceptor.

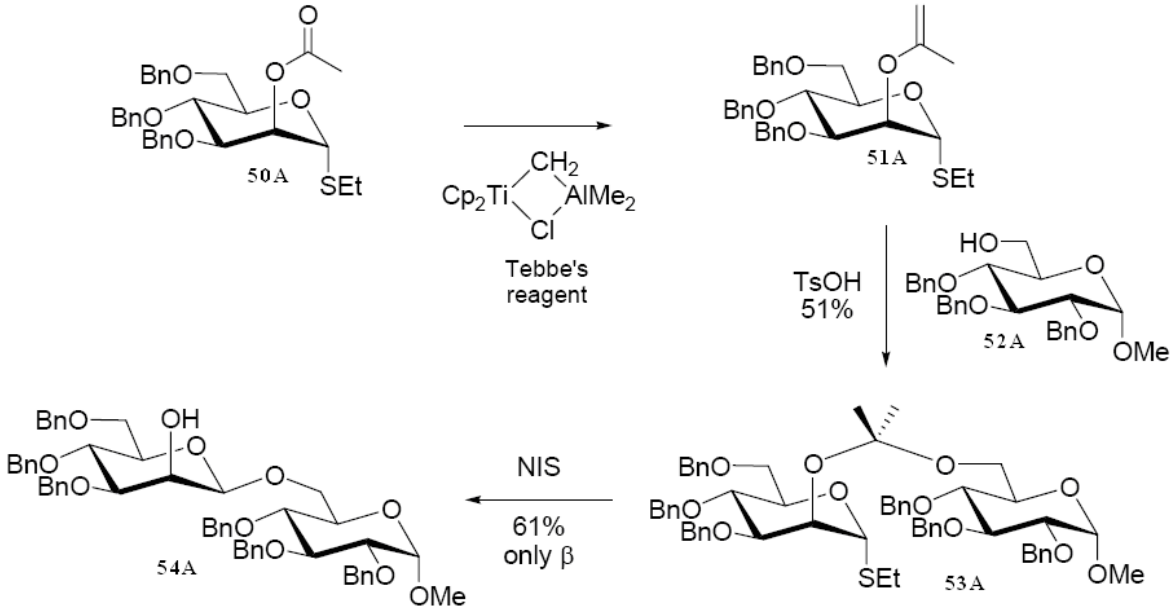
Glucuronic acid **42A** adopts a $^4C_1$ conformation with the *C*-4 hydroxyl group equatorially oriented. Locking the conformation of the glycosyl acceptor in a $^1C_4$ conformation allowed the completely selective preparation of the desired *cis*-glycoside. Coupling glycosyl tricholoroacetimidate **41A** with acceptor **44A** resulted exclusively in formation of the α-linked disaccharide **45A** in very good yield.

The **intramolecular aglycone delivery (IAD)** method is a new and effective strategy developed to improve stereocontrol and yields in difficult glycosylations. It was introduced by Hindsgaul and coworkers for the preparation of β-D-mannopyranosides.[116] The strategy involves the initial covalent attachment of the glycosyl acceptor to a group on *O*-2 of the glycosyl donor (**Scheme 28**). Activation of the anomeric leaving group in the tethered derivative **46A** by an electrophile is then expected to proceed intramolecularly *via* a concerted mechanism. Thus, the derivative **46A** results in formation of **48A** via **47A**. On quenching with water, **48A** releases *O*-2 and yields the glycoside **49A**.



Scheme 28 Intramolecular Aglycone Delivery.

This concept was implemented using isopropylidene ketal type tethering. As shown in **Scheme 29**, the 2-*O*-acetyl thioglycoside **50A** was transformed into the isoprenyl ether **51A** using Tebbe's reagent. Acid-catalyzed addition of the glycosyl acceptor **52A** afforded the tethered derivative **53A**. Glycosylation by activation of the thioglycoside with NIS afforded the β-mannopyranoside **54A** with excellent stereoselectivity.



Scheme 29 Intramolecular Aglycone Delivery Using Isopropylidene Ketal Tethering.

The method worked well on simple molecules; however its exstension to higher oligosaccharides and complex structures had limited success.[117] Numerous variations of the above intramolecular glycosylation were studied, including changes in the position of linkers and variations in the length, the type and the rigidity of the linker.[118]

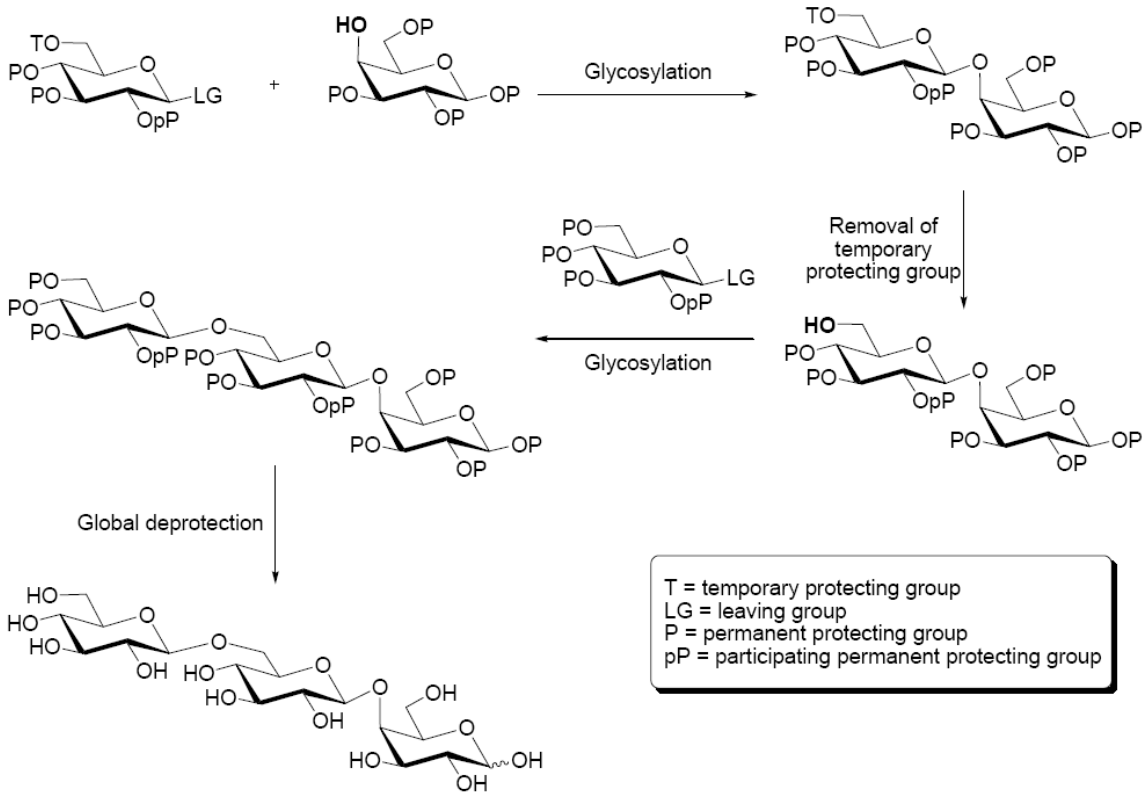
Regioselectivity of Glycosidation Reactions

Glycosylation reactions have to fulfil the essential requirement of regioselectivity. This issue is generally settled by the use of protection strategies. Protecting group manipulations represent an essential aspect of all total syntheses of organic molecules. This is particularly true in oligosaccharide synthesis, because of the multifunctional nature of carbohydrates. Most of the functional groups present on these molecules are of the same sort - hydroxyl groups – and necessitate regioselective protection strategies. As previously anticipated, all the functional groups that could potentially compete with the desired nucleophile in the attack on glycosyl donor are, generally, suitably protected.[119] When a simple disaccharide has to be synthesized, theoretically, only one kind of protecting group can be used for both reaction partners. Even in this simple case, however, regioselective protecting group manipulations have to be exerted on both molecules, either to differentiate the anomeric center from the other hydroxyl groups of glycosyl donor and to regioselectively protect all the nucleophilic groups on the acceptor but the one desired. All the protecting groups used in carbohydrate chemistry have to be stable in glycosylation conditions and must be installed and removed without compromising the stability of both saccharide ring and the sensitive glycosidic bond.

These requirements limit the number of protecting groups that are used in carbohydrate chemistry, if compared with those used in other fields of organic chemistry. On the other hand, like in any other area of organic synthesis, in oligosaccharide syntheses it's extremely crucial to rely on a wide range of protecting groups, in order to project efficient synthetic strategies.

By far, the most important protecting groups in carbohydrate chemistry are those used for the protection of hydroxyl groups, including the anomeric hemiacetal. Amino-protecting groups (for amino-deoxy sugars) and carboxyl protection (for uronic acids) are also of interst. Several procedures can be followed for installation and cleavage also in regioselective fashion[120] of the most important protecting groups used in carbohydrate chemistry.

In oligosaccharide synthesis beyond the level of disaccharides, **temporary and permanent** protecting groups must frequently be distinguished. Permanent protecting groups will remain through all synthetic steps until the liberation of final target oligosaccharide. The removal of temporary protecting groups during the synthetic sequence will reveal a free hydroxyl group, most often to produce a glycosyl acceptor ready for glycosylation (**Scheme 30**).



Scheme 30 Schematic Synthesis of a Trisaccharide.

The two different types of protecting groups require different qualities. It must be possibile to introduce and remove permanent groups in bulk with regiocontrol and high efficiency. Obviously, they should be stable to conditions used for the removal (and introduction) of temporary groups. In the synthesis of branched structures or structures with substituents (phosphates, sulfates, acetates, etc.), it might be required the preparation of building blocks whose hydroxyl groups have to be differentiated from each other by orthogonal sets of temporary protecting groups. The idea of **orthogonal protection** was defined by Baranay and Mettifield as "a set of completely independent classes of protection groups, such that each class can be removed in any order and in the presence of all other classes".[121]

Preferably only one type of permanent protecting group should be used, to allow only one final deprotection step, an aspiration seldom possible to realize. Very few of the large numbers of protecting groups available fulfil the criteria for permanent protecting groups. More or less only acetates, benzoates, benzyl ethers, benzylidene and isopropylidene acetals have the stability and, at the same time, the efficient introduction/deprotection properties needed to make them suitable for this purpose.

For effectively synthesize complex oligosaccharidic targets, it's clear that differently protected precursors have to be prepared. For this scope, it's essential to dispose of synthetic

methodologies for distinguishing between the several hydroxyl groups present on the saccharidic backbone in order to regioselectively install a given protection on a determinate position.[122] General considerations on the reactivity of the various hydroxyl groups present on the sugar ring have to be discussed. In aldo-hexo-pyranoses three different kind of hydroxyl groups can be distinguished: the hemiacetalic at *C*-1, the primary at *C*-6, and three secondary hydroxyl groups at *C*-2, *C*-3 and *C*-4. The reactivity of the hemiacetalic OH is clearly different from the others. Unlike the other positions, the anomeric center in acidic conditions undergoes nucleophilc attack and, because of this, can be easily differentiated. Installation of a temporary protecting group at the anomeric position in Fischer conditions is generally the first operation of a multi-step building block synthesis. Most of the procedures for protecting groups installation exploit the nucleophilicity of the hydroxyl functions of the sugars. In these cases the primary position is appreciably more reactive than the other non-anomeric positions. The primary alchool can be effectively chemoselectively functionalized with a bulky protecting group (such as DMT, TBDMS, TIPS, etc.) in the presence of free secondary hydroxyl groups. The ability of distinguishing between the three secondary position is strongly dependent by their configuration. Consistent with well-known generalizations from cyclohexane chemistry, equatorial secondary hydroxyl groups of pyranoid compounds tend to react more readily than axial groups.

Oligosaccharide Synthesis

For the successful synthesis of oligosaccharides, both chemical reactions and tactics are important concerns. All the methodologies developed for effectively promote, stereo- and regio-chemically direct glycosylation reactions have to be skilfully combined in order to achieve the desired oligosaccharide targets in high yields and reasonable time. For the efficient synthesis of oligosaccharides, **stepwise** or **convergent** methods can be employed (**Figure 11**).

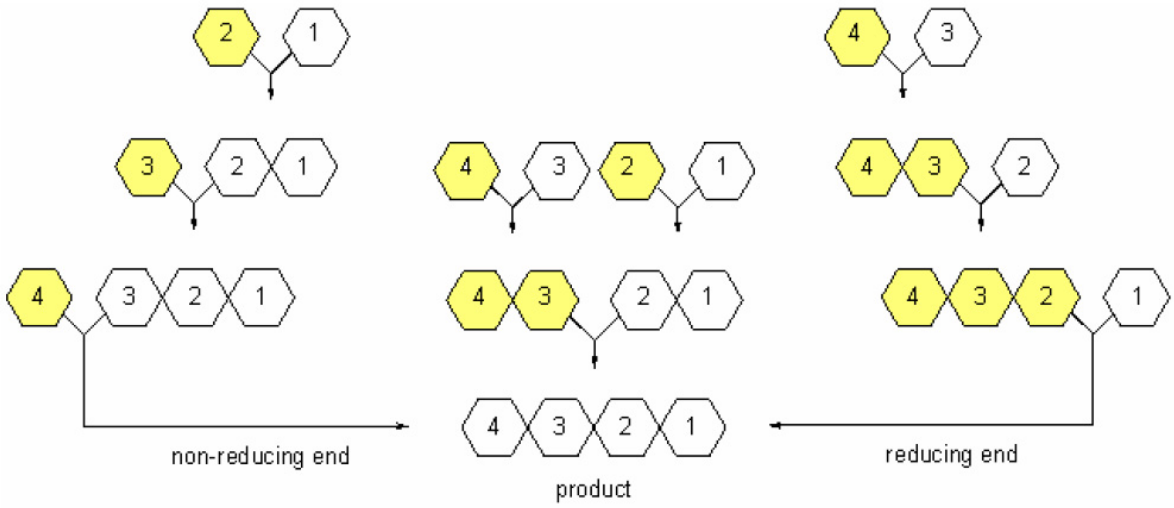
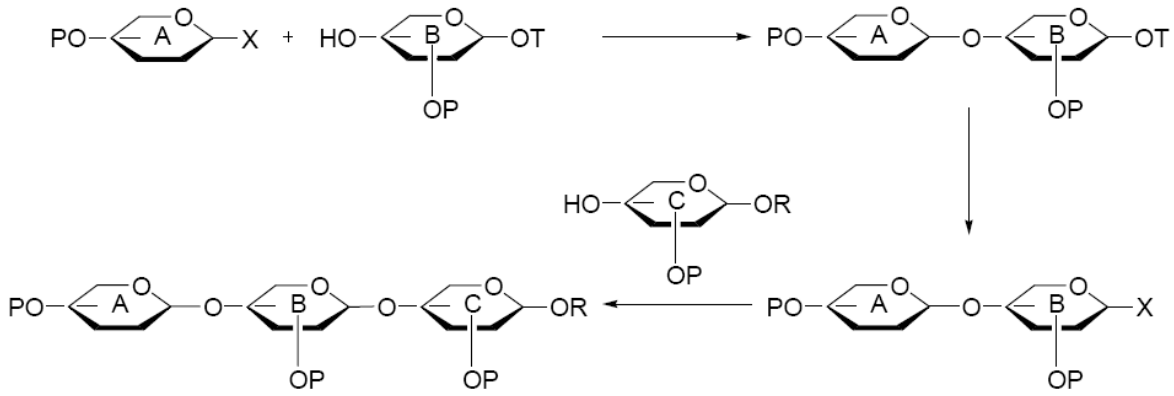


Figure 11 Stepwise and Convergent Methods in the Synthesis of Oligosaccharides.

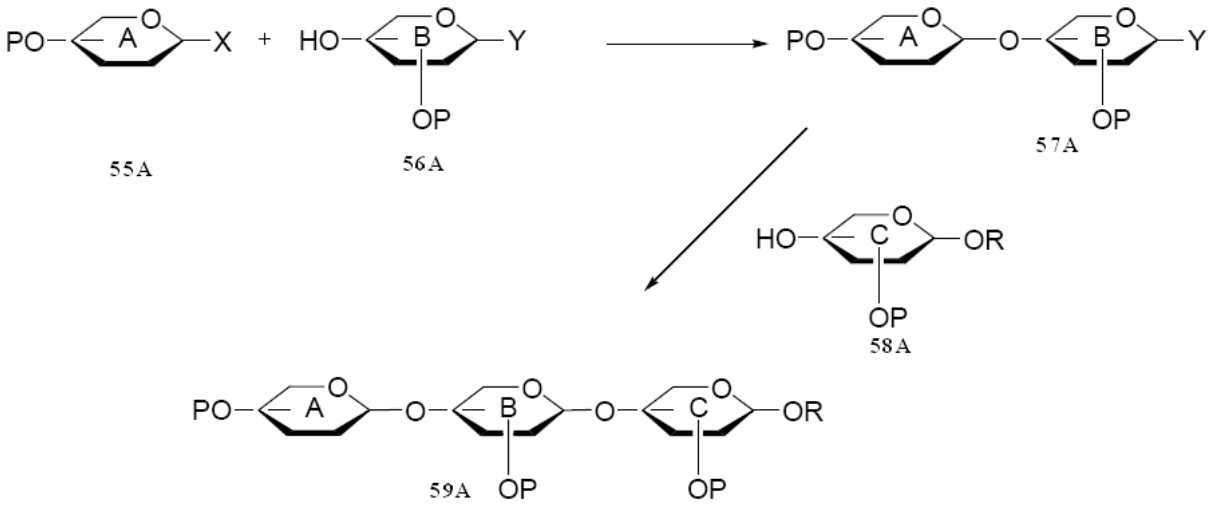
In the stepwise format the synthesis might start either from the reducing or the nonreducing end. The first approach is generally more convenient. Because of their reactivity, during glycosylations most glycosyl donors often undergo side-reactions (hydrolysis, rearrangement, etc.). Thus, in order to maximize coupling yields, they are used in slight excess compared with glycosyl acceptors. Starting from the non-reducing end implies the use of oligosaccharide donors and, therefore, the waste of precious oligosaccharide structures in case of decomposition. The use of monosaccharide donors and oligosaccharide acceptors is preferable instead. Unreacted glycosyl acceptors can be easily recovered from the glycosylation medium and directly reused. Hydrolysis or decomposition products require more synthetic steps to be converted into the parent glycosyl donors. The recent development of new anomeric protecting groups and some substituent groups that can be easily converted into leaving groups, however, has enabled the alternative format (starting from the non-reducing end) to be used. The concept of stepwise synthesis is especially important for the construction of relatively small oligomers, but the convergent format is preferably employed for the synthesis of larger saccharides, especially in the syntheses of oligosaccharides

possessing repeating units in their structures. Furthermore, block syntheses reduce the overall number of steps and the convergent nature of this strategy makes it more efficient. Also, block syntheses afford greater flexibility in synthetic design. Specifically critical steps can be performed at early stages on smaller molecules, thereby facilitating chromatographic separations. In block syntheses, the reducing end unit of a block has to fulfil opposite requirements. It should be stable enough to serve as a glycosyl acceptor in the synthesis of the block and, at the same time, it should be reactive enough to serve as glycosyl donor in the assembly of the oligosaccharide from the blocks. Several strategies have been adopted to settle this issue. One solution to this problem is to **exchange the anomeric substituent** after the synthesis of the block. During the synthesis of the block, the reducing end is protected by a temporary protecting group (T), that is then removed converting the block into a glycosyl donor with a leaving group (X) at the reducing end (**Scheme 31***)*.



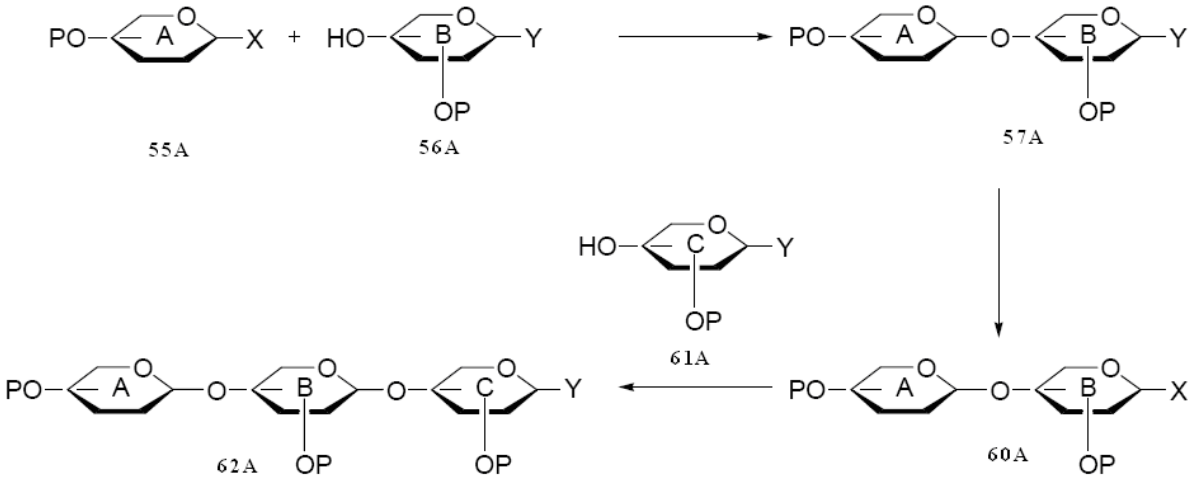
Scheme 31 Block Synthesis by Reactivation via Exchange of the Anomeric Substituent.

A drawback of this strategy is that the conversion of the block into a glycosyl donor requires several steps, which are especially undesirable in the case of larger fragments. An alternative approach uses **different types of glycosyl donors** in sequential glycosylation steps. As **Scheme 32** shows, the key intermediate **56A** carries an unprotected hydroxyl and has an anomeric substituent (Y) that withstands glycosylation with donor **55A**. After glycosylation, the newly generated block **57A** can be used directly as a donor, without any replacement of the anomeric substituent, to provide the oligosaccharide **59A**. An example of this strategy is reported in **Scheme 15** of this chapter.



Scheme 32 Block Synthesis by Sequential Glycosylations with Different Types of Glycosyl Donors.

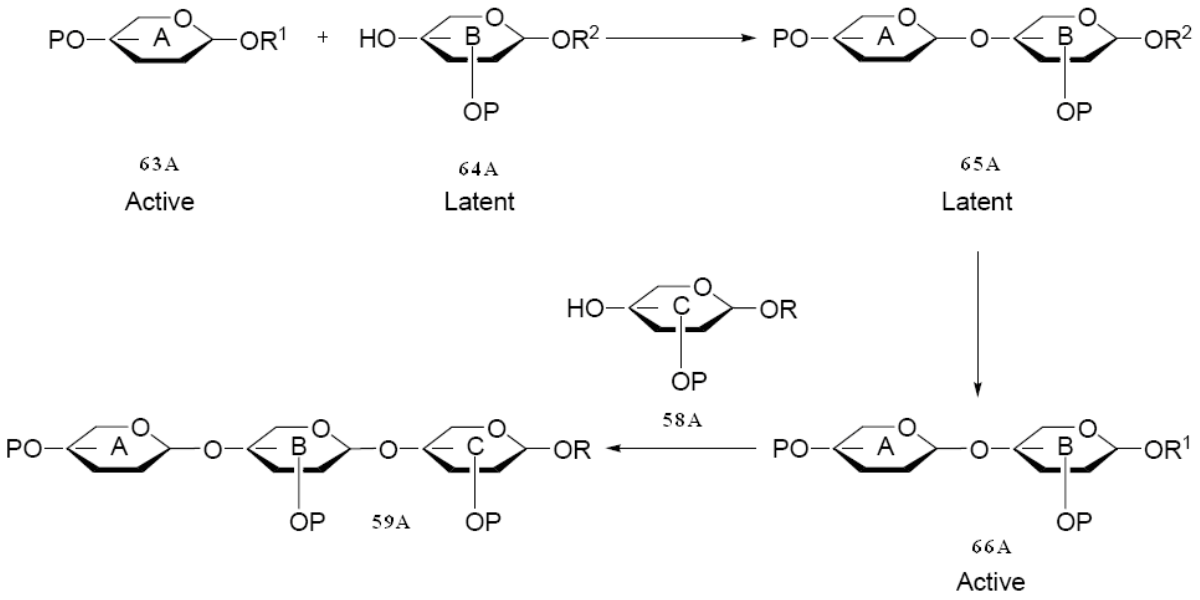
Nicolaou and coworkers proposed the **two-stage activation** strategy,[34] where two types of anomeric substituents are used. One type, having Y at the anomeric center, serves as glycosyl acceptor (**56A**), the other one, possessing X, is used as glycosyl donor **55A** (**Scheme 33**).



Scheme 33 Block Two-Stage Activation.

After glycosylating **56A** with **55A**, the anomeric substituent Y in the coupling product **57A** is converted back into X (**60A**), so the resulting block can be used as a donor in further glycosylations. Using acceptor **61A** of the same type as before makes the process suitable for further reiteration. Nicolaou used glycosyl fluorides as glycosyl donors and thioglycosides as acceptors and the procedure took advantage of the ready conversion of thioglycoside into glycosyl fluorides with NBS and DAST, as also shown in **Scheme 4** in this chapter.

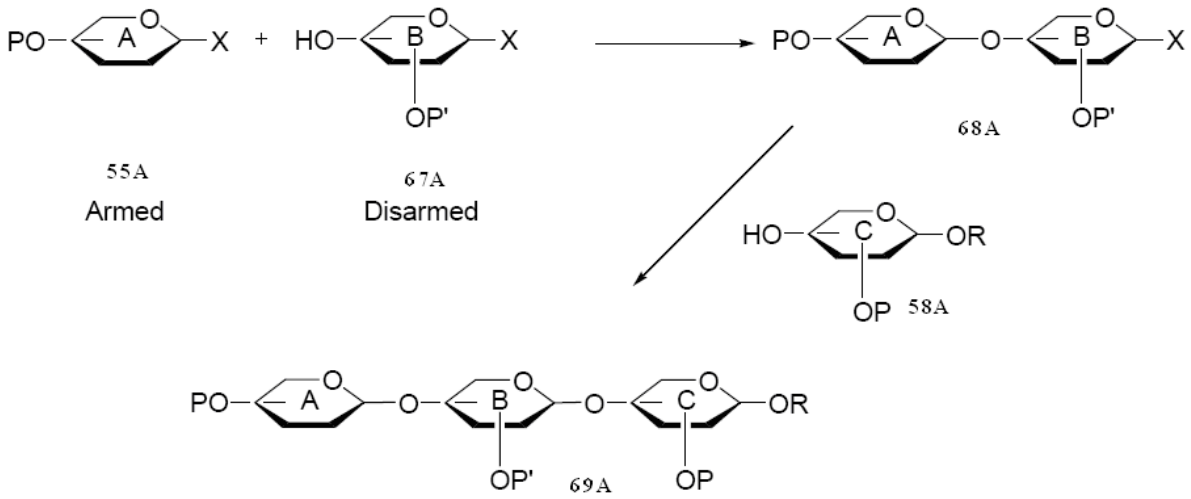
In ***active-latent*** glycosylation strategy, the glycosyl donor capability of an acceptor is turned on by a slight chemical modification in its aglycone. Glycosylation of the latent compound **64A** by the active donor **63A** affords the latent disaccharide **65A** (**Scheme 34**).



Scheme 34 Active-Latent Glycosylation.

Conversion of disaccharide aglycone (R^2) into an active form (R^1), transforms **65A** into active glycosyl donor **66A** that can be used in further chain elongations. This approach has been used by Danishefsky in iterative glycosylations using glycals as latent compounds and 1,2-anhydro sugars as active glycosyl donors, as depicted in **Scheme 14** in this chapter.

The ***armed-disarmed*** concept can also be counted among the several glycosylation strategies used in block syntheses. As shown in **Scheme 35**, the armed glycosyl donor **55A** can be coupled with the disarmed **67A** without self condensation of the latter. The resulting disarmed compound **68A** can be used as a glycosyl donor in further coupling, either by arming it, by exchanging the protecting groups, or by using a more powerful promoter capable of activating the disarmed compound. Besides general synthetic strategies, some new methods and techniques are also worthy of discussion. In the traditional approaches of oligosaccharide synthesis, the product of a glycosylation reaction had to be isolated and it required some chemical transformations to make it suitable for the next glycosylation reaction.



Scheme 35 Block Armed-Disarmed Glycosylation.

In some of the synthetic strategies that it will be showed in **Chapter E**, **Chapter F** and herein described, such as in the sequential and in the armed-disarmed glycosylations, the product of one glycosylation reaction is used directly in the next coupling reaction. This opened the way for omitting the isolation step and performing multiple glycosylations in a **one-pot** fashion (**Figure 12**).

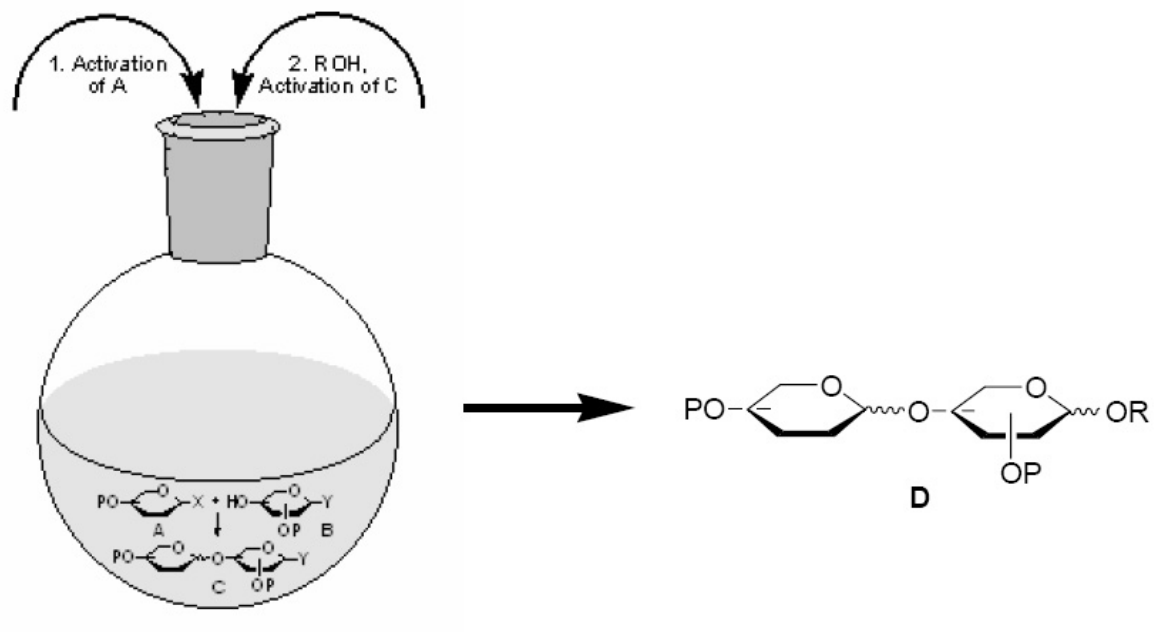
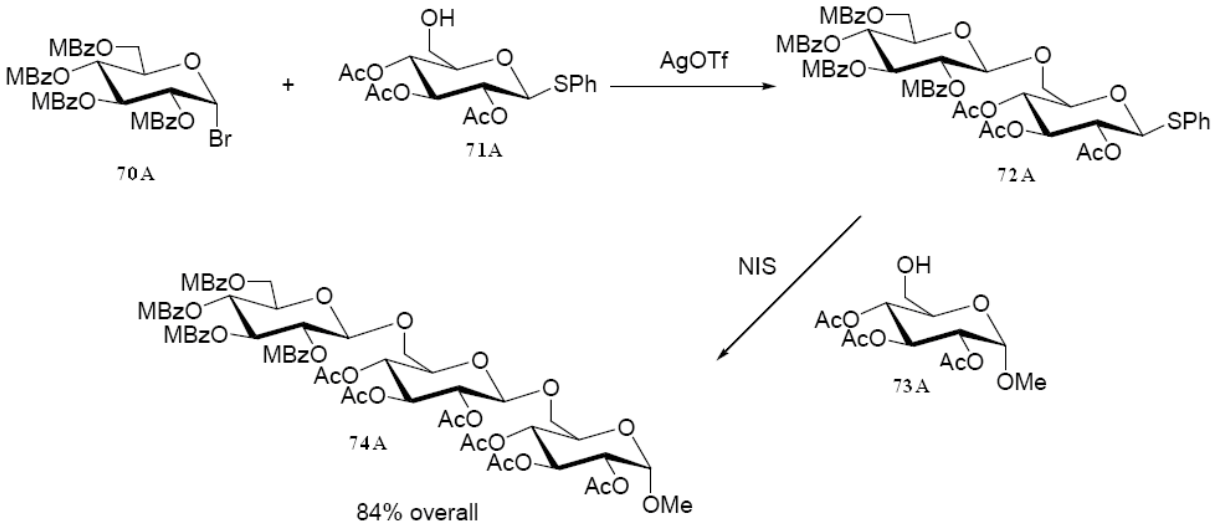


Figure 12 General Scheme of One-Pot Glycosylation.

Several glycosylation strategies can be performed in a one-pot manner. Often different types of glycosyl donors are employed in one-pot sequential glycosylations. Generally, the orthogonality between the different classes of the used donors is not required. Glycosylation

are performed starting from the non reducing end, sequentially activating glycosyl donors with increasing stability. The first one-pot glycosylation sequence using this approach performed the progressive glycosylation of thioglycoside acceptor **71A** by glycosyl bromide **70A**, and then of *O*-glycoside **73A** by the newly formed thioglicoside donor **72A** (glycosyl bromide → thioglycoside → *O*-glycoside) (**Scheme 36**).[123]



Scheme 36 One-pot Sequential Glycosylation Using Different Types of Glycosyl Donors.

Similar one-pot glycosylation sequences were performed using glycosyl trichloroacetimidate → thioglycoside → *O*-glycoside; glycosyl fluoride → thioglycoside → *O*-glycoside or glycosyl phosphate → thioglycoside → glycal.

Armed-disarmed type glycosylations can also be readily performed in a one-pot fashion. In this case the leaving group on the glycosyl donors is always the same. The control of the chemoselectivity is exerted by tuning the glycosyl donor reactivities through suitable protection strategies. The ability to control glycosyl donor reactivity by careful selection of hydroxyl protecting groups is one of the underlying principles of **programmable one-pot oligosaccharide syntheses**. Wong and coworkers set up a procedure for determining glycosyl donor reactivity by a competitive HPLC experiment.[9] Donors and acceptors with donor capability (thioglycosides with one hydroxyl group exposed) with various protecting group patterns provided a set of building blocks with diverse reactivities. The relative reactivity values (RRVs), as observed by HPLC, were tabulated in a database, from which the computer program 'Optimer' was created. After the user has selected an oligosaccharide structure, the program lists the best combination of building blocks for its preparation. With this strategy, oligosaccharides containing three to six monosaccharides are rapidly assembled in minutes or hours by mixing the selected building blocks in sequence, with the most reactive first.

‘Optimer’ has been successfully applied to the synthesis of linear and branched oligosaccharide structures, as well as to the construction of a 33-membered oligosaccharide library.[124]

References

1. Taylor M. E., Drickamer K. in *Introduction to Glycobiology*, Oxford University Press: New York, **2006**.

2. Lowe, J. B., in *The molecular basis of blood diseases*, Eds.: Stamatoyannopolous, G., Nienhuis, a. W., Majerus, P. W., Varmus, H., Saunders, Philadelphia, **1987**, chap 8.

3. Lehmann J. in *Carbohydrates-Structure and Biology-*, Thieme, Stuttgart·New York: **1998**.

4. a) Rudd, P. M.; Elliot, T.; Cresswell, P.; Wilson, I. A.; Dwek, R. A. S*cience* **2001**, *291*, 2370; b) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683; c) Feizi, T. *Curr. Opin. Struct. Biol.* **1993**, *3*, 701; d) Rosen, S. D.; Bertozzi, C. R. *Curr. Biol.* **1996**, *6*, 261; e) Varki, A. *Glycobiology* **1993**, *3*, 97; f) Philips, M. L.; Nudelman, E.; Gaeta, F. C. A.; Perez, M.; Singal, A. K.; Hakomori, S.; Paulson, J. C. *Science* **1990**, *250*, 1130; g) Lasky, L. A. *Science* **1992**, *258*, 964; Miller, D. J.; Macek, M. B.; Schur, B. D. *Nature* **1992**, *357*, 589; h) Feizi, T. *Nature* **1985**, *314*, 53.

5. a) Treves, A. J.; Carnaud, C.; Tranin, N.; Feldman, M.; Cohen, I. R. *Eur. J. Immunol.* **1974**, *4*, 722; b) Fujimoto, S.; Greene, M. I.; Sehon, A. H. *J. Immunol.* **1976**, *116*, 791; c) Naor, D. *Adv. Cancer. Res.* **1979**, *29*, 45; d) Dye, E. S.; North, R. J. *J. Exp. Med.* **1981**, *154*, 1033; e) Kirchner, H.; Chused, T. M.; Herberman, R. B.; Holden, H. T.; Lavrin, D. H. *J. Exp. Med.* **1974**, *139*, 1473.

6. *Carbohydrate-based Drug Discovery*, Wong C. –H., Ed., Wiley-VCH: Weinheim, **2003**.

7. Hirabayashi, J.; Kasai, K.-I. *Trends in Glycoscience and Glycotechnology*, **2000**, 63, 1.

8. Plante, O. J.; Palmacci, E. R.; Seeberger, P. H. *Science* **2001**, *291*, 1523.

9. Zhang, Z.; Ollmann, I. R.; Ye, X. –S.; Wishnat, R.; Baasov, T.; Wong, C. –H. *J. Am. Chem. Soc.* **1999**, *121*, 734.

10. *Carbohydrates in Chemistry and Biology*, Part II Vol.2, Ernst B., Hart G. W., Sinaÿ P., Eds, Wiley-VCH: Weinheim, **2000**.

11. a) *Carbohydrates in Chemistry and Biology*, Part II Vol.2, Ernst B., Hart G. W., Sinaÿ P., Eds, Wiley-VCH: Weinheim, **2000**; b) *The Organic Chemistry of Sugars*, Levy D. E., Fügedi, P., Eds., Taylor & Francis: Boca Raton, **2006**.

12. a) Koenigs, W.; Knorr, E. *Ber. Dtsch. Chem. Ges*. **1901**, *34*, 957; b) Wulff, G.; Röhle, G. *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 157; c) Igarashi, K. *Adv. Carbohydr. Chem. Biochem.* **1977**, *34*, 243.

13. Garegg, P. J.; Johansson, R.; Samuelsson, B. *Acta Chem. Scand. B* **1982**, *36*, 249.

14. a) Helferich, B.; Wedemeyer, K. -F. *Liebigs Ann. Chem.* **1949**, *563*, 139; b) Helferich, B.; Jung, K. -H. *Liebigs Ann. Chem.* **1954**, *589*, 77; c) Helferich, B.; Berger, A. *Chem. Ber.* **1957**, *90*, 2492.

15. Schroeder, L. R.; Green, J. W. *J. Chem. Soc. C* **1966**, 530.

16. Bock, K.; Medal, M. *Acta Chem. Scand. B* **1983**, *37*, 775.

17. Conrow, R. B.; Bernstein, S. *J. Org. Chem.* **1971**, *36*, 863.

18. a) Bredereck, H.; Wagner, A.; Faber, G.; Ott, H. *Chem. Ber.* **1959**, *92*, 1135; b) Bredereck, H.; Wagner, A.; Kuhn, H.; Ott, H. *Chem. Ber.* **1960**, *93*, 1201; c) Bredereck, H.; Wagner, A.; Geissel, D.; Gross, P.; Hutten, U.; Ott, H. *Chem. Ber.* **1962**, *95*, 3056; d) Bredereck, H.; Wagner, A.; Geissel, D.; Ott, H. *Chem. Ber.* **1962**, *95*, 3064.

19. a) Lemieux, R. U.; Takeda, T.; Chung, B. Y. *ACS. Symp. Ser.* **1976**, *39*, 90; b) Hanessian, S.; Banoub, J. *Carbohydr. Res.* **1977**, *53*, C13.

20. Paulsen, H.; Lockhoff, O. *Chem. Ber.* **1981**, *114*, 3102.

21. Garegg, P. J.; Ossowski, P. *Acta Chem. Scand. B* **1983**, *37*, 249.

22. van Boeckel, C. A. A.; Beetz, T. *Recl. Trav. Chim. Pays-Bas* **1987**, *106*, 596.

23. Ogawa, T.; Matsui, M. *Carbohydr. Res.* **1976**, *51*, C13.

24. Higashi, K.; Nakayama, K.; Soga, T.; Shioya, E.; Uoto, K.; Kusama, T. *Chem. Pharm. Bull.* **1990**, *38*, 3280.

25. Leimieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056.

26. Mukaiyama, T.; Murai, Y.; Shoda, S. -Y. *Chem. Lett.* **1981**, 431.

27. a) Shimizu, M.; Togo, H.; Yokoyama, M. *Synthesis* **1998**, 799; b) Toshima, K. In *Glycoscience – Chemistry and Chemical Biology*, Fraser-Reid, B., Tatsuta, K., Thiem, J., Eds., Springer Verlag, Berlin, Heidelberg, 2001, pp.584-625.

28. Posner, G. H.; Haines, S. R. *Tetrahedron Lett.* **1985**, *26*, 5.

29. a) Ogawa, T.; Takahashi, Y. *Carbohydr. Res.* **1985**, *138*, C5; b) Takahashi, Y.; Ogawa, T. *Carbohydr. Res*. **1987**, *164*, 277.

30. Hashimoto, S.; Hayashi, M.; Noyori, R. *Tetrahedron Lett.* **1984**, *25*, 1379.

31. a) Nicolaou, K. C.; Chucholowski, A.; Dolle, R. E.; Randall, J. L. *J. Chem. Soc. Chem. Commun.* **1984**, 1155; b) Kunz, H.; Sager, W. *Helv. Chim. Acta* **1985**, *68*, 283; c) Kunz, H.; Waldmann, H. *J. Chem. Soc. Chem. Commun.* **1985**, 638.

32. a) Dobarro-Rodriguez, A.; Trumtel, M.; Wessel, H. P. *J. Carbohydr. Chem.* **1992**, *11*, 255; b) Wessel, H. P. *Tetrahedron Lett.* **1990**, *31*, 6863; c) Wessel, H. P.; Ruiz, N. *J. Carbohydr. Chem.* **1991**, *10*, 901.

33. a) Jona, H.; Mandai, H.; Chavasiri, W.; Takeuchi, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 291; b) Mukaiyama, T.; Jona, H.; Takeuki, K. *Chem. Lett.* **2000**, 696; c) Jona, H.; Takeuki, K.; Mukaiyama, T. *Chem. Lett.* **2000**, 1278.

34. Nicolaou, K.C.; Dolle, R.E.; Papahatjis, D. P. *J. Am. Chem. Soc.* **1984**, *106*, 4189.

35. Barena, M. I.; Echarri, R.; Castillon, S. *Synlett* **1996**, 675.

36. Fischer, E.; Fischer, H. *Ber. Dtsch. Chem. Ges.* **1910**, *43*, 2521.

37. Glycosyl iodides are object of **Chapter B** and in part of **Charter D**, for more insights in their preparation and use in glycosylation reactions **Chapter B**.

38. Fisher, E.; Delbrück, K. *Ber.* **1909**, *42*, 1476.

39. a) Horton, D.; Hutson, D. H. *Adv. Carbohydr. Chem.* **1963**, *18*, 123; b) Norberg, T. in *Modern methods in Carbohydrate Synthesis*, Khan, S. H., O'Neill, R. A., Eds., Harwood Academic Publishers, **1995**, pp 82-106; c) Garegg, P. J. *Adv. Carbohydr. Chem. Biochem.* **1997**, *52*, 179.

40. a) Ferrier, R. J.; Furneaux, R. H. *Carbohydr. Res.* **1976**, *52*, 63; b) Dasgupta, F.; Garegg, P. J. *Acta Chem. Scand.* **1989**, *43*, 471.

41. a) Horton, D. *Methods Carbohydr. Chem.* **1963**, *2*, 433; b) Valerio, S.; Iadonisi, A.; Adinolfi, A.; Ravidà, A. *J. Org. Chem.* **2007**, *72*, 6097.

42. Ferrier, R. J.; Hay, R. W.; Vethaviyasar, N. A. *Carbohydr. Res.* **1973**, *27*, 55.

43. a) Tsai, T. Y. R.; Jin, H.; Wiesner, K. A. *Can. J. Chem.* **1984**, *62*, 1403; b) van Cleve, J. W. *Carbohydr. Res.* **1979**, *70*, 161; c) Garegg, P. J.; Henrichson, C.; Norberg, T. *Carbohydr. Res.* **1983**, *116*, 162.

44. a) Hanessian, S.; Bacquet, C.; Lehong, N. *Carbohydr. Res.* **1980**, *80*, C17; b) Nicolaou, K. C.; Seitz, S. P.; Papahatjis, D. P. *J. Am. Chem. Soc.* **1983**, *105*, 2430.

45. a) Lönn, H. *Carbohydr. Res.* **1985**, *139*, 105; b) Lönn, H. *Carbohydr. Res.* **1985**, *139*, 115; c) Lönn, H. *J. Carbohydr. Chem.* **1987**, *6*, 301.

46. a) Andersson, F.; Fügedi, P.; Garegg, P. J.; Nashed, M. *Tetrahedron Lett.* **1986**, *27*, 3919; b) Fügedi, P. in *e-EROS, Electronic Encyclopedia of Reagents for Organic Synthesis*, Paquette, L. A., Ed., Wiley Interscience, New York, **2002**, http://www.mrw.interscience.wiley.com/eros/eros_articles_fs.html.

47. a) Griffin, G. W.; Bandara, N. C.; Clarke, M. A.; Tsang, W. –S.; Garegg, P. J.; Oscarson, S.; Silwanis, B. A. *Heterocycles* **1990**, *30*, 939; b) amatore, C.; Jutand, A.; Mallet, J. –M.; Meyer, G.; Sinaÿ, P. *J. Chem. Soc. Chem. Commun.* **1990**, 718; c) Balavoine, G. Greg, A.; Fischer, J. –C.; Lubineau, A. *Tetrahedron Lett.* **1990**, *31*, 5761; d) Marra, A.; Amatore, J. –M.; Amatore, C.; Sinaÿ, P. *Synlett* **1990**, 572.

48. a) Veeneman, G. H.; van Boom, J. H. *Tetrahedron Lett.* **1990**, *31*, 275; b) Zuurmond, H. M.; van der Laan, S. C.; van der Marel, G. A.; van Boom, J. H. *Carbohydr. Res.* **1991**, *215*, C1; c) Smid, P.; de Ruiter, G. A.; van der Marel, G. A.; Rombouts, F. M.; van Boom, J. H. *J. Carbohydr. Chem.* **1991**, *10*, 833.

49. Veeneman, G. H.; van Leeuwen, S. H.; Zuurmond, H.; van Boom, J. H. *J. Carbohydr. Chem.* **1990**, *9*, 783.

50. Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.*. **1990**, *31*, 1331.

51. a) Konradsson, P.; Mootoo, D. R.; McDevitt, R. E.; Fraser-Reid, B. *J. Chem. Soc. Chem. Commun.* **1990**, 270; b) Konradsson, P.; Udodong, U. E.; Fraser-Reid, B. *Tetrahedron Lett.* **1990**, *31*, 4313.

52. Aloui, M.; Fairbanks, A. J. *Synlett* **2001**, 797.

53. Codèe, J. D. C.; Litjens, R. E. J. N. ; van den Bos, L. J.; Overkleft, H. S.; van der Marel, G. A. *Chem. Soc. Rev.* **2005**, *34*, 769-782.

54. a) Mukaiyama, T.; Nakatsuka, T.; Shoda, S. *Chem. Lett.* **1979**, 487; b) Gama, Y.; Yasumoto, A. *Chem. Lett.* **1993**, 319.

55. a) Demchenko, A. V.; Kamat, M. N.; De Meo, C. *Synlett* **2003**, 1287; b) Demchenko, A. V.; Malysheva, N. N.; De Meo, C. *Org. Lett.* **2003**, *5*, 455.

56. Chen, Q.; Kong, F. *Carbohydr. Res.* **1995**, *272*, 149.

57. Garegg, P. J.; Oscarson, S.; Szönyi, M. *Carbohydr. Res.* **1990**, *205*, 125.

58. a) Oscarson, S.; Tedebarck, D.; Turek, D. *Carbohydr. Res.* **1997**, *159*, 159; b) Wang, L. – X.; Sakiri, N.; Kezukura, H. *J. Chem. Soc. Perkin I* **1990**, 1677; c) Krog-Jensen, C.; Oscarson, S. *J. Org. Chem.* **1996**, *61*, 1234.

59. a) Das, S. K.; Ghosh, R.; Roy, N. *J. Carbohydr. Chem.* **1993**, *12*, 693; b) Zuurmond, H. M.; van der Laan, S. C.; van der Marel, G. A.; van Boom, J. H. *Carbohydr. Res.* **1991**, *215*, c1.

60. a) Fügedi, P.; Garegg, P. J.; Lönn, H.; Norberg, T. Glycoconjugate J. **1987**, 4, 97; b) Garegg, P. J. Adv. Carbohydr. Chem. Biochem. **1997**, 52, 179.

61. Schmidt, R. R.; Michel, J. Angew. Chem. Int. Ed. Engl. **1980**, 19, 731.

62. Schmidt, R. R.; Michel, J. Tetrahedron Lett. **1984**, 25, 821.

63. a) Yu, B.; Tao, H. *Tetrahedron Lett.* **2001**, *42*, 2405; b) Yu, B.; Tao, H. *J. Org. Chem.* **2002**, *67*, 9099.

64. Schimdt, R. R.; Michel, J.; Roos, M. *Liebigs Ann. Chem.* **1984**, 1343.

65. Adinolfi, M.; Barone, G.; Iadonisi, A.; Schiattarella, M. *Synlett* **2002**, 269.

66. Adinolfi, M.; Iadonisi, A.; Ravidà, A.; Schiattarella, M. *J. Org. Chem.* **2005**, *70*, 5316.

67. Tamura, K.; Mizukami, H.; Maeda, K.; Watanabe, H.; Uneyama, K. *J. Org. Chem.* **1993**, *58*, 32.

68. Cai, S.; Yu, B. Org. Lett. 2003, 5, 3827.

69. Schmidt, R. R.; Grundler, G. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 781.

70. Adinolfi, M.; Barone, G.; Iadonisi, A.; Schiattarella, M. *Synlett* **2002**, 269.

71. Adinolfi, M.; Barone, G.; Guariniello, L.; Iadonisi, A. *Tetrahedron Lett.* **2000**, *41*, 9005.

72. a) Adinolfi, M.; Barone, G.; Iadonisi, A.; Mangoni, L.; Schiattarella, M. *Tetrahedron Lett.* **2001**, *42*, 5967; b) Adinolfi, M.; Barone, G.; Iadonisi, A.; Schiattarella, M. *Tetrahedron Lett.* **2002**, *43*, 5573.

73. Adinolfi, M.; Barone, G.; Iadonisi, A.; Schiattarella, M. *Org. Lett.* **2003**, *5*, 987.

74. Adinolfi, M.; Iadonisi, A.; Ravidà, A.; Valerio, S. *Tetrahedron Lett.* **2006**, *47*, 2595.

75. Adinolfi, M.; Iadonisi, A.; Schiattarella, M. *Tetrahedron Lett.* **2003**, *44*, 6479.

76. a) Adinolfi, M.; Iadonisi, A.; Ravidà, A. *Synlett* **2006**, 583; b) S. Valerio, M. Adinolfi, A. Iadonisi, A. Pastore, *J. Org. Chem.* **2008**, *73*, 4496-4503. The results of this second work are described with more details in **Chapter E**.

77. Nakajima, N.; Saito, M.; Kudo, M.; Ubukata, M. *Tetrahedron* **2002**, *58*, 3579.

78. Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21.

79. a) Cramer, F.; Hennrich, N. *Chem. Ber.* **1961**, *94*, 976; b) Zhu, T.; Boons, G. –J. *Carbohydr. Res.* **2000**, *329*, 709.

80. Schmidt, R. R.; Toepfer, A. *Tetrahedron Lett.* **1991**, *32*, 3353.

81. Halcomb, R. L.; Danishefsky, S. J.; *J. Am. Chem. Soc.* **1989**, *111*, 6661.

82. Danishefsky, S. J.; Bilodeau, M. T. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1380.

83. Gervay, J.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 5448.

84. Liu, K. K. C.; Danishefsky, S. J. *J. Org. Chem.* **1994**, *59*, 1892.

85. a) Bayer, T. A.; Sadler, J. E.; Rearick, J. I.; Paulson, J. C.; Hill, R. L. *Adv. Enzymol. Relat. Areas Mol. Biol*. **1981**, *52*, 23; b) Heidlas, J. E.; Williams, K. W.; Whitesides, G. M. *Acc. Chem. Res*. **1992**, *25*, 307.

86. Hashimoto, S.; Honda, T.; Ikegami, S. *J. Chem. Soc. Chem. Commun.* **1989**, 685.

87. Plante, O. J.; Palmacci, E. R.; Andrade, R. B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2001**, *123*, 9545.

88. a) Hariprasad, V.; Singh, G.; Tranoy, I *Chem. Commun.* **1998**, 2129; b) Singh, G.; Vankayalapati, H. *Tetrahedron: Asymmetry* **2000**, *11*, 125; c) Vankayalapati, H.; Singh, G. *J.*

Chem. Soc. Perkin. Trans.1 **2000**, 2187; d) Vankayalapati, H.; Singh, G.; Tranoy, I. *Tetrahedron: Asymmetry* **2001**, *12*, 1373.

89. a) Love, K. R.; Andrade, R. B.; Seeberger, P. H. *J. Org. Chem.* **2001**, *66*, 8165; b) Bosse, F.; Marcaurelle, L. A.; Seeberger, P. H. *J. Org. Chem.* **2002**, *67*, 6659; c) Swanson, E. R.; Seeberger, P. H. *Org. Lett.* **2003**, *24*, 4717; d) Love, K. R.; Seeberger, P. H. *Angew. Chem. Int. Ed.* **2004**, *43*, 602.

90. See *Chapter 8* in PhD thesis of Dr. Alessandra Ravidà.

91. Love, K. R.; Seeberger, P. H. *Angew. Chem. Int. Ed.* **2004**, *43*, 602.

92. a) Martin, T. J.; Schmidt, R. R. *Tetrahedron Lett.* **1992**, *33*, 6123; b) Müller, T.; Schneider, R.; Schmidt, R. R. *Tetrahedron Lett.* **1994**, *35*, 4763.

93. a) Kondo, H.; Ichikawa, Y.; Wong, C. –H. *J. Am. Chem. Soc.* **1992**, *114*, 8748; b) Sim, M. M.; Kondo, H.; Wong, C –H.; *J. Am. Chem. Soc.* **1993**, *115*, 2260; c) Kondo, H.; Aoki, S.; Ichikawa, Y.; Halcomb, R. L.; Ritzen, H.; Wong, C. –H. *J. Org. Chem. Soc.* **1994**, *59*, 864.

94. a) Watanabe, Y.; Nakamoto, C.; Ozaki, S. *Synlett* **1993**, 115; b) Watanabe, Y.; Nakamoto, C.; Yamamoto, T.; Ozaki, S. *Tetrahedron* **1994**, *50*, 6523.

95. Corey, E. J.; Wu, Y. –J. *J. Am. Chem. Soc.* **1993**, *115*, 8871.

96. a) Lauplicher, L.; Sajus, H.; Thiem, J. *Synthesis* **1992**, 1133; b) Bielawska, H.; Michalska, M. *Tetrahedron Lett.* **1998**, *39*, 9761.

97. a) Hashimoto, S.; Honda, T.; Ikegami, S. *Tetrahedron Lett.* **1990**, *31*, 4769; b) Hashimoto, S.; Sakamoto, H.; Honda, T.; Ikegami, S. *Tetrahedron Lett.* **1997**, *38*, 5181.

98. Fraser-Reid, B.; Konradsson, P.; Mootoo, D. R.; Udodung, U. *J. Chem. Soc. Chem. Commun.* **1988**, 823.

99. Konradsson, P.; Mootoo, D. R.; McDevitt, R. E.; Fraser-Reid, B. *J. Chem. Soc. Chem. Commun.* **1990**, 270.

100. Fraser-Reid, B.; Udodung, U.; Wu, Z.; Ottosson, H.; Merritt, J. R.; Rao, C. S.; Roberts, C.; Madsen, R. *Synlett* **1992**, 927.

101. Mootoo, D. R.; Konradsson, P.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1989**, *111*, 8540.

102. Kahne, D.; Walzer, S.; Cheng, Y.; van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881.

103. Crich, D.; Sun, S. *Tetrahedron* **1998**, *54*, 8321.

104. Brown, D. S.; Ley, S. V.; *Tetrahedron Lett.* **1988**, *29*, 4873.

105. a) Adinolfi, M.; Barone, G.; Guariniello, L.; Iadonisi, A. *Tetrahedron Lett.* **2000**, *41*, 9005; b) Adinolfi, M.; Barone, G.; Iadonisi, A.; Mangoni, L.; Schiattarella, M. *Tetrahedron Lett.* **2001**, *42*, 5967.

106. Mootoo, D. R.; Konradsson, P.; Udodung, U.; Fraser-Reid, B. *J. Am. Chem. Soc.* **1988**, *110*, 5583.

107. Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056.

108. a) Wulff, G.; Röhle, G. *Angew. Chem. In. Ed. Eng.* **1974**, *3*, 157; b) Schmidt, R. R.; Rüker, E. *Tetrahedron Lett.* **1980**, *21*, 1421; c) Schmidt, R. R.; Behrendt, M.; Toepfer, A. *Synlett* **1990**, 694; d) Demchenko, A.; Stauch, T.; Boons, G. –J. *Synlett* **1997**, 818.

109. a) Pougny, J. –R.; Sinaÿ, P. *Tetrahedron Lett.* **1976**, *45*, 4073; b) Ratcliffe, A. J.; Fraser-Reid, B. *J. Chem. Soc. Perkin Trans. I* **1990**, 747.

110. Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217.

111. Crich, D.; Smith, M. *J. Am. Chem. Soc.* **2001**, *123*, 9015.

112. Crich, D.; Chandrasekera, N. S. *Angew. Chem. Int. Ed.*. **2004**, *43*, 5386.

113. Haines, A. H. Adv. *Carbohydr. Chem. Biochem*. **1976**, *33*, 11.

114. Spijker, N. M.; van Boeckel, C. A. A. *Angew. Chem. Int. Ed.* **1991**, *30*, 180.

115. Orgueira, H. A.; Bartolozzi, A.; Schell, P. Seeberger, P. H. *Angew. Chem. Int. Ed.* **2002**, *41*, 2128.

116. Barresi, F.; Hindsgaul, O. *J. Am. Chem. Soc.* **1991**, *113*, 9376.

117. Barresi, F.; Hindsgaul, O. *Can. J. Chem.* **1994**, *72*, 1447.

118. a) Ito, Y.; Ogawa, T. *Angew. Chem. Int. Ed.* **1994**, *33*, 1765; b) Steward, C. M. P.; Cumpstey, I.; Aloui, M.; Ennis, S. C.; Redgrave, A. J.; Fairbanks, A. J. *Chem. Commun.* **2000**, 1409; c) Jung, K. –H.; Müller, M.; Schmidt, R. R. *Chem. Rev.* **2000**, *100*, 4423.

119. See **Scheme 2** of Chapter A.

120. a) Green, T.; Wuts, P. G. M., *Protective Groups in Organic Synthesis*, 3rd ed., Wiley, New York, **1999**; b) Kocienski, P. *Protecting Groups*, Georg Thieme Verlag, Stuttgart, **2000**.

121. Barany, G.; Merrifield, R. B.; *J. Am. Chem. Soc.* **1977**, *116*, 7363.

122. For a wide treatment of selective manipulations on saccharide backbone: Collins, P., Ferrier, R. In *Monosaccharides -Their Chemistry and Their Role in Natural Products*-, John Wiley & Sons: Chichester, **1995**.

123. Yamada, H.; Harada, T.; Miyazaki, H.; Takahashi, T. *Tetrahedron Lett.* **1994**, *35*, 3979.

124. Ye, X. –S.; Wong, C. –H. *J. Org. Chem.* **2000**, *65*, 2410.

Chapter B

Straightforward access to 2-*O*-deprotected allyl glycosides by $BiBr_3$-promoted activation of peracetylated glycosyl iodides.

Introduction

Chemical manipulation of monosaccharide functional groups is the fundamental initial stage for accessing the building-blocks needed for oligosaccharide synthesis or, more in general, for preparing useful precursors of chiral synthetic targets. The desired differentiation of the several hydroxyl groups of a sugar molecule often implies multiple synthetic steps in which the appropriate variety of protecting groups is installed and then suitably elaborated according to the synthetic requirement. These processes can be time-consuming, as several synthetic operations and related purifications should be performed. Therefore, over the last year, some effort has been devoted towards the development of expeditious synthetic procedures providing rapid differentiation of monosaccharide protecting groups through multiple stages performed sequentially without any purification of intermediates.[1] In this regard, herein it was reported a simple and rapid protocol for accessing monosaccharides bearing the versatile allyl group at the anomeric position, a free hydroxyl group at *C*-2, and acetyls on the other carbinolic positions. The approach relies on the feasible activation of glycosyl iodides with the use of sub-stoichiometric amounts of $BiBr_3$.

Results and discussion

The procedure was disclosed in the course of an investigation aimed at finding catalytic activators of per-acetylated glycosyl iodides to be employed in glycosidations as an alternative to known current protocols requiring excess amounts of expensive or not environmentally friendly promoters such as AgOTf or Hg(II) salts.[2] These precursors, despite their instability to both thermal conditions and light exposure, have been widely employed in carbohydrate chemistry as useful synthetic intermediates. In fact glycosyl iodides can be rapidly generated in situ within a few minutes by exposing commercially available peracetylated sugars to the combined system I_2/Et_3SiH according to a procedure developed in our laboratories a few years ago.[3a] As it will be shown in **Chapter D**, the combined system I_2/Et_3SiH is also able to afford partially protected mono- and disaccharides starting from densely *O*-benzylated glycosides. Glycosyl iodides can be produced, starting from 1-*O*-acylated precursors, also with other reactant system such as HI 55-58%/Ac_2O,[3b] catalytic amounts of BiI_3 in the presence of Me_3SiI or $MeSiCl_3$,[3c] Me_3SiI,[3d] I_2/thiolacetic acid or I_2/1,3-propanedithiol,[3e]

I_2/HMDS[3f]. This class of glycosyl halides can be also obtained from hemiacetals, under neutral conditions by using iodoenamines[3g] or with a polymer bound triarylphospahe-iodine complex and imidazole.[3h] Additionally, glycosyl phosphates, imidates, trifluoroacetates, chlorides, and bromides are converted under neutral conditions into the respective glycosyl iodides by treatment with LiI or NaI in 1 M solutions of $LiClO_4$ in DCM.[3i] Few examples in the literature report that glycosyl iodides can be synthesized also from glycosyl phosphites,[3j] from densely *O*-trimethylsylilated glycosides[3k] and from 1,2-*O*-ketene acetal.[3l] This class of glycosyl halides can be employed as crude products, after a simple extractive work-up, in sequential one-pot schemes allowing the preparation of useful building blocks necessary for oligosaccharide assembly, such as 1,2-ethylidenes, 1,2-orthoesters, glycals, thio- and selenoglycosides[3a,4] (**Figure 1**).

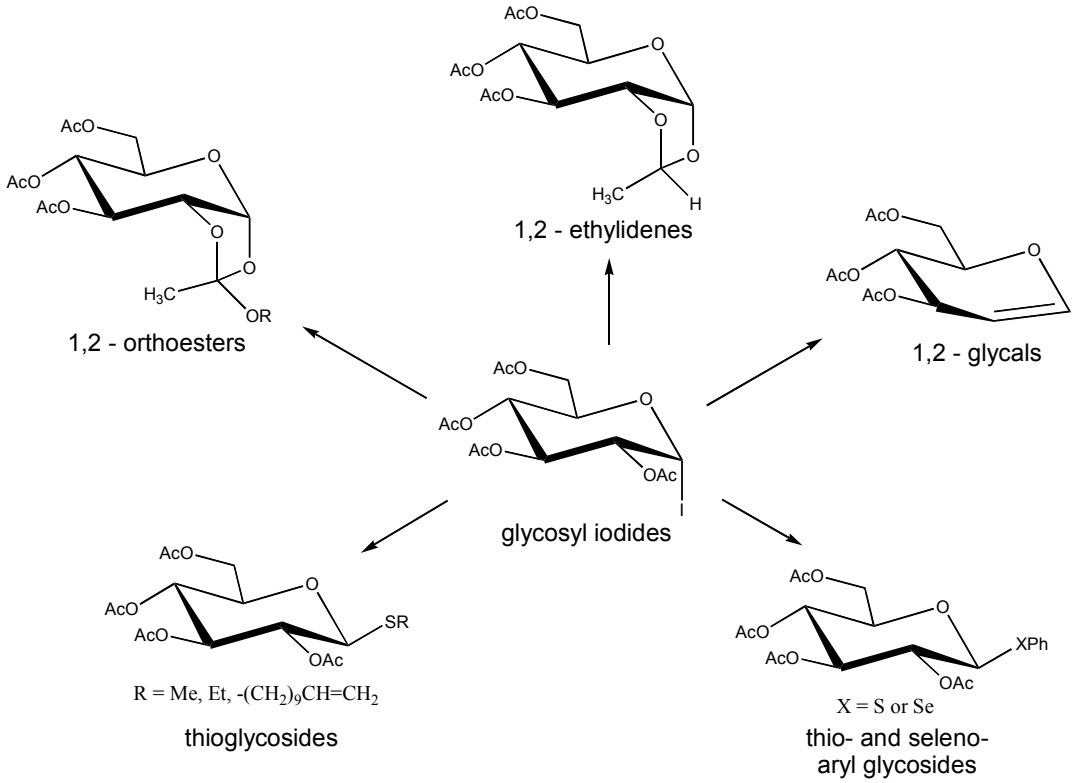
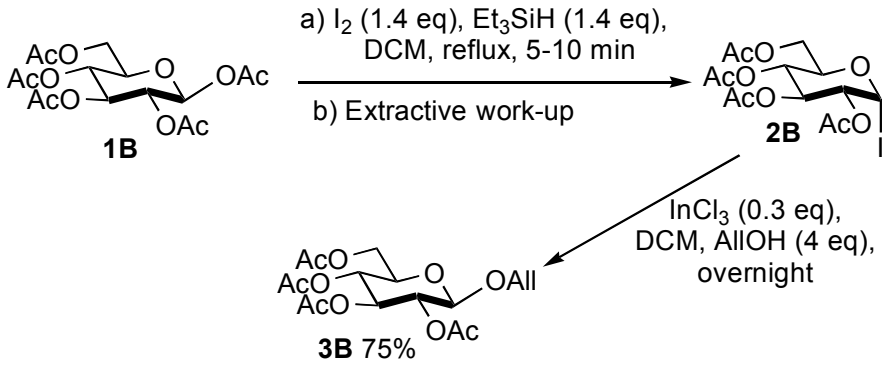


Figure 1

As expected, sub-stoichiometric amounts of $InCl_3$ (a known activator of glycosyl bromides)[5] are capable of promoting in high yield the anomeric allylation of glucosyl iodide **2B** with the predicted 1,2-*trans*-selectivity arising from a vicinal participation effect (**Scheme 1**).



Scheme 1 $InCl_3$-promoted activation of glycosyl iodide **2B**.

In searching for alternative catalytic reagents of higher reactivity, several bismuth(III) salts were examined whose catalytic halophilic reactivity had been evidenced in some useful synthetic transformations such as Friedel-Crafts alkylations[6a, 6b] (**Figure 2** and **3**) and 5-*exo*-trig cyclization via halide activation[6c] (**Figure 4**).

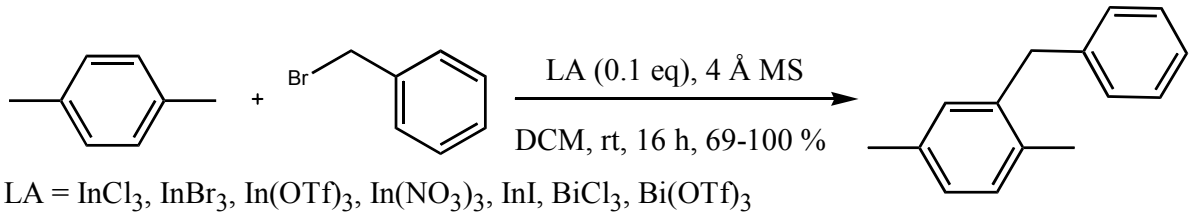


Figure 2

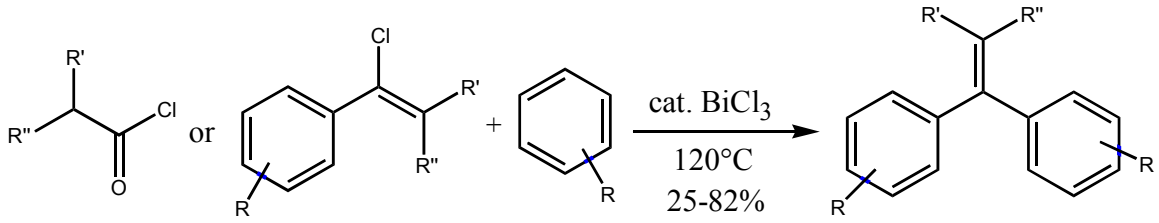


Figure 3

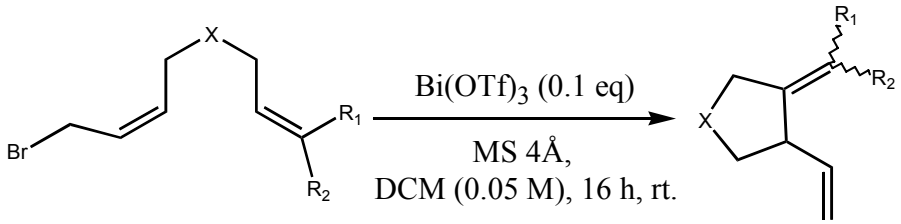
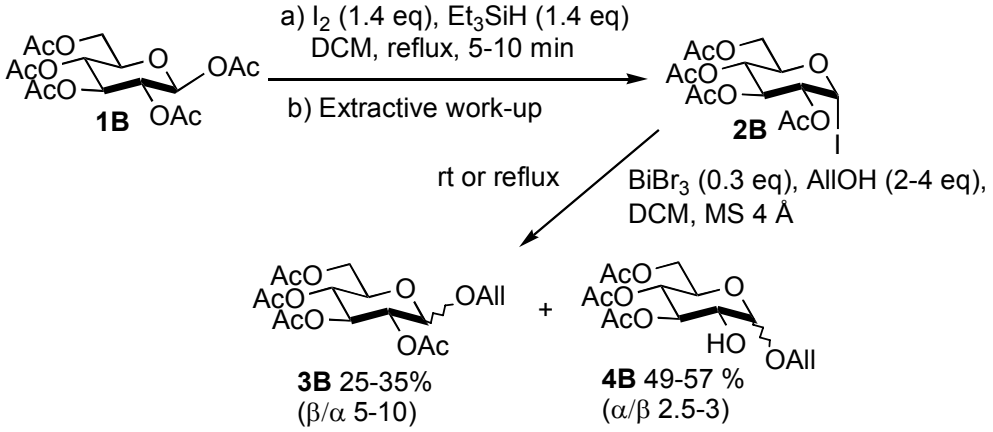


Figure 4

When $BiBr_3$ was used, the reaction outcome was rather different than with $InCl_3$, and a mixture of products was recovered in which allyl glycoside **4B**, deprotected at *O*-2, predominated over minor, although not negligible, amounts of peracetylated allyl glycoside **3B** (**Scheme 2**).

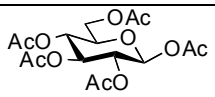
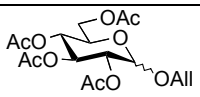
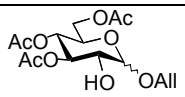
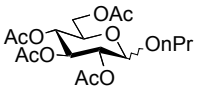
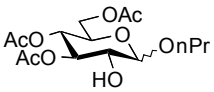
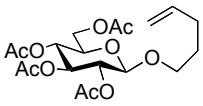
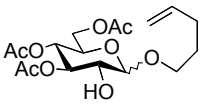
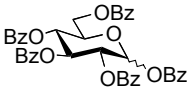
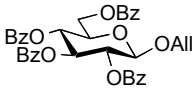
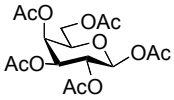
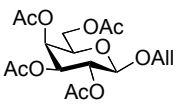
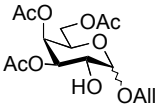
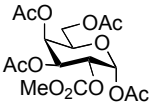
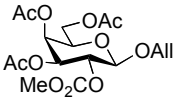
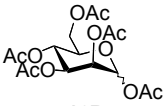
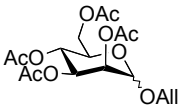
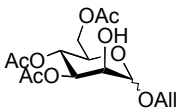
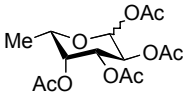
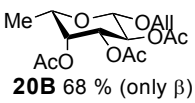
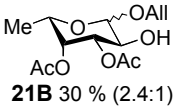
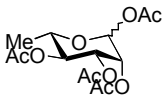
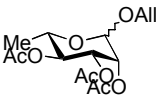
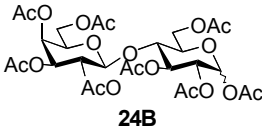
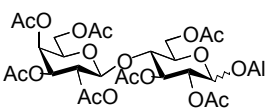
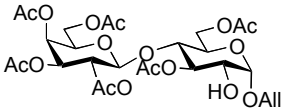


Scheme 2 $BiBr_3$-promoted activation of glycosyl iodide **2B**.

As shown in **Scheme 2**, the composition of the reaction mixture was examined under a variety of conditions (reactions at rt or in refluxing DCM, with 2 or 4 equivalents of allyl alcohol). The best yield of the 2-*O*-deprotected compound **4B** (57 %) was achieved with 4 eq of allyl alcohol in refluxing DCM, and in the presence of freshly activated 4 Å molecular sieves. Remarkably, under these conditions the reaction is sufficiently fast (ca 90 minutes) so that the whole synthetic sequence shown in **Scheme 2** can be performed within a few hours. Other solvents (1,2-dichloroethane, toluene, dioxane, acetonitrile) were also tested, but lower yields were invariably obtained. The anomeric profile of the obtained allylated products was also interesting: while compound **4B** was obtained with some predominance of the α-anomer, the peracetylated allyl glycoside **3B** was obtained with predominant, though not exclusive β-selectivity. Given that the allyl group is frequently used for anomeric transient protection, the described two steps sequence appeared of synthetic value because it achieved the rapid chemical discrimination of the anomeric, the *O*-2, and the remaining oxygenated positions. From a literature survey it appeared that a similar transformation can be carried out with a slight improved yield (63% of **4B**, β/α 3:1) by treating penta-*O*-acetyl-β-glucose with allyl alcohol (4 eq) in the presence of a stochiometric excess of $BF_3{\cdot}OEt_2$ (1.5 eq).[7] However, the overall reaction takes much longer times (overnight) than required by the here presented sequential procedure. Equally prolonged times (and high temperatures) have been very recently reported to be required by several zeolites for inducing similar transformations (glycosidation with concomitant 2-*O* deprotection) in the coupling of β-configured peracetylated sugars with either phenols or long-chain alcohols.[8] In contrast to the above mentioned $BF_3{\cdot}OEt_2$-based procedure, the anomeric profile observed in this latter approach was analogous to that obtained under the here described conditions. Further sparse examples of glycosidations proceeding with 2-*O* deacetylation of the glycosyl donor have been

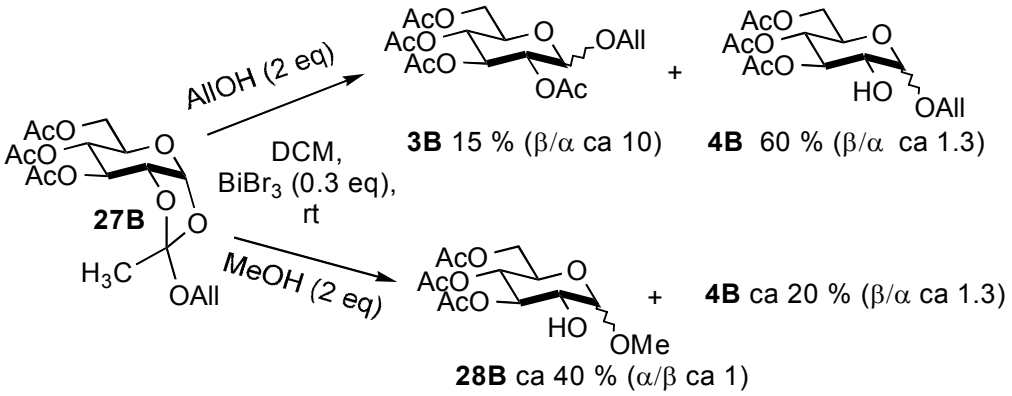
occasionally described as minor side processes.[9] Once established the best reaction conditions, the scope of the procedure was examined with a wide range of alternative saccharidic precursors (**Table 1**). With peracetylated galactose and mannose precursors the yields of the corresponding 2-OH allyl glycosides were again of synthetic interest, albeit lower than with glucose (**Table 1**, entries 5 and 8 vs entry 1). Notably, a lower yield of 2-*O*-deprotected product was obtained when commercial acetobromo galactose was used in place of the corresponding iodinated precursor (entries 6 and 5, respectively). Acetylated 6-deoxy sugars such as L-rhamnose or fucose were instead found to afford a large predominance of the peracetylated 1,2-*trans* allyl glycosides (entries 9 and 10). Adoption of an alternative 2-*O*-acyl group such as benzoyl (entry 4), or a methoxycarbonyl[10] (entry 7) suppressed, under otherwise identical conditions, the process of 2-*O*-deprotection, and was effective in the exclusive generation of the corresponding 1,2-*trans* glycosides. These latter results indicate that $BiBr_3$–promoted anomeric allylation without 2-*O*-deprotection can also be usefully achieved under suitable structural conditions of the substrates, and this may offer an alternative to protocols based on Fischer glycosidations, that require toxic and high-boiling allyl alcohol as the solvent. The use of alternative primary acceptors (*n*-propanol, *n*-pentenyl alcohol) in place of allyl alcohol was also tested with a *gluco*-configured acetylated precursor and it did not result in a remarkably different reaction mixture composition (compare entries 2 and 3 with entry 1), although the best results in the 2-*O*-deprotection were obtained with allyl alcohol. An especially interesting result was obtained with a disaccharide such as D-lactose, which afforded the 2-*O*-deprotected product in very good overall yield and α-selectivity (entry 11). It should be noted that in previously reported approaches[7,8] of 2-*O*-deprotective glycosidation no disaccharide was surveyed. Additionally, only per-acetylated β-configured *galacto*- and *gluco* sugars, more prone to the acid-promoted anomeric activation, were used in those procedures, whereas the present protocol can be generally independent of the anomeric configuration of the starting compound, the initial iodination step being efficient with both anomers.[3]

Table 1 $BiBr_3$-promoted activation of glycosyl halides[a]

Entry	Starting compound	Products Yield (α/β)
1	 **1B**	 **3B** 35 % (1:10)  **4B** 57 % (3.0:1)
2[b]	**1B**	 **5B** 29 % (1:4.7)  **6B** 45 % (2.7:1)
3[c]	**1B**	 **7B** 35 % (only β)  **8B** 43 % (2.9:1)
4	 **9B**	 **10B** 61 % (only β)
5	 **11B**	 **12B** 48 % (only β)  **13B** 45 % (1.3:1)
6[d]	**11B**	**12B** 51 % (only β) **13B** 35 % (1.6:1)
7	 **14B**	 **15B** 66 % (only β)
8	 **16B**	 **17B** 25 % (3.7:1)  **18B** N. D.[e]
9	 **19B**	 **20B** 68 % (only β)  **21B** 30 % (2.4:1)
10	 **22B**	 **23B** 74 % (4.5:1)
11	 **24B**	 **25B** 29 % (1:6)  **26B** 48 % (only α)

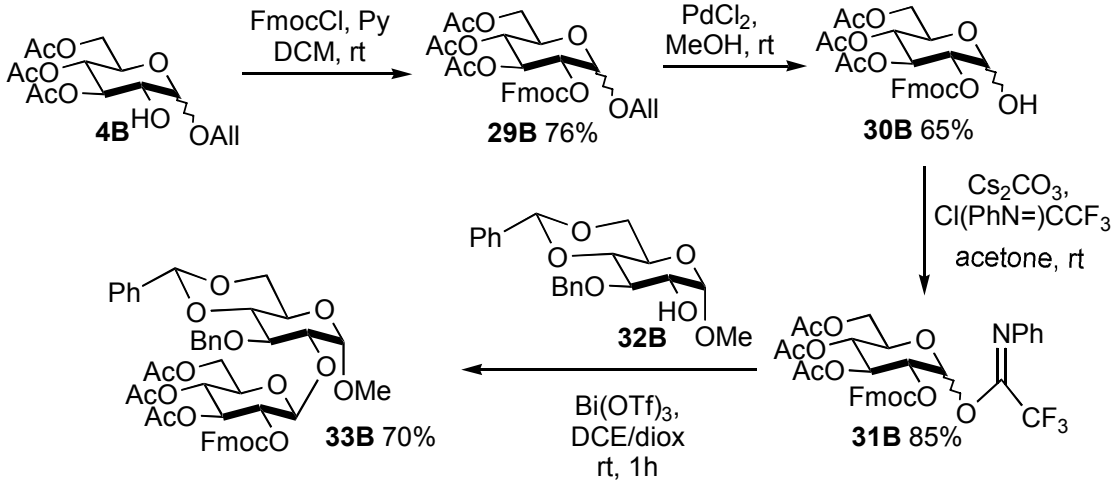
[a] General conditions: sugar, I_2 (1.4 eq), Et_3SiH (1.4 eq), refluxing DCM. Exctractive work-up, then: glycosyl iodide, allyl alcohol (4 eq), 4Å MS, $BiBr_3$ (0.3 eq), DCM, reflux. [b] *n*-Propanol used in place of allyl alcohol. [c] *n*-Pentenyl alcohol used in place of allyl alcohol. [d] Tetraacetyl bromo galactose was used in place of the corresponding iodide. [e] The isolated yield could not been determined as the anomeric products were contaminated by inseparable 2,3,4,6-tetra-*O*-acetyl mannopyranose. Estimated yield by NMR: ca 35 % (α/β ca 1).

After having established the scope and the limitations of the protocol, some experiments were performed to gain some mechanistic information on the process. First, allyl 2,3,4,6-tetra-*O*-acetyl galactopyranoside was exposed to the typical reaction conditions above described, and no appreciable 2-*O*-deacetylation was detected, evidencing that the removal of the acetyl group is not occurring after allylation of the anomeric position. In a second experiment, allyl orthoester **27B**, prepared via the corresponding iodide **2B**,[3] was exposed to $BiBr_3$ and allyl alcohol (**Scheme 3**). Interestingly, this treatment led to a mixture of allylated compounds **3B** and **4B** within short times even at room temperature, with a more large relative predominance of 2-*O*-deprotection but a lower α-selectivity. The outcome of this experiment is highly suggestive of an allylated orthoester as one of the feasible intermediates generated in the rate-determining step in which $BiBr_3$ promotes the activation of the anomeric iodide. In order to ascertain the origin of the aglycon moiety in the final product, allyl orthoester **27B** was treated under the same conditions previously adopted but in the presence of methanol rather than allyl alcohol as the external nucleophile. The product profile (**Scheme 3**) displayed a predominant, albeit not exclusive, content of methyl glycosides, which implies that the aglycon can be provided from the reaction medium and it's not necessarily incorporated into the initial orthoester intermediate.



Scheme 3 $BiBr_3$-promoted activation of orthoester **27B**.

Due to the interest in the search of 2-*O*-participating groups (as it will be shown in **Chapter F**) serving in $Bi(OTf)_3$-promoted 1,2-*trans* glycosidations[11] and amenable to selective removal in the presence of acetyls, it took advantage of the present procedure for the straightforward access to **4B**, a useful precursor of the 2-*O*-Fmoc trifluoroacetimidate donor **31B** (**Scheme 4**).



Scheme 4 Synthesis of donor **31B** and its coupling with acceptor **32B**.

The Fmoc group was initially installed on compound **4B**, and the resulting compound **29B** was submitted to a sequence of anomeric deallylation and installation of the (*N*-phenyl)trifluoroacetimidate leaving group.[12] $Bi(OTf)_3$-catalyzed coupling[11] with model acceptor **32B** smoothly afforded disaccharide **33B** in good yield (70%).

Conclusions

In conclusion, it was shown that the sequence of anomeric iodination and $BiBr_3$-promoted activation of the intermediate glycosyl iodides can afford within short times useful saccharidic building-blocks unprotected at 2-OH and bearing the selectively removable allyl anomeric group. Suitable structural conditions of substrates (6-deoxy sugars or use of benzoyl or methoxycarbonyl 2-*O*-participating groups) switch the preferential process to a glycosidation without concomitant 2-*O*-deprotection.

Experimental Section

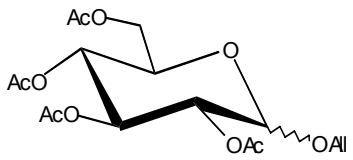
General methods and Material

Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded in $CDCl_3$ (internal standard, for ^{1}H: $CHCl_3$ at δ 7.26; for ^{13}C: $CDCl_3$ at δ 77.0) on Varian spectrometers at 200 or 300 MHz and 50 or 75 MHz, respectively, or on a Bruker Avance 400 spectrometer at 400 MHz. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. ^{1}H NMR assignments were based on homo-decoupling experiments. Analytical thin layer chromatography (TLC) was performed on aluminium plates precoated with Silica Gel 60 F_{254} as the adsorbent. The plates were developed with 5% H_2SO_4 ethanolic solution and then heating to 130°C. Column chromatography was performed on Kieselgel 60 (63-200 mesh). When specified, anhydrous solvents stored over molecular sieves (purchased from Aldrich) were used. Glycosidation promoter bismuth(III) triflate was coevaporated three times in toluene and dried under vacuum for 30-45 minutes before being dissolved in the presence of freshly activated 4Å with dioxane.

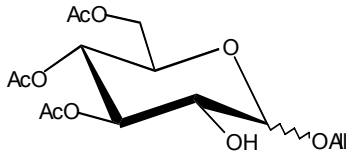
Typical Procedure for $BiBr_3$-Promoted Allylation: To a solution of peracetylated glucose (110 mg, 0.28 mmol) in dichloromethane (4 mL) were sequentially added iodine (102 mg, 0.40 mmol) and triethylsilane (62.5 µL, 0.40 mmol; *caution*: exothermic reaction). After stirring for 5 min at reflux temperature, TLC analysis (petroleum ether/ethyl acetate, 6:4) displayed completion of the reaction.

After cooling to room temperature, the mixture was diluted with dichloromethane and washed with a solution of saturated sodium hydrogen carbonate containing a minimal amount of sodium thiosulfate for reducing the residual amount of iodine. The aqueous phase was extracted with dichloromethane, and the collected organic phase was dried with sodium sulfate and concentrated in vacuo. Freshly activated 4 Å molecular sieves were added to the residue, and the mixture was suspended in anhydrous dichloromethane (4 mL). Allyl alcohol (4 equiv.) and BiBr3 (37 mg, 0.084 mmol) were then added, and the mixture was heated at reflux until TLC analysis (petroleum ether/ethyl acetate, 4:6) displayed

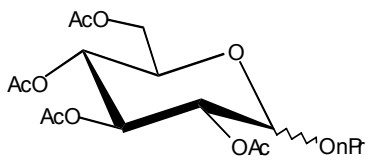
complete consumption of the UV/Vis detectable glycosyl iodide (ca. 80 min). Some drops of pyridine were added, and the mixture was filtered through a short pad of silica gel (ethyl acetate), and the residue from the filtered liquor was chromatographed by silica gel flash chromatography (petroleum ether/ethyl acetate, 6:4) to yield peracetylated allyl glycoside **3B** (40 mg, 37%; α/β, 1:10), and 2-*O*-free allyl glycoside **4B** (55 mg, 57%; α/β, 3:1).



Allyl 2,3,4,6-tetra-*O*-acetyl-α,β-D-glucopyranoside (3B)[7]. Foam (ca α/β 1:10 anomeric mixture). Data for the β-anomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.94-5.74 (m, 1 H, -CH_2CH=CH_2), 5.26 (dd, ^3J = 17.4 Hz, ^2J = 1.2 Hz, 1 H, -CH_2CH=$CH_{cis}H_{trans}$), 5.20 (t, $J_{3,4} = J_{2,3} =$ 9.3 Hz, 1 H, 3-H), 5.19 (dd, ^3J = 10.4 Hz, ^2J = 1.2 Hz, 1 H, -CH_2CH=$CH_{cis}H_{trans}$), 5.08 (t, $J_{3,4} = J_{4,5} =$ 9.3 Hz, 1 H, 4-H), 5.01 (dd, $J_{1,2}$ = 7.8 Hz, 1 H, 2-H), 4.55 (d, 1 H, 1-H), 4.37-4.29 (dd, ^3J = 4.8 Hz, ^2J = 13.2 Hz, 1 H, -CH_aH_bCH=CH_2), 4.25 (dd, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6a}$ = 4.6 Hz, 1 H, 6_a-H), 4.13 (dd, $J_{5,6b}$ = 2.4 Hz, 1 H, 6_b-H), 4.12-4.03 (dd, ^3J = 6.0 Hz, ^2J = 13.2 Hz, 1 H, CH_aH_bCH=CH_2), 3.72-3.64 (m, 1H, 5-H), 2.08, 2.04, 2.01, 1.99 (4 x s, 12 H, 4 x -$COCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5, 170.1, 169.2, 169.1, 133.2, 117.5, 99.4 (C-1), 72.7, 71.6, 71.1, 69.8, 68.3, 61.8, 20.4 ppm. $C_{17}H_{24}O_{10}$ (388.37): calcd C 52.57, H 6.23; found C 52.40, H 6.10.

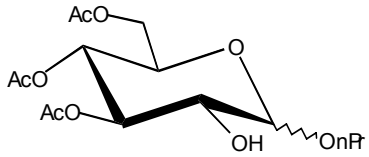


Allyl 3,4,6-tri-*O*-acetyl-α,β-D-glucopyranoside (4B)[7]. Oil (ca α/β 3.0:1 anomeric mixture). Data for the α-anomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.00-5.80 (m, 1 H, -CH_2CH=CH_2), 5.30 (m, ^3J = 17.1 Hz, ^2J = 1.5 Hz, 1 H, -CH_2CH=$CH_{cis}H_{trans}$), 5.24 (m, ^3J = 10.2 Hz, ^2J = 1.5 Hz, 1 H, -CH_2CH=$CH_{cis}H_{trans}$), 5.22 (t, $J_{3,4} = J_{2,3} =$ 9.7 Hz, 1 H, 3-H), 4.99 (t, $J_{4,5} =$ 9.7 Hz, 1 H, 4-H), 4.95 (d, $J_{1,2}$ = 3.9 Hz, 1 H, 1-H), 4.36-4.01 (m, 2 H, -CH_2CH=CH_2), 4.24 (dd, $J_{6a,6b}$ = 12.3 Hz, $J_{5,6a}$ = 4.5 Hz, 1 H, 6_a-H), 4.04 (dd, $J_{5,6b}$ = 2.1 Hz, 1 H, 6_b-H), 3.99-3.93 (m, 1 H, 5-H), 3.71-3.62 (m, 1 H, 2-H), 2.23 (d, $J_{2,OH}$ = 7.5 Hz, 1H, OH-2), 2.06, 2.04, 2.00 (3 x s, 9 H, 3 x -$COCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.0, 170.5, 169.5, 132.9, 118.5, 97.3 (C-1), 73.3, 70.7, 69.0, 67.9, 67.6, 61.8, 20.7 ppm. Significative signals of the β-anomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.09 (t, $J_{2,3} = J_{3,4} =$ 9.6 Hz, 1 H, 3-H), 4.39 (d, $J_{1,2}$ = 8.1 Hz, 1 H, 1-H), 3.57 (m, 1 H, 2-H) ppm. $C_{15}H_{22}O_9$: calcd C 52.02, H 6.40; found C 51.80, H 6.31.

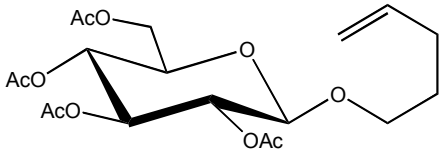


***n*-Propyl 2,3,4,6-tetra-*O*-acetyl-α,β-D-glucopyranoside (5B)[13] .** Oil (ca α/β 1:4.7 anomeric mixture). Data for the β-anomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.16 (t, $J_{2,3} = J_{3,4} =$ 9.6 Hz, 1 H, 3-H), 5.04 (t, $J_{4,5} =$ 9.6 Hz, 1 H, 4-H), 4.94 (dd, $J_{1,2}$ = 8.1 Hz, $J_{2,3} =$ 9.6 Hz, 1 H, 2-H), 4.45 (d, 1 H, 1-H), 4.22 (dd, $J_{6a,6b}$ = 12.0 Hz, $J_{5,6a}$ = 4.5 Hz, 1 H, 6_a-H), 4.08 (dd, $J_{5,6b}$ = 2.2 Hz, 1 H, 6_b-H), 3.85-3.74 (m, 1 H), 3.69-3.61 (m, 1 H, 5-H), 3.44-3.32 (m, 1 H), 2.04, 1.98, 1.97, 1.96 (4 x s, 12 H, 4 x -$COCH_3$), 1.6-1.4 (m, 2 H, -

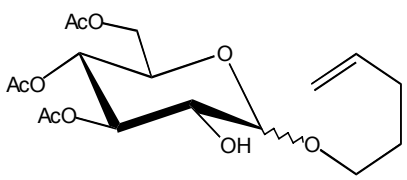
$OCH_2CH_2CH_3$), 0.85 (t, ^3J = 6.9 Hz, 3 H, -$OCH_2CH_2CH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5, 170.1, 169.2, 169.1, 100.7 (C-1), 72.7, 71.6, 71.2, 70.2, 68.4, 61.9, 22.5, 20.5, 10.1 ppm. $C_{17}H_{26}O_{10}$: calcd C 52.30, H 6.71; found C 52.00, H 6.55.



***n*-Propyl 3,4,6-tri-*O*-acetyl-α,β-D-glucopyranoside (6B).** Oil (ca α/β 2.7:1 anomeric mixture). Data for the α-anomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ = ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.18 (t, $J_{3,4} = J_{2,3} = 9.6$ Hz, 1 H, 3-H), 4.95 (t, $J_{4,5} = 9.6$ Hz, 1 H, 4-H), 4.87 (d, $J_{1,2} = 3.9$ Hz, 1 H, 1-H), 4.21 (dd, $J_{6a,6b} = 12.3$ Hz, $J_{5,6a} = 4.5$ Hz, 1 H, 6_a-H), 4.02 (dd, $J_{5,6b} = 2.1$ Hz, 1 H, 6_b-H), 3.98-3.88 (m, 1 H, 5-H), 3.75-3.40 (m, 3 H, 2-H and –$OCH_2CH_2CH_3$), 2.41 (d, $J_{2,OH} = 7.4$ Hz, 1 H, 2-OH), 2.04, 2.03, 1.98 (3 x s, 9 H, 3 x –$COCH_3$), 1.73-1.53 (m, 2 H, –$OCH_2CH_2CH_3$), 0.92 (t, ^3J = 7.5 Hz, 3 H, –$OCH_2CH_2CH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.0, 170.6, 169.6, 98.1 (C-1), 73.4, 70.7, 70.4, 68.1, 67.5, 62.0, 22.6, 20.5, 10.5 ppm. Significative signals of the β-anomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.07 (t, $J_{3,4} = J_{2,3} = 9.6$ Hz, 1 H, 3-H), 4.97 (t, $J_{4,5} = 9.6$ Hz, 1 H, 4-H), 4.31 (d, $J_{1,2} = 7.8$ Hz, 1 H, 1-H) ppm. $C_{15}H_{24}O_9$: calcd C 51.72, H 6.94; found C 51.45, H 6.75.

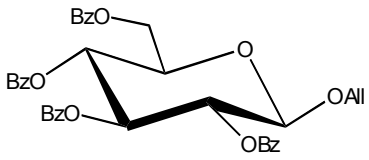


***n*-Pentenyl 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranoside (7B)[14].** Solid. $[\alpha]^{25}_D$ = -17.2 ° (c= 0.6, $CHC1_3$), m.p.= 47 °C (light petroleum: diethyl ether). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.86-5.67 (m, 1 H, -CH_2CH=CH_2), 5.18 (t, $J_{3,4} = J_{2,3} = 9.4$ Hz, 1 H, 3-H), 5.06 (t, $J_{3,4} = J_{4,5} = 9.4$ Hz, 1 H, 4-H), 4.99 (dd, ^3J = 16.9 Hz, 2 J = 1.8 Hz, 1 H, -CH_2CH=$CH_{cis}H_{trans}$), 4.96 (dd, $J_{1,2} = 7.9$ Hz, 1 H, 2-H), 4.95 (dd, ^3J = 9.9 Hz, ^2J = 1.8 Hz, 1 H, -CH_2CH=$CH_{cis}H_{trans}$), 4.47 (d, 1 H, 1-H), 4.24 (dd, $J_{6a,6b} = 12.3$ Hz, $J_{5,6a}$ = 4.8 Hz, 1 H, 6_a-H), 4.11 (dd, $J_{5,6b} = 2.5$ Hz, 1 H, 6_b-H), 3.90-3.81 (dt, ^3J = 6.1 Hz, ^2J = 9.6 Hz, 1 H, -$OCH_aH_bCH_2CH_2CH$=CH_2), 3.71-3.63 (m, 1 H, 5-H), 3.53-3.43 (dt, ^3J = 6.6 Hz, ^2J = 9.6 Hz, 1 H, -$OCH_aH_bCH_2CH_2CH$=CH_2), 2.06, 2.02, 2.00, 1.98 (4 x s, 12 H, 4 x -$COCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5, 170.2, 169.3, 169.2, 137.7, 115.0, 100.8 (C-1), 72.9, 71.8, 71.4, 69.2, 68.6, 62.0, 29.8, 28.6, 20.5 ppm. $C_{19}H_{28}O_{10}$: calcd C 54.80, H 6.78; found C 54.53, H 6.65.

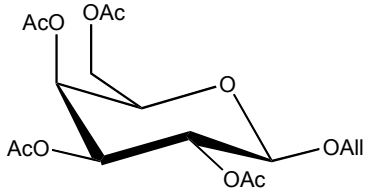


***n*-Pentenyl 3,4,6-tri-*O*-acetyl-α,β-D-glucopyranoside (8B).** Oil (ca α/β 2.9:1 anomeric mixture). Data for the α-anomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.87-5.70 (m, 1 H,

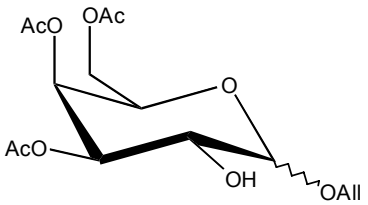
-CH_2CH=CH_2), 5.19 (t, $J_{3,4} = J_{2,3} = 9.6$ Hz, 1 H, 3-H), 5.02 (dd, $^3J = 17.1$ Hz, $^2J = 1.8$ Hz, 1 H, -CH_2CH=$CH_{cis}H_{trans}$), 5.02-4.90 (m, 2 H, -CH_2CH=$CH_{cis}H_{trans}$ and 4-H), 4.87 (d, $J_{1,2} = 3.6$ Hz, 1 H, 1-H), 4.23 (dd, $J_{6a,6b} = 12.3$ Hz, $J_{5,6a} = 4.5$ Hz, 1 H, 6_a-H), 4.04 (dd, $J_{5,6b} = 2.4$ Hz, 1 H, 6_b-H), 3.97-89 (m, 1 H, 5-H), 3.78-3.69 (dt, $^3J = 6.7$ Hz, $^2J = 9.9$ Hz, 1 H, -$CH_aH_bCH_2CH_2CH$=CH_2), 3.69-3.59 (m, 1 H, 2-H), 3.53-3.43 (dt,$^3J = 6.4$ Hz, $^2J = 9.6$ Hz, 1 H, -$CH_aH_bCH_2CH_2CH$=CH_2), 2.60 (br. s, 1 H, 2-OH), 2.05 (x 2), 2.00 (3 x s, 9 H, 3 x -$COCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.0, 170.5, 169.5, 137.6, 115.2, 98.3, 73.5, 70.8, 68.2 (x 2), 67.7, 62.1, 30.2, 28.4, 20.6 ppm. Significative signals of the β-anomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.09 (t, $J_{3,4} = J_{2,3} = 9.9$ Hz, 1 H, 3-H), 4.32 (d, $J_{1,2} = 7.8$ Hz, 1 H, 1-H) ppm. $C_{17}H_{26}O_9$: calcd C 54.54, H 7.00; found C 54.32, H 6.87.



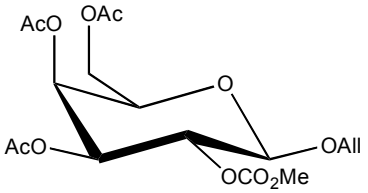
Allyl 2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranoside (10B)[15]**.** Foam $[\alpha]^{24}_D$ = +50.7 (c 1.1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.30-7.20 aromatic protons), 5.96 (t, $J_{3,4} = J_{2,3} = 9.6$ Hz, 1 H, 3-H), 5.80-5.66 (m, 2 H, -CH_2CH=CH_2 and 4-H), 5.62 (t, 1 H, 2-H), 5.24 (d, $^3J = 17.4$ Hz, 1 H, CH_2CH=$CH_{cis}H_{trans}$), 5.14 (d, $^3J = 10.5$ Hz, 1 H, -CH_2CH=$CH_{cis}H_{trans}$), 4.95 (d, $J_{1,2} = 8.1$ Hz, 1 H, 1-H), 4.68 (dd, $J_{6a,6b} = 11.8$ Hz, $J_{5,6b} = 2.8$ Hz, 1 H, 6_b-H), 4.60-4.05 (4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 166.1, 165.8, 165.2, 165.1, 133.5, 133.3, 133.2 (x 2), 133.1, 129.8-128.3, 117.9, 99.8 (C-1), 73.0, 72.2, 71.9, 70.1, 69.8, 63.2 ppm. $C_{37}H_{32}O_{10}$: calcd C 69.80, H 5.07; found C 69.65, H 5.21.



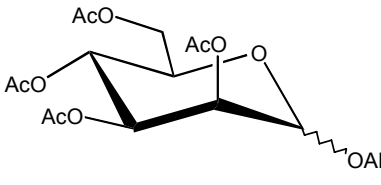
Allyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside (12B)[16]**.** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.90-5.70 (m, 1 H, -CH_2CH=CH_2), 5.35 (dd, $J_{3,4} = 3.3$ Hz, $J_{4,5} = 1.0$ Hz, 1 H, 4-H), 5.24 (dd, $^3J = 17.1$ Hz, $^2J = 1.5$ Hz, 1 H, -CH_2CH=$CH_{cis}H_{trans}$), 5.20 (dd, $J_{1,2} = 7.5$ Hz, $J_{2,3} = 10.5$ Hz, 1 H, 2-H), 5.17 (dd, $^3J = 10.5$ Hz, $^2J = 1.5$ Hz, 1 H, -CH_2CH=$CH_{cis}H_{trans}$), 4.99 (dd, 1 H, 3-H), 4.49 (d, 1 H, 1-H), 4.37-4.27 (m, 1 H), 4.15 (dd, $J_{6a,6b} = 12.6$ Hz, 1 H, 6-H), 4.11-4.03 (m, 2 H), 3.87 (br. t, $J_{5,6a} = J_{5,6b} = 6.6$ Hz, 1 H, 5-H), 2.11, 2.02, 2.01, 1.94 (4 x s, 12 H, 4 x -$COCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 170.1, 170.0, 169.3, 133.2, 117.4, 99.9 (C-1), 70.8, 70.5, 69.9, 68.7, 66.9, 61.2, 20.5 ppm. $C_{17}H_{24}O_{10}$: calcd C 52.57, H 6.23; found C 52.35, H 6.10.



Allyl 3,4,6-tri-*O*-acetyl-α,β-D-galactopyranoside (13B)[17]**.** Oil (ca α/β 1.3:1 anomeric mixture). Data for the α-anomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.00-5.80 (m, 1 H, -CH_2CH=CH_2), 5.36 (dd, $J_{3,4}$ = 3.0 Hz, $J_{4,5}$ = 1.2 Hz, 1 H, 4-H), 5.29 (dd, ^3J = 17.1 Hz, ^2J = 1.2 Hz, 1 H, -CH_2CH=$CH_{cis}H_{trans}$), 5.22 (dd, ^3J = 10.5 Hz, ^2J = 1.2 Hz, 1 H, -CH_2CH=$CH_{cis}H_{trans}$), 5.11 (dd, $J_{2,3}$ = 10.5 Hz, 1 H, 3-H), 4.99 (d, $J_{1,2}$ = 3.9 Hz, 1 H, H-1), 4.30-4.00 (m, 5 H, 5-H, 6-H_2 and -CH_2CH=CH_2), 3.80 (m, 1 H, 2-H), 2.70 (bs, 1 H, 2-OH), 2.10, 2.01 (x2) (2 x s, 9 H, 3 x -$COCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.6, 170.3, 170.0, 133.0, 118.3, 97.6 (C-1), 70.6, 68.9, 68.1, 66.9, 66.7, 61.7 (C-6), 20.6, 20.5 ppm. Significative signals of the β-anomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.89 (dd, $J_{3,4}$ = 3.3 Hz, $J_{2,3}$ = 10.5 Hz, 1 H, 3-H), 4.38 (d, $J_{1,2}$ = 7.5 Hz, 1 H, 1-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ =101.9 (C-1) ppm. $C_{15}H_{22}O_9$: calcd C 52.02, H 6.40; found C 51.85, H 6.30.

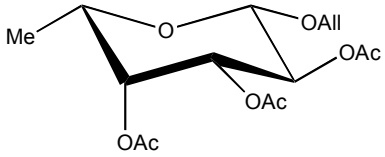


Allyl 3,4,6-tri-*O*-acetyl-2-*O*-methoxycarbonyl-β-D-glucopyranoside (15B). Oil. $[\alpha]^{25}_D$ = +7.5 (c 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.90-5.72 (m, 1 H, -CH_2CH=CH_2), 5.35 (bs, 1 H, 4-H), 5.22 (m, ^3J = 17.4 Hz, ^2J = 1.2 Hz, 1 H, -CH_2CH=$CH_{cis}H_{trans}$), 5.14 (m, ^3J = 10.5 Hz, ^2J = 1.2 Hz, 1 H, -CH_2CH=$CH_{cis}H_{trans}$), 4.98-4.97 (m, overlapped signals, 2 H, 1-H and 3-H), 4.50 (1H, dd, $J_{1,2}$ = $J_{2,3}$ = 3.9 Hz, 1 H, H-2), 4.35-4.00 (m, 4 H, 6-H_2 and -CH_2CH=CH_2), 3.86 (t, $J_{5,6a}$ = $J_{5,6b}$ = 6.9 Hz, 1 H, 5-H), 3.75 (s, 3 H, -OCH l_3), 2.08, 1.98, 1.93 (3 x s, 9 H, 3 x -$COCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 170.0, 169.8, 154.7, 133.1, 117.4, 99.8 (C-1), 72.8, 70.6, 70.4, 70.0, 66.9, 61.0, 55.0, 20.4 ppm. $C_{17}H_{24}O_{11}$: calcd C 50.49, H 5.98; found C 50.25, H 6.04.

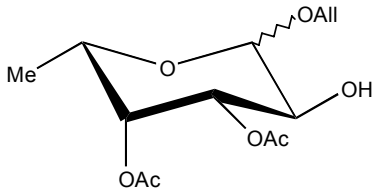


Allyl 2,3,4,6-tetra-*O*-acetyl-α,β-D-mannopyranoside (17B)[18]**.** Oil (ca α/β 3.7:1 anomeric mixture). Data for the α-anomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.00-5.80 (m, 1 H, -CH_2CH=CH_2), 5.35 (dd, $J_{3,4}$ = 10.2 Hz, 1-H, 3-H), 5.29 (dd, ^3J = 17.1 Hz, ^2J = 1.2 Hz, 1 H, -CH_2CH=$CH_{cis}H_{trans}$), 5.27 (t, $J_{4,5}$ = 10.2 Hz, 1 H, 4-H), 5.24 (dd, $J_{2,3}$ = 3.1 Hz, 1 H, 2-H), 5.22 (dd, ^3J = 10.5 Hz, ^2J = 1.2 Hz, 1 H, CH_2CH=$CH_{cis}H_{trans}$), 4.85 (d, $J_{1,2}$ = 1.5 Hz, 1 H, 1-H), 4.27 (dd, $J_{6a,6b}$ = 12.1 Hz, $J_{5,6a}$ = 5.2 Hz, 1 H, 6_a-H), 4.22-4.12 (bdd, ^3J = 5.4 Hz, ^2J = 13.2 Hz, 1 H, -CH_aH_bCH=CH_2), 4.11-3.95 (m, 3 H, 6_b-H, -CH_aH_bCH=CH_2 and 5-H), 2.13, 2.09, 2.02, 1.97 (4 x s, 12 H, 4 x -$COCH_3$) ppm. ^{13}C NMR

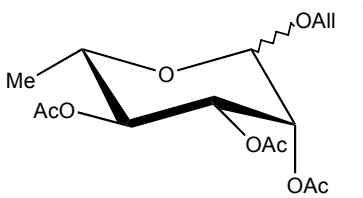
(75 MHz, $CDCl_3$): δ = 170.6, 170.0, 169.7, 169.6, 132.9, 118.3, 96.5 (C-1), 69.6, 69.0, 68.6, 68.5, 66.2, 62.4, 20.6 ppm. Significative signals of the β-anomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.48 (dd, $J_{1,2}$ = 0.9 Hz, $J_{2,3}$ = 3.6 Hz, 1 H, 2-H), 5.26 (t, $J_{3,4} = J_{4,5}$ = 9.6 Hz, 1 H, 4-H), 5.04 (dd, 1-H, 3-H), 4.68 (d, 1 H, 1-H), 3.68-3.60 (m, 1 H, 5-H), 2.19, 2.09, 2.04, 1.99 (4 x s, 12 H, 4 x -$COCH_3$) ppm. $C_{17}H_{24}O_{10}$: calcd C 52.57, H 6.23; found C 52.35, H 6.15.



Allyl 2,3,4-tri-*O*-acetyl-β-L-fucopyranoside (20B). Oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.83-5.68 (m, 1 H, -CH_2CH=CH_2), 5.23-5.05 (m, 4 H, -CH_2CH=CH_2 , 4-H and 2-H), 4.93 (dd, $J_{3,4}$ = 3.3 Hz, $J_{2,3}$ = 10.5 Hz, 1 H, 3-H), 4.41 (d, $J_{1,2}$ = 8.1 Hz, 1 H, 1-H), 4.32-4.20 (m, ^3J = 4.5 Hz, ^2J = 13.5 Hz, 1 H, -CH_aH_bCH=CH_2), 4.05-3.95 (m, ^3J = 6.0 Hz, ^2J = 13.5 Hz, 1 H, -CH_aH_bCH=CH_2), 3.73 (q, $J_{5,6}$ = 6.6 Hz, 1-H, 5-H), 2.08, 1.96, 1.88 (3 x s, 9 H, 3 x -$COCH_3$), 1.13 (d, 3 H, 6-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.4, 169.9, 169.2, 133.4, 117.0, 99.6 (C-1), 71.1, 70.0, 69.5, 68.8, 68.7, 20.5, 20.4, 20.3, 15.8 ppm. $C_{15}H_{22}O_8$: calcd C 54.54, H 6.71; found C 54.35, H 6.65.

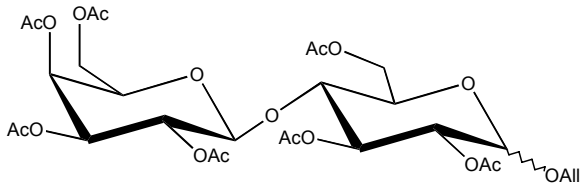


Allyl 3,4-di-*O*-acetyl-α,β-L-fucopyranoside (21B). Oil (ca α/β 2.4:1 anomeric mixture). Data for the α-anomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.95-5.80 (m, 1 H, -CH_2CH=CH_2), 5.35-5.20 (m, 3 H, -CH_2CH=CH_2 and 4-H), 5.11 (dd, $J_{3,4}$ = 3.3 Hz, $J_{2,3}$ = 10.5 Hz, 1 H, 3-H), 4.94 (d, $J_{1,2}$ = 3.6 Hz, 1 H, 1-H), 4,25-3.95 (m, 3 H, -CH_2CH=CH_2 and 5-H), 3.91 (bdd, 1 H, 2-H), 2.61 (bs, 1 H, 2-OH), 2.12, 2.01 (2 x s, 6 H, 2 x -$COCH_3$), 1.10 (d, $J_{5,6}$ = 6.3 Hz, 3 H, 6-H_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5 (x 2), 133.3, 118.0, 97.7 (C-1), 71.2 (x 2), 68.8, 66.9, 64.8, 20.8, 20.6, 15.8 ppm. Significative signals of the β-anomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.89 (dd, $J_{3,4}$ = 3.3 Hz, $J_{2,3}$ = 10.5 Hz, 1 H, 3-H), 4.34 (d, $J_{1,2}$ = 8.1 Hz, 1 H, 1-H), 2.11, 2.01 (2 x s, 6 H, 2 x -$COCH_3$), 1.18 (d, $J_{5,6}$ = 6.3 Hz, 3 H, 6-H_3) ppm. $C_{13}H_{20}O_7$: calcd C 54.16, H 6.91; found C 54.21, H 6.80.

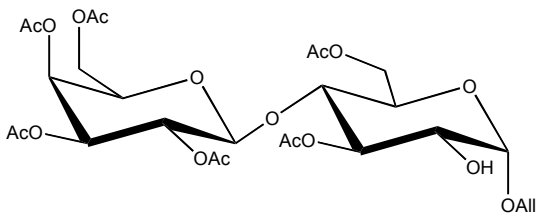


Allyl 2,3,4-tri-*O*-acetyl-α,β-L-rhamnopyranoside (23B)[19]. Oil (ca α/β 4.5:1 anomeric mixture). Data for the α-anomer, ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.96-5.70 (m, 1 H, -CH_2CH=CH_2), 5.23 (dd, ^3J = 17.2 Hz, ^2J = 1.5 Hz, 1 H, -CH_2CH=$CH_{cis}H_{trans}$), 5.20 (dd, $J_{2,3}$ = 3.4 Hz, $J_{3,4}$ = 9.7 Hz, 1 H, 3-H), 5.18 (dd, $J_{1,2}$ = 1.8 Hz, 1 H, 2-H), 5.15 (dd, ^3J = 10.1 Hz, ^2J = 1.5 Hz, 1 H, -CH_2CH=$CH_{cis}H_{trans}$), 4.99 (t, $J_{4,5}$ = 9.7 Hz, 1 H, 4-H), 4.70 (d, 1 H,

1-H), 4.18-3.88 (m, 2-H, -CH_2CH=CH_2), 3.88-3.74 (m, 1 H, 5-H), 2.07, 1.98, 1.91 (3 x s, 9 H, 3 x -$COCH_3$), 1.15 (d, $J_{5,6}$ = 6.2 Hz, 3 H, 6-CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 169.9, 169.8, 169.7, 133.1, 117.8, 96.3 (C-1), 70.9, 69.7, 68.9, 68.1, 66.2, 20.6. β-anomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.92-5.77 (m, 1 H, -CH_2CH=CH_2), 5.44 (d, $J_{2,3}$ = 3.0 Hz, 1 H, 2-H), 5.24 (dd, ^3J = 17.5 Hz, ^2J = 1.5 Hz, 1 H, -CH_2CH=$CH_{cis}H_{trans}$), 5.19 (dd, ^3J = 10.5 Hz, ^2J = 1.5 Hz, 1 H, -CH_2CH=C$H_{cis}$$H_{trans}$), 5.03 (t, $J_{3,4}$ = $J_{4,5}$ = 10.2 Hz, 1 H, 4-H), 4.97 (dd, 1 H, 3-H), 4.63 (s, 1 H, 1-H), 4.32 (dd, ^3J = 4.8 Hz, ^2J = 12.9 Hz, 1 H, -C$H_a$$H_b$CH=$CH_2$), 4.07 (dd, ^3J = 6.3 Hz, ^2J = 12.9 Hz, 1 H, -$CH_a$$H_b$CH=$CH_2$), 3.55-3.42 (m, 1 H, 5-H), 2.16, 2.03, 1.96 (3 x s, 9 H, 3 x -$COCH_3$), 1.26 (d, $J_{5,6}$ = 6.0 Hz, 3 H, 6-CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1 (x 3), 133.2, 118.0, 96.9 (C-1), 71.1, 70.7, 70.5, 70.0, 69.1, 20.8, 20.7, 20.5, 17.4 ppm. $C_{15}H_{22}O_8$: calcd C 54.54, H 6.71; found C 54.40, H 6.60.

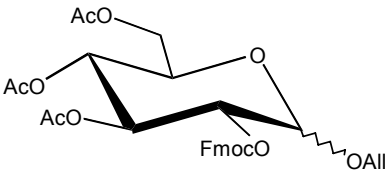


Allyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-acetyl-α,β-D-glucopyranoside (25B)[20]**.** Foam (ca α/β 1:6 anomeric mixture). Data for the β-anomer, ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.93-5.70 (m, 1 H, -CH_2CH=CH_2), 5.31 (bd, $J_{3,4}$ = 3.4 Hz, 1 H, 4′-H), 5.23 (dd, ^3J = 17.3 Hz, ^2J = 1.6 Hz, 1 H, -CH_2CH=$CH_{cis}H_{trans}$), 5.16 (t, $J_{2,3}$ = $J_{3,4}$ = 9.6 Hz, 1 H, 3-H), 5.15 (dd, ^3J = 10.6 Hz, ^2J = 1.6 Hz, 1 H, -CH_2CH=C$H_{cis}$$H_{trans}$), 5.07 (dd, $J_{1,2}$ = 7.9 Hz, $J_{2,3}$ = 10.4 Hz, 1 H, 2′-H), 4.92 (dd, 1 H, 3′-H), 4.89 (br. dd, $J_{1,2}$ = 8.0 Hz, $J_{2,3}$ = 9.6 Hz, 1 H, 2-H), 4.53-4.42 (2 x d, 2 H, 1-H and 1′-H), 4.34-3.92 (m, 6 H), 3.84 (brt, $J_{5,6a}$ = $J_{5,6b}$ = 6.8 Hz, 1 H, 5′-H), 3.77 (t, $J_{3,4}$ = $J_{4,5}$ = 9.3 Hz, 1 H, 4-H), 3.63-3.50 (m, 1 H, 5-H), 2.11, 2.09, 2.02, 2.01 (x 2), 2.00, 1.92 (7 x s, 21 H, 7 x –$COCH_3$) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.2 (x 2), 170.0, 169.8, 169.6, 169.4, 168.8, 133.2, 117.5, 100.9 (C-1′), 99.2 (C-1), 76.2, 72.8, 72.5, 71.6, 70.9, 70.6, 69.9, 69.1, 66.6, 62.0, 60.8, 20.6 ppm. $C_{29}H_{40}O_{18}$: calcd C 51.48, H 5.96; found C 51.13, H 5.78.

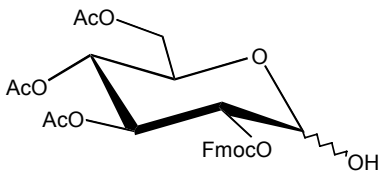


Allyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl-(1→4)-3,6-di-*O*-acetyl-α-D-glucopyranoside (26B). Oil. $[\alpha]^{25}_D$ = +62.3 (c 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.97-5.80 (m, 1 H, -CH_2CH=CH_2), 5.37-5.15 (m, 4 H, 4′-H, -CH_2CH=CH_2, 3-H), 5.06 (dd, $J_{1,2}$ = 7.6 Hz, $J_{2,3}$ = 10.4 Hz, 1 H, 2′-H), 4.89 (dd, $J_{3,4}$ = 3.3 Hz, 1 H, 3′-H), 4.86 (d, $J_{1,2}$ = 3.4 Hz, 1 H, 1-H), 4.47 (d, 1 H, 1′-H), 4.40 (dd, $J_{5,6a}$ =

5.6 Hz, $J_{6a,6b}$ = 11. 6 Hz, 1 H, 6a-H), 4.21-3.80 (m, 7 H, 6b-H, 6′-H_2, 5- H, OCH_2-CH=CH_2 and 2-H), 3.64 (t, $J_{3,4} = J_{4,5}$ = 9.6 Hz, 1 H, 4-H), 3.56-3.47 (bt, $J_{5,6a} = J_{5,6b}$ = 7.8 Hz, 1 H, H-5′), 2.74 (brs, 1 H, 2-OH), 2.11, 2.08 (x 2), 2.01 (x 2), 1.92 (6 x s, 18 H, 6 x –$COCH_3$) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.6, 170.2, 170.1, 170.0, 169.9, 168.9, 133.0, 118.3, 100.8 (C-1′), 97.0 (C-1), 76.1, 73.2, 70.9, 70.3, 68.9 (x 2), 68.3, 66.5, 62.0, 60.7 (x 2), 20.7, 20.5 ppm. $C_{27}H_{38}O_{17}$: calcd C 51.10, H 6.04; found C 50.95, H 5.83.

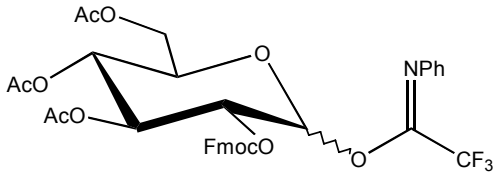


Allyl 2-(fluorenyl)methyloxycarbonyl-3,4,6-tri-*O*-acetyl-α,β-D-glucopyranoside (29B). To a solution of **4B** (248 mg, 0.72 mmol) in anhydrous DCM (8 mL) were sequentially added pyridine (0.64 mL, 8.0 mmol) and FmocCl (259 mg, 1.0 mmol). When the reaction was complete (ca 3 h), the mixture was diluted with DCM and washed with water. The aq phase was re-extracted with DCM, and the collected organic phases were dried and concentrated under vacuo. The residue was purified by silica-gel flash chromatography (eluent: petroleum ether/ethyl acetate mixtures) to yield **29B** (oil, 311 mg, 76 % yield) as an anomeric mixture (α/β 6:1). **29B** α-anomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80-7.28 (aromatic protons), 5.97-5.82 (m, 1 H, -CH_2C*H*=CH_2), 5.59 (t, $J_{2,3} = J_{3,4}$ = 9.7 Hz, 1 H, 3-H), 5.34 (dq, ^3J = 17.2 Hz, $^2J = {}^4J$ = 1.5 Hz, 1 H, -CH_2CH=$CH_{cis}H_{trans}$), 5.22 (dq, ^3J = 10.3 Hz, $^2J = {}^4J$ = 1.5 Hz, 1 H, -CH_2CH=CH_{cis}H$_{trans}$), 5.17 (d, $J_{1,2}$ = 3.6 Hz, 1 H, 1-H), 5.09 (t, $J_{3,4} = J_{4,5}$ = 9.7 Hz, 1 H, 4-H), 4.79 (dd, 1 H, 2-H), 4.44-4.01 (m, 8 H), 2.10, 2.04, 2.01 (3 x s, 9 H, 3 x –$COCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 169.8, 169.6, 154.1, 143.0, 142.9, 141.1 (x 2), 132.9, 127.8-119.9, 118.1, 94.6 (C-1), 73.8, 70.2, 69.9, 68.8, 68.5, 67.3, 61.7, 46.4, 20.5, 20.4 ppm. Significative signals of the β-anomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.32 (t, $J_{2,3} = J_{3,4}$ = 9.7 Hz, 1 H, 3-H), 5.11 (t, $J_{4,5}$ = 9.7 Hz, 1 H, 4-H), 4.88 (br. dd, $J_{1,2}$ = 7.9 Hz, 1 H, 2-H), 4.64 (d, 1 H, 1-H), 3.76-3.68 (m, 1 H, 5-H), 2.09, 2.03, 1.97 (3 x s, 9 H, 3 x –$COCH_3$) ppm. $C_{30}H_{32}O_{11}$: calcd C 63.37, H 5.67; found C 63.14, H 5.75.



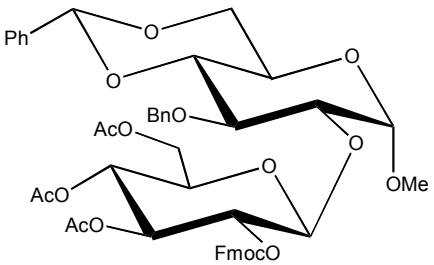
2-(Fluorenyl)methyloxycarbonyl-3,4,6-tri-*O*-acetyl-D-glucopyranose (30B). To a solution of **29B** (320 mg, 0.56 mmol) in 4:1 DCM/MeOH (5 mL), was added $PdCl_2$ (13 mg, 0.07 mmol). The mixture was stirred for 10 h at rt, concentrated, resuspended in DCM/MeOH 95:5, and then filtered through a short pad of silica-gel. The filtered liquor was concentrated and the residue purified by silica-gel flash chromatograhphy (eluent: petroleum ether/ethyl acetate mixtures) to yield **30B** (oil, 193 mg,

65 % yield) as an anomeric mixture (α:β 3.5). **30B** α-anomer,[1]H NMR (300 MHz, $CDCl_3$): δ = 7.80-7.28 (aromatic protons), 5.61 (t, $J_{2,3} = J_{3,4} = 9.7$ Hz, 1 H, 3-H), 5.50 (bs, 1 H, 1-H), 5.09 (t, $J_{3,4} = J_{4,5} = 9.6$ Hz, 1 H, 4-H), 4.78 (dd, $J_{1,2} = 3.6$ Hz, 1 H, 2-H), 4.40-4.04 (m, 6 H), 2.07, 2.02, 1.99 (3 x s, 9 H, 3 x –$COCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.8, 170.1, 169.7, 154.2, 143.0, 142.9, 141.1 (x 2), 127.8-120.0, 89.8 (C-1), 74.3, 70.2, 69.7, 68.4, 67.0, 61.8, 46.4, 20.6 ppm. Significative signals of the β-anomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.32 (t, $J_{2,3} = J_{3,4} = 9.7$ Hz, 1 H, 3-H), 3.79-3.71 (m, 1 H, 5-H) ppm. $C_{27}H_{28}O_{11}$: calcd C 61.36, H 5.34; found C 61.12, H 5.18.



2-*O*-(Fluorenyl)methyloxycarbonyl-3,4,6-tri-*O*-acetyl-α,β-D-glucopyranosyl (N-Phenyl)trifluoroacetimidate (31B).

To a solution of **30B** (106 mg, 0.20 mmol) in acetone (4 mL) were sequentially added at 0 °C Cs_2CO_3 (74 mg, 0.23 mmol) and (*N*-phenyl)trifluoroacetimidoyl chloride (50 mL, 0.40 mmol). The mixture was allowed to warm to rt and after 1 h from the start the solvent was removed under vacuo. The residue was purified via column chromatography on neutral aluminium oxide (Brockman grade 2, eluent: petroleum ether/ethyl acetate mixtures) to yield **31B** (oil, 119 mg, yield 85%) as an anomeric mixture (α/β 2.5:1). **31B** α-anomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.80-6.75 (aromatic protons), 6.74 (bs, 1 H, H-1), 5.66 (t, $J_{2,3} = J_{3,4} = 9.9$ Hz, 1 H, 3-H), 5.23 (t, $J_{4,5} = 9.9$ Hz, 1 H, 4-H), 5.05 (dd, $J_{1,2} = 3.3$ Hz, 1 H, 2-H), 4.50-4.10 (m, 6 H), 2.14, 2.11, 2.09 (3 x s, 9 H, 3 x –$COCH_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 169.7, 169.4, 154.0, 143.0, 142.8, 141.2, 128.7, 127.9, 127.1, 125.0, 124.5, 120.0, 119.1, 91.8 (C-1), 73.0, 70.6, 67.6, 61.2, 46.3, 20.5 ppm. Significative signals of the β-anomer, ^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.90 (bs, 1 H, H-1), 5.39 (t, $J_{2,3} = J_{3,4} = 9.9$ Hz, 1 H, 3-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 94.2 (C-1). $C_{35}H_{32}F_3NO_{11}$: calcd C 60.09, H 4.61; found C 59.90, H 4.50.



Methyl 2-*O*-(fluorenyl)methyloxycarbonyl-3,4,6-tri-*O*-acetyl-β-D-glucopyranosyl-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (33B).

Donor **31B** (35 mg, 0.05 mmol) and acceptor **32B** (13 mg, 0.035 mmol) were coevaporated three times in anhydrous toluene and then dried in vacuo for 30 minutes. The mixture was then dissolved at 0 °C (ice bath) under argon with anhydrous DCE (1 mL) in the presence of freshly activated 4 Å AW

molecular sieves. After stirring for 15 minutes, a solution of $Bi(OTf)_3$ in dioxane (17 mg/mL, 135 μL, 3.5 μmol) was added. After further 10 minutes the ice bath was removed and the mixture was left under stirring until TLC analysis displayed the consumption of the donor (ca 90 min from the addition of the promoter). The reaction was quenched with pyridine, and the mixture was filtered through a short pad of silica gel. The residue from the filtered liquor was submitted to silica-gel flash chromatography (eluent: toluene/acetone 7:1) to yield disaccharide **32B** as a foam (21 mg, 70% yield). **32B**: $[\alpha]^{25}_D$ = +29.3 (c 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.70-7.20 (aromatic protons), 5.56 (s, 1H, benzylidene acetal CH), 5.27 (t , $J_{2,3} = J_{3,4}$ = 9.7 Hz, 1 H, 3'-H), 5.09 (t, $J_{4,5}$ = 9.7 Hz, 1 H, 4'-H), 4.97 (d, $J_{1,2}$ = 7.5 Hz, 1 H, 1'-H), 4.93 (dd, 1 H, 2'-H), 4..83 (d, $J_{1,2}$ = 3.6 Hz, 1 H, 1-H), 4.72 (s, 2 H, benzyl CH_2), 4.40 (dd, ^3J = 7.8 and 10.5 Hz, 1 H, Fmoc –OCH_2CH), 4.32-4.06 (m, 5 H, overlapped signals), 3.98 (t, $J_{2,3} = J_{3,4}$ = 9.7 Hz, 1 H, 3-H), 3.86 (td, ^3J = 4.5 and 9.7 Hz, 1 H, 5-H), 3.80-3.70 (m, 2 H, 2-H and 6ax-H), 3.70-3.65 (m, 1H, 5'-H), 3.60 (t, 1 H, 4-H), 3.42 (s, 3 H, -OCH_3), 2.09, 2.03, and 1.94 (3 x s, 9 H, , 3 x –$COCH_3$) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 170.4, 170.0, 169.2, 169.4, 154.1, 133.1, 143.2, 142.9, 141.2, 138.3, 137.4, 128.9-127.2, 126.0, 125.0, 129.0, 101.3 (x2) (C-1' and benzylidene acetal CH), 100.1 (C-1), 82.3, 79.5, 77.7, 77.2, 75.4, 75.2, 72.8, 71.9, 70.2, 69.1, 68.5, 62.2, 61.9, 55.4, 46.5, 20.6, 20.5 (x2). $C_{48}H_{50}O_{16}$: calcd C 65.30, H 5.71; found C 65.05, H 5.53.

References

1. C.-C. Wang, J.-C. Lee, S.-Y. Luo, S. S. Kulkarni, Y.-W. Huang, C.-C. Lee, K.-L. Chang, S.-C. Hung, *Nature*, **2007**, *446*, 896; b) A. Francais, D. Urban, J.-M. Beau, *Angew. Chem. Int. Ed*. **2007**, *46*, 8662.

2. Glycosyl iodides are generally activated by stoichiometric reagents. For some examples: a) M. J. Hadd, J. Gervay, *Carbohydr. Res.* **1999**, *320*, 61. b) J. A. Perrie, J. R. Harding, C. King, D. Sinnott, A. V. Stachulski, *Org. Lett.* **2003**, *5*, 4545. c) S. M. Lamm, J. Gevay-Hague, *J. Org. Chem.* **2005**, *70*, 8773. d) W. Du, J. Gevay-Hague *Org. Lett.* **2005**, *7*, 2063.

3. a) M. Adinolfi, A. Iadonisi, M. Schiattarella, A. Ravidà, *Tetrahedron Lett*. **2003**, *44*, 7863. b) Ness, R. K.; Fletcher, H. G.; Hudrson, C. S. *J. Am. Chem. Soc.* **1950**, *72*, 2200. c) Montero, J.-L.; Winum, J.-Y; Leydet, A.; Kamal, M.; Pavia, A. A.; Roque, J.-P. Carbohydr. Res. **1997**, *297*, 175. d) Gervay, J.; Nguyen, T. N.; Hadd, M. J. Carbohydr. Res. **1997**, *300*, 119. e) Chervin, S. M.; Abada, P.; Koreeda, M. *Org. Lett.* **2000**, *2*, 369. f) Mukhopadhyay, B.; Ravindranathan Kartha K. P.; Russell D. A.; Field R. A. *J. Org. Chem.* **2004**, *69*, 7758. g) Ernst, B.; Winkler, T. Tetrahedron Lett. **1989**, *30*, 3081. h) Caputo, R.; Kunz, H.; Mastroianni, D.; Palumbo, G.; Pedatella, S.; Solla, F. *Eur. J. Org. Chem.* **1999**, *11*, 3147. i) Schmid, U.; Waldmann, H. *Liebigs Annalen – Reuceil* **1997**, *12*, 2573. j) Tanaka, H.; Sakamoto, H.; Nakamura, A. S. S.; Nakajima, M.; Hashimoto, S. *Chem. Comm.* **1999**, *13*, 1259. k) Bhat, A. S.; Gervay, J. *Org. Lett.* **2001**, *3*, 2081. l) Ko, Y.-J.; Shim, S.-B.; Shin, J.-H. *Org. Lett.* **2009**, *11*, 609.

4. a) M. Adinolfi, A. Iadonisi, A. Pezzella, A. Ravidà, *Synlett* **2005**, 1848; b) S. Valerio, A. Iadonisi, M. Adinolfi, A. Ravidà, *J. Org. Chem.* **2007**, *72*, 6097.

5.] D. Mukherjee, P. K. Ray, U. S. Chowdhury, *Tetrahedron* **2001**, *57*, 7701.

6. a)M. Kaneko, R. Hayashi, G. R. Cook, *Tetrahedron Lett.* **2007**, *48*, 7085. b) H. Sun, R. Hua, S. Chen, Y. Yin *Advanced Synthesis & Catalysis*, **2006**, *348*, 1919. c) R. Hayashi, G. R. Cook *Tetrahedron Lett.* **2008**, *49*, 3888.

7. M.-Z. Liu, H.-N. Fan, Z.-W. Guo, Y.-Z. Hui, *Carbohydr. Res.* **1996**, *290*, 233.

8. a) U. Aich, D. Loganathan, *Carbohydr. Res.* **2006**, *341*, 19; b) U. Aich, D. Loganathan, *Carbohydr. Res.* **2007**, *342*, 704.

9. a) F. Coutrot, E. Busseron, J.-L. Montero, *Org. Lett.* **2008**, *10*, 753. b) G.Gu, G. Wei, Y. Du, *Carbohydr. Res.* **2004**, *339*, 1155. c) Y. Xing, J. Ning, *Tetrahedron: Asymmetry*

2003, *14*, 1275. d) T. Nukada, A. Berces, D. M. Whitfield, *J. Org. Chem.* **1999**, *64*, 9030. e) T. Murakami, Y. Sato, M. Shibakami, *Carbohydr. Res.* **2008**, *343*, 1297.

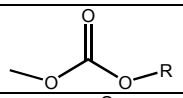
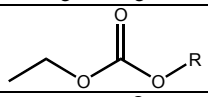
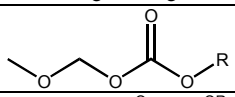
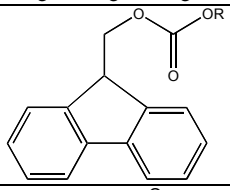
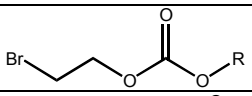
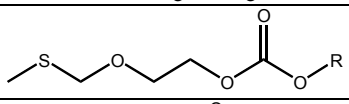
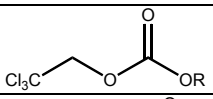
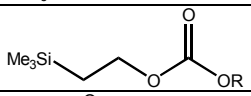
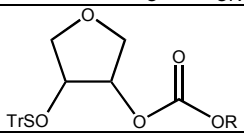
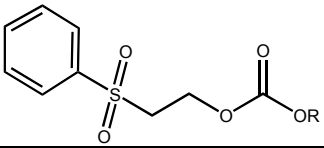
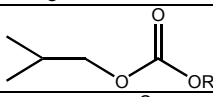
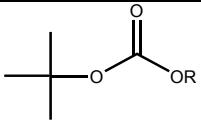
10. M. Adinolfi, G. Barone, A. Iadonisi, L. Mangoni, M. Schiattarella, *Tetrahedron Lett.* **2001**, *42*, 5967-5969.
11. M. Adinolfi, A. Iadonisi, A. Ravidà, S. Valerio, *Tetrahedron Lett.* **2006**, *47*, 2595.
12. B. Yu, H. Tao, *Tetrahedron Lett*. **2001**, *42*, 2405.
13. W. A. R. van Heeswijk, H. G. J. Visser, J. F. G.Vliegenthart, *Carbohydr. Res.* **1977**, *58*, 494.
14. R. Rodebaugh, B. Fraser-Reid, *Tetrahedron*, **1996**, *52*,7663.
15. G. Sureshkumar, S. Hotha, *Tetrahedron Lett.* **2007**, *48*, 6564.
16. W. Steffan, C. Vogel, H. Kristen, *Carbohydr. Res.* **1990**, *204*, 109.
17. M. Izumi, O. Tsuruta, S. Harayama, H. Hashimoto *J. Org. Chem.* **1997,** *62,* 9928.
18. a) J.-P. Utille, B. Priem, *Carbohydr. Res.* **2000**, *329*, 431. b) Y. A. Lin, J. M. Chalker, N. Floyd, G. J. L.Bernardes, B. G. Davis *J. Am. Chem. Soc.* **2008,** *130,* 9642.
19. a) M. T. Campos-Valdes, J. R. Marino-Albernas, V. Verez-Bencomo, *J. Carb. Chem.* **1987**, *6*, 509. b) P. Westerduin, P. E. Dr Haan, M. J. Dees, J. H. van Boom, *Carbohydr. Res.* **1988**, *280*, 195.
20. K. Okamoto, T. Kondon, T. Goto, *Tetrahedron* **1987**, *43*, 5919.

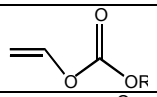
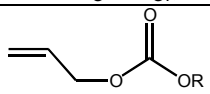
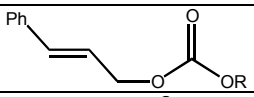
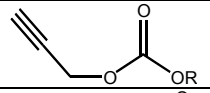
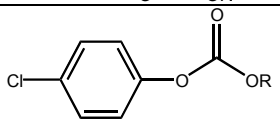
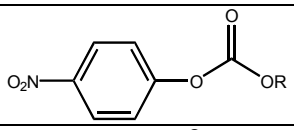
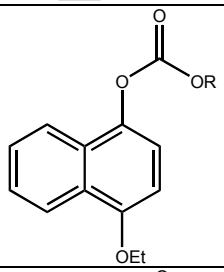
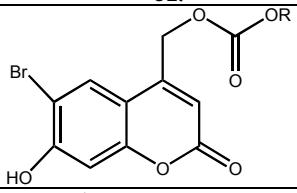
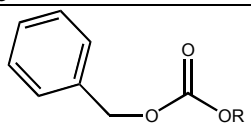
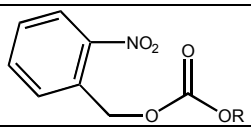
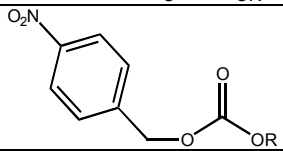
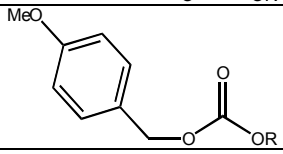
Chapter C

A selective and operationally simple approach for removal of methoxy-, allyloxy- and benzyloxycarbonyl groups from carbinols.

Introduction

Alkoxycarbonyl groups have long been extensively used in the protection of amino functionalities. However their application to carbinol functions is only currently receiving a wide interest as it was widely showed in **Table 1**[4a], especially in carbohydrate chemistry.[1]

Name of the alkyl carbonate	Structure	Cleavage
Methyl carbonate		Basic solvolysis
Ethyl carbonate		Basic solvolysis
Methoxymethyl carbonate		Basic solvolysis Acid solvolysis
9-Fluorenylmethyl carbonate (Fmoc-OR)		TEA,Py
Bromoethyl carbonate (BEC-OR)		Zn, AcOH
2-(Methylthiomethoxy)ethyl carbonate (MTMEC-OR)		$Hg(ClO_4)_2$, 2,4,6-collidine, acetone, H_2O (9:1); then NH_3, dioxane, H_2O (1:1).
2,2,2-Trichloroethyl carbonate (Troc-OR)		Zn, AcOH; Sm, I_2, MeOH; In, NH_4Cl, H_2O, MeOH.
2-(Trimethylsilyl)ethyl carbonate (TMSEC-OR, Teoc-OR)		TBAF 0.2 M, THF; $ZnCl_2$, DCM.
Cis-[4-[[(-Methoxytrityl)sulfenyl]oxy]tetrahydrofuran-3-yl]oxy carbonate (MTFOC-OR)		I_2 0.5 M, Py, H_2O 9:1 v:v
2-(Phenylsulfonyl)ethyl carbonate (Psec-OR)		TEA, py
Isobutyl carbonate		AcOH, reflux
t-Butyl carbonate (BOC)		TFA, DCM

Vinyl carbonate		Basic hydrolysis
Allyl carbonate (Alloc-OR)		$Pd(Ph_3P)_4$ (cat.), $HCOONH_4$; $Pd(Ph_3P)_4$ (cat.), Bu_3SnH; $PdCl_2(Ph_3P)_2$ (cat.), dimedone; $Pd(Ph_3P)_4$ (cat.), $NaBH_4$, EtOH.
Cinnamyl carbonate		-2.3 V, Hg, MeCN
Propargyl carbonate (Poc-OR)		$[BnNEt_3]_2MoS_4$, MeCN
p-Chlorophenyl carbonate (CPC-OR)		LiOOH, THF/H_2O, 0°C
p-Nitrophenyl carbonate		Imidazole (cat.), H_2O/dioxane
4-Ethoxy-1-Naphthyl carbonate		-1.6 V, C-anode, acetone/H_2O
6-Bromo-7-hydroxycoumarin-4-ylmethyl carbonate (Bhcmoc-OR)		*hv*, H_2O
Benzyl carbonate (Cbz-OR)		H_2, Pd/C, EtOH; cycloexadiene, Pd/C (cat.), DMF; -2.7 V, R_4NX, DMF; Basic hydrolysis; CAN or TBAF or TFA or HBr or HCl; $NaBrO_3$, $Na_2S_2O_4$, $AcOEt/H_2O$.
o-Nitrobenzyl carbonate		*hv*, pH 7
p-Nitrobenzyl carbonate		H_2, Pd/C, EtOH, dioxane, H_2O, K_2HPO_4; electrolytic reduction.
p-Methoxybenzyl carbonate		Ph_3CBF_4, 0°C; DDQ; strong acids.

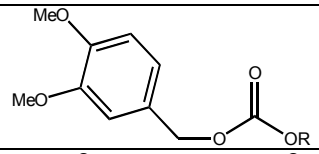
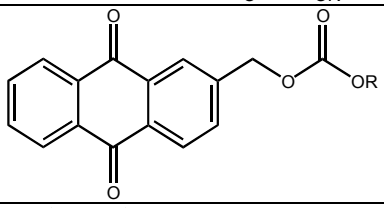
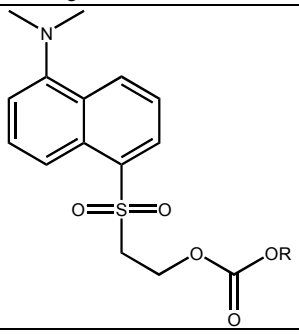
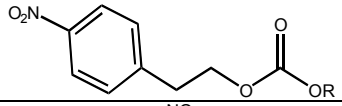
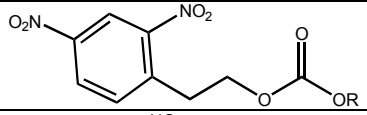
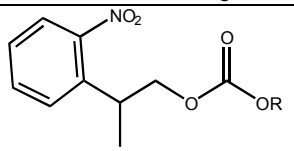
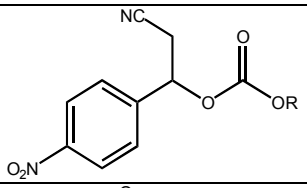
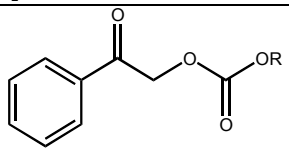
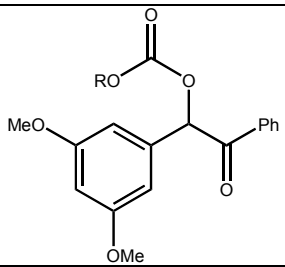
3,4-Dimethoxybenzyl carbonate		Ph_3CBF_4, 0°C; DDQ; strong acids.
Anthraquinon-2-ylmethyl carbonate (Aqmoc-OR)		*hv*, H_2O/THF
2-Dansylethyl Carbonate (Dnseoc-OR)		DBU, MeCN
2-(4-Nitrophenyl)ethyl carbonate (Npeoc-OR)		*hv*; Basic solvolysis
2-(2,4-Dinitrophenyl)ethyl carbonate (Dnpeoc-OR)		Basic solvolysis
2-(2-Nitrophenyl)proyl carbonate (NPPOC-OR)		*hv*, MeOH/H_2O
2-Cyano-1-phenylethyl carbonate (Cpeoc-OR)		DBU 0.1 M, MeCN
Phenacyl carbonate		*hv*, *N*-methylcarbazole
3',5'-Dimethoxybenzoin carbonate (DMB-O_2COR)		*hv*, THF

Table 1

Other relevant synthetic applications based on the use of alkoxycarbonylated carbinols are:

- substitutions or rearrangements of *O*-alkoxycarbonylated allyl alcohols promoted by palladium catalysis[2] (**Figure 1**)

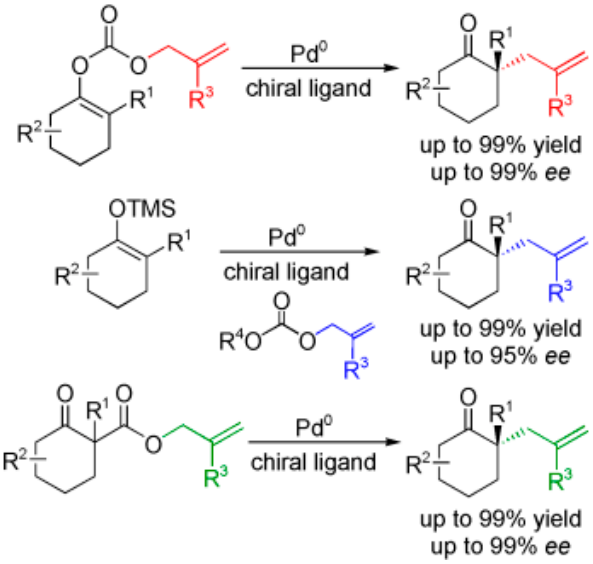


Figure 1

- masking of aldehyde or ketone carbonyl groups via *O*-methoxycarbonylation of cyanohydrins[3] (**Figure 2**).

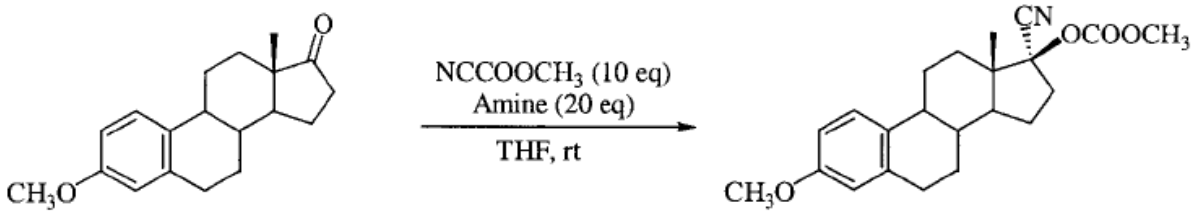


Figure 2

One of the most relevant advantages of alkoxycarbonyl groups is their easy installation on carbinols under mild basic conditions compatible with a wide range of functionalities.[1] Alkoxycarbonyl groups can be removed under two different cleavage pathways. The first pathway is an acyl nucleophilic substitution process which is the basis of many solvolytic methods that confer little advantage to carbonates as protecting groups. In general, the conditions needed to attack esters are also efficient for carbonates[3] although these latter are less reactive than esters towards basic solvolysis owing to the reduced electrophilicity of the carbonyl group due to the resonance deactivation generated by two oxygens substituents.[4b] The second pathway is based on a common general mechanism entailing an initial alkyl scission followed by spontaneous loss of CO_2 (**Figure 3**).[4a] In this way, several alkoxycarbonyl groups, i.e. allyloxycarbonyl (Alloc), benzyloxycarbonyl (Z), fluorenylmethoxycarbonyl (Fmoc) groups, can be selectively removed under specific

conditions. Alternative cleavage pathways resembling an acyl nucleophilic substitution have instead been applied to de-*O*-methoxycarbonylation.[3,5]

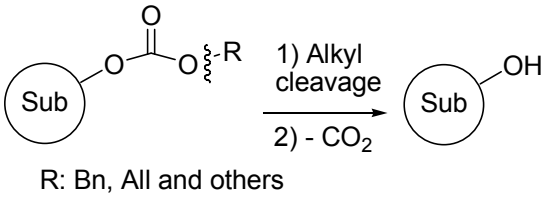


Figure 3 Common general mechanism for removal of many alkoxycarbonyl groups from alcohols

Over the last years my research group has been appreciating numerous advantages in using the methoxycarbonyl group in carbohydrate chemistry. Actually it can be quantitatively and quickly installed on saccharidic carbinols to yield products easily purified by a simple extractive work-up. The adopted protocol, based on the use of cheap methyl chloroformate and TMEDA, is also suited for the regioselective protection of diols.[6] In addition, methoxycarbonyl groups can be removed under Zemplen conditions at rates comparable with those of acetyls,[5] thus representing an effective alternative to the use of sterically encumbered acyl groups which are installed and removed under more forced conditions. In this regard, methoxycarbonyl was found to serve as an excellent non bulky participating group in 1,2-*trans* glycosidations conducted under very mild acidic conditions[7] where 1,2-orthoester coupling products predominated on adopting conventional acyl protecting groups.[8] In contrast, in the experience of my research group allyloxy- and benzyloxycarbonyl groups were found to be less effective in inducing 1,2-*trans* selective glycosidations because of their trend to furnish undesired cyclic 1,2-carbonates[9]; differently, 9-fluorenylmethoxycarbonyl groups required the best α-selective glycosidation solvent mixture ($PhCH_3/Et_2O$ 4:1) to afford 1,2-*trans* mannosides in high yield and stereocontrol as it will show in **Chapter F**.

Due to the emerged manifold advantages of methoxycarbonyl group and in order to expand the scope of methoxycarbonyl as transient protecting groups in oligosaccharide synthesis, the current work has been spurred by the search for deprotection conditions compatible with the stability of acyl protecting groups.

Results and discussion

Since a carboxylic ester possesses a hard center (carboxyl carbon) and a soft center (carbinol carbon), using the principles of hard/soft acid base theory,[19,20] hard nucleophiles are predicted to show a preference for attack on the carboxy carbon (hard-hard interaction) rather than the carbinol carbon (hard-soft interaction) (**Figure 4).**

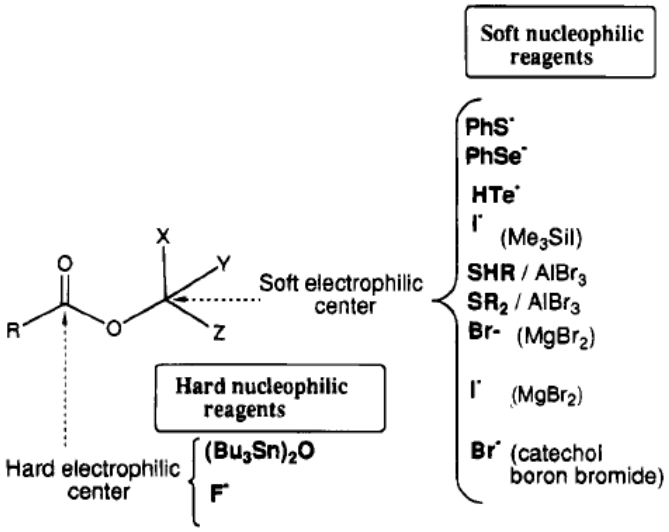


Figure 4

In evaluating the various hard nucleophiles which are available, "naked" fluoride anion[21] is one choice. Similarly, pertinent internal bifunctional systems consisting of a hard acid and a hard nucleophile should attack the carboxylic ester at the carboxy center rather than at the carbinol center and, therefore, accomplish acyl-oxygen cleavage without affecting the stereochemistry of a chiral center at the carbinol carbon. On the other hand, the alternative approach of cleaving esters via nucleophilic attack at the carbinol carbon under non-hydrolytic conditions in non-hydroxylic solvents can be employed. Thiophenoxide, alkanethiolate, trithio-carbonate, ethanedithiolate, sulfide, phenyl selenide, hydrogen selenide, and telluride anions are representative of the soft nuclephile class. Besides, the most widely used combination systems, consisting of a hard acid and a soft nucleophile, are: trimethylsilyl iodide, aluminium halide-ethanethiol, aluminium halide-dialkyl sulfide, aluminium triiodide, magnesium bromide, magnesium iodide, and catechol boron bromide.

Additionally, methyl esters can be cleaved with different reactant system based on:

1. a Lewis acid in the presence of a nucleophilic additive such as $AlBr_3$/tetrahydrothiophene (**Figure 5**), $AlCl_3/Me_2S$;[4a]

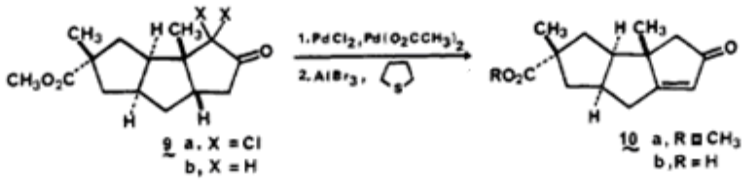


Figure 5

2. a Lewis acid where a ligand of the acidic species promotes the alkyl cleavage such as $AlCl_3/C_6H_5N(Me)_2$, BCl_3;[4a]

3. a powerful nucleophile reacting in dipolar aprotic solvent such as NaCN/HMPA, Cs_2CO_3/PhSH/DMF, catalytic KF or K_2CO_3/PhSH/NMP 190°C (**Figure 6**), *n*-PrSLi/HMPA (**Figure 7**), Ph_3SiSH/ Cs_2CO_3/2,6-di-*t*-butylcresol/DMF (**Figure 8**);[4a]

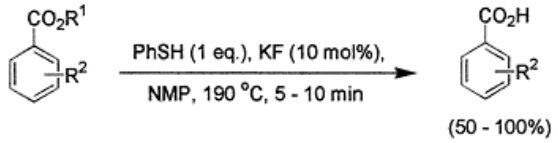


Figure 6 Ester *O*-alkyl cleavage are carried out chemoselectively under non-hydrolytic neutral condition in high yields.

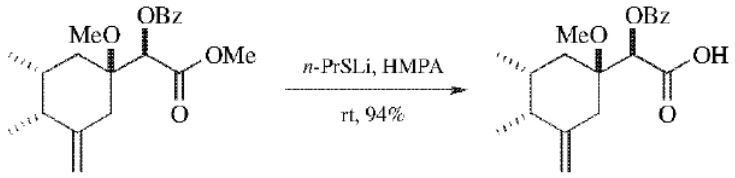


Figure 7

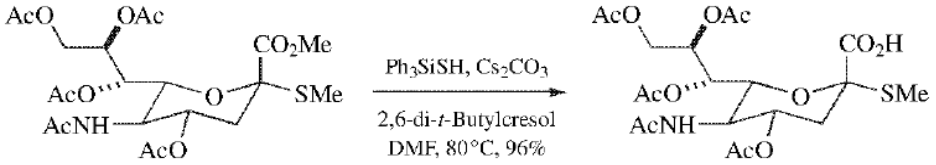


Figure 8

4. other reactant system: $NaBH_4/I_2$, LiI/Py reflux (**Figure 9**), $(CH)_3SiOK$/THF (**Figure 10**), $[MeTeAlMe_2]_2$/toluene (**Figure 11**), $(Bu_3Sn)_2O$/benzene, Me_3SnOH/1,2-DCE (**Figure 12**), $NaOCH_2CH_2CN$/THF (**Figure 13**).[4a]

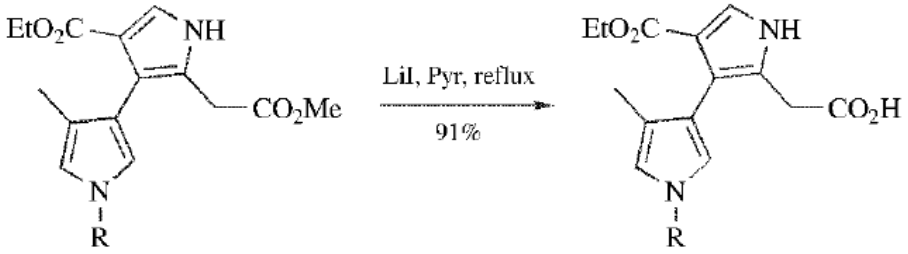


Figure 9

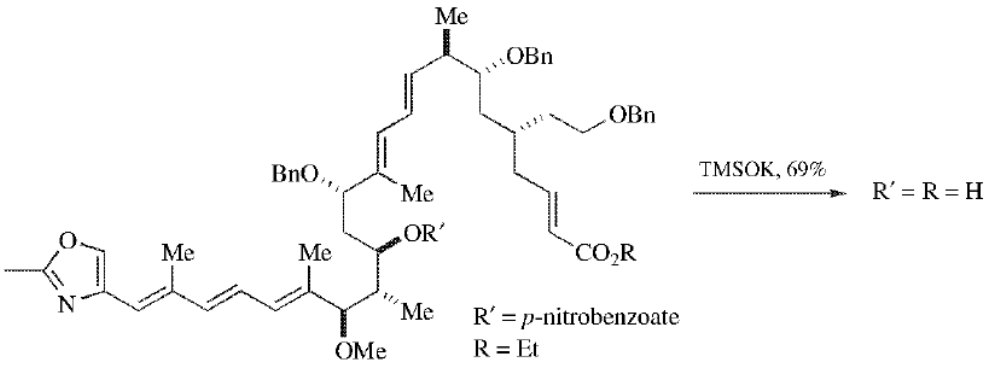


Figure 10 $(CH)_3SiOK$, in ether or in THF, often cleaves methyl esters when conventional hydrolysis fails. It was even found effective for cleavage of an ethyl ester when other methods failed. Hindered esters are cleaved with this reagent.

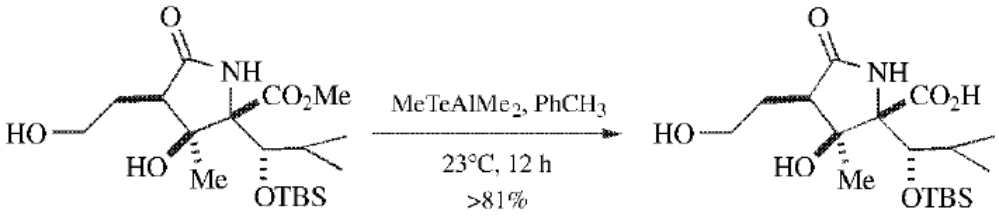


Figure 11

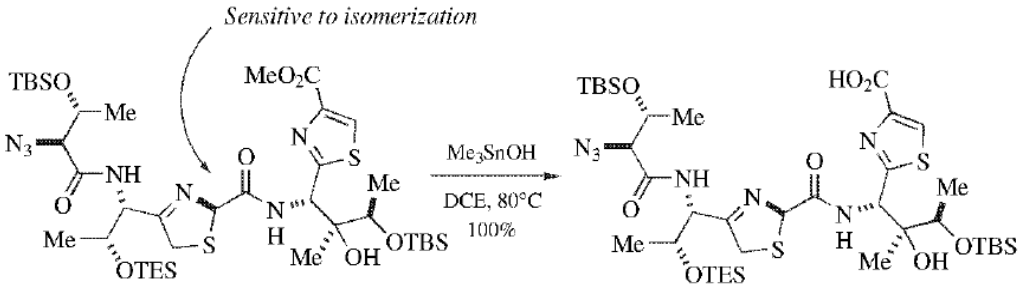


Figure 12

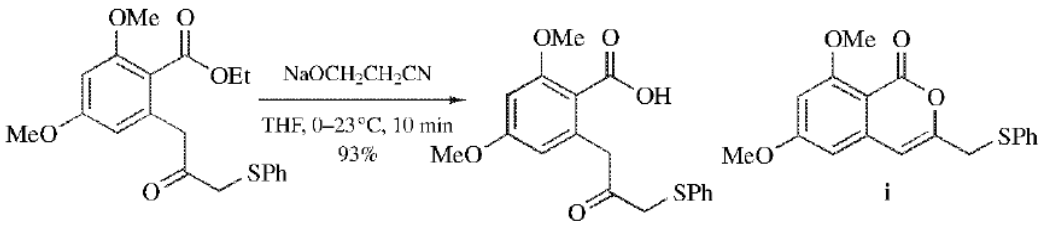
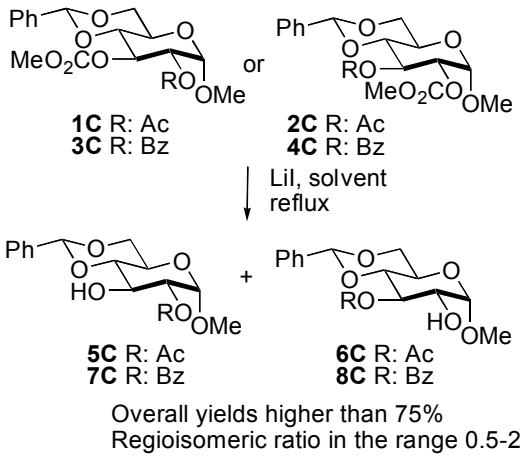


Figure 13 This method was used to prevent formation of coumarin **i**.

Because of the obvious structural analogy between a methyl ester and a methyl carbonate, the most practical methodologies were investigated out of those described for cleaving methyl esters by an alkyl scission mechanism. A single example of methoxycarbonyl removal from a phenol with the system thiophenol/cesium carbonate in DMF is indeed reported,[10] but in preliminary experiments it did not prove very effective on such densely functionalized substrates as **1C** and **2C** (**Scheme 1**). On the other hand, use of LiI in either refluxing ethyl acetate[11] or refluxing pyridine[12] appeared as an experimentally more convenient alternative. Both protocols were thereby initially examined on model compounds **1C** and **2C** purposely protected with a methoxycarbonyl adjacent to an acetylated position (**Scheme 1**).

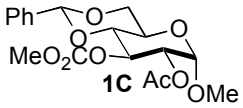
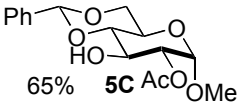
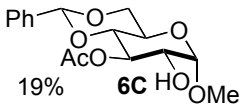
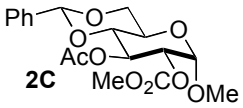
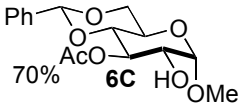
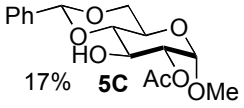
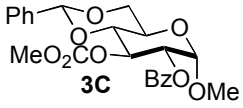
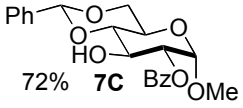
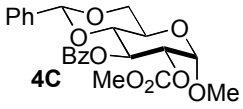
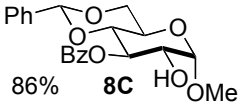
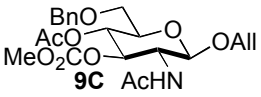
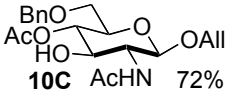
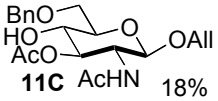
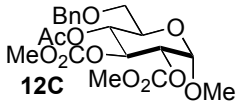
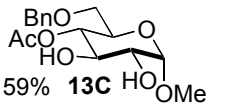
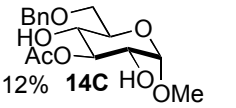
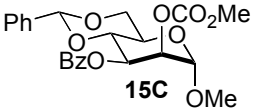
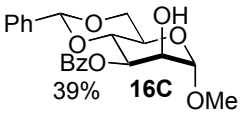
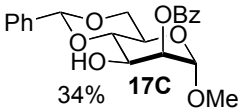
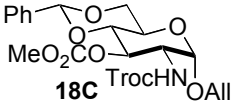
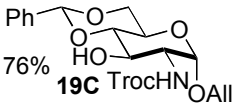
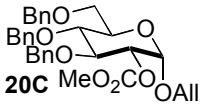
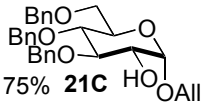
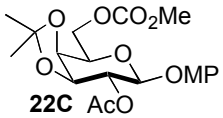
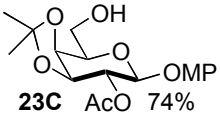
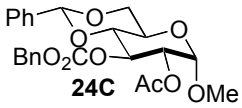
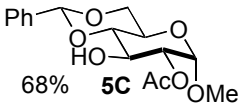
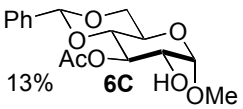
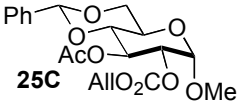
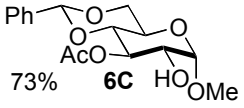
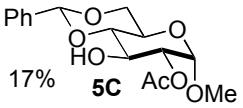
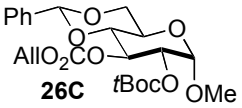
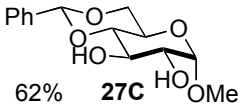
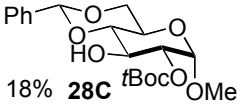


Scheme 1 Removal of methoxycarbonyl groups from *O*-acylated model substrates.

As a matter of fact, use of high-boiling pyridine was found necessary to guarantee a high yielding deprotection within short times, whereas longer reaction times and higher amounts of LiI were needed in refluxing ethyl acetate. Not unexpectedly, in all cases the desired deprotections were accompanied by rearrangement processes, so that, regardless of the structure of the starting compound, comparable amounts of 2-*O*- and 3-*O*-acetylated products were observed (**Scheme 1**). Interestingly, the extent of the acyl transfer was not significantly reduced when the vicinal acetyl group was replaced by the benzoyl functionality, well known for being much more reluctant to rearrangement processes (**Scheme 1**).[13] Reasoning that the initially produced lithium alkoxide intermediate might cause the aforementioned

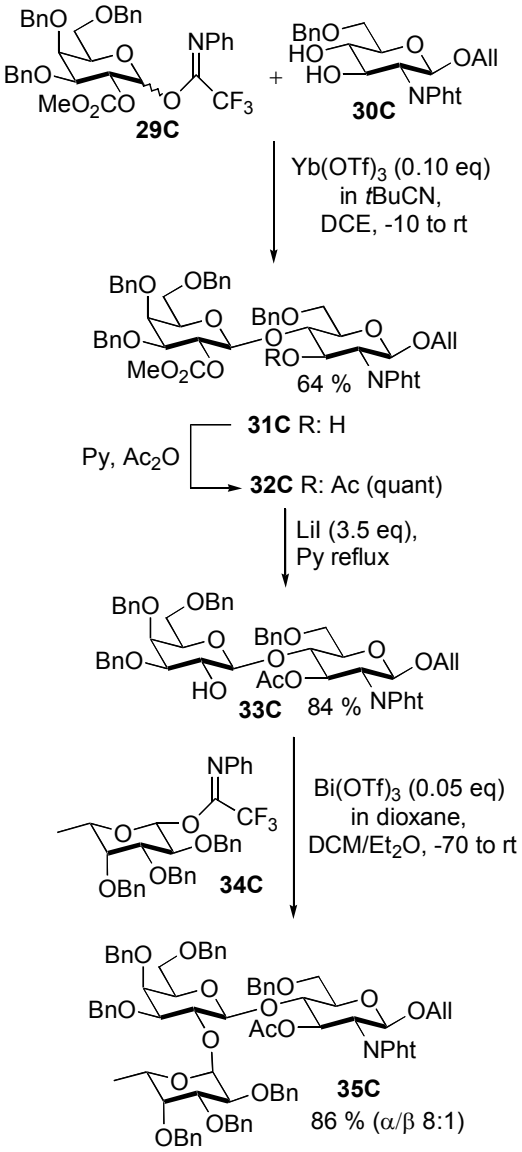
transacylation, a stoichiometric excess of an acid as weak as acetic acid (5 eq) was added to the reaction medium containing a lower excess of LiI (3 eq) with the aim of minimizing the transacylation process. As a matter of fact, this simple procedural modification led to a significant reduction of the acetyl transfer (compare **Scheme 1** and **Table 2**, entries 1-2) whereas the intramolecular *trans*-benzoylation was practically suppressed with the *gluco*-precursors **3C** and **4C** (**Table 2**, entries 3-4). In contrast, the benzoyl shift could not be avoided in the *manno*-precursor **15C** due to the *syn*-relation of *O*-2 and *O*-3 (entry 7). These improved conditions were then tested on a range of protected saccharidic derivatives (**Table 2**). The protocol proved effective at removing methoxycarbonyl group in the presence of a variety of different functionalities widely adopted in carbohydrate chemistry, including amino sugars *N*-derivatized with an acetyl (entry 5), a Troc (entry 8) and a phtalimido group (see below in **Scheme 2**). The procedure also worked well for removing allyloxy- and benzyloxycarbonyl groups (entries 11 and 12), as expected from an alkyl substitution mechanism. Interestingly, a benzyloxycarbonyl (Z) could be smoothly cleaved in the presence of a benzylidene (entry 11), whereas the routinely used hydrogenolytic removal[1f] of the benzyloxycarbonyl group would affect the benzylidene functionality. Furthermore, other functions sensitive to hydrogenolysis conditions, benzyl and allyl ethers, were instead stable under the here proposed conditions (entries 5, 6, 9). Very interestingly, reaction in entry 13 shows that *tert*-buthoxycarbonyl (*t*-Boc) also proved to be a cleavable protecting group under the optimized conditions, even though in this case the direct involvement of the iodide anion in the scission step should be excluded on the basis of steric considerations. The procedure was operationally very simple and in all cases reactions took a few hours (generally less than 4 hours). Besides the deprotection products, unreacted starting material generally represented the main saccharidic component of the crude reaction mixture. Removal of a methoxycarbonyl from the nitrogen of 1,3,4,6-*O*-acetyl glucosamine was also attempted and resulted in the recovery of the starting material to indicate the chemoselectivity of the reported conditions.[14]

Table 2 Removal of alkoxycarbonyl groups by the LiI/AcOH system.

Entry	Substrates	Products and yield		Time (min)
1	 **1C**	 65% **5C**	 19% **6C**	100
2	 **2C**	 70% **6C**	 17% **5C**	90
3	 **3C**	 72% **7C**		180
4	 **4C**	 86% **8C**		120
5[a]	 **9C**	 **10C** 72%	 **11C** 18%	90
6[b]	 **12C**	 59% **13C**	 12% **14C**	100
7	 **15C**	 39% **16C**	 34% **17C**	300
8	 **18C**	 76% **19C**		240
9	 **20C**	 75% **21C**		240
10	 **22C**	 **23C** 74%		150
11	 **24C**	 68% **5C**	 13% **6C**	160
12	 **25C**	 73% **6C**	 17% **5C**	60
13	 **26C**	 62% **27C**	 18% **28C**	300

General conditions: LiI (3 eq), AcOH (5 eq), pyridine, reflux. [a] Regiosiomers obtained as an inseparable mixture. Yields evaluated by ^{1}H NMR. [b]Conditions: LiI (6 eq), AcOH (10 eq), pyridine, reflux. Minor regioisomer **14C** could not be separated from the major one (**13C**). Yields evaluated by ^{1}H NMR.

The feasible selective removal of methoxycarbonyl group was usefully exploited in the synthesis of protected trisaccharide **35C**, a common trisaccharide motif incorporated into *N*-glycans. In pursuing our interest for the use of moisture stable glycosidation promoters, initial coupling between galactosyl donor **29C** and acceptor **30C** was best performed under the activation of catalytic $Yb(OTf)_3$ added as a solution in pivalonitrile (**Scheme 2**).[15] The reaction afforded in satisfying yield (64 %) the desired 4-*O*-linked disaccharide **31C** together with minor amounts (ca 10%) of the 3-*O*-linked disaccharide.[16] Acetylation of **31C** yielded protected lactosamine **32C** that was then submitted to the proposed de-*O*-methoxycarbonylation protocol to give **33C** in a very good yield (84 %). This latter was coupled with the fucosyl donor **34C** under catalytic activation with $Bi(OTf)_3$[17] to yield the desired trisaccharide building-block **35C** in high yield and α-selectivity.



Scheme 2 Synthesis of trisaccharide **35C**.

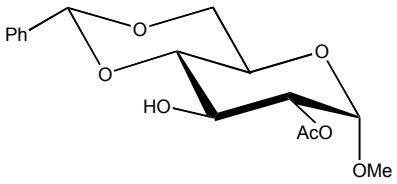
Conclusions

In conclusion in this chapter it has been described an operationally simple approach[18] for the selective removal of methoxy-, allyloxy- and benzyloxycarbonyl carbonyl groups from alcohols. Combined use of LiI and acetic acid minimizes or even suppresses concomitant trans-acylation processes. In addition, this procedure is compatible with a wide range of functional groups which could be otherwise affected under previously reported cleavage conditions. The developed protocol offers a very useful option in designing synthetic routes towards highly functionalized carbohydrate targets.

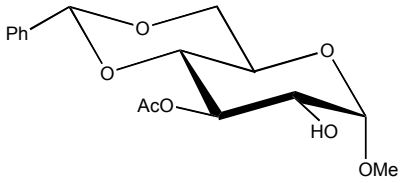
Experimental Section

General methods and Material

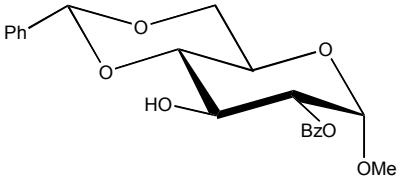
Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded in $CDCl_3$ (internal standard, for ^{1}H: $CHCl_3$ at δ 7.26; for ^{13}C: $CDCl_3$ at δ 77.0) on Varian spectrometers at 200 or 500 MHz and 50 or 125 MHz, respectively, or on a Bruker Avance 400 spectrometer at 400 MHz. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. ^{1}H NMR assignments were based on homo-decoupling experiments. MALDI-MS spectra were recorded in the positive mode: compounds were dissolved in acetonitrile at a concentration of 0.1 mg/mL and one microliter of these solutions were mixed with one microliter of a 20 mg/mL solution of 2,5-dihydroxybenzoic acid in 7:3 CH_3CN/H_2O. Analytical thin layer chromatography (TLC) was performed on aluminium plates precoated with Silica Gel 60 F_{254} as the adsorbent. The plates were developed with 5% H_2SO_4 ethanolic solution and then heating to 130°C. Column chromatography was performed on Kieselgel 60 (63-200 mesh). When specified, anhydrous solvents stored over molecular sieves (purchased from Aldrich) were used. Glycosidation promoters bismuth(III) triflate and ytterbium(III) triflate were coevaporated three times in toluene and dried under vacuum for 30-45 minutes before being dissolved in the presence of freshly activated 4Å with dioxane and pivalonitrile, respectively.



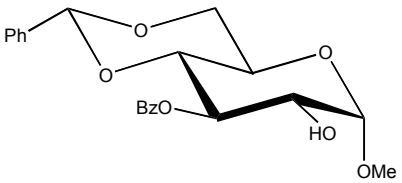
Methyl 2-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (5C). White solid; $[\alpha]^{26}_D$ +107.5° (c 1.2, $CHCl_3$). Lit[22]: $[\alpha]_D$ +108.7° (c 3, $CHCl_3$). M.p. 132-133 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.30 (aromatic protons), 5.53 (s, 1H, benzylidene acetal CH), 4.93 (d, $J_{1,2}$ = 3.6 Hz, 1H, H-1), 4.78 (1H, t, $J_{2,3}$ = 9.6 Hz, H-2), 4.28 (1H, dd, $J_{5,6eq}$ = 4.0 Hz, $J_{6eq,6ax}$ = 10.0 Hz, H-6eq), 4.15 (1H, t, $J_{3,4}$ = 10.0 Hz, H-3), 3.85 (1H, td, $J_{4,5}$ = $J_{5,6ax}$ = 10.0 Hz, H-5), 3.74 (1H, t, H-6ax), 3.65 (1H, dd, H-2), 3.53 (1H, t, H-4), 3.39 (3H, s, 1-OCH_3), 2.14 (3H, s, -$COCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 (-*C*OCH_3), 136.9 (aromatic C); 129.2, 128.3 and 126.2 (aromatic CH); 101.9 (benzylidene acetal CH), 97.4 (C-1), 81.2, 73.5, 68.8, 68.5, 61.9, 55.3 (1-OCH_3), 20.08 (-CO*C*H_3). $[M + Na]^+$ calcuId 347.11, found 347.25. Anal. Calcd. for $C_{16}H_{20}O_7$: C, 59.25, H, 6.22. Found: C, 59.00; H, 6.34.



Methyl 3-*O*-acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (6C). White solid; $[\alpha]^{26}_D$ +111.5° (c 1.0, $CHCl_3$). M.p. 175-176 °C (lit[23] 176-177 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (aromatic protons), 5.49 (1H, s, benzylidene acetal CH), 5.32 (1H, t, $J_{2,3} = J_{3,4} = 9.6$ Hz, H-3), 4.80 (1H, d, $J_{1,2} = 3.6$ Hz, H-1), 4.30 (1H, dd, $J_{5,6eq} = 4.8$ Hz, $J_{6eq,6ax} = 10.0$ Hz, H-6eq), 3.85 (1H, td, $J_{4,5} = J_{5,6ax} = 10.0$ Hz, H-5), 3.75 (1H, t, H-6ax), 3.65 (1H, dd, H-2), 3.58 (1H, t, H-4), 3.46 (3H, s, 1-OCH_3), 2.12 (3H, s, -$COCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1 (-*C*OCH_3), 137.0 (aromatic C); 129.1, 128.2 and 126.2 (aromatic CH); 101.5 (benzylidene acetal CH), 100.1 (C-1), 78.6, 72.3, 71.8, 68.9, 62.7, 55.6 (1-OCH_3), 21.0 (-CO*C*H_3). $[M + Na]^+$ calcuId 347.11, found 347.30. Anal. Calcd. for $C_{16}H_{20}O_7$: C, 59.25, H, 6.22. Found: C, 59.06; H, 6.37.

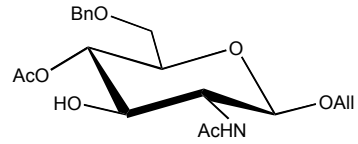


Methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (7C). White solid; $[\alpha]^{26}_D$ +113.0° (c 1.1, $CHCl_3$). Lit[1]: $[\alpha]^{24}_D$ +118.3° (c 2.1, $CHCl_3$). M.p. 170-171 °C (lit[24] 170.3-170.6 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-7.35 (aromatic protons), 5.57 (1H, s, benzylidene acetal CH), 5.08 (1H, d, $J_{1,2} = 3.6$ Hz, H-1), 5.05 (1H, dd, $J_{2,3} = 9.6$ Hz, H-2), 4.37-4.30 (2H, overlapped signals, H-3 and H-6eq), 4.02 (1H, td, $J_{4,5} = J_{5,6ax} = 10.0$ Hz, $J_{5,6eq} = 4.8$ Hz, H-5), 3.79 (1H, t, $J_{6ax,6eq} = 10.0$ Hz, H-6ax), 3.62 (1H, t, H-4), 3.39 (3H, s, 1-OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2 (-*C*OPh), 137.0 and 133.3 (aromatic C); 129.9, 129.5, 129.2, 128.4, 128.3, 128.1, 126.3 (aromatic CH); 102.0 (benzylidene acetal CH), 97.8 (C-1), 81.4, 74.1, 68.9, 68.8, 62.0; 55.4 (1-OCH_3). $[M + Na]^+$ calcuId 409.13, found 409.05. Anal. Calcd. for $C_{21}H_{22}O_7$: C, 65.28, H, 5.74. Found: C, 65.05; H, 5.90.

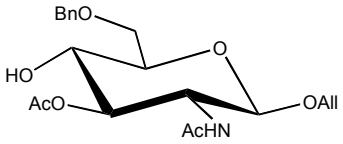


Methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (8C). White solid; $[\alpha]^{26}_D$ +36.5° (c 1.3, $CHCl_3$). M.p. 215-216 °C (lit[3] 216.6-217.0 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10-7.30 (aromatic protons), 5.60 (1H, t, $J_{2,3} = J_{3,4} = 9.6$ Hz, H-3), 5.53 (1H, s, benzylidene acetal CH), 4.86 (1H, d, $J_{1,2} = 3.6$ Hz, H-1), 4.34 (1H, dd, $J_{5,6eq} = 3.6$ Hz, $J_{6eq,6ax} = 10.0$ Hz, H-6eq), 3.95 (1H, td, $J_{4,5} = J_{5,6ax} = 10.0$ Hz, H-5), 3.90-3.70 (3H, overlapped, H-2, H-4 and H-6ax), 3.49 (3H, s, 1-OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6 (-*C*OPh), 136.9 and 133.0 (aromatic C); 129.8, 128.9, 128.2, 128.1,

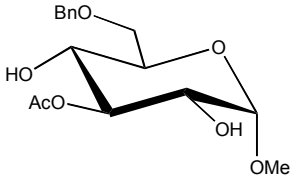
126.1 (aromatic CH); 101.5 (benzylidene acetal CH), 99.5 (C-1), 78.8, 73.0, 72.0, 68.9, 62.7; 55.5 (1-OCH_3). $[M + Na]^+$ calculd 409.13, found 409.25. Anal. Calcd. for $C_{21}H_{22}O_7$: C, 65.28, H, 5.74. Found: C, 65.10; H, 5.85.



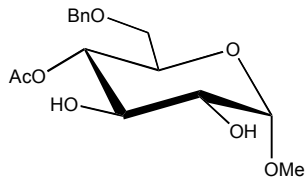
Allyl 2-acetamido-4-*O*-acetyl-6-*O*-benzyl-2-deoxy-β-D-glucopyranoside (10C). ^1H NMR (400 MHz, $CDCl_3$) δ 7.30-7.25 (aromatic protons), 5.90-5.75 (1H, m, -C*H*=CH_2), 5.26 (1H, bd, J_{trans} = 17.2 Hz, -CH=$CH_{cis}H_{trans}$), 5.17 (1H, bd, J_{cis} = 10.2 Hz, -CH=C$H_{cis}H_{trans}$), 4.86 (1H, t, $J_{3,4} = J_{4,5}$ = 9.6 Hz, H-4), 4.62 (1H, d, $J_{1,2}$ = 8.8 Hz, H-1), 4.53 and 4.49 (2H, 2xd, J_{gem} = 12.0 Hz, -CH_2Ph), 4.35-4.30 (1H, m, -C$H_a$$H_b$CH=$CH_2$), 4.10-4.05 (1H, m, -$CH_a$$H_b$CH=$CH_2$), 3.95-3.85 (1H, m, H-3), 3.65-3.50 (4H, overlapped signals, H-2, H-5 and H_2-6), 1.99 and 1.97 (6H, 2xs, 2x –$COCH_3$). ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.1 and 170.5 (2x –*C*OCH_3), 155.2 (-*C*O_2CH_3), 137.7 (aromatic C), 133.6 (-*C*H=CH_2), 128.3 and 127.7 (aromatic CH), 117.7 (-CH=*C*H_2), 99.3 (C-1), 73.4 (x2), 72.4, 72.1, 69.8, 69.2; 57.7 (C-2), 23.3 (–NHCO*C*H_3), 20.8 (–OCO*C*H_3). **10C** and **11C** were obtained as an inseparable mixture (**10C**/**11C** 4:1).



Allyl 2-acetamido-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-β-D-glucopyranoside (11C). Significant signals of **BF**: ^1H NMR (400 MHz, $CDCl_3$) δ 5.03 (1H, t, J = 9.2 and 10.4 Hz, H-3), 2.07 and 1.92 (6H, 2xs, 2x –$COCH_3$). $[M + Na]^+$ calculd 416.12, found 416.00. Anal. Calcd. for $C_{20}H_{27}NO_7$: C, 61.06, H, 6.92. Found: C, 60.85; H, 6.85.

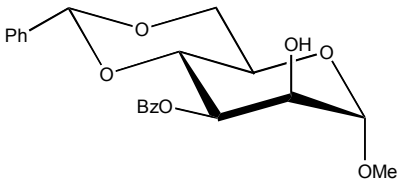


Methyl 3-*O*-acetyl-6-*O*-benzyl-α-D-glucopyranoside (14C). Significant signals: ^1H NMR (400 MHz, $CDCl_3$) δ 5.06 (1H, t, $J_{2,3}$ = $J_{3,4}$ = 9.6 Hz, H-3), 4.78 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1), 4.63-4.55 (2H, AB, J = 12.0 Hz, -CH_2Ph), 3.44 (3H, s, -OCH_3), 2.14 (3H, s, -$COCH_3$). Compound **14C** could not be separated from the major regioisomer **13C**.

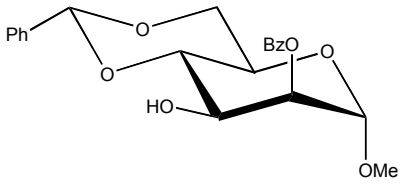


Methyl 4-*O*-acetyl-6-*O*-benzyl-α-D-glucopyranoside (13C). Oil, $[\alpha]^{28}_D$ +81.7° (c 1.2, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.25 (aromatic protons), 4.93 (1H, t, $J_{3,4} = J_{4,5}$ = 10.0 Hz, H-4), 4.82 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1), 4.59 and 4.50 (2H, AB, J = 12.0 Hz, -CH_2Ph), 3.90-3.80 (1H, m, H-5), 3.81 (1H, t, $J_{2,3}$ = 9.5 Hz, H-3), 3.63 (1H, bdd, H-2), 3.56-3.49 (2H, m, H_2-6), 3.44 (3H, s, -OCH_3), 3.14 and 2.77 (2H, 2x bs, OH-2 and OH-3), 1.98

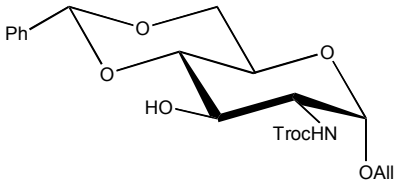
(3H, s, -$COCH_3$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8 (-*C*OCH_3), 137.7 (aromatic C); 128.3, 127.8, and 127.7 (aromatic CH), 99.0 (C-1), 73.4, 72.8, 72.6, 71.1, 68.7, 68.5, 55.4 (1-OCH_3), 20.8 (-CO*C*H_3). $[M + Na]^+$ calcuId 349.13, found 349.34. Anal. Calcd. for $C_{16}H_{22}O_7$: C, 58.89, H, 6.79. Found: C, 58.70; H, 6.91.



Methyl 3-*O*-benzoyl-4,6-*O*-benzylidene-α-D-mannopyranoside (16C). Solid, $[\alpha]^{28}_D$ -22.3° (c 1.0, $CHCl_3$). Lit[25]: $[\alpha]_D$.-24° (c 1.3, CH_2Cl_2). M.p. 131-132 °C (lit[3] 131-132 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.25 (aromatic protons), 5.61 (1H, s, benzylidene acetal CH), 5.54 (1H, bd, $J_{3,4}$ = 10.0 Hz, H-3), 4.77 (1H, bs, H-1), 4.35-4.25 (3H, overlapped signals; H-2, H-4, and H-6 eq), 4.05-3.95 (1H, m, H-5), 3.91 (1H, t, H-6ax), 3.43 (3H, s, -OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6 (COPh), 137.2 and 133.2 (aromatic C); 129.8, 128.9, 128.4, 128.3, and 126.0 (aromatic CH), 101.8 and 101.6 (benzylidene acetal CH and C-1), 76.0, 71.5, 69.5, 68.8, 63.7, 55.0 (1-OCH_3). $[M + Na]^+$ calcuId 409.13, found 409.27. Anal. Calcd. for $C_{21}H_{22}O_7$: C, 65.28, H, 5.74. Found: C, 65.02; H, 5.90.

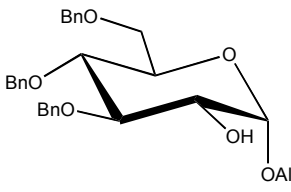


Methyl 2-*O*-benzoyl-4,6-*O*-benzylidene-α-D-mannopyranoside (17C). Foam, $[\alpha]^{27}_D$ -35.2° (c 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.10-7.40 (aromatic protons), 5.66 (1H, s, benzylidene acetal CH), 5.46 (1H, bd, $J_{1,2}$ = 1.5 Hz, $J_{2,3}$ = 3.4 Hz, H-2), 4.84 (1H, d, H-1), 4.38-4.30 (2H, overlapped signals), 4.04 (1H, t), 3.96-3.86 (2H, overlapped signals), 3.43 (3H, s, -OCH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.0 (COPh), 137.1 and 133.4 (aromatic C); 129.9-128.3, and 126.2 (aromatic CH), 102.2 and 99.6 (benzylidene acetal CH and C-1), 79.4, 72.5, 68.8, 67.4, 63.3, 55.2 (1-OCH_3). $[M + Na]^+$ calcuId 409.13, found 409.08. Anal. Calcd. for $C_{21}H_{22}O_7$: C, 65.28, H, 5.74. Found: C, 65.08; H, 5.85.

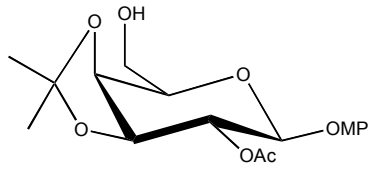


Allyl 4,6-*O*-benzylidene-2-deoxy-2-[(2,2,2-trichloroethoxy)carbonylamino]-α-D-glucopyranoside (19C). Solid, $[\alpha]^{28}_D$ +55.4° (c 1.0, $CHCl_3$). Lit[26]: $[\alpha]_D$.+59.5° (c 1.04, $CHCl_3$). M.p. (MeOH) 167-168 °C (lit[5] 168 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.20 (aromatic protons), 6.00-5.80 (1H, m, -C*H*=CH_2), 5.55

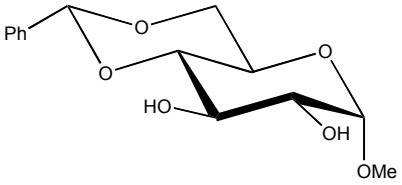
(1H, s, benzylidene acetal CH), 5.38 (1H, d, $J_{NH,2}$ = 8.0 Hz, 2-NH), 5.31 (1H, bd, J_{trans} = 17.2 Hz, -CH=CH$_{cis}$*H$_{trans}$*), 5.24 (1H, bd, J_{cis} = 10.4 Hz, -CH=C*H$_{cis}$*H$_{trans}$), 4.93 (1H, d, $J_{1,2}$ = 2.8 Hz, H-1), 4.82 and 4.68 (2H, AB, J_{gem} = 10.8 Hz, -CH_2CCl_3), 4.27 (1H, dd, $J_{5,6eq}$ = 4.4 Hz, $J_{6ax,6eq}$ = 10.0 Hz, H-6 eq), 4.23-4.18 (1H, m, -C*H$_a$*H$_b$CH=CH_2), 4.05-4.00 (1H, m, -CH$_a$*H$_b$*CH=CH_2), 4.00-3.80 (3H, overlapped signals), 3.75 (1H, t, J = 10.2 Hz), 3.57 (1H, t, J = 9.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.8 (-NH*C*OCH_2CCl_3), 137.0 (aromatic C), 133.2 (-*C*H=CH_2), 129.3, 128.4, and 126.4 (aromatic CH), 118.3 (-CH=*C*H_2), 101.9 (benzylidene acetal CH), 97.0 (C-1), 81.8, 74.7, 69.8, 68.7, 68.6 62.6; 55.7 (C-2). $[M + Na]^+$ calculd 504.04, found 504.17. Anal. Calcd. for $C_{19}H_{22}Cl_3NO_7$: C, 47.27, H, 4.59. Found: C, 47.08; H, 4.70.



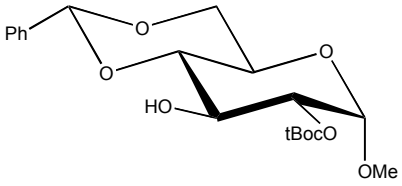
Allyl 3,4,6-tri-*O*-benzyl-α-D-glucpyranoside (21C). Solid, $[\alpha]^{28}_D$ +86.7° (c 1.0, $CHCl_3$). Lit[27]: $[\alpha]_D$ +93.3° (c 1, $CHCl_3$). M.p. 71-72 °C (lit[6] 71.5-73.5 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.00 (aromatic protons), 6.00-5.80 (1H, m, -C*H*=CH_2), 5.33 (1H, dq, J_{trans} = 17.2 Hz, -CH=CH$_{cis}$*H$_{trans}$*), 5.23 (1H, bd, J_{cis} = 9.2 Hz, -CH=C*H$_{cis}$*H$_{trans}$), 4.98 (1H, d, $J_{1,2}$ = 3.6 Hz, H-1), 5.00-4.50 (6H, 3x AB, 3x –CH_2Ph), 4.35-4.20 (1H, m, -C*H$_a$*H$_b$CH=CH_2), 4.10-4.05 (1H, m, -CH$_a$*H$_b$*CH=CH_2), 3.85-3.75 (4H, overlapped signals), 3.75-3.65 (2H, overlapped signals). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 138.1, and 137.9 (aromatic C), 133.5 (-*C*H=CH_2), 128.3-127.6 (aromatic CH), 117.8 (-CH=*C*H_2), 97.5 (C-1), 83.3, 77.4, 75.3, 74.9, 73.4, 72.9, 70.6, 68.4 (x2). $[M + Na]^+$ calculd 513.24, found 513.33. Anal. Calcd. for $C_{30}H_{34}O_6$: C, 73.45, H, 6.99. Found: C, 73.21; H, 7.05.



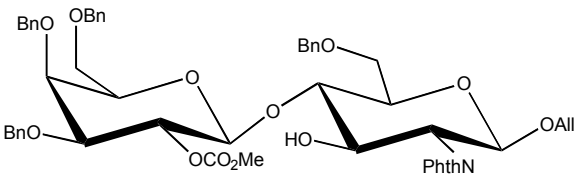
***p*-Methoxyphenyl 2-*O*-acetyl-3,4-*O*-isopropylidene-β-D-galactopyranoside (23C).** Oil, $[\alpha]^{28}_D$ +16.2° (c 1.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95-6.75 (aromatic protons), 5.20 (1H, t, $J_{1,2}$ = $J_{2,3}$ = 8.0 Hz, H-2), 4.82 (1H, d, H-1), 4.30-4.17 (2H, overlapped signals, H-3 and H-4), 4.55-3.90 (2H, m, H-5 and H-6a), 3.75 (3H, s,–OCH_3), 2.12 (3H, s, -$COCH_3$), 1.59 and 1.34 (6H, 2xs, isopropylidene methyls). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6 (-$COCH_3$), 155.3 and 151.0 (aromatic C); 118.1 and 114.5 (aromatic CH), 110.9 (-*C*$(CH_3)_2$), 99.5 (C-1), 77.0, 73.6 (x2), 72.5, 62.0, 55.5 (-OCH_3), 27.5 and 26.3 (-C(*C*$H_3)_2$), 21.2 (-CO*C*H_3). $[M + Na]^+$ calculd 349.14, found 349.32. Anal. Calcd. for $C_{16}H_{22}O_7$: C, 58.89, H, 6.79. Found: C, 58.81; H, 6.93.



Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (27C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.30 (aromatic protons), 5.51 (1H, s, benzylidene acetal CH), 4.73 (1H, d, $J_{1,2}$ = 4.0 Hz, H-1), 4.27 (1H, dd, $J_{5,6eq}$ = 4.4 Hz, $J_{6eq,6ax}$ = 9.6 Hz, H-6eq), 3.90 (1H, t, $J_{2,3} = J_{3,4}$ = 9.6 Hz, H-3), 3.78 (1H, td, $J_{5,6eq}$ = 5.6 Hz, $J_{4,5} = J_{5,6ax}$ = 10.0 Hz, H-5), 3.71 (1H, t, H-6ax), 3.58 (1H, dd, H-2), 3.45 (1H, t, H-4), 3.42 (3H, s, 1-OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.0 (aromatic C); 129.2, 128.3 and 126.3 (aromatic CH); 101.9 (benzylidene acetal CH), 99.9 (C-1), 80.9, 72.7, 71.4, 68.9, 62.3, 55.4 (1-OCH_3). $[M + Na]^+$ calcuId 405.15, found 405.20. Anal. Calcd. for $C_{14}H_{18}O_6$: C, 59.57, H, 6.43. Found: C, 59.30; H, 6.35.

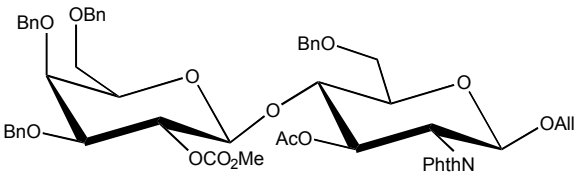


Methyl 2-*O*-*tert*-butoxycarbonyl-4,6-*O*-benzylidene-α-D-glucopyranoside (28C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55-7.30 (aromatic protons), 5.54 (1H, s, benzylidene acetal CH), 5.00 (1H, d, $J_{1,2}$ = 3.6 Hz, H-1), 4.58 (1H, dd, $J_{2,3}$ = 9.6 Hz H-2), 4.28 (1H, dd, $J_{5,6eq}$ = 4.4 Hz, $J_{6eq,6ax}$ = 9.6 Hz, H-6eq), 4.18 (1H, t, $J_{3,4}$ = 9.6 Hz, H-3), 3.84 (1H, td, $J_{5,6eq}$ = 4.8 Hz, $J_{4,5} = J_{5,6ax}$ = 10.0 Hz, H-5), 3.75 (1H, t, H-6ax), 3.55 (1H, t, H-4), 3.40 (3H, s, 1-OCH_3), 1.50 (9H, s, -$C(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.9 (CO), 136.9 (aromatic C); 129.1, 128.2 and 126.2 (aromatic CH); 101.9 (benzylidene acetal CH), 97.5 (C-1), 82.9, 81.1, 75.9, 68.7, 68.5, 62.0, 55.3 (1-OCH_3), 27.6 (-$C(CH_3)_3$). $[M + Na]^+$ calcuId 405.16, found 405.25.



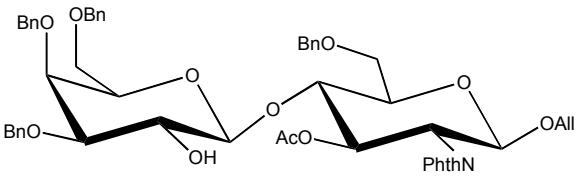
Allyl 2-*O*-methoxycarbonyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-6-*O*-benzyl-2-deoxy-2-(phthalimido)-β-D-glucopyranoside (31C). A mixture of donor **29C**[7] (84 mg, 0.12 mmol) and diol **30C**[28] (36 mg, 84 μmol) was coevaporated three times with anhydrous toluene (3 x 2 mL), and then dried in vacuo for 30 minutes. After adding 4Å AW 300 MS, the mixture was dissolved under argon with DCE (2 mL), cooled to -10 °C, and stirred for 15 min. A solution of $Yb(OTf)_3$ in pivalonitrile (0.047 M, 0.2 mL, 9.4 μmol) was then added, and the mixture was allowed to gradually warm to rt. After two hours the reaction was quenched with some drops of pyridine and the mixture filtered on a short plug of silica gel repeatedly washed with DCM/MeOH/acetonitrile 85:10:5. The filtrate was concentrated, and the residue purified by silica-gel flash-chromatography (eluent: petroleum ether/ethyl

acetate from 3:1 to 7:3) to yield disaccharide **31C** as an oil (50 mg, 64 % overall yield). Foam. $[\alpha]^{27}_{D}$ +4.8° (c 0.87, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.90-7.15 (aromatic protons), 5.80-5.65 (1H, m, -C*H*=CH_2), 5.22 (1H, d, $J_{1,2}$ = 8.5 Hz, H-1), 5.17 (1H, t, $J_{1,2}$ = $J_{2,3}$ = 8.5 Hz, H-2′), 5.12 (1H, bd, J_{trans} = 18.0 Hz, -CH=$CH_{cis}H_{trans}$), 5.03 (1H, bd, J_{cis} = 10.0 Hz, -CH=C$H_{cis}H_{trans}$), 4.95-4.20 (8H, 4x AB, 4x -CH_2Ph), 4.47 (1H, bt, $J_{2,3}$ = $J_{3,4}$ = 10.0 Hz, H-3), 4.39 (1H, d, H-1′), 4.30-4.20 (2H, overlapped signals, H-2 and -C$H_a$$H_b$CH=$CH_2$), 4.05 (1H, bdd, J_{vic} = 6.0 Hz, J_{gem} = 13.0 Hz, -$CH_a$$H_b$CH=$CH_2$), 3.85 (1H, bd, $J_{3,4}$ = 2.5 Hz, H-4′), 3.81 (3H, s, -CO_2CH_3), 3.80-3.65 (4H, overlapped signals), 3.70-3.40 (3H, overlapped signals). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.9 (phtalimido *C*O), 155.1 (–*C*O_2CH_3); 138.5, 138.0, 137.6, 137.3 (aromatic C); 133.8 (-*C*H=CH_2), 128.7-123.3 (aromatic CH), 117.2 (-CH=*C*H_2), 101.7 (C-1′), 97.3 (C-1), 82.7, 82.2, 75.6, 74.5, 74.1, 73.7, 73.6, 73.2, 74.5 (x2), 69.7, 69.6, 68.5, 68.3; 55.9 and 55.0 (C-2 and –OCH_3). $[M + Na]^+$ calcuId 952.35, found 952.50. Anal. Calcd. for $C_{53}H_{55}NO_{14}$: C, 68.45, H, 5.96. Found: C, 68.21; H, 5.85.

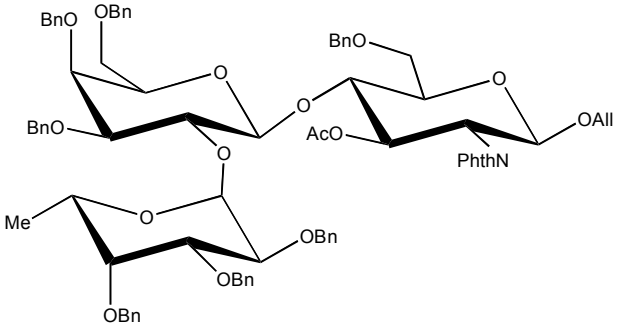


Allyl 2-*O*-methoxycarbonyl-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-(phthalimido)-β-D-glucopyranoside (32C). To a solution of disaccharide **31C** (39 mg, 0.042 mmol) in pyridine (0.8 mL) was added acetic anhydride (0.4 mL) and the solution was kept overnight at rt . The mixture was diluted with DCM and the organic phase was washed with water. The organic phase was dried with sodium sulphate, concentrated in vacuo and the residue was repeatedly coevaporated with toluene to give disaccharide **32C** (41 mg, quantitative yield) which was directly submitted to the next deprotection step. $[\alpha]^{23}_{D}$ +15.4° (c 1.5, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.15 (aromatic protons), 5.80-5.65 (1H, m, -C*H*=CH_2), 5.71 (1H, dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 9.6 Hz, H-3), 5.37 (1H, d, $J_{1,2}$ = 8.4 Hz, H-1), 5.12 (1H, qd, J_{trans} = 16.8 Hz, -CH=$CH_{cis}H_{trans}$), 5.03 (1H, bd, J_{cis} = 10.0 Hz, -CH=C$H_{cis}H_{trans}$), 5.01 (1H, dd, $J_{1,2}$ = 8.0 Hz, $J_{2,3}$ = 10.0 Hz, H-2′), 4.70-4.35 (8H, 4x AB, 4x -CH_2Ph), 4.43 (1H, d, H-1′), 4.30-4.25 (1H, m, -C$H_a$$H_b$CH=$CH_2$), 4.24 (1H, dd, H-2), 4.05-4.00 (1H, m, -$CH_a$$H_b$CH=$CH_2$), 4.01 (1H, t, $J_{4,5}$ = 9.6 Hz, H-4), 3.89 (1H, bd, $J_{3,4}$ = 2.8 Hz, H-4′), 3.90-3.75 (2H, m, 3.79 (3H, s, -CO_2CH_3), 3.70-3.65 (1H, m, H-5), 3.60-3.48 (2H, m, H_2-6′), 3.37-3.34 (2H, overlapped signals, H-3′ and H-5′), 1.75 (3H, s, -$COCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0 (–*C*OCH_3), 167.8 (phtalimido *C*O), 154.9 (–*C*O_2CH_3); 138.5, 138.3, 137.8, 137.7 (aromatic C); 133.6 (-*C*H=CH_2), 128.4-127.2 (aromatic CH), 117.4

(-CH=*C*H_2), 100.6 (C-1′), 97.1 (C-1), 80.5, 76.0, 75.7, 74.6, 74.4, 73.4, 73.2, 73.1, 72.5, 72.0, 71.3, 70.0, 68.0, 67.8, 55.0, 54.9, 20.5 (–CO*C*H_3). $[M + Na]^+$ calculd 994.37, found 994.65.



Allyl 3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-(phthalimido)-β-D-glucopyranoside (33C). Disaccharide **32C** (41 mg, 0.042 mmol) and LiI (20 mg, 0.15 mmol) were dissolved in pyridine (0.4 mL) and to the resulting solution was added acetic acid (12.5 μL, 0.21 mmol). The resulting mixture was refluxed for 4 hours, afterthen the reaction vessel was cooled to rt. The mixture was diluted with DCM and the organic phase was washed with water. The aqueous phase was re-extracted with DCM and ethyl acetate. Collected organic phases were dried and concentrated in vacuo to give a residue which was purified by silica gel flash-chromatography (eluent: petroleum ether/ethyl acetate 7:3) to yield **33C** (32 mg, 84 %) as a foam. Foam. $[\alpha]^{26}_D$ +25.0° (c 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85-7.10 (aromatic protons), 5.78 (1H, dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 9.2 Hz, H-3), 5.80-5.65 (1H, m, -C*H*=CH_2), 5.37 (1H, d, $J_{1,2}$ = 8.4 Hz, H-1), 5.13 (1H, bd, J_{trans} = 17.2 Hz, -CH=$CH_{cis}H_{trans}$), 5.03 (1H, bd, J_{cis} = 10.4 Hz, -CH=$CH_{cis}H_{trans}$), 4.90-4.35 (8H, 4x AB, 4x -CH_2Ph), 4.35 (1H, d, $J_{1,2}$ = 7.6 Hz, H-1′), 4.35-4.20 (2H, overlapped signals -CH_aH_bCH=CH_2 and H-2), 4.15-4.00 (3H, overlapped signals; H-2, H-6a and -CH_aH_bCH=CH_2), 3.89 (1H, bd, $J_{3,4}$ = 2.4 Hz, H-4′), 3.88-3.80 (2H, overlapped signals, H-6b and H-2′), 3.78-3.73 (1H, m, H-5), 3.57 (1H, t, $J_{5,6a}$ = $J_{6a,6b}$ = 8.8 Hz, H-6′a), 4.53-3.40 (2H, overlapped signals, H-5 and H-6′b), 3.34 (1H, dd, $J_{2,3}$ = 9.6 Hz, H-3′), 1.76 (3H, s, -$COCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2 (-*C*OCH_3), 167.9 (phtalimido *C*O), 138.6, 138.1 (x2), 137.9, 137.7 (benzyl aromatic C); 133.6 (-*C*H=CH_2), 128.7-123.3 (aromatic CH), 117.4 (-CH=*C*H_2), 103.3 (C-1′), 97.3 (C-1), 81.6, 76.0, 74.4, 73.4 (x3), 72.8, 72.2, 71.7 (x2), 70.0, 68.3, 68.1, 54.9 (C-2), 20.5 (-CO*C*H_3). $[M + Na]^+$ calculd 936.37, found 936.62. Anal. Calcd. for $C_{53}H_{55}NO_{13}$: C, 69.65, H, 6.07. Found: C, 69.32; H, 5.95.



Allyl 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-β-D-galactopyranosyl-(1→4)-3-*O*-acetyl-6-*O*-benzyl-2-deoxy-2-(phthalimido)-β-D-glucopyranoside (**35C**). A mixture of donor 34C[7] (35.2 mg, 0.056 mmol) and acceptor 33C (26.0 mg, 0.028 mmol) was coevaporated three times with anhydrous toluene (3 x 2 mL), and then dried in vacuo for 30 minutes. After adding 4Å AW 300 MS, the mixture was dissolved under argon with DCM/Et_2O 4:1 (1.5 mL) at -10 °C, and stirred for 15 min. The mixture was then cooled to -70 °C and a solution of $Bi(OTf)_3$ in dioxane (0.019 M, 75 μL, 1.4 μmol) was then added. The mixture was allowed to gradually warm to rt and after 4.5 hours the reaction was quenched with some drops of pyridine and the mixture filtered on a short plug of silica gel repeatedly washed with DCM/MeOH/acetonitrile 85:10:5. The filtrate was concentrated, and the residue purified by silica-gel flash-chromatography (eluent: toluene/ethyl acetate from 9:1 to 7:1) to yield trisaccharide 35C as a foam (32.5 mg, α/β 8:1, 86 % overall yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85-7.10 (aromatic protons), 5.78 (1H, dd, $J_{2,3}$ = 10.4, $J_{3,4}$ = 9.2 Hz, H-3), 5.80-5.65 (1H, m, -C*H*=CH_2), 5.66-5.62 (2H, overlapped signals, H-1″ and H-3), 5.34 (1H, d, $J_{1,2}$ = 8.5 Hz, H-1), 5.14 (1H, bd, J_{trans} = 17.5 Hz, -CH=$CH_{cis}H_{trans}$), 5.05 (1H, bd, J_{cis} = 10.5 Hz, -CH=C$H_{cis}H_{trans}$), 5.00-4.35 (14H, 7x AB, 7x -CH_2Ph), 4.37 (1H, d, $J_{1,2}$ = 7.6 Hz, H-1′), 4.35-4.25 (3H, overlapped signals), 4.10-4.00 (4H, overlapped signals), 3.90 (1H, bd, $J_{3,4}$ = 2.4 Hz, H-4′), 3.85-3.65 (4H, overlapped signals), 3.60-3.45 (4H, overlapped signals), 3.40 (1H, t, J = 6.5 Hz), 1.69 (3H, s, -$COCH_3$), 1.31 (3H, d, $J_{5,6}$ = 7.0 Hz, H3-6″). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3 (-*C*OCH_3), 167.9 (phtalimido *C*O); 139.0, 138.9, 138.6 (x2), 138.2, 138.0, 137.8 (benzyl aromatic C); 134.0 (bs, aromatic phtalimido C), 133.6 (-*C*H=CH_2), 128.7-123.3 (aromatic CH), 117.3 (-CH=*C*H_2), 103.4 (C-1′), 97.5 and 97.1 (C-1 and C-1″), 84.0, 79.2, 78.2, 75.8, 75.6, 74.8, 74.4, 73.5, 72.9, 72.8, 72.5, 72.2, 72.1, 71.0, 70.8, 70.0, 68.2, 68.0, 66.5, 54.8 (C-2), 20.5 (-CO*C*H_3). $[M + Na]^+$ calcuId 1352.57, found 1352.70. Anal. Calcd. for $C_{80}H_{83}NO_{17}$: C, 72.22, H, 6.29. Found: C, 72.01; H, 6.50

References

1. For some examples: (a) Sridhar, P. R.; Chandrasekaran, S. *Org. Lett.* **2002**, *4*, 4731-4733; (b) Morere, A.; Mouffouk, F.; Jeanjean A.; Leydet, A. Montero J. L. *Carbohydr. Res.* **2003**, *338*, 2409-2412; (c) Tanaka, H.; Amaya, T.; Takahashi T. *Tetrahedron Lett.* **2003**, *44*, 3053-3057; (d) Orgueira, H. A.; Bartolozzi, A.; Schell, P.; Litjens, R.E. J. N.; Palmacci, E. R.; Seeberger, P. H. *Chem. Eur. J.* **2003**, *9*, 140-169; (e) Adinolfi, M.; Iadonisi, A.; Ravidà, A.; Schiattarella, M. *Synlett* **2004**, 275-278; (f) Ko, K. S.; Jaipuri, F. A.; Pohl, N. L. *J. Am. Chem. Soc.* **2005**, *127*, 13162-13163; (g) de Oliveira, R. N.; Cottier, L.; Sinou, D.; Srivastavab, R. M. *Tetrahedron* **2005**, *61*, 8271-8281; (h) Kim, J. H.; Yang, H.; Khot, V.; Whitfield, D.; Boons, G.-J. *Eur. J. Org. Chem.* **2006**, 5007-5028.
2. For a recent review: Mohr, J. T.; Stoltz, B. M. *Chem. Asian. J.* **2007**, *2*, 1476-1491.
3. (a) Poirier, D.; Berthiaume, D.; Boivin, R. P. *Synlett* **1999**, 1423-1425; (b) Berthiaume, D.; Poirier, D. *Tetrahedron* **2000**, *56*, 5995-6003.
4. (a) Wuts, P. G. M.; Greene, T. W. *Greene's Protective groups in organic synthesis*; Wiley & Sons, 2007. (b) Kocienski, P. *Protecting Groups*, Georg Thieme Verlag, Stuttgart, **2000**.
5. Adinolfi, M.; Iadonisi, A.; Pezzella, A.; Ravidà, A. *Synlett* **2005**, 1848-1852.
6. Adinolfi, M.; Barone, G.; Iadonisi, A.; Guariniello, L. *Tetrahedron Lett.* **2000**, *41*, 9305-9309.
7. (a) Adinolfi, M.; Barone, G.; Iadonisi, A.; Mangoni, L.; Schiattarella, M. *Tetrahedron Lett.* **2001**, *42*, 5967-5969; (b) Adinolfi, M.; Barone, G.; Iadonisi, A.; Schiattarella, M. *Org. Lett.* **2003**, *5*, 987-989. For an application to a biologically relevant target: Adinolfi, M.; Iadonisi, A.; Ravidà, A.; Schiattarella, M. *J. Org. Chem.* **2005**, *70*, 5316-5319.
8. For a recent example of a sterically bulky participating groups for 1,2 *trans*-glycosidations: Szpilman, A. M.; Carreira, E. M. *Org. Lett.* **2009**, *11*, 1305-1307.
9. For a recent report on the generation of saccharidic cyclic carbonates arising from participation effects: Crich, D.; Hu, T.; Cai, F. *J. Org. Chem.* **2008**, *73*, 8942-8953.
10. Bouzbouz, S.; Kirschleger, B. *Synthesis*, **1994**, 714-718.
11. For some examples: (a) Mayato, C.; Dorta, R. L.; Vazquez, J. T. *Tetrahedron Lett.* **2008**, *49*, 1396-1398; (b) Fisher, J. W.; Trinkle, K. L. *Tetrahedron Lett.* **1994**, *35*, 2505-2508; (c) Biron, E.; Kessler, H. *J. Org. Chem.* **2005**, *70*, 5183-5189.
12. For some examples: (a) Borch, R. F.; Grudzinskas, C. V.; Peterson, D. A.; Weber, L. D. *J. Org. Chem.* **1972**, *37*, 1141-1145; (b) Wade, J. J.; Hegel, R. F.; Toso, C. B. *J. Org. Chem.* **1979**, *44*, 1811-1816; (c) Magnus, P.; Gallagher T. *J. Chem. Soc., Chem. Commun*. **1984**, 389-390; (d) Sun, B.; Srinivasan, B.; Huang, X. *Chem. Eur. J.* **2008**, *14*, 7072-7081.

13. Haines, A. H. *Adv. Carbohydr. Chem. Biochem.* **1976**, *33*, 11.
14. For the use of *N*-methoxycarbonylated sugars in carbohydrate chemisrty: Yeung, B. K. S.; Adamski-Werner, S. L.; Bernard, J. B.; Poulenat, G.; Petillo, P. A. *Org. Lett.* **2000**, *2*, 3135-3138.
15. Adinolfi, M.; Iadonisi, A.; Ravidà, A. *Synlett* **2006**, 583-586.
16. For the effect of the *N*-phtalimido group on regioselective glycosidations of glucosamine acceptors: (a) Ellervik, U.; Magnusson, G. *J. Org. Chem.* **1998,** *63,* 9314-9322; (b) Bohn, M. L.; Colombo, M. I.; Pisano, P. L.; Stortz, C. A.; Rùveda, E. A. *Carbohydr. Res.* **2007**, 342, 2522-2536.
17. Adinolfi, M.; Iadonisi, A.; Ravidà, A.; Valerio, S. *Tetrahedron Lett.* **2006**, *47*, 2595-2599.
18. Experimental procedure: The saccharidic compound (0.3 mmol) and LiI (120 mg, 0.9 mmol) were dissolved in pyridine (1.4 mL) and to the resulting solution was added acetic acid (90 μL, 1.5 mmol). The resulting mixture was refluxed for the times indicated on Table 2, after then the vessel was cooled to rt. The mixture was diluted with DCM and the organic phase was washed with water. The aqueous phase was re-extracted with DCM and ethyl acetate. Collected organic phases were dried and concentrated in vacuo to give a residue which was purified by silica gel flash-chromatography (eluent: petroleum ether/ethyl acetate mixtures).
19. (a) Pearson, R. G. *J. Am. Chem. SOC.* **1963**, *85*, 3533. (b) Hudson, R. F. *Coordination Chemistry Reviews* **1966**, 89. (c) Saville, B. *Angew. Chem., Znt. Ed. Engl.* **1967**, *6*, 928. (d) Pearson, R. G.; Songstad, J. *J. Am. Chem. SOC.* **1967**, *89*,1827. (e) Pearson, R. G.; Songstad, J. *J. Org. Chem.* **1967**, *32*, 2899. (f) Parr, R. G.; Pearson, R. G. *J. Am. Chem. SOC.* **1983**, *105*, 7512. (g) Pearson R. G. *J. Am. Chem. SOC.* **1988**, *110*, 7684. (h) Pearson, R. G. *J. Org. Chem.* **1989**, *54*, 1423. (i) Pearson, R. G. *Acc. Chem. Res.* **1993**, *26*, 250.
20. For a review see: (a) Pearson, R. G. *Hard and Soft Acids and Bases*; Dowden, Hutchinson, & Ross Inc.: Stroudsberg, 1973. (b) Ho, T. L. *Hard and Soft Acids and Bases Principle in Organic Chemistry*; Academic Press: New York, 1977. (c) Ho, T. L. *Chem. Rev.* **1976**, *75*, 1.
21. The only unsolvated ("naked") fluoride anions that have proven reliable are tetramethylammonium fluoride, phosphazenium fluoride, and *N*,*N*,*N*-trimethyl-1-adamantylammonium fluoride, see: (a) Mascaretti, 0. A. *Aldrichimica Acta* **1993**, *26*, 47. (b) Harmon, K. M.; Southworth, B. A.; Wilson, K. E.; Keefer, P. K. *J. Org. Chem.* **1993**, 58, 7294.

22. C.-C.; Wang,; J.-C Lee, S.-Y. Luo; S. S. Kulkarni,; Y.-W. Huang,; C.-C. Lee; Chang, K.-L.; S.-C..Hung, *Nature* **2007**, *446*, 896.

23. R. W. Jeanloz; D. A. Jeanloz *J.Am. Chem. Soc.* **1957**, *79*, 2579.

24. Cheuk, S.; Stevens, E. D; Wang, G. *Carbohydr. Res.* **2009**, *344*, 417.

25. Crich, D.; Sun S.; Brunckova J. *J. Org. Chem.* **1996,** *61,* 605.

26. Oikawa, M.; Wada, A.; Yoshizaki, H.; Fukase, K.; Kusumoto, S. *Bull. Chem. Soc. Jap.* **1997**, *70*, 1435.

27. Gent, P. A.; Gigg, R. *Carbohydr. Res.* **1976**, *49*, 325.

28. Sato, S.; Ito, Y.; Nukada, T.; Nakahara, Y.; Ogawa, T. *Carbohydr. Res.* **1987**, *167*, 197.

Chapter D

Easy and versatile approach for regioselective de-*O*-benzylation of protected sugars based on the I_2/Et_3SiH combined system.

Introduction

Benzyl is one of the most used protecting groups in organic synthesis for carbinol derivatization.[1] Several advantages justify the popularity of this protecting group: a) the protection step can occur under either acidic or basic conditions; b) a benzyl group can be installed on the multiple sites of molecules equipped with several functional groups such as carbohydrates; c) the protecting group is stable to a wide range of chemical conditions and is removable under mild conditions.[1] Hydrogenolysis is the commonest option for de-*O*-benzylation and it is especially suitable for the total deprotection of poli-*O*-benzylated substrates. Consequently, benzyl protecting groups are frequently employed in organic synthesis for polihydroxylated targets and their removal is often performed at advanced stages of the synthetic schemes. Protected carbohydrates are frequently exploited as convenient precursors of chiral compounds[2] through synthetic schemes routinely relying on *O*-benzylated intermediates. In addition, the use of *O*-benzylated saccharidic derivatives is also functional in tuning the reactivity of carbohydrate building-blocks in glycosidation chemistry: a large number of examples highlights the "arming" effect of benzyl groups on both glycosyl donors and acceptors in comparison with the depressed reactivity of sugars equipped with "disarming" acyl groups.[3] Furthermore, benzyl groups are also widely used in stereocontrolled glycosidations where protecting but non-participating groups are needed on the glycosyl donor.[4]

Rapid access to partially protected building-blocks is one of the most important goals[5] in modern organic synthesis: on this regard, several procedures of regioselective de-*O*-benzylation of densely *O*-benzylated saccharidic precursors have been described in the literature. Among these, only a few examples are relying on controlled hydrogenolysis,[6] whereas most approaches require acidic conditions. Indeed, the regioselecetive de-*O*-benzylation of saccharidic compounds can be effected with stoichiometric amounts of strong and sensitive Lewis acids such as $SnCl_4$ or $TiCl_4$,[7] (**Figure 1**) excess amounts of alanes (DIBAL, TIBAL, etc) at high temperatures[8,9] (**Figure 2**) or under microwave activation,[10] BCl_3 at low temperature,[11] excess amounts of $CrCl_2$ and LiI at high temperature.[12]

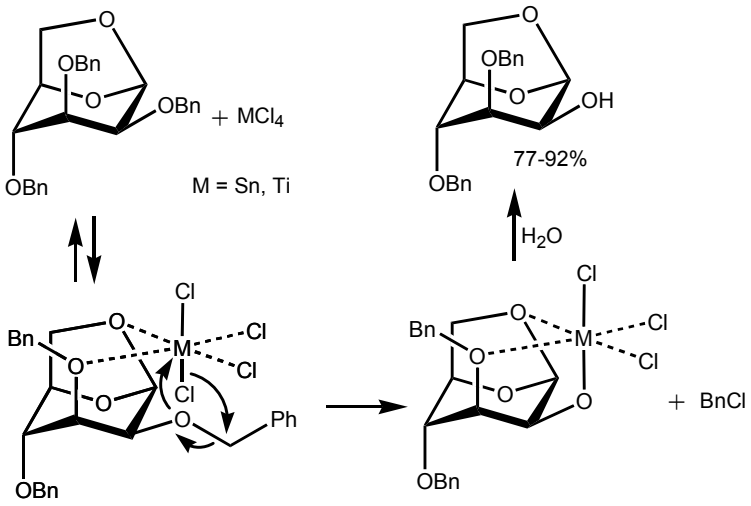


Figure 1

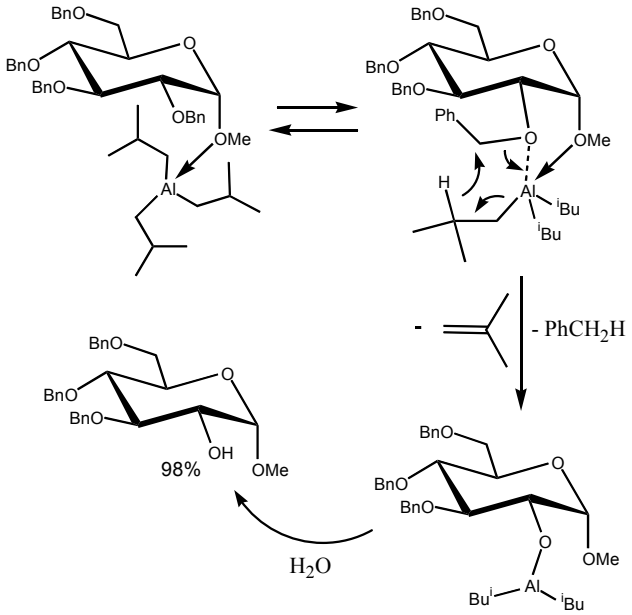
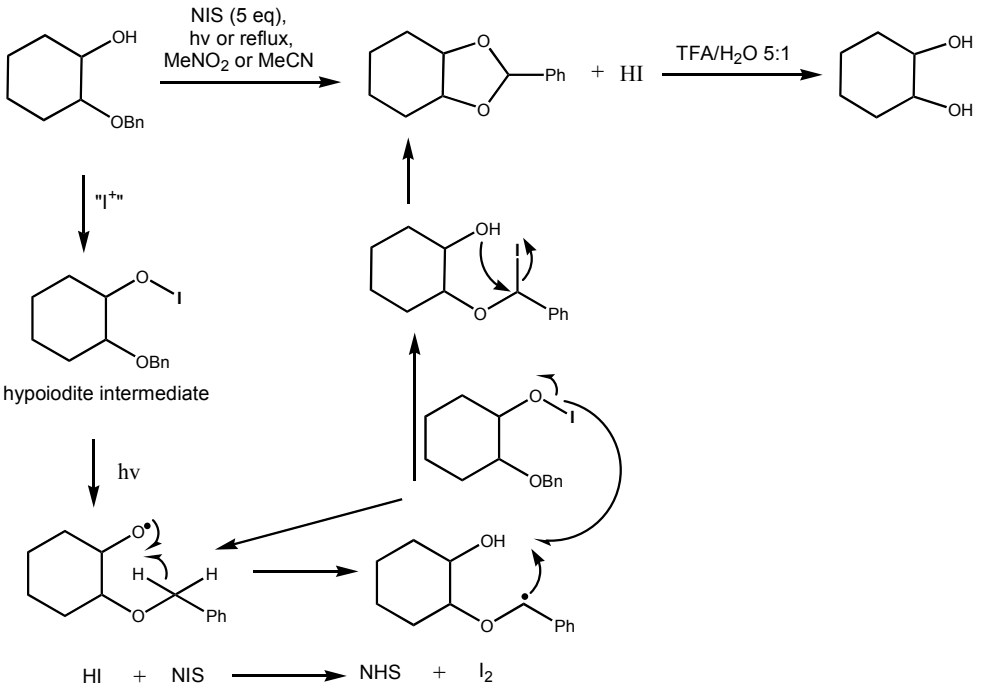


Figure 2

In these cases regioselectivity is critically dependent on the possibility of the saccharidic substrate to generate a chelated structure with the Lewis acid present in each reagent system, whereas benzyl removal is accomplished by a nucleophilic agent introduced either as the counter anion of the chelated metal or as an independent species. Chelation control can also serve in regioselective de-*O*-benzylation of non-saccharidic substrates under acidic conditions.[13] Other regioselective de-*O*-benzylation approaches for carbohydrates are requiring pre-existence of suitable functionalities, such as a free hydroxyl group[14] (**Figure 3**) or an allyl group,[15] adjacent to the site to be *O*-deprotected (**Figure 4**).



Proposed mechanism for the formation of benzylidene derivatives.

Figure 3

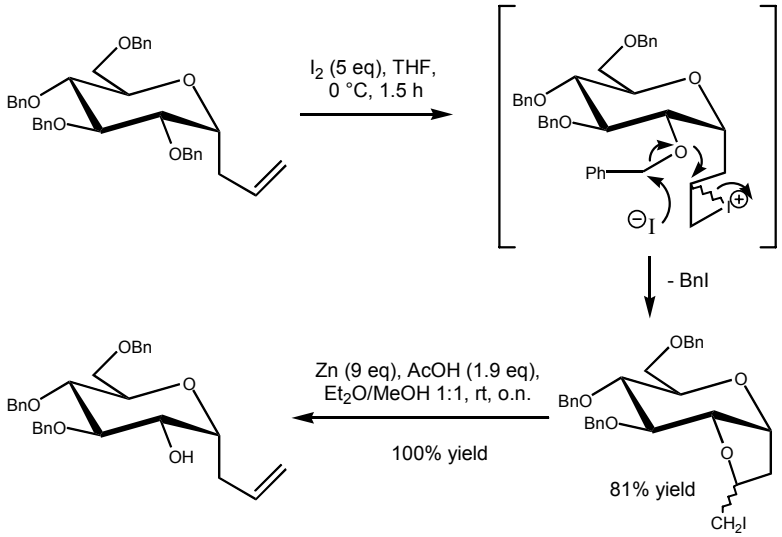


Figure 4

Very recently Crich and Vinogradova have shown that highly benzylated *manno*- and *rhamno*- derivatives can be deprotected with moderate selectivity at *O*-4 by treatment with a stoichiometric oxidant as DDQ[16] (**Figure 5**).

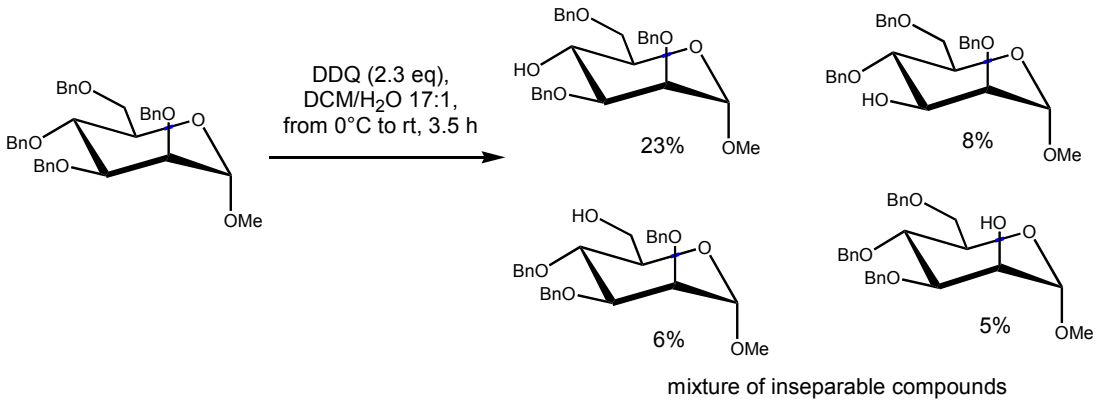


Figure 5 Facile oxidative cleavage of 4-*O*-benzyl ethers with dichlorodicyanoquinone in Rhamno- and Mannopyranosides.

Primary positions can be de-*O*-benzylated (and concomitantly triethylsilylated) with excellent regioselectivity on prolonged exposure of benzylated mono-, di- and trisaccharides to the $Et_3SiH/Co_2(CO)_8$ combined system at high temperature under CO.[17] Acetolysis is another approach often leading to selective de-*O*-benzylation (and concomitant acetylation) of primary positions, but in this case cleavage of glycosidic bonds can be a potential trouble.[18] TMSI has also been reported to produce selective de-*O*-benzylation of primary carbinols (via the corresponding trimethylsilyl ethers).[19]

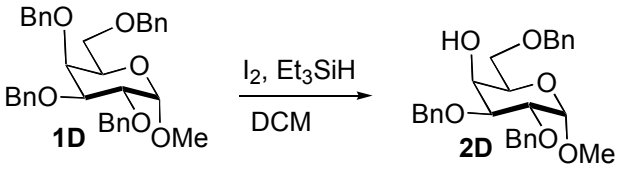
In this chapter it was described the wide and unprecedented scope of the I_2/Et_3SiH combined system in regioselective de-*O*-benzylation of sugars. This reagent permits the smooth generation of anhydrous HI and several useful applications were already established in our laboratory: for example, the combination of I_2 (stoichiometric) and Et_3SiH (catalytic) turned out to be an effective activating system for trihaloacetimidate glycosyl donors[20] and it was successively exploited by Takahashi and co-workers in their protocols aimed at the stereoselective synthesis of 2,6-dideoxy β-glycosides.[21] An analogous stoichiometric combination of these reagents in methanol was also found effective for the cleavage of benzylidene acetals.[22] Additionally, stoichiometric amounts of both I_2 and Et_3SiH allow glycosyl iodides to be generated from 1-*O*-acylated precursors within a few minutes: as it was shown in **Chapter B**, this rapid step has been incorporated into several sequential procedures leading to a variety of useful saccharidic intemediates such as 1,2-orthoesters,[23] -ethylidenes,[23] glycals,[23] thio- and seleno-glycosides,[24] 2-*O*-deprotected allyl glycosides,[25] as well as glycoconjugates with estradiol[26] or melanogenic 5,6-dioxyindole.[27] Further synthetically useful applications of I_2/Et_3SiH were also reported by other groups for the regioselective reductive opening of benzylidenes,[28] the reductive Ferrier rearrangement of glycals,[29] and the Friedel-Crafts cyclization of aryl-substituted propargyl alcohols.[30]

Reaction of Et_3SiH and I_2 provides HI and Et_3SiI under very simple experimental conditions.[31] Given that HI and Me_3SiI are known agents for ether cleavage,[19,32,33] the feasible application of the convenient I_2/Et_3SiH system in the deprotection of carbohydrates has been explored, with a special focus on the difficult issue of regioselective de-*O*-benzylation of sugars.

Results and discussion

Preliminary experiments examined the behaviour of tetra-*O*-benzylated methyl α-glycopyranosides in the presence of a slight stoichiometric excess of I_2 and Et_3SiH in DCM. The regioselective de-*O*-benzylation of these substrates immediately appeared as a feasible task when working at low temperature. Galactoside **1D** displayed high propensity to be deprotected at *O*-4 (**Scheme 1**) and it was chosen as the model compound for optimizing several experimental parameters such as the order of addition of reagents, their stoichiometry, the reaction temperature (**Table 1**). These experiments evidenced the effectiveness of the most experimentally convenient procedure (addition of Et_3SiH to a preformed DCM solution containing I_2 and the substrate). Other solvents such as toluene, 1,2-dichloroethane, acetonitrile and dioxane were found much less suitable for the purpose as sluggish reactions were observed. Investigation on the stoichiometry of the reagents revealed that a slight excess of both of them is required for obtaining high conversion of the starting material (compare entries 4-8 with entries 1-3). Use of less than one equivalent of either reagent provided incomplete de-*O*-benzylation (entries 1, 2) to suggest that only HI, and not Et_3SiI, is responsible for deprotection (see below for other evidences on this point). The temperature range was found critical for maximizing the yield while allowing the reaction to proceed at an elevated rate. Actually, TLC analysis suggested that further deprotection of mono de-*O*-benzylated products was competitive enough with the initial de-*O*-benzylation step of the fully protected saccharidic reagent. Thus, temperature control of the reaction medium was pivotal for tuning the course of all these potential processes. Under the optimized conditions (entry 6), D-*galacto* precursor **1D** provided the 4-OH derivative **2D** in an appreciable isolated yield (60 %) in only 15 minutes at the temperature range of -20 – -10 °C. Upon further warming the yield of **2D** decreased owing to formation of higher amounts of multiple de-*O*-benzylation products. In comparison with other known procedures for regioselective de-*O*-benzylation of sugars, the here proposed approach looked advantageous under several aspects such as reaction rapidity, use of a slight stoichiometric excess of cheap and easy to handle

reagents, and recourse to non demanding experimental precautions (no inert atmosphere was actually required for high yields to be achieved).



Scheme 1 Regioselective de-*O*-benzylation of model compound **1D**.

Table 1: optimization of de-*O*-benzylation conditions.

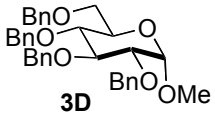
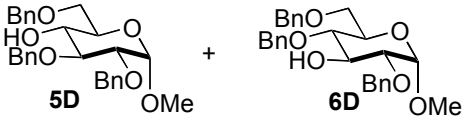
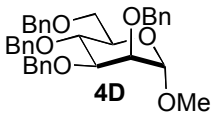
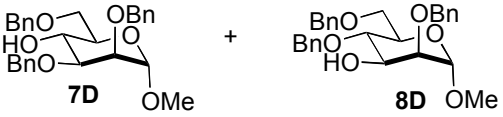
Entry	Eq of I_2	Eq of Et_3SiH	T(°C)	Time (min)	Isolated yield of 2D (%) (conversion)
1	0.5	0.5	-20	60	29
2	0.5	1.0	-20 to -5	60	35 (42)
3	1.0	1.0	-20 to -15	50	43
4	1.25	1.25	-25 to 0	60	48
5	1.25 [a]	1.25 [a]	-20	30	45 (67)
6	1.25	1.25	-20 to -10	15	60
7	1.25	1.25	-20	15	50
8	1.25	1.25	-15	15	55

General conditions: Et_3SiH was added at the indicated temperature to a solution of **1D** and I_2 in anhydrous DCM. The reaction was quenched at the final temperature by addition of pyridine. [a] I_2 and Et_3SiH were premixed in DCM and the resulting solution was added to **1D** dissolved in DCM.

The procedure was then applied to *gluco*- and *manno*- precursors **3D** and **4D** (**Table 2**). Predominance of the the 4-OH regioisomer was again recorded but in both cases the corresponding 3-OH regioisomer was isolated together with the main product as an inseparable mixture. The regioselectivity ratio was strongly dependent on the precursor and

was much higher for the *manno* precursor **4D** (**7D**/**8D** 8:1) than for the *gluco* derivative **3D** (**5D**/**6D** 3.8:1). Interestingly, in these cases de-*O*-benzylation started at lower temperatures than with the *galacto* precursor, but gradual warming of the reaction medium ensured the completion in relatively short times.

Table 2: De-*O*-benzylation of tetra-*O*-benzylated *gluco*- and *manno*-pyranoside precursors.

Entry	Reagent	Time (min)	T (°C)	Products, combined yields (conversion), regiosomeric ratio
1	 **3D**	70	-55 to -30	 **5D** + **6D** 43 % (56 %), **5D**:**6D** 3.8
2	**3D**	270	-55 to -30	41 % (61 %), **5D**:**6D** 2.5
3[a]	**3D**	265	-60 to -20	31 %, **5D**:**6D** 3
4[a]	**3D**	170	-60 to -30	29 %, **5D**:**6D** 2
5	 **4D**	75	- 40 to -10	 **7D** + **8D** 44 % (60 %), **7D**:**8D** 8

General conditions: Et_3SiH (1.25 eq) was added to a solution of **3D** or **4D** and I_2 (1.25 eq) in anhydrous DCM at the starting temperature. The reaction was quenched at the final temperature by addition of pyridine. [a] Experiment was performed in DCM/n-Exhane 9:1. [b] Experiment was performed in the presence of activated 4Å MS.

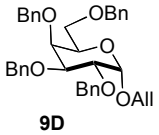
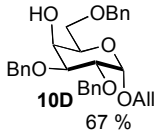
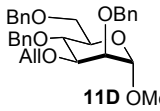
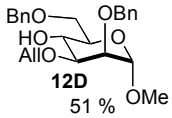
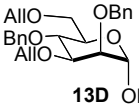
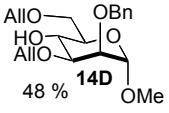
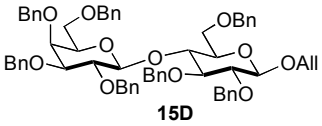
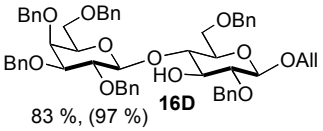
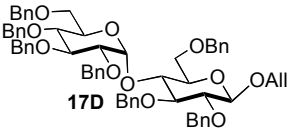
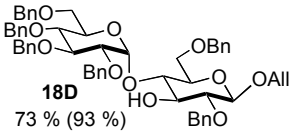
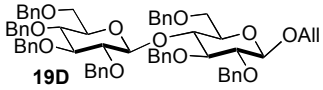
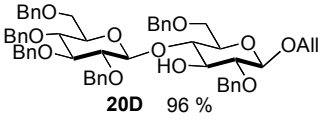
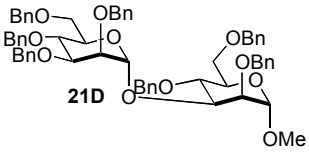
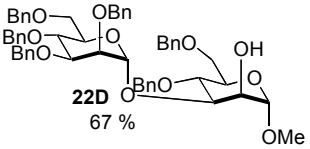
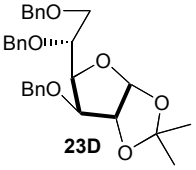
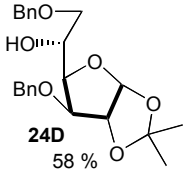
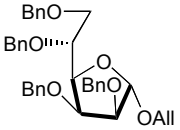
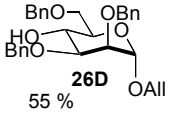
It is also significant that the inseparable mixture of **7D** and **8D** was recently obtained in a sensibly lower yield (31 %) and regioselectivity (**7D**:**8D** less than 5) upon treatment of **4D** with DDQ.[16a] Other saccharidic precursors bearing multiple benzyl protecting groups have been then screened and further interesting results emerged (**Table 3**). Like α-methyl glycosides (**Tables 1 and 2**), α-allyl glycosides proved compatible with the protocol (compare entry 1 of **Table 3**, with entry 6 of **Table 1**) thus offering a useful extension of the reaction scope in view of the wider chemical versatility of allyl aglycons. The stability of allyl

groups installed on non-anomeric carbinols also led to an improved regioselectivity in de-*O*-benzylation of *manno*-configured sugars, for which partially *O*-allylated precursors can be effectively prepared by stannylidene-mediated protections.[34] As shown in entries 2 and 3 of **Table 3**, 4-*O* deprotection of 3-*O*-allylated derivatives **11D** and **13D** occurred in satisfying yield and high regioselectivity: unlike the behaviour of the corresponding 3-*O*-benzylated counterpart **4D** (**Table 2**, entry 2), no products freed at 3-OH were detected from these 3-*O*-allylated precursors.

Rather surprising was the result obtained from allyl lactoside **15D** (**Table 3**, entry 4) which was deprotected in a very good yield at O-3 (*gluco* moiety) rather than at the expected position O-4′ (*galacto* moiety). This outcome eluded the trend inferred from entries in **Tables 1 and 2** (predominance of 4-OH products in all cases), and the previously observed higher reactivity of glucose *vs* galactose (compare activation temperatures in **Tables 1 and 2**) was initially considered to account for the apparently anomalous result. This hypothesis was immediately contradicted by results obtained from other disaccharide precursors **17D**, **19D**, and **21D** (**Table 3**, entries 5-7): regardless of the nature of saccharidic components, these compounds were still selectively deprotected at a secondary carbinol of the reducing terminus adjacent to the glicosidic bond. Very interestingly, the 3-*O*-linked manno disaccharide **21D** (entry 7) was preferentially deprotected at the axial *O*-2, *cis*-oriented to the encumbered 3-*O*-glycosylated position, rather than at *O*-4. Notably, the deprotection yields of disaccharides were typically higher than with monosaccharide precursors despite the larger number of potential deprotection events. Also worthy of note is the stability of the glycosidic linkages on the disaccharides under the employed acidic conditions, despite the "arming" effect of the benzyl protecting groups that is expected to facilitate the acid-promoted scission of inter-saccharidic linkages.[35]

As with monosaccharides and disaccharide precursors, furanoside derivatives also displayed a peculiar regioselectivity trend. Glucofuranoside **23D** (**Table 3**, entry 8) was selectively de-*O*-benzylated to give the 5-OH regiosiomer **24D** in a yield (58 %) comparable with that obtained with $TiCl_4$.[7b] This was the only found case where the Et_3SiH/I_2 system gave both yield and regioselectivity similar to other previously established procedures. Mannofuranoside **25D** (**Table 3**, entry 9) was also debenzylated at O-5, but in this case the putative furanoside intermediate free at O-5 evolved to give pyranoside **26D**[36] free at O-4 and minor amounts of an unidentified product (ca 10%) with neither a free hydroxyl group nor the allyl aglycon.[37]

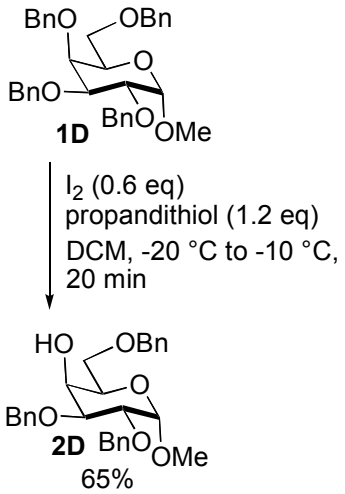
Table 3: Regioselective de-*O*-benzylation of pyranoside or furanoside monosaccharides, and disaccharides.

Entry	Reagent	T (°C) and time	Products and isolated yields (conversion)
1	 **9D**	- 40 to - 25 50 min	 **10D** 67 %
2	 **11D**	- 60 to 0 2.5 h	 **12D** 51 %
3	 **13D**	- 65 to - 5 2.5 h	 **14D** 48 %
4	 **15D**	-15 25 min	 **16D** 83 %, (97 %)
5	 **17D**	- 60 to - 20 1 h	 **18D** 73 % (93 %)
6	 **19D**	- 60 to - 20 1.5 h	 **20D** 96 %
7	 **21D**	- 65 to + 10 2.5 h	 **22D** 67 %
8	 **23D**	- 60 to - 20 1 h	 **24D** 58 %
9	 **25D**	- 60 to - 20 75 min	 **26D** 55 %

General conditions: Et_3SiH (1.25 eq) was added to a solution of the benzylated sugar and I_2 (1.25 eq) in anhydrous DCM at the starting temperature. The reactions were quenched by addition of pyridine (entries 1-3) or solid $NaHCO_3$ (2.5-5 eq) at the final temperature.

At this stage, a general survey of the obtained results and their comparison with previously reported approaches indicated an unprecedented direction of regioselectivity. As mentioned above, only 4-*O* deprotection of monosaccharides was somehow resemblant of the results described by Crich (stoichiometric DDQ), whose applicability is however restricted to date only to *manno*- and *rhamno*-configured substrates. [16a]

In order to better explain the origin of the obtained regioselectivity, some investigation was devoted to ascertain whether HI was the actual agent responsible of the deprotection. To this purpose, *galacto* precursor **1D** was treated with a mixture of I_2 and propandithiol according to the procedure described by Koreeda and coworkers some years ago for the in situ generation of anhydrous HI.[38] As expected, the reaction afforded once more the free 4-OH galacto derivative **2D** in high yield upon exposure to 0.6 eq of I_2 and 1.2 eq of propandithiol (**Scheme 2**). Under these conditions the reaction rate and the yield were both similar to those observed with I_2 and Et_3SiH.



Scheme 2 Regioselective de-*O*-benzylation of model compound **1D** with I_2 and propandithiol.

This outcome supports the hypothesis that the in situ generated HI acts as the actual de-*O*-benzylation agent.[32] On the other hand, the negligible contribution of Et_3SiI to the process is supported by the reported stability at 0 °C of saccharide benzyl ethers upon exposure to Me_3SiI (reasonably more reactive than Et_3SiI in ether cleavage) under the conditions adopted for the synthesis of glycosyl iodides of per-*O*-benzylated sugars.[39] Additionally, in sharp contrast with all the results found with the I_2/Et_3SiH system, the regioselectivity of Me_3SiI-mediated de-*O*-benzylations leads to preferential modification of the sterically more accessible primary positions.[19] As a matter of fact, only in the reaction described in entry 3 of **Table 3** did we isolate minor amounts (5 %) of the 4-*O*-triethylsilylated ether of **14D**.

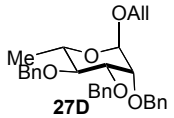
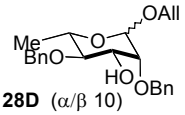
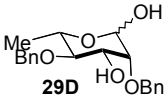
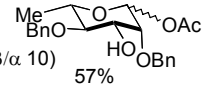
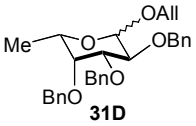
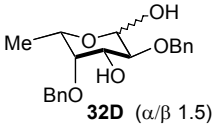
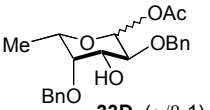
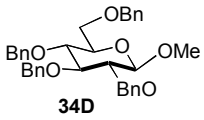
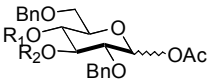
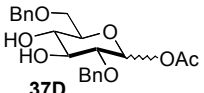
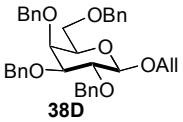
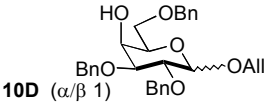
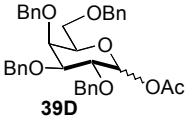
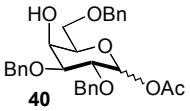
On the basis of these evidences and according to a well established general mechanism of ether scission,[32b] HI is expected to activate the benzyloxy group by *O*-protonation to favour the subsequent benzyl removal by nucleophilic attack by the iodide anion (and release of the alcohol). Consistently, benzyl iodide was isolated as a by-product of the reactions.

Once identified the actual promoter of the process, some consideration was made to rationalize the origin of the observed regioselectivity. Unlike many of the previously reported methods operating under Lewis acid conditions, HI-induced de-*O*-benzylation can not be regioselectively controlled by chelation effects. On the other hand, it can be observed that in all examined cases the liberation of the least accessible carbinols was favored and in no case *O*-benzylated primary positions were significantly affected. Thus, a reasonable mechanistic sketch could suggest that initial HI-promoted *O*-protonation might occur reversibly at the most basic secondary benzyloxy groups, and the following de-*O*-benzylation step, promoted by the nearby iodide anion, may be somehow kinetically controlled by the relief of the steric strain associated with the expulsion of the benzyl group. This effect could account for either the preferential deprotection (**Tables 1** and **2**) at the 4-*O*-position, the most encumbered for pyranoside monosaccharides, and the highest level of regioselectivity associated with the removal of the axially oriented galactose 4-*O*-benzyl group (compare **Table 1** and **2**). Furthermore, the apparently anomalous behaviour of disaccharide derivatives (**Table 3**, entries 4-7) can actually be consistent with this hypothesis if the steric crowding around the benzylated carbinol group flanking a glycosidation site is acknowledged. A similar reasoning can also rationalize the liberation of 5-OH on the furan derivatives (**Table 3**, entries 8 and 9), which fortuitously, in the case of entry 8, provides a result similar to a de-*O*-benzylation occurring under chelation control of the regioselectivity. Some literature cases of acid-promoted ether or acetal scissions seem to be governed by the "steric strain release effect" here invoked.[40]

To further extend the substrate scope of the reaction, other kind of precursors such as 2,3,4-tri-*O*-benzylated 6-deoxy pyranosides or β-configured 2,3,4,6-tetra-*O*-benzylated glycopyranosides were exposed to the I_2/Et_3SiH system. Initial experiments appeared frustrating as complex mixtures were obtained (TLC analysis). However, upon pyridine or lutidine quenching, the TLC profile of the reaction mixtures got almost simpler and most products displayed higher mobility than during the course of the reaction. This apparently strange observation was ascribed to the feasible "in situ" generation of glycosyl iodide intermediates as a consequence of the higher anomeric reactivity of 6-deoxyglycosides and β-*O*-linked glycosides, which could result in a fast HI-promoted expulsion of the aglycon

alcohol. Glycosyl iodides of "armed" densely *O*-benzylated sugars are poorly stable, so that they are very likely degraded under the TLC elution conditions to give more polar hydrolysis products. Experiments conducted with varied amounts of I_2 and Et_3SiH evidenced that anomeric iodination was faster than de-*O*-benzylation at any site, and thus part of the I_2/Et_3SiH reagent was consumed for this process. Interestingly, quenching of the reactions with bases as mild as pyridine or lutidine induced the reattachment of the initial aglycon alcohol with poor selectivity, so to give mixtures of α and β glycosides starting from anomerically pure substrates. These observations led us to foresee that addition of sufficient amounts of I_2 and Et_3SiH could induce a concomitant de-*O*-benzylation process together with the faster anomeric iodination. Thus, upon quenching the reaction would yield partially protected derivatives as anomeric mixtures. This overall result could be indeed very useful if the synthetic elaboration of the sugar entails subsequent removal of the aglycon, as for example in the preparation of glycosyl donors for oligosaccharide synthesis.

Table 4: Regioselective de-*O*-benzylation of 6-deoxy glycopyranosides and monosaccharide β-pyranosides

Entry	Reagent	T (°C) and time	Quenching conditions	Products and yields (conversion)
1	 **27D**	-60 to 0 2 h	A	 **28D** (α/β 10) 42 % (52 %)
2	**27D**	-60 to 0 2 h	B	**28D** (α/β 1) 40 % (50 %)
3	**27D**	-60 to 0 2 h	C	 **29D** + **28D** 38 % (43 %) 17 % (20 %)
4	**27D**	-60 to 0 1 h	D	 **30D** (β/α 10) 57%
5	 **31D**	-65 to 0 2 h	C	 **32D** (α/β 1.5) 61 %
6	**31D**	-65 to 0 2 h	D	 **33D** (α/β 1) 67 %[a]
7	 **34D**	-25 to -5 1 h	D	 **35D** R_1: H, R_2: OBn **36D** R_1: OBn, R_2: H 31 % (**35D**/**36D** ca 2)  **37D** 19 %[a]
8	 **38D**	-60 to - 10 80 min	A	 **10D** (α/β 1) 50 % (62 %)
9	 **39D**	-30 to -15 40 min	D	 **40** 46D %

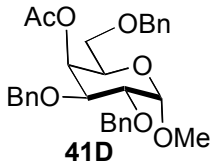
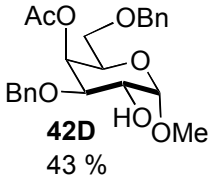
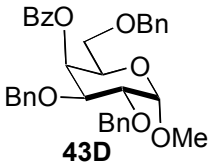
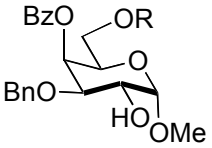
General conditions: Et_3SiH (1.8 eq) was added at the starting temperature to a solution of the benzylated sugar and I_2 (1.8-2.1 eq) in anhydrous DCM. The mixture was allowed to warm up to the final temperature. The reaction was quenched at the final temperature according to the following conditions A-D, and then the reaction vessel was allowed to warm to rt. Condition A: allyl alcohol (5 eq) and $NaHCO_3$ (5 eq); B: allyl alcohol (5 eq) and lutidine (5 eq); C: sat aq sodium carbonate; D: solution of lutidine (7 eq) and acetic acid (4 eq) in DCM. [a]Product slightly contaminated by an unidentified regiosomer.

After several experiments, the use of 1.8 equivalents of both I_2 and Et_3SiH emerged as the best option for performing regioselective de-*O*-benzylation of sugars especially reactive at the anomeric positions. Application of such conditions to the L-*rhamno* precursor **27D** (**Table 4**, entries 1-4) resulted in the regioselective deprotection at *O*-3, whereas prevalent *O*-4 deprotection had been previously recorded in the presence of the bulkier benzyloxy group at *C*-6 (**Table 2**, entry 2) or through the DDQ metodology.[16a] Differentiated quenching conditions (**Table 4**, conditions A-D) were also developed in order to tune the anomeric composition of the product, or even to change the nature of the anomeric substituent. These data evidence that reattachment of the aglycon alcohol can proceed with variable stereoselectivity according to the nature of the base (**Table 4**, entries 1 and 2). On the other hand, hydrolysis of the iodide was also carried out by quenching with saturated aq sodium bicarbonate (**Table 4**, entry 3) even though partial reattachment of the original alcohol aglycon was also recorded. Even more interestingly, the aglycon of the starting compound could be exchanged for a synthetically versatile acetate group upon quenching with a DCM solution of premixed acetic acid and lutidine (**Table 4**, entry 4). The quenching with pyridine, applied in the initial experiments on precursors unaffected at the anomeric position by I_2/Et_3SiH (**Tables 1-3**), was soon abandoned after the formation of consistent amounts of glycosyl pyridinium species eroded the overall yield of the process.

Application of the procedures to L-fucose confirmed the higher amenability of 6-deoxy sugars to *O*-3 deprotection with concurrent modification at the anomeric position (**Table 4**, entries 5-6). Interestingly, per-*O*-benzylated β-glucoside **34D** and β-galactoside **38D** also revealed anomeric reactivity towards I_2 and Et_3SiH (**Table 4**, entries 7 and 8) as shown by the aglycon exchange in entry 7 and the partial anomerization in entry 8. The de-*O*-benzylation regioselectivity was consistent with that of the corresponding α-pyranoside precursors (compare with **Tables 1** and **2**), and not negligible amounts of 3,4-diol **37D** (slightly contaminated by another 1-*O*-acetylated derivative) were also isolated from the *gluco* precursor. The 1-*O*-acetylated *galacto* derivative **39D** (**Table 4**, entry 9), highly prone to anomeric iodination with I_2/Et_3SiH,[23] also reacted with a regioselectivity mirroring the behaviour of the corresponding α-methyl glycoside **1D** (**Table 1**). At this stage it's interesting to recall that in the case of β-*O*-allylated disaccharides **15D**, **17D**, and **19D** (**Table 3**, entries 4-6) no evidence of HI-promoted de-*O*-allylation had been recorded. This evidence highlights that de-*O*-benzylation of disaccharide substrates is much faster than their anomeric iodination, in stark contrast with the behaviour of monosaccharide β-glycosides.

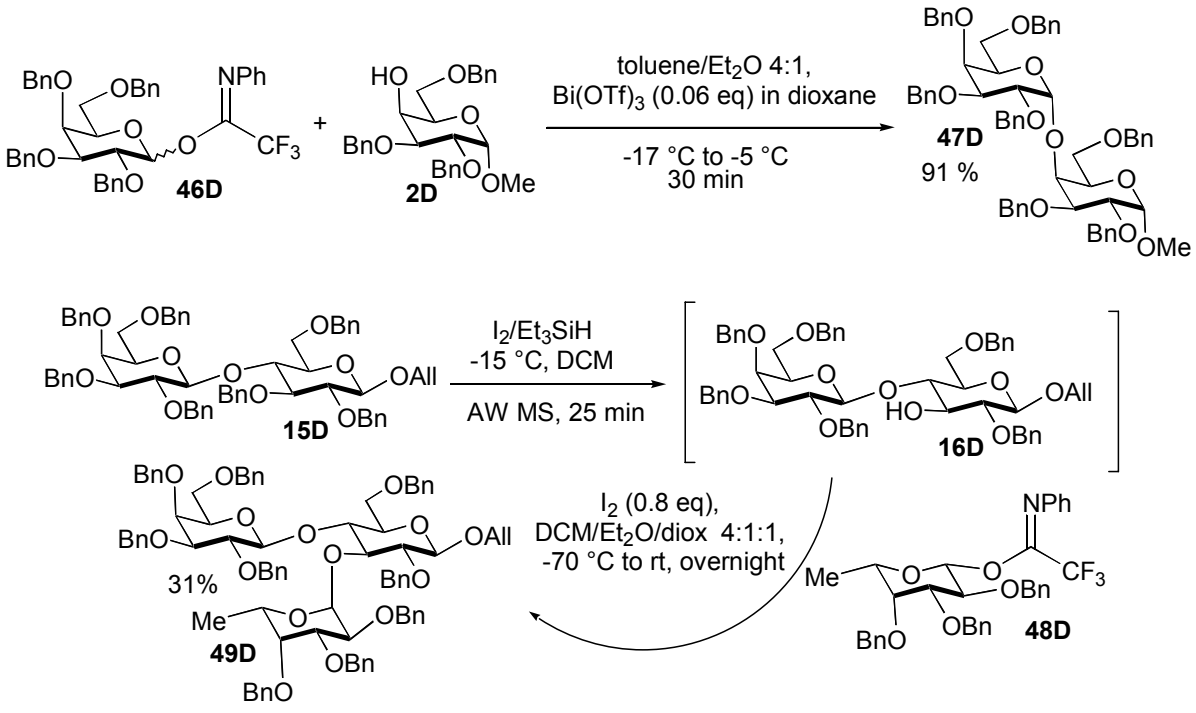
A further extension of the reaction scope was pursued by examining the effect of acyl protecting groups on substrates bearing multiple benzyl groups. The electron withdrawing aptitude of acyl groups was expected to reduce the basic character of adjacent benzylated oxigens thus interfering with the preliminary protonation of the benzyloxy group necessary for triggering the iodide-induced benzyl removal. Consistently, this effect could switch the normal regioselectivity (controlled by steric factors) to favor deprotection of the carbinol sites more distant from the acyloxy groups. To assay this effect, compound **2D** was readily acetylated or benzoylated under standard conditions to yield derivatives **41D** and **43D** (**Table 5**). Both derivatives were exposed to the I_2/Et_3SiH system at low temperature. Interestingly, the regioselectivity of the process was really influenced by the presence of the ester functionality, the less proximal benzyl group at *O*-2 being preferentially removed in synthetically useful yields (entries 1 and 2). In these cases minor but not negligible amounts of pure by-products were isolated. In particular, compound **41D** (entry 1) also gave the 6-*O*-debenzylation product in 12 % yield as well as minor amounts (less than 10 %) of the 3-*O*-deprotected derivative. This was the only case in which liberation of the primary carbinol was observed at an appreciable extent. Starting from compound **43D** (entry 2), the liberation of 2-OH was partially accompanied by 6-*O*-triethylsilylation (17% yield). As mentioned above, triethylsilylation of benzylated substrates is an uncommon event upon treatment with the I_2/Et_3SiH. The directing effect of acyl groups on regioselectivity further expands the synthetic potential of the method: selective 2-*O*-deprotections, which were never observed starting from per-*O*-benzylated monosaccharides (**Tables 1, 2** and **3**), were now possible starting from 4-*O*-acylated precursors.

Table 5: Regioselective de-*O*-benzylation of 4-*O*-acylated galactopyranosides.

Entry	Reagent	Time (min)	Temp (°C)	Product and yield (%)
1	 **41D**	1.5 h	-20 to -5	 **42D** 43 %
2	 **43D**	45 min	-20 to -5	 **44D** R: Bn 46 % **45D** R: TES 17 %

General conditions: Et_3SiH (1.25 eq) was added to a solution of **41D** or **43D** and I_2 (1.25 eq) in anhydrous DCM at the starting temperature. The reaction was quenched at the final temperature by addition of pyridine.

The usefulness of the methodology as a tool to streamline the synthesis of biologically useful oligosaccharides was demonstrated with the application of acceptors **2D** and **16D**, rapidly prepared in high yields as shown above. Coupling of acceptor **2D** with galactosyl trifluoroacetimidate[41] donor **46D** under $Bi(OTf)_3$ catalytic activation[42] quickly afforded protected galabiose **47D** (**Scheme 3**) in a very high yield and α-selectivity. Galabiose is contained in a range of biologically relevant oligosaccharide sequences, and this disaccharide fragment is frequently investigated for his potential role in tuning the adhesion of pathogenic bacteria.[43] In another application, the de-*O*-benzylation procedure was incorporated into a one-pot sequence yielding the Lewis X mimic **49D** where the glucosamine residue is replaced by a glucose (**Scheme 3**).[44] For this purpose, fully protected lactose **15D** was readily deprotected at *O*-3 as shown in **Table 3** (entry 4), thenafter the fucosyl imidate **48D**[45] was directly added to the reaction vessel with an additional amount of iodine.[20,46,47] The procedure afforded **49D** in an acceptable 31 % overall yield and to the best of our knowledge this is the first example in which a benzyl ether cleavage is applied to a one-pot sequence for oligosaccharide synthesis. Indeed, reductive opening of benzylidenes is the most pursued strategy for liberating a carbinol position in one-pot protocols of carbohydrate derivatization and oligosaccharide synthesis. [5,48]



Scheme 3 Application of regioselectively deprotected products in the synthesis of biologically relevant oligosaccharides.

Conclusion

In this chapter it was demonstrated that the I_2/Et_3SiH combined system is a very useful reagent to effect regioselective de-*O*-benzylation of highly *O*-benzylated substrates. HI generated in situ appears to be the actual promoter of the process. Synthetically useful regioselectivity is frequently achieved to give partially protected building-blocks otherwise accessible only through longer synthetic sequences. The obtained results show that sterically hindered benzyl groups are preferentially removed and the relief of steric strain appears as the main factor ruling the regioselectivity. This effect could explain other known selective processes of ether or acetal scission occurring under acidic conditions and might be exploited in designing new selective acid promoted processes. Consistently with this mechanistic view, for each group of examined substrates a well defined regioselectivity trend was observed: tetra-*O*-benzylated hexopyranoside monosaccharides are preferentially deprotected at *O*-4, hexofuranosides at *O*-5, 6-deoxy pyranosides at *O*-3, per-*O*-benzylated disaccharides at a secondary carbinol site of the reducing terminus adjacent to the glycosidic bond. Interestingly, the regioselectivity of the process can also be switched by insertion of acyl protecting groups on the substrate that results in the de-*O*-benzylation at the farthest site from the acylated position.

Application of the reagent system (with an appropriate stoichiometry) to substrates especially reactive at the anomeric position (6-deoxy glycopyranosides and monosaccharide β-pyranosides) causes rapid anomeric iodination at low temperature besides de-*O*-benzylation. However, the intermediate glycosyl iodides thus generated are reactive enough to be converted into a variety of synthetically useful products upon suitable quenching.

As demonstrated in the synthesis of the Lewis X mimic **49D**, the de-*O*-benzylation protocol can also be incorporated into one-pot procedures of oligosaccharide synthesis with an unprecedented use of benzyl as a transient protecting group.

In addition to its wide applicative scope, the disclosed protocol exhibits a broad range of practical advantages over many of the current methodologies of regioselective de-*O*-benzylations: reactions proceed rapidly at low temperatures and are performed without adopting inert atmosphere, the reagents are cheap and easy to handle and can be used in only slight stoichiometric excesses.

Experimental Section

General methods and Material

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (internal standard, for ^{1}H: $CHCl_3$ at δ 7.26; for ^{13}C: $CDCl_3$ at δ 77.0) ^{1}H NMR assignments were based on homo-decoupling experiments or bidimensional experiments. MALDI-MS spectra were recorded in the positive mode: compounds were dissolved in acetonitrile at a concentration of 0.1 mg/mL and one microliter of these solutions were mixed with one microliter of a 20 mg/mL solution of 2,5-dihydroxybenzoic acid in 7:3 CH_3CN/H_2O. Analytical thin layer chromatography (TLC) was performed on aluminium plates pre-coated with Silica Gel 60 F_{254} as the adsorbent. The plates were developed with 5% H_2SO_4 ethanolic solution and then heating to 130°C. Column chromatography was performed on silica gel (63-200 mesh). Glycosidations were performed with commercial anhydrous solvents.

Structural assignment of de-*O*-benzylation products was supported by their acetylation and observation of the consequent downfield acetylation shift at ^{1}H NMR. The most significant data (downfield carbinol signals) are included in the NMR description of each compound that was acetylated.

General procedure of de-*O*-benzylation with I_2 and Et_3SiH

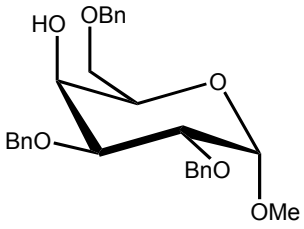
Anhydrous DCM (16-20 mL/mmol I_2) was added to the poli-*O*-benzylated derivative and I_2 at room temperature (see Tables for the relative amounts of reagents). After complete dissolution the mixture was cooled to the starting temperature of the reaction (see Tables) and then Et_3SiH (see Tables for the relative amount) was added by a syringe. The reaction mixture was allowed to gradually warm or maintained at the same temperature (Tables) until TLC analysis displayed the optimal extent of conversion. The reaction was quenched as indicated in the Tables. In the case of condition A (**Table 4**), allyl alcohol (5 eq) and solid $NaHCO_3$ (5 eq) were sequentially added. In the case of condition B, allyl alcohol (5 eq) and lutidine (5 eq) were sequentially added. In the case of condition C, sat aq sodium carbonate (5 mL/mmol I_2) was added. In the case of condition D, a solution of lutidine (7 eq) and acetic acid (4 eq) in DCM (3 mL/mmol I_2). The mixture was allowed to warm to rt and was then diluted with DCM. The organic phase washed with water containing sodium thiosulfate (to remove residual amounts of iodine). Water phase was re-extracted with DCM, and collected organic phases were dried and concentrated in vacuo. Silica-gel flash chromatography (eluent: hexane/ethyl acetate mixtures) yielded the de-*O*-benzylated products reported in the tables.

Procedure for the synthesis of galabiose disaccharide 47D

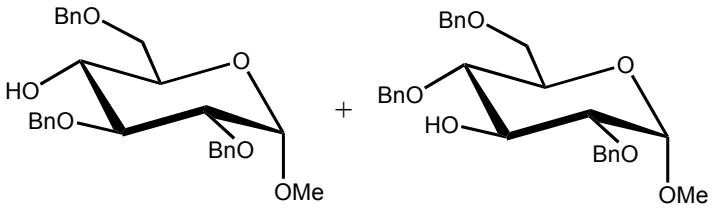
Trifluroacetrimidate donor **46D** (30 mg, 0.042 mmol) and acceptor **2D** (14 mg, 0.030 mmol) were co-evaporated three times with toluene (3 x 0.5 mL) and dried under vacuum. After adding 4Å AW 300 MS, the mixture was dissolved under argon with 4:1 toluene/Et_2O (1.5 mL), cooled to -17 °C, and stirred for 15 min. A solution of $Bi(OTf)_3$ in dioxane (14.5 mg/mL, 80 μL, 1.8 μmol) was then added, and the temperature was allowed to raise up to -5 °C over 30 minutes. Pyridine was added to quench the reaction and the mixture was filtered on a short plug of silica gel (eluent: DCM/MeOH/CH_3CN 85:10:5), concentrated and purified by silica gel flash chromatography (eluent: hexane/ethyl acetate from 85:15 to 4:1) to yield **47D** as an oil (27 mg, 91 % yield).

One-pot synthesis of Lewis X mimic 49D

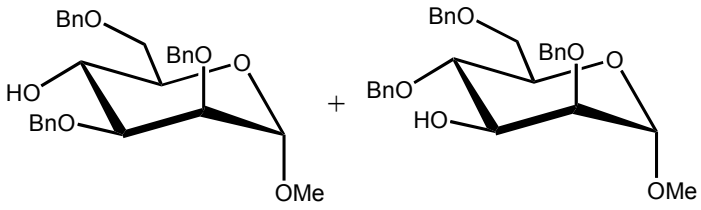
Protected lactose **15D** (23 mg, 0.023 mmol) was co-evaporated three times with toluene (3 x 0.5 mL) and dried under vacuum. The reaction vessel was purged with argon and then 4Å AW 300 MS, dry DCM (0.58 mL) and iodine (7 mg, 0.028 mmol) were sequentially added. After stirring for 10 min at rt, the vessel was cooled to – 15 °C and then Et_3SiH (4.5 μL, 0.028) was added by a syringe. After 25 minutes at -15 °C, the mixture was cooled to -78 °C and then a solution of fucosyl donor **48D** (42 mg, 0.069 mmol) in DCM/Et_2O/dioxane 2:1:1 (2 mL) was added, followed by a solution of I_2 (4.7 mg, 0.018 mmol) in DCM (0.27 mL). The temperature was allowed to raise up to rt overnight. The reaction was quenched with solid $NaHCO_3$ and the mixture was filtered on a short plug of silica gel (eluent: DCM/MeOH/CH_3CN 85:10:5), concentrated and purified by silica gel flash chromatography. The filtered liquor was washed with diluted aq thiosulfate and the organic phases were collected, dried and concentrated. The residue was chromatographed with *n*-pentane/ethyl acetate (from 10:1 to 6.5:1) to obtain an oil containing trisaccharide **49D** contaminated with minor amounts of fucose self-coupling by products. PLC purification of this crude mixture (eluent: toluene/ethyl acetate 7.5:1) afforded pure **49D** as an oil (9 mg, 31% overall yield).



Methyl 2,3,6-tri-*O*-benzyl-α-D-galactopyranoside (2D). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.15 (aromatic H), 4.70 (1H, d, $J_{1,2}$ = 3.2 Hz, H-1), 4.85-4.55 (6H, 3 x AB,3x –CH_2Ph), 4.07 (1H, bs, H-4), 3.93 (1H, bt, $J_{5,6a} = J_{5,6b}$ = 6.0 Hz, H-5), 3.90-3.87 (2H, overlapped, H-2 e H-3), 3.75 (1H, dd, $J_{6a,6b}$ = 10.0 Hz, H-6a), 3.69 (1H, dd, H-6b), 3.40 (3H, s, 1-OCH_3), 2.62 (1H, bs, 4-OH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.4, 138.2, 138.0 (aromatic C); 128.5-127.6 (aromatic CH), 98.6 (C-1), 77.6, 75.8, 73.6, 73.5, 72.7, 69.6, 68.4, 68.1, 55.3 (-OCH_3). Significant signals of acetylated **2D** at δ 5.62 (d, 1H, $J_{3,4}$ = 2.4 Hz, H-4), 2.08 (3H, s, -$COCH_3$). MS (MALDI-TOF) calcd for ($C_{28}H_{32}O_6Na^+$) 487.21, found 487.5.



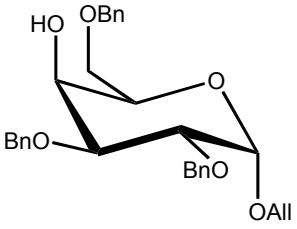
Methyl 2,3,6-tri-*O*-benzyl-α-D-glucopyranoside (5D) and Methyl 2,4,6-tri-*O*-benzyl-α-D-glucopyranoside (6D). (regioisomeric mixure **5D**/**6D** 3.8). ^{1}H NMR ($CDCl_3$, 500 MHz) significant signals of **5D** at δ 4.63 (1H, d, $J_{1,2}$ = 3.6 Hz, H-1), 3.79 (1H, t, $J_{2,3} = J_{3,4}$ = 9.6 Hz, H-3), 3.60 (1H, bt, $J_{4,5}$ = 9.6 Hz, H-4), 3.53 (1H, dd, H-2), 3.39 (3H, s, 1-OCH_3), 2.41 (1H, bs, 4-OH). Significant signals of **6D** at δ 4.66 (1H, d, $J_{1,2}$ = 3.6 Hz, H-1), 4.07 (1H, bt, $J_{2,3} = J_{3,4}$ = 9.6 Hz, H-3), 3.41 (1H, dd, H-2), 3.34 (3H, s, 1-OCH_3), 2.45 (1H, bs, 4-OH). Significant signals of acetylated **5D** at δ 5.02 (d, 1H, $J_{3,4}$ = 9.6 Hz, H-4), 1.81 (3H, s, -$COCH_3$). Significant signals of acetylated **6D** at δ 5.51 (d, 1H, $J_{3,4}$ = 10.0 Hz, H-4), 1.93 (3H, s, -$COCH_3$). ^{13}C NMR ($CDCl_3$, 125 MHz) signals of **5D** at δ 138.7, 137.9 (x2) (aromatic C), 128.5-127.5 (aromatic CH), 98.1 (C-1), 81.4, 79.5, 75.4, 73.5, 73.1, 70.6, 69.8, 69.4, 55.2 (-OCH_3). Significant signal of **6D** at δ 97.5 (C-1). MS (MALDI-TOF) calcd for ($C_{28}H_{32}O_6Na^+$) 487.21, found 487.4.



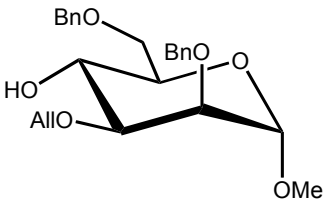
Methyl 2,3,6-tri-*O*-benzyl-α-D-mannopyranoside (7D) and Methyl 2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (8D).

7D and **8D** (regioisomeric mixure **7D**/**8D** 8).^{1}H NMR ($CDCl_3$, 400 MHz) signals of **7D** at δ 7.40-7.20 (aromatici), 4.79 (1H, s,

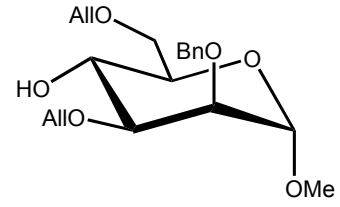
H-1), 4.75-4.49 (6H, 3 x AB, 3x –CH_2Ph), 4.05 (1H, t, $J_{3,4}$ = $J_{4,5}$ = 9.6 Hz, H-4), 3.82-3.73 (4H, segnali sovrapposti, H-2, H-5, H-6a, H-6b), 3.70 (1H, dd, $J_{2,3}$ = 3.2 Hz, H-3), 3.34 (3H, s, 1-OCH_3), 2.53 (1H, bs, 4-OH). Significant signals of **8D** at δ 4.83 (1H, bs, H-1). ^{13}C NMR ($CDCl_3$, 125 MHz) signals of **7D** at δ 138.4 (x3) (aromatic C), 128.4-127.4 (aromatic CH), 99.0 (C-1), 79.6, 73.8, 73.5, 72.6, 71.7, 71.3, 70.3, 67.7, 54.8 (-OCH_3). MS (MALDI-TOF) calcd for ($C_{28}H_{32}O_6Na^+$) 487.21, found 487.1.



Allyl 2,3,6-tri-*O*-benzyl-α-D-galactopyranoside (10D). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.20 (aromatic H), 5.94-5.90 (1H, m, -OCH_2-C*H*=CH_2), 5.29 (1H, dd, J_{trans} = 17.2 Hz, J_{gem} = 1.6 Hz, -OCH_2-CH=$CH_{cis}H_{trans}$), 5.18 (1H, dd, J_{cis} = 10.4 Hz, J_{gem} = 1.2 Hz, –OCH_2-CH=C$H_{cis}H_{trans}$), 4.86 (1H, d, $J_{1,2}$ = 3.2 Hz, H-1), 4.87-4.56 (6H, 3 x AB, 3x –CH_2Ph), 4.07 (1H, bs, H-4), 4.18-3.99 (2H, m, -OCH_2-CH=CH_2), 3.95 (1H, bt, $J_{5,6a}$ = $J_{5,6b}$ = 5.8 Hz, H-5), 3.90-3.84 (2H, overlapped signals, H-2 e H_2-3), 3.72 (1H, dd, $J_{6a,6b}$ = 12.8 Hz, H-6a), 3.66 (1H, dd, H-6b), 2.57 (1H, bs, 4-OH). Significant signals of acetylated **10D** at δ 5.62 (1H, bs, $J_{3,4}$ = 3.2 Hz, H-4), 2.05 (3H, s, -$COCH_3$). MS (MALDI-TOF) calcd for ($C_{20}H_{34}O_6Na^+$) 513.23, found 513.6.

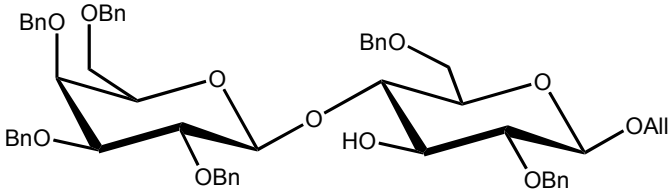


Methyl 3-*O*-allyl-2,6-di-*O*-benzyl-α-D-mannopyranoside (12D). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43-7.26 (m, aromatic H), 5.98-5.86 (m, 1H, -C*H*=CH_2), 5.30 (1H, dd, J_{trans} = 17.2 Hz, J_{gem} = 1.5 Hz, -CH_2CH=$CH_{cis}H_{trans}$), 5.20 (dd, 1H, J_{cis} = 10.4 Hz, -CH_2CH=C$H_{cis}H_{trans}$), 4.79 (d, 1H, $J_{1,2}$ = 1.6 Hz, H-1), 4.73-4.60 (4H, 2 x AB, 2 x –CH_2Ph), 4.61 (1H, d, J_{gem} = 12.1 Hz, -CH_2Ph), 4.10-3.95 (2H, m, -C$H_a$$H_b$CH=$CH_2$ and H-4), 3.85-3.71 (5H, m), 3.62 (1H, dd, $J_{2,3}$ = 3.1 Hz, $J_{3,4}$ = 9.5 Hz, H-3), 3.37 (s, 3H, -OMe). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.23, 138.20 (aromatic C), 134.6 (-*C*H=CH_2), 128.3-127.5 (aromatic CH), 117.2 (-CH=*C*H_2), 99.2 (C-1), 79.2, 73.6, 73.5, 72.6, 71.3, 70.5, 70.4, 67.7, 54.8 (-OMe). Significant signals of acetylated **12D** at δ 5.31 (1H, t, $J_{3,4}$ = $J_{4,5}$ = 10.0 Hz, H-4), 1.98 (3H, s, -$COCH_3$). MS (MALDI-TOF) calcd for ($C_{24}H_{30}O_6Na^+$) 437.20, found 437.3.

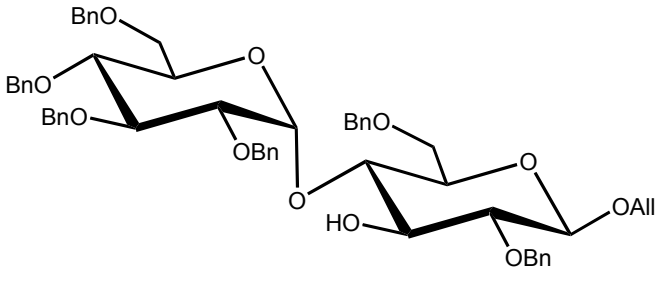


Methyl 3,6-di-*O*-allyl-2-*O*-benzyl-α-D-mannopyranoside (14D). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40-7.20 (m, aromatic H), 5.98-5.87 (m, 2H, 2 x -C*H*=CH_2), 5.33-5.25 (m, 2H, 2 x -

$CH_2CH{=}CH_{cis}H_{trans}$), 5.23-5.15 (m, 2H, 2 x -$CH_2CH{=}CH_{cis}H_{trans}$), 4.78 (d, 1H, $J_{1,2}$ = 1.5 Hz, H-1), 4.70 (2H, s, -CH_2Ph), 4.10-3.93 (m, 5H, 2 x -$CH_2CH{=}CH_2$ and H-4), 3.81-3.67 (m, 4H), 3.60 (dd, 1H, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 10.0 Hz, H-3), 3.36 (s, 3H, -OMe), 2.61 (bs, 1H, 4-O*H*). ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.2 (aromatic C), 134.64, 134.60 (2 x -*C*H=CH_2), 128.3-127.6 (aromatic CH), 117.2, 117.0 (2 x -CH=*C*H_2), 99.2 (anomeric CH), 79.2, 73.5, 72.6, 72.5, 71.2, 70.5, 70.4, 67.7, 54.8 (-OMe). MS (MALDI-TOF) calcd for ($C_{20}H_{28}O_6Na^+$) 387.18, found 387.3.

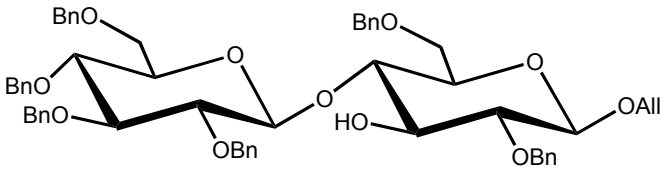


Allyl 2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,6-di-*O*-benzyl-β-D-glucopyranoside (16D). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.45-7.10 (aromatici), 6.00-5.90 (1H, m, -OCH_2-C*H*=CH_2), 5.33 (1H, bd, J_{trans} = 17.2 Hz, J_{gem} = 1.6 Hz, -OCH_2-$CH{=}CH_{cis}H_{trans}$), 5.19 (1H, dd, J_{cis} = 10.4 Hz, J_{gem} = 1.5 Hz, –OCH_2-$CH{=}CH_{cis}H_{trans}$), 4.41 (1H, d, $J_{1.2}$ = 7.2 Hz, H-1'), 4.31 (1H, d, $J_{1.2}$ = 7.2 Hz, H-1), 4.95-4.30 (13H, 6 x –CH_2Ph and –$OCH_aH_bCH{=}CH_2$), 4.13 (1H, bdd, J_{gem} = 12.8 Hz, J_{vic} = 5.6 Hz, –$OCH_aH_bCH{=}CH_2$), 3.85 (1H, d, $J_{3,4}$ = 2.4 Hz, H-4'), 3.83-3.73 (3H), 3.65-3.55 (2H), 3.53-3.45 (4H), 3.35 (1H, dd, H-2, $J_{2,3}$ = 9.2 Hz, H-2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.93, 138.42, 138.37, 138.33, 138.09, 137.54 (aromatic C), 134.1 (-*C*H=CH_2), 128.5-127.3 (aromatic CH), 117.1 (-CH=*C*H_2), 103.7 and 102.0 (C-1 and C-1′), 82.4, 81.6, 81.4, 78.9, 75.4, 75.2, 74.7, 74.6, 74.2, 73.6 (x2), 73.2, 73.0, 72.9, 70.3, 68.8, 68.5. Significant ^{1}H NMR signals of acetylated **16D** at δ 5.13 (1H, t, $J_{2.3}$ = $J_{3,4}$ = 9.6 Hz, H-3), 2.05 (3H, s, -$COCH_3$). MS (MALDI-TOF) calcd for ($C_{57}H_{62}O_{11}Na^+$) 946.42, found 946.2.

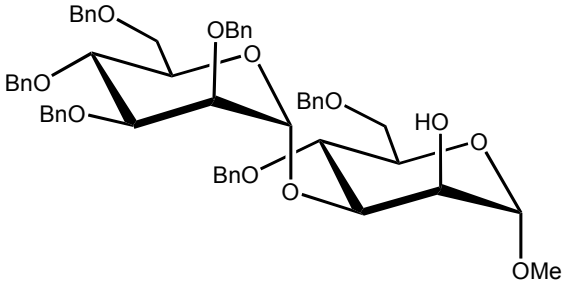


Allyl 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranosyl-(1→4)-2,6-di-*O*-benzyl-β-D-glucopyranoside (18D). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.00 (aromatic H), 6.00-5.80 (1H, m, -C*H*=CH_2), 5.35 (1H, dq, J_{trans} = 17.2 Hz, J_{gem} = 1.6 Hz, -$CH{=}CH_{cis}H_{trans}$), 5.21 (1H, dq, J_{cis} = = 10.8 Hz, -$CH{=}CH_{cis}H_{trans}$), 4.99 (1H, d, $J_{1,2}$ = 3.6 Hz, H-1′), 4.45 (1H, $J_{1,2}$ = 7.6 Hz, H-1), 5.00-4.40 (13 H, 6 x AB, 6 x CH_2Ph and –$CH_aCH_bCH{=}CH_2$), 4.15 (1H, m, –$CH_aCH_bCH{=}CH_2$), 4.00 (1H, t, $J_{1,2}$ = 9.6 Hz, H-3′), 3.83

(1H, m, H-5′), 3.83-3.75 (2H), 3.67 (1H, dd, J = 5.6 and 11.2 Hz), 3.64-3.50 (4H), 3.46-3.43 (2H), 3.38 (1H, dd, $J_{2,3}$ = 10.2 Hz, H-2′). ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.77, 138.49, 138.40, 138.1, 137.8, 137.0 (6 x aromatic C), 134.1 (-*C*H=CH_2), 128.4-127.2 (aromatic CH), 117.1 (-CH=*C*H_2), 102.3 and 100.6 (C-1 and C-1′), 82.1, 81.7, 80.7, 79.6, 75.6, 75.0, 74.4, 74.2, 73.4, 73.2, 71.3, 70.3, 69.2, 68.3. Significant ^{1}H NMR signals of acetylated **18D** at δ 5.31 (1H, t, $J_{2,3}$ = $J_{3,4}$ = 9.2 Hz, H-3), 1.82 (3H, s, -$COCH_3$). MS (MALDI-TOF) calcd for ($C_{57}H_{62}O_{11}Na^+$) 946.42, found 946.5.

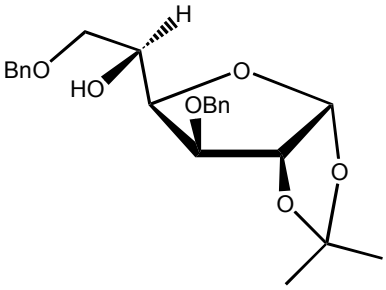


Allyl 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-(1→4)-2,6-di-*O*-benzyl-β-D-glucopyranoside (20D). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.50-7.05 (aromatic H), 6.00-5.85 (1H, m, -C*H*=CH_2), 5.35 (1H, bd, J_{trans} = 17.6 Hz, -CH=$CH_{cis}H_{trans}$), 5.20 (1H, bd, J = 10.6 Hz, -CH=C$H_{cis}H_{trans}$), 4.46 (1H, d, $J_{1,2}$ = 7.6 Hz, H-1), 4.40 (1H, d, $J_{1,2}$ = 7.6 Hz, H-1′), 4.90-4.30 (13 H, 6 x AB, 6 x –CH_2Ph and –C$H_a$$CH_b$CH=$CH_2$), 4.15 (1H, m, –$CH_aCH_b$CH=$CH_2$), 3.80-3.70 (3H), 3.68-3.50 (7H), 3.45-3.37 (2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.0, 138.3 (x2), 138.1, 137.9, 137.7 (aromatic C), 134.1 (-*C*H=CH_2), 128.4-127.2 (aromatic CH), 117.1 (-CH=*C*H_2), 103.2 and 102.1 (C-1 and C-1′), 84.7, 81.8, 81.5, 81.2, 77.7, 75.6, 75.3, 75.1, 74.9, 74.7, 74.6, 74.3, 73.6, 73.1, 70.2, 68.7. Significant signals of acetylated **20D** at δ 5.15 (1H, t, $J_{2,3}$ = $J_{3,4}$ = 9.2 Hz, H-3), 1.93 (3H, s, -$COCH_3$). MS (MALDI-TOF) calcd for ($C_{57}H_{62}O_{11}Na^+$) 946.42, found 946.6.

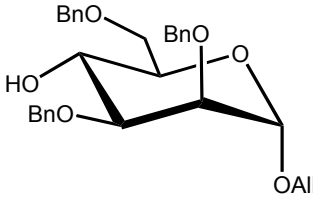


Methyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl-(1→3)-4,6-di-*O*-benzyl-α-D-mannopyranoside (22D). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.50-7.00 (aromatic H), 5.03 (1H, bs, H-1′), 4.47 (1H, bs, H-1), 4.82-4.32 (12H, 6 x –CH_2Ph), 4.20 (1H, bt, J = 8.5 Hz, H-5), 4.13 (1H, bs, sharper signal with D_2O, H-2), 3.88 (1H, dd, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 9.0 Hz, H-3), 3.76 (1H, bd, $J_{5,6a}$ = 8.0 Hz, H-6a), 3.75-3.60 (6H), 3.56 (1H, bs, exchange with D_2O, OH-2), 3.51 (1H, J = 8.5 Hz, H-6b), 3.28 (3H, s, -OCH_3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.6, 138.4, 138.23, 138.17, 138.10, 137.6 (aromatic C), 128.3-127.2 (aromatic CH), 101.3 and 99.3 (C-1 and C-1′), 82.4, 80.0, 75.6, 75.3, 74.9, 74.8, 73.9, 73.6, 73.4, 72.7, 72.1, 72.0, 71.2, 69.8, 69.3,

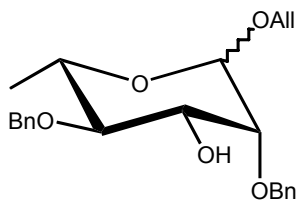
69.1, 54.7. Significant signals of acetylated **22D** at δ 5.24 (1H, bs, H-2), 2.16 (3H, s, -$COCH_3$). MS (MALDI-TOF) calcd for ($C_{55}H_{60}O_{11}Na^+$) 919.40, found 919.2.



3,6-Di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (24D). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35-7.31 (aromatic H), 5.92 (1H, d, $J_{1,2}$ = 3.6 Hz, H-1), 4.70-4.53 (5H, 2x –CH_2Ph and H-2), 4.20-4.10 (3H, overlapped signals, H-3, H-4 and H -5), 3.75 (1H, dq, $J_{6a,6b}$ = 10.0 Hz, $J_{5,6a}$ = 2.8 Hz, H-6a), 3.61 (1H, dq, $J_{5,6b}$ = 5.7 Hz, H-6b), 2.67 (1H, d, $J_{5\text{-}OH}$ = 4.7 Hz, 5-OH), 1.48 and 1.29 (6H, 2 x s, 2 x-CH_3). Significant signals of acetylated **24D** at δ 5.32 (1H, m, H -5), 2.01 (3H, s, -$COCH_3$). MS (MALDI-TOF) calcd for ($C_{23}H_{28}O_6Na^+$) 423.18, found 423.2.

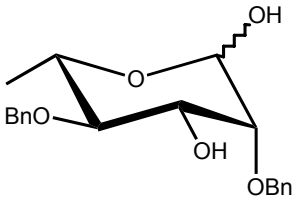


Allyl 2,3,6-tri-*O*-benzyl-α-D-mannopyranoside (26D). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.10 (aromatic H), 5.95-5.80 (1H, m, -$CH_2C\mathit{H}$=CH_2), 5.26 (1H, dq, J_{trans} = 15.6 Hz, J_{all} = J_{gem} = 1.6 Hz, -CH_2CH=$CH_{cis}\mathit{H}_{trans}$), 5.19 (1H, dq, J_{cis} = 10.6 Hz, J_{all} = J_{gem} = 1.6 Hz, -CH_2CH=$C\mathit{H}_{cis}H_{trans}$), 4.95 (1 H, d, $J_{1,2}$ = 1.6 Hz, 1-H), 4.70-4.50 (6 H, 3 x AB, 3 x -CH_2Ph), 4.23-4.17 (1H, m, -$C\mathit{H}_aH_b$CH=CH_2), 4.11-4.04 (1H, m, H-5), 4.02-3.94 (1H, m, -$CH_a\mathit{H}_b$CH=CH_2), 3.85-3.75 (5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1 (x3) (aromatic C), 133.7 (-CH=CH_2), 128.3-127.5 (aromatic CH), 117.2 (-CH=CH$_2$), 97.2 (C-1), 79.6, 73.9, 73.4, 72.5, 71.8, 71.5, 70.3, 67.8. Significant signals of acetylated **26D** at δ 5.34 (1H, t, $J_{3,4}$ = $J_{4,5}$ = 9.6 Hz, H-4), 1.94 (3H, s, -$COCH_3$). MS (MALDI-TOF) calcd for ($C_{20}H_{34}O_6Na^+$) 513.23, found 513.5.

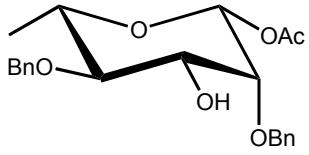


Allyl 2,4-di-*O*-benzyl-α,β-L-rhamnopyranoside (28D). ^{1}H NMR ($CDCl_3$, 400 MHz) signals of the α-anomer at δ 7.40-7.10 (aromatici), 6.00-5.80 (1H, m, -C*H*=CH_2), 5.28-5.10 (2H, m, -CH=CH_2), 4.87 (1H, bs, H-1), 4.92-4.55 (4H, 2 x AB, 2 x –CH_2Ph), 4.14 (1H, m, -$C\mathit{H}_aH_b$CH=CH_2), 4.00-3.85 (2H, m, H-3 and -$CH_a\mathit{H}_b$CH=CH_2), 3.76 (1H, bd, $J_{2,3}$ = 3.2 Hz, H-2), 3.65 (1H, m, H-5), 3.34 (1H, t, $J_{3,4}$ = $J_{4,5}$ = 9.6 Hz, H-4), 1.34 (3H, d, J_{vic} = 6.4 Hz, CH_3-6). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.5, 137.7 (aromatic C), 133.7 (*C*H=CH_2), 128.5-127.6 (aromatic CH), 117.2 (CH=*C*H$_2$), 96.0 (C-1), 82.3, 78.6, 75.1, 73.0, 71.6, 67.7, 67.2, 18.0. ^{1}H NMR ($CDCl_3$, 400 MHz) significant signals of the β-anomer at δ 4.50 (1H, s,

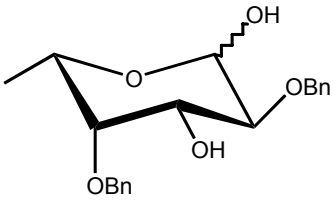
H-1), 3.84 (1H, d, $J_{2,3}$ = 3.6 Hz, H-2), 3.62 (1H, dd, $J_{3,4}$ = 8.8 Hz, H-3), 3.50-3.35 (2H, overlapped signals, H-4 and H-5), 1.39 (3H, d, J_{vic} = 6.0 Hz, CH_3-6). Significant signals of acetylated **28Dα** at δ 5.21 (1H, dd, $J_{2,3}$ = 3.4 Hz, $J_{3,4}$ = 9.6 Hz, H-3), 1.96 (3H, s, -$COCH_3$). MS (MALDI-TOF) calcd for ($C_{23}H_{28}O_5Na^+$) 407.19, found 407.4.



2,4-Di-*O*-benzyl-L-rhamnopyranose (29D). (anomeric mixture α/β ca 2.5:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.10 (aromatic H), 5.23 (1H, d, $J_{1,2}$ =1.2 Hz, H-1 α), 4.75 (1H, bs, H-1 β), 4.95-4.60 (-CH_2Ph a and β), 4.01 (1H, dd, $J_{2,3}$ = 3.6 Hz, $J_{3,4}$ = 9.2 Hz, H-3 α), 3.90 (1H, dd, J = 6.0 and 10.0 Hz, H-5 α), 3.83 (1H, dd, $J_{2,3}$ = 3.2 Hz, H-2 β), 3.83 (1H, dd, $J_{2,3}$ = 3.6 Hz, H-2 α), 3.73 (1H, m, H-5 β), 3.36 (2H, t, J = 9.6 Hz, H-4 α and β), 1.38 (3H, d, J = 6.0 Hz, CH_3-6 β), 1.33 (3H, d, J = 6.4 Hz, CH_3-6 α). ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.5, 138.2, 138.9, 137.8 (aromatic C), 93.8 (C-1 β), 91.9 (C-1 α), 82.2, 81.5, 78.7, 75.7, 75.0, 74.7, 73.2, 71.5, 71.2, 67.4, 18.1. MS (MALDI-TOF) calcd for ($C_{20}H_{24}O_5Na^+$) 367.15, found 367.3.

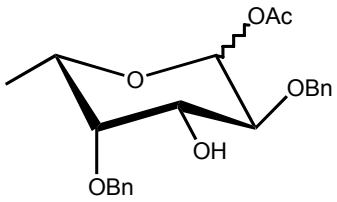


Acetyl 2,4-di-*O*-benzyl-β-L-rhamnopyranoside (30D). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40-7.10 (aromatic protons), 5.67 (1H, s, H-1), 5.02-4.66 (4H, 2 x AB, 2 x –CH_2Ph), 3.88 (1H, d, $J_{2,3}$ = 3.5 Hz, H-2), 3.75 (1H, m, H-3), 3.46 (1H, m, H-5), 3.32 (1H, t, $J_{3,4}$ = $J_{4,5}$ = 10.0 Hz, H-4), 2.33 (1H, d, J = 9.0 Hz, OH-3), 2.14 (3H, s, -$COCH_3$), 1.39 (3H, d, J = 6.0 Hz, CH_3-6). ^{13}C NMR (50 MHz, $CDCl_3$) δ 168.9 (-$COCH_3$), 138.2 and 137.9 (aromatic C), 128.5-127.7 (aromatic CH), 93.1 (C-1), 81.5, 77.5, 75.3, 75.1, 73.9, 72.4, 21.0, 17.9. MS (MALDI-TOF) calcd for ($C_{22}H_{26}O_6Na^+$) 409.16, found 409.5.

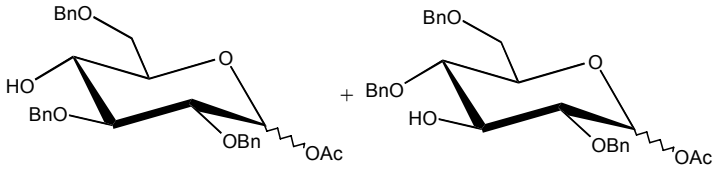


2,4-Di-*O*-benzyl-L-fucopyranose (32D). (anomeric mixture α:β ca 1.5). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.40-7.10 (aromatic protons), 5.30 (1H, bs, H-1 α), 5.00-4.70 (-CH_2Ph α and β), 4.63 (1H, t, J = 7.2 Hz, H-1 β), 4.17 (1H, bq, J_{vic} = 6.8 Hz, H-5 α), 4.04 (1H, m, H-3), 3.77 (1H, dd, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 9.6 Hz, H-2), 3.72-3.60 (H-4 α, H-3 and H-5 β), 3.59 (1H, bd, $J_{3,4}$ = 3.2 Hz, H-4 β), 3.50 (1H, dd, $J_{2,3}$ = 9.6 Hz, H-2 β), 3.00 (1H, d, $J_{1,OH}$ = 7.2 Hz, OH-1 β), 2.76 (1H, d, $J_{1,OH}$ = 2.0 Hz, OH-1 α), 2.29 (1H, d, $J_{3,OH}$ = 4.8 Hz, OH-3 β), 2.18 (1H, d, $J_{3,OH}$ = 5.6 Hz, OH-3 α), 1.26 (3H, d, J = 6.4 Hz,

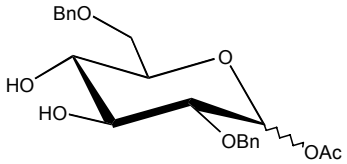
CH_3-6 β), 1.21 (3H, d, J = 6.8 Hz, CH_3-6 α). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3 and 137.8 (aromatic C), 128.6-127.6 (aromatic CH), 97.6 (C-1 β), 91.1 (C-1 α), 80.8, 79.5, 78.5, 75.6, 74.6, 74.3, 72.9, 71.0, 70.3, 66.5 16.9, 16.8. MS (MALDI-TOF) calcd for ($C_{20}H_{24}O_5Na^+$) 367.15, found 367.2.



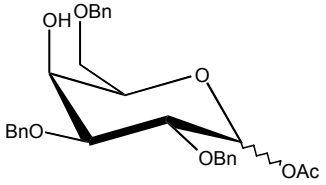
Acetyl 2,4-di-*O*-benzyl-α,β-L-fucopyranoside (33D). (anomeric mixture α:β ca 1.0). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.41 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1 α), 5.53 (1H, d, $J_{1,2}$ = 8.0 Hz, H-1 β), 4.87-4.52 (-CH_2Ph α and β), 4.03 (2H, m, H-3 and H-5 α), 3.91 (1H, dd, $J_{2,3}$ = 10.4 Hz, H-2 α), 3.78-3.68 (4H, H-4 α, H-2, H-3 and H-5 β), 3.59 (1H, d, $J_{3,4}$ = 3.6 Hz, H-4 β), 2.28 (1H, d, $J_{3,OH}$ = 4.0 Hz, OH-3 α), 2.25 (1H, d, $J_{3,OH}$ = 5.0 Hz, OH-3 β), 2.10 and 2.06 (6H, 2 xs, –$COCH_3$ α and β), 1.25 and 1.19 (6H, 2 x d, J = 7.5 Hz, CH_3-6 α and β). ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.5 and 169.4 (-*C*OCH_3 α and β), 138.3, 138.2, 138.1 and 137.6 (aromatic C), 128.6-127.4 (aromatic CH), 94.2 (C-1 β), 90.1 (C-1 α), 79.0, 78.6, 78.5, 75.8, 75.6, 74.8, 74.4, 72.8, 71.7, 70.5, 69.0, 21.0 (x2), 16.7 (x2). MS (MALDI-TOF) calcd for ($C_{22}H_{26}O_6Na^+$) 409.16, found 409.5.



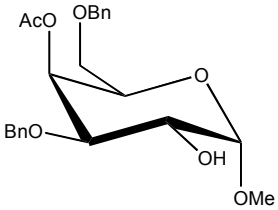
Acetyl 2,3,6-tri-*O*-benzyl-α,β-D-glucopyranoside (35D) and Acetyl 2,4,6-tri-*O*-benzyl-α,β-D-glucopyranoside (36D). (regiosiomeric mixture **35D**/**36D** ca 2.5). ^{1}H NMR ($CDCl_3$, 500 MHz) significant signals of **35Dα** at δ 6.39 (1H, d, $J_{1,2}$ = 3.0 Hz, H-1), 5.03-4.56 (3 x -CH_2Ph), 3.87 (1H, m, H-5), 3.81 (1H, t, $J_{2,3}$ = $J_{3,4}$ = 9.0 Hz, H-3), 3.80-3.66 (4H), 2.60 (1H, bs, OH-4), 2.20 (3H, s, -$COCH_3$). Significant signals of acetylated **35Dα** at δ 6.34 (1H, d, $J_{1,2}$ = 3.4 Hz, H-1), 5.12 (1H, t, $J_{3,4}$ = $J_{4,5}$ = 9.4 Hz, H-4), 2.17 and 1.84 (6H, 2 x s, 2 x -$COCH_3$). ^{1}H NMR ($CDCl_3$, 500 MHz) significant signals of **36Dα** at δ 6.41 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1), 4.08 (1H, bt, $J_{2,3}$ = $J_{3,4}$ = 9.0 Hz, H-3), 3.58 (1H, dd, H-2), 2.25 (1H, bs, OH-3), 2.14 (3H, s, -$COCH_3$). Significant signals of acetylated **36Dα** at δ 6.36 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1), 5.46 (1H, t, $J_{2,3}$ = $J_{3,4}$ = 9.0 Hz, H-3), 2.13 and 1.93 (6H, 2 x s, 2 x -$COCH_3$). MS (MALDI-TOF) calcd for ($C_{29}H_{32}O_7Na^+$) 515.20, found 515.4.



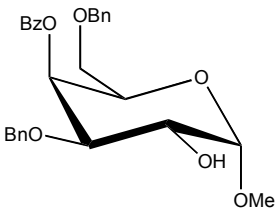
Acetyl 2,6-di-*O*-benzyl-α,β-D-glucopyranoside (37D). (anomeric mixture α:β ca 5.0). ^{1}H NMR ($CDCl_3$, 500 MHz) signals of the α anomer at δ 6.41 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1), 4.73-4.54 (4H, 2 x AB, 2 x -CH_2Ph), 3.90 (1H, t, $J_{2,3} = J_{3,4}$ = 9.5 Hz, H-3), 3.84 (1H, m, H-5), 3.76-3.65 (3H, overlapped signals, H-4 and CH_2-6), 3.50 (1H, dd, $J_{2,3}$ = 9.5 Hz, H-3), 2.13 (3H, s, -$COCH_3$). Significant signals of acetylated **37Dα** at δ 6.35 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1), 5.37 (1H, t, $J_{2,3} = J_{3,4}$ = 9.5 Hz, H-3), 5.12 (1H, t, $J_{4,5}$ = 9.5 Hz, H-4), 2.16, 2.00 and 1.90 (6H, 2 x s, 2 x -$COCH_3$). MS (MALDI-TOF) calcd for ($C_{22}H_{26}O_7Na^+$) 425.16, found 425.3.



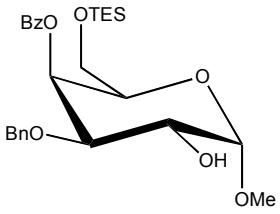
Acetyl 2,3,6-tri-*O*-benzyl-α,β-D-galactopyranoside (40D). (anomeric mixture α:β ca 1.0). ^{1}H NMR ($CDCl_3$, 400 MHz) significant signals at δ 6.41 (1H, d, $J_{1,2}$ = 2.8 Hz, H-1 α), 5.59 (1H, d, $J_{1,2}$ = 8.0 Hz, H-1 β), 4.19 and 4.13 (2H, 2 x bs, H-4 α and β), 2.14 and 2.07 (6H, 2 x s, 2 x –$COCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) significant signals at δ 94.1 (C-1 β), 90.4 (C-1 α), 80.9, 77.5, 77.2, 75.3, 74.6, 73.7, 73.6, 73.2, 72.6, 72.3, 70.9, 69.0, 68.5, 67.5, 66.4, 21.0 (x2). Significant ^{1}H NMR signals of acetylated **40D** at δ 6.39 (1H, d, $J_{1,2}$ = 3.5 Hz, H-1), 5.72 and 5.67 (2H, 2 x bs, H-4 α and β), 5.63 (1H, d, $J_{1,2}$ = 7.6 Hz, H-1 β), 2.14, 2.11 and 2.08 (x2) (12H, 3 x s, 4 x –$COCH_3$). MS (MALDI-TOF) calcd for ($C_{29}H_{32}O_7Na^+$) 515.20, found 515.1.



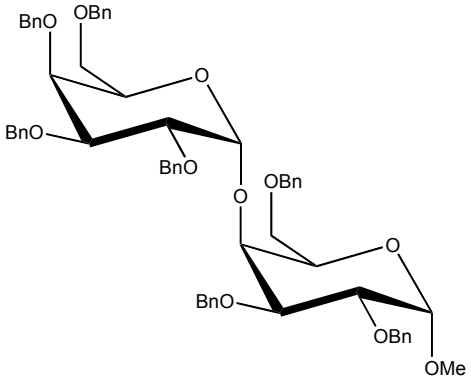
Methyl 4-*O*-acetyl-3,6-di-*O*-benzyl-α-D-galactopyranoside (42D). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.15 (aromatic H), 5.61 (1H, bd, $J_{3,4}$ = 3.2 Hz, H-4), 4.87 (1H, d, $J_{1,2}$ = 3.6 Hz, H-1), 4.80-4.40 (4H, 2 x AB, 2 x –CH_2Ph), 4.07 (1H, bt, $J_{5,6a} = J_{5,6b}$ = 6.4 Hz, H-5), 3.94 (1H, bdd, $J_{2,3}$ = 10.0 Hz, H-2), 3.72 (1H, dd, H-3), 3.55-3.45 (2H, m, CH_2-6), 3.43 (3H, s, -OCH_3), 2.08 (3H, s, -$COCH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.3 (-*C*OCH_3), 137.6 (x2) (aromatic C), 128.4-127.6 (aromatic CH), 99.4 (C-1), 76.4, 73.6, 71.5, 68.3, 67.9, 67.2, 55.5, 20.8. Significant signals of acetylated **42D** at δ 5.63 (1H, bd, $J_{3,4}$ = 2.8 Hz, H-4), 5.09 (1H, dd, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 10.4 Hz, H-2), 2.09 and 2.08 (6H, 2 x s, 2 x –$COCH_3$). MS (MALDI-TOF) calcd for ($C_{23}H_{28}O_7Na^+$) 439.18, found 439.3.



Methyl 4-*O*-benzoyl-3,6-di-*O*-benzyl-α-D-galactopyranoside (44D). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10-7.10 (aromatic H), 5.87 (1H, bd, $J_{3,4}$ = 2.8 Hz, H-4), 5.00 (1H, d, $J_{1,2}$ = 3.6 Hz, H-1), 4.90-4.43 (4H, 2 x AB, 2 x $-CH_2Ph$), 4.19 (1H, bt, $J_{5,6a} = J_{5,6b}$ = 6.4 Hz, H-5), 4.09 (1H, bdd, $J_{2,3}$ = 10.0 Hz, H-2), 3.85 (1H, dd, H-3), 3.70-3.55 (2H, m, CH_2-6), 3.48 (3H, s, $-OCH_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.7 (-COPh), 137.6 and 133.1 (aromatic C), 129.9-127.6 (aromatic CH), 99.5 (C-1), 76.5, 73.6, 71.4, 68.6 (x2), 68.3, 67.7, 55.5. Significant signals of acetylated **44D** at δ 5.89 (1H, bd, $J_{3,4}$ = 2.8 Hz, H-4), 5.20 (1H, dd, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 10.4 Hz, H-2), 2.04 (3H, s, $-COCH_3$). MS (MALDI-TOF) calcd for ($C_{28}H_{30}O_7Na^+$) 501.20, found 501.4.

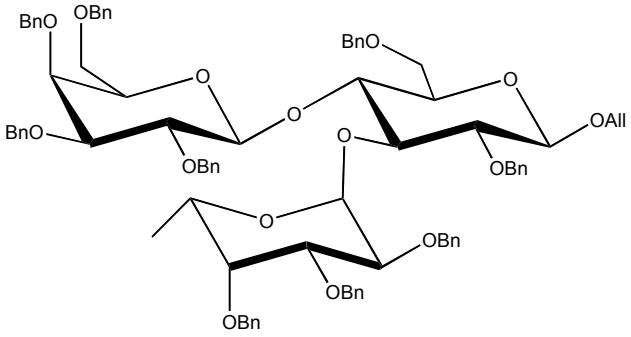


Methyl 4-*O*-benzoyl-3-*O*-benzyl-6-*O*-triethylsilyl-α-D-galactopyranoside (45D). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.10-7.10 (aromatic H), 5.85 (1H, bd, $J_{3,4}$ = 2.8 Hz, H-4), 4.95 (1H, d, $J_{1,2}$ = 3.6 Hz, H-1), 4.91-4.49 (2H, AB, J_{gem} = 11.2 Hz, $-CH_2Ph$), 4.07 (1H, dd, $J_{2,3}$ = 10.0 Hz, H-2), 4.03 (1H, bt, $J_{5,6a} = J_{5,6b}$ = 6.4 Hz, H-5), 3.85 (1H, dd, H-3), 3.70 (2H, d, CH_2-6), 3.48 (3H, s, $-OCH_3$), 0.90 (9H, t, J_{vic} = 8.0 Hz,$-Si(CH_2C\mathit{H}_3)_3$), 0.55 (6H, q, $Si(C\mathit{H}_2CH_3)_3$). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.7 (-COPh), 133.1 (aromatic C), 130.0-127.6 (aromatic CH), 99.4 (C-1), 76.8, 71.5, 70.1, 68.7, 67.4, 61.5, 55.4, 6.62, 4.23. Significant signals of acetylated **45D** at δ 5.86 (1H, bd, $J_{3,4}$ = 2.8 Hz, H-4), 5.20 (1H, dd, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 10.4 Hz, H-2), 2.09 (3H, s, $-COCH_3$). MS (MALDI-TOF) calcd for ($C_{27}H_{38}O_7SiNa^+$) 525.24, found 525.4.



Methyl 2,3,4,6-tetra-*O*-benzyl-α-D-galactopyranosyl-(1→4)-2,3,6-tri-*O*-benzyl-α-D-galactopyranoside (47D). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40-7.00 (aromatic protons), 5.01 (1H, $J_{1,2}$ = 3.2 Hz, H-1′), 4.73 (1H, $J_{1,2}$ = 3.2 Hz, H-1), 4.99-4.55 (12 H, 6 x AB, 6 x $-CH_2Ph$), 4.43 (1H, bdd, J = 5.6 and 9.2 Hz), 4.24 (1H, s), 4.13 (1H, bs, 2H), 4.08 (1H, dd, J = 2.4 and 9.2 Hz), 3.95-3.80 (4H), 3.60-3.45 (2H), 3.39 (3H, s, $-OCH_3$), 3.24 (1H, dd, J = 4.8 and 8.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.98, 138.95, 138.75, 138.67, 138.5, 138.2, 138.1 (6 x aromatic C), 128.3-127.2 (aromatic CH), 100.3 and 98.7 (C-1 and C-1′), 79.5, 77.9, 77.2, 76.6, 75.1, 74.9, 74.6, 74.1, 73.3, 73.1, 72.9, 72.6, 72.2,

69.5, 69.3, 68.2, 67.8, 55.3. MS (MALDI-TOF) calcd for $(C_{62}H_{66}O_{11})^+$ 1009.45, found 1009.7.



Allyl 2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl-(1→3)-2,3,4,6-tetra-*O*-benzyl-β-D-galactopyranosyl-(1→4)-2,6-di-*O*-benzyl-β-D-glucopyranoside (49D). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.42-7.00 (aromatic protons), 5.92-5.81 (1H, m, -C*H*=CH_2), 5.65 (1H, d, $J_{1,2}$ = 4.0 Hz, H-1 Fuc), 5.26 (1H, dd, J_{trans} = 17.0 Hz, J_{gem} = 1.5 Hz, -OCH_2-CH=$CH_{cis}H_{trans}$), 5.14 (1H, dd, J_{cis} = 11.0 Hz, J_{gem} = 1.5 Hz, –OCH_2-CH=C$H_{cis}H_{trans}$), 5.08-4.34 (22 H, 9 x AB, 9 x –CH_2Ph, H-5 Fuc, 2 H-1 and –C$H_a$$CH_b$CH=$CH_2$), 4.51 (1H, d, $J_{1,2}$ = 7.0 Hz, H-1 Glc), 4.44 (1H, d, $J_{1,2}$ = 7.5 Hz, H-1 Gal), 4.15 (1H, t, J = 9.5 Hz, H-4 Glc), 4.08 (1H, bdd, J_{gem} = 13.0 Hz, J_{vic} = 6.0 Hz, –$OCH_a$$H_b$CH=$CH_2$), 4.02-3.94 (4H, m), 3.92 (1H, dd, $J_{2,3}$ = 10.0 Hz, H-2 Fuc), 3.80 (1H, t, J = 9.0 Hz, H-5 Gal), 3.76-3.70 (2H, m, H-6), 3.67 (1H, bdd, $J_{2,3}$ = 10.0 Hz, H-2 Gal), 3.60 (1H, bdd, $J_{2,3}$ = 9.0 Hz, H-2 Glc), 3.41 (1H, dd, $J_{3,4}$ = 3.0 Hz, H-3 Gal), 3.39-3.35 (1H, m, H-5 Glu), 3.34-3.30 (2H, m, H_2-6 Glc), 1.14 (3H, d, $J_{5,6}$ = 6.5 Hz, H_3-6 Fuc). ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.3, 139.2, 139.0, 138.9, 138.7, 138.5, 138.4 (x2), 137.9 (9 x aromatic C), 128.3-127.2 (aromatic CH), 134.0 (*C*H=CH_2), 128.7-126.3 (aromatic CH), 117.2 (CH=*C*H_2), 102.9, 102.2, and 97.6 (anomeric C), 82.8, 82.4, 80.1, 79.6, 78.8, 75.8, 75.5, 75.4, 75.3 (x2), 75.0, 73.9, 73.3 (x3), 73.0, 72.9, 72.7, 72.4, 72.2, 70.2, 68.0, 67.8, 65.8; 16.8 (Fuc C-6). MS (MALDI-TOF) calcd for $(C_{84}H_{90}O_{15})^+$ 1361.62, found 1361.4.

References

1. Greene, T. W.; Wuts, P. G. M. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; John Wiley & Sons: Hoboken, NJ, 2007; pp 102-120.

2. Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem. Int. Ed.* **2001**, *40*, 1576-1624.

3. Fraser-Reid, B.; Wu, Z.; Udodong, U. E.; Ottosson, H. B. *J. Org. Chem.* **1990**, *55*, 6068-6070. For a recent review on oligosaccharide synthesis: Zhu, X.; Schmidt, R. R. *Angew. Chem. Int. Ed.* **2009**, *48*, 1900-1934.

4. (a) Demchenko, A. V. *Synlett* **2003**, 1225-1240. (b) Mydock, L.K.; Demchenko, A. V. *Org. Bio. Chem.* **2010**, *8*, 497-510.

5. (a) Wang, C.-C.; Lee, J.-C.; Luo, S.-Y.; Kulkarni, S. S.; Huang, Y.-W.; Lee, C.-C.; Chang, K.-L.; Hung S.-C. *Nature*, **2007**, *446*, 896-899. (b) Francais, A.; Urban, D.; Beau, J.-M. *Angew. Chem. Int. Ed.* **2007**, *46*, 8662-8665. (c) Wang, C.-C.; Kulkarni, S. S.; Lee, J.-C.; Luo, S.-Y.; Hung S.-C. *Nature Protocols* **2008**, *3*, 97-113.

6. (a) Beaupere, D.; Boutbaiba, I.; Wadouachi, A.; Frechou, C.; Demailly, G.; Uzan, R. *New J. Chem.* **1992**, *16*, 405-411. (b) Bieg, T.; Szeja, W. *Carbohydr. Res.* **1990**, *205*, C10-C11: (c) Beaupere, D.; Boutbaiba, I.; Demailly, G.; Uzan, R. *Carbohydr. Res.* **1988**, *180*, 152-155. (d) Cruzado, M. C.; Martin-Lomas, M. *Tetrahedron Lett.* **1986**, *27*, 2497-2500.

7. (a) Martin, O.; Kurz, K. G.; Rao, S. P. *J. Org. Chem.* **1987**, *52*, 2922-2925. (b) Hori, H.; Nishida, Y.; Ohrui, H.; Meguro, H. *J. Org. Chem.* **1989**, *54*, 1346-1353. (c) Bouali, A.; Boullanger, P.; Lafont, D.; Fenet, B. *Carbohydr. Res.* **1992**, *228*, 81-93.

8. (a) Jia, C.; Zhang, Y.; Zhang, L.-H.; Sinay, P.; Sollogoub, M. *Carbohydr. Res.* **2006**, *341*, 2135-2144. (b) Lecourt, T.; Herault, A.; Pearce, A. J.; Sollogoub, M.; Sinay, P. *Chem. Eur. J.* **2004**, *10*, 2960-2971. (c) Roizel, B. C.; Cabianca, E.; Rollin, P.; Sinay, P. *Tetrahedron* **2002**, *58*, 9579-9583.

9. For applications to benzylated cyclodextrins: (a) Pearce, A. J.; Sinay, P. *Angew. Chem. Int. Ed.* **2000**, *39*, 3610-3612. (b) Bistri, O.; Sinay, P.; Sollogoub, M. *Tetrahedron Lett.* **2005**, *46*, 7757-7760. (c) Bistri, O.; Sinay, P.; Jimenez-Barbero, J.; Sollogoub, M. *Chem Eur. J.* **2007**, *13*, 9757-9774. (d) Guieu, S.; Sollogoub, M *J. Org. Chem.* **2008**, *73*, 2819-2828. (e) Lopez, O.; Bols, M. *Tetrahedron* **2008**, *64*, 7587-7593. (f) Guieu, S.; Sollogoub, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 7060-7063. (g) Rawal, G. K.; Rani, S.; Ling, C. –C. *Tetrahedron*

Lett. **2009**, *50*, 4633-4636. (h) Rawal, G.; Rani, S.; Ward, S.; Ling, C.-C. *Org. Biomol. Chem.* **2010**, *8*, 171-180. (i) Guieu, S.; Zaborova, E.; Bleriot, Y.; Poli, G.; Jutand, A.; Madec, D.; Prestat, G.; Sollogoub, M. *Angew. Chem. Int. Ed.* **2010**, *49*, 2314-2318.

10. Zaborova, E.; Bleriot, Y.; Sollogoub, M. *Tetrahedron Lett.* **2010**, *51*, 1254-1256.

11. (a) Xie, J.; Menand, M.; Valery, J.-M. *Carbohydr. Res.* **2005**, *340*, 481-487.

12. Falck, J. R.; Barma, D. K.; Venkataraman, S. K.; Baati, R.; Mioskowski, C. *Tetrahedron Lett.* **2002**, *43*, 963-966.

13. (a) Kawana, M. *Chem. Lett.* **1981**, *10*, 1541-1544. (b) Casas, C. P.; Yamamoto, H.; Yamato, T. *J. Chem. Res.* **2005**, 694-696. (c) Haraldsson, G. G.; Baldwin, J. E. *Tetrahedron* **1997**, *53*, 215-224.

14. (a) Madsen, J.; Bols, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 3177-3178. (b) Madsen, J.; Viuf, C.; Bols, M. *Chem. Eur. J.* **2000**, *6*, 1140-1146.

15. (a) Cipolla, L.; Lay, L.; Nicotra, F. *J. Org. Chem.* **1997**, *62*, 6678-6691. (b) Lay, L.; Cipolla, L.; La Ferla, B.; Peri, F.; Nicotra, F. *Eur. J. Org. Chem.* **1999**, 3337-3340. (c) Cipolla, L.; La Ferla, B.; Lay, L.; Peri, F.; Nicotra, F. *Tetrahedron: Asymmetry* **2000**, *11*, 295-303.

16. (a) Crich, D.; Vinogradova, O. *J. Org. Chem.* **2007**, *72*, 3581-3584. For previous examples of DDQ-mediated regioselective de-*O*-benzylation of sugars: (b) Cabianca, E.; Tatibouet, A.; Rollin, P. *Pol. J. Chem.* **2005**, *79*, 317-322.

17. Yin, Z.-J.; Wang, B.; Li, Y.-B.; Meng, X.-B.; Li, Z-J. *Org. Lett.* **2010**, *12*, 536-539.

18. (a) Allerton, R.; Fletcher, H. G., Jr. *J. Am. Chem. Soc.* **1954**, *76*, 1757–1760. (b) Ganem, B.; Small, V. R., Jr. *J. Org. Chem.* **1974**, *39*, 3728–3730. (c) Eby, R.; Sondheimer, S. J.; Schuerch, C. *Carbohydr. Res.* **1979**, *73*, 273–276. (d) Sakai, J.-I.; Takeda, T.; Ogihara, Y. *Carbohydr. Res.* **1981**, *95*, 125–131. (e) Angibeaud, P.; Utille, J.-P. *Synthesis* **1991**, 737–738. (f) Yang, G.; Ding, X.; Kong, F. *Tetrahedron Lett.* **1997**, *38*, 6725–6728. (g) Brar, A.; Vankar, Y. D. *Tetrahedron Lett.* **2006**, *47*, 5207–5210.

19. Klemer, A.; Bieber, M.; Wilbers, H. *Liebigs Ann. Chem.* **1983**, 1416-1421.

20. Adinolfi, M.; Barone, G.; Iadonisi, A.; Schiattarella, M. *Synlett* **2002**, 269-270.

21. (a) Tanaka, H.; Yoshizawa, A.; Takahashi, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 2505-2507. (b) Tanaka, H.; Yoshizawa, A.; Chijiwa, S.; Ueda, J.; Takagi, M.; Shin-Ya, K.; Takahashi, T. *Chem. Eur. J.* **2009**, *4*, 1114-1125. (c) Tanaka, H.; Yamaguchi, S.; Yoshizawa, A.; Takagi, M.; Shin-Ya, K.; Takahashi, T. *Chem. Asian. J.* **2010**, *5*, 1407-1424.

22. Adinolfi, M.; De Napoli, L.; Di Fabio, G.; Iadonisi, A.; Montesarchio, D.; Piccialli, G. *Tetrahedron* **2002,** *52*, 6697-6704.

23. Adinolfi, M.; Iadonisi, A.; Ravidà, A.; Schiattarella, M. *Tetrahedron Lett.***2003,** *44*, 7863-7866.

24. Valerio, S.; Iadonisi, A.; Adinolfi, M.; Ravidà, A. *J. Org. Chem.* **2007**, *72*, 6097-6106.

25. Pastore, A.; Adinolfi, M.; Iadonisi, A. *Eur. J. Org. Chem.* **2008**, 6206-6212.

26. Adinolfi, M.; Iadonisi, A.; Pezzella, A.; Ravidà, A. *Synlett* **2005**, 1848-1852.

27. Pezzella, A.; Iadonisi, A.; Valerio, S.; Panzella, L.; Napolitano, A.; Adinolfi, M.; d'Ischia, M. *J. Am. Chem. Soc.* **2009**, *131*, 15270-15275.

28. Panchadhayee, R.; Misra, A. K. *Synlett* **2010**, 1193-1196.

29. Yadav, J. S.; Reddy, S. B. V.; Premalatha, K.; Swamy, T. *Tetrahedron Lett.***2005,** *46*, 2687-2690.

30. Subba Reddy, B. V.; Brahma Reddy, B.; Raghavendra Rao, K. V.; Yadav, J. S. *Tetrahedron Lett.* **2010,** *51*, 5697-5700.

31. Deans, D. R.; Eaborn, C. *J. Chem. Soc.* **1954**, 3169-3173.

32. For the use of HI in ether cleavage: (a) Smith, C. A.; Grutzner, J. B. *J. Org. Chem*. **1976**, *41***,** 367-370. (b) Bhatt, V. M.; Kulkarni, S. U. *Synthesis* **1983**, 249-282.

33. For the use of TMSI in ether cleavage: Jung, M. E.; Lyster, M. A. *J. Org. Chem*. **1977**, *42***,** 3761-3764.

34. Yang, G. B.; Kong, F.-Z.; Zhou, S. H. *Carbohydr. Res.* **1991**, *211*, 179-182.

35. Per-*O*-benzylated saccharose, containing a more acid-labile glycosidic linkage, was actually decomposed upon exposure to iodine and Et_3SiH at low temperature.

36. Adinolfi, M.; Giacomini, D.; Iadonisi, A.; Quintavalla, A.; Valerio, S. *Eur. J. Org. Chem.* **2008**, 2895-2899.

37. In a reasonable hypothesis, the 5-OH furanoside intermediate could be involved in an intramolecular *trans*-acetalation with expulsion of allyl alcohol and generation of a 1,5-anhydro bicyclo structure.

38. Chervin, S. M.; Abada, P.; Koreeda, M. *Org. Lett.* **2000**, *2*, 369-372.

39. Gervay, J.; Hadd M. J. *Carbohydr. Res.* **1999**, *320*, 61-69.

40. Vickery, E. H.; Pahler, L. F.; Eisenbraun, E. J. *J. Org. Chem.* **1979**, *44*, 4444–4446. (b) Hendel, J. L.; Wang, J.-W.; Jackson, T. A.; Hardmeier, K.; De Los Santos, R.; Auzanneau, F.-I. *J. Org. Chem.* **2009**, *74*, 8321–8331.

41. Yu, B.; Sun, J. *Chem. Commun.* **2010**, 4668-4679.

42. Adinolfi, M.; Iadonisi, A.; Ravidà, A.; Valerio, S. *Tetrahedron Lett.* **2006,** *47*, 2595-2599.

43. (a) Kitov, P. I.; Shimizu, H.; Homans, S. W.; Bundle, D. R. *J. Am. Chem. Soc.* **2003**, *125*, 3284-3294. (b) Joosten, J. A. F.; Loimaranta, V.; Appeldoorn, C. C. M. Haataja, S.; Maate, F. A. E.; Liskamp, R. M. J.; Finne, J.; Pieters, R. J. *J. Med. Chem.* **2004,** *47,* 6499-6508. (c) Salminen, A.; Loimaranta, V.; Joosten, J. A. F.; Khan, A. S.: Hacker, J.; Pieters, R. J.; Finne, J. *J. Antimicrobial Chemotherapy* **2007**, *60*, 495–501.

44. For other examples of synthetic efforts towards analogue Lewis X mimics: (a) Tsukida, T.; Yoshida, M.; Kurokawa, K.; Nakai, Y.; Achiba, T.; Kiyoi, T.; Kondo, H. *J. Org. Chem.* **1997**, *62*, 6876–6881. (b) Asnani, A.; Auzanneau, F.-I. *Carbohydr. Res.* **2008**, *343*, 1653–1664.

45. Adinolfi, M.; Iadonisi, A.; Ravidà, A.; Schiattarella, M. *J. Org. Chem.* **2005**, *70*, 5316-5319.

46. Kharta, R. K. P.; Karkkainen, T. S.; Marsh, S. J.; Field, R. A. *Synlett* **2001,** 260-261.

47. Adinolfi, M.; Iadonisi, A.; Ravidà, A.; Schiattarella, M. *Synlett* **2004,** 275-278.

48. Vohra, Y.; Vasan, M.; Venot, A.; Boons, G.-J. *Org. Lett.* **2008**, *10*, 3247–3250.

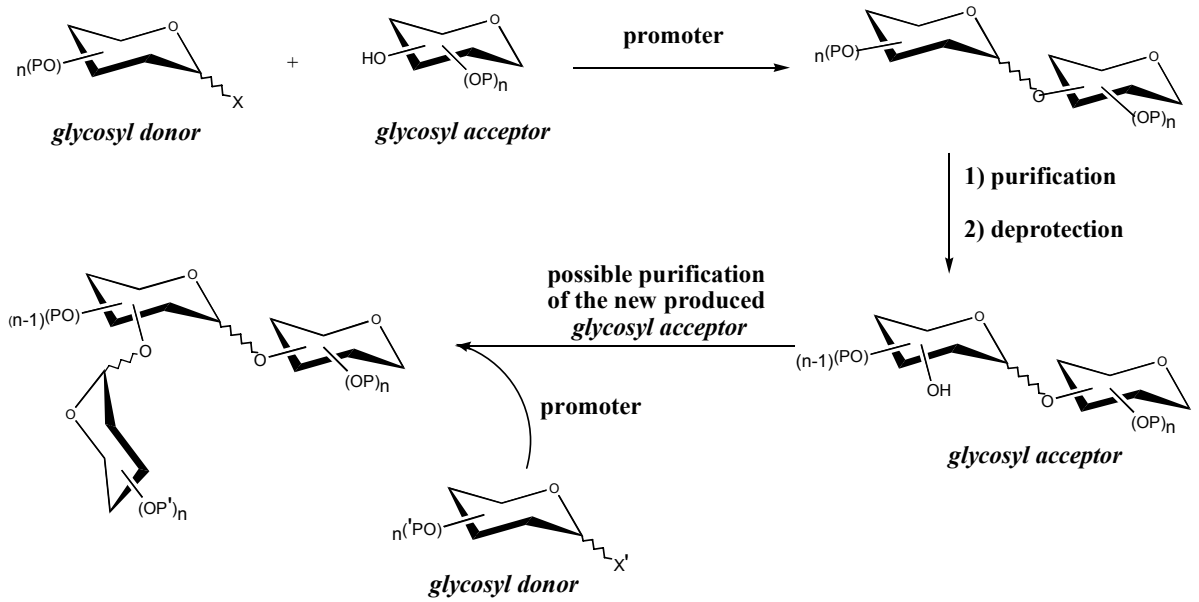
Chapter E

Sequential One-Pot Glycosidations Catalytically Promoted: an Unprecedented Strategy in Oligosaccharide Synthesis for the Straightforward Assemblage of the Antitumor PI-88 Pentasaccharide

Introduction

Over the last years the therapeutic impact of oligosaccharides has been widely recognized by the scientific community as demonstrated by the increasing number of biomedical applications[1] (such as the investigation of the role of carbohydrates in a immune response, pathogenesis and for the generation of carbohydrate-based drugs). Unfortunately, isolation of oligosaccharides from natural sources is very tedious because they are generally present as complex micro-heterogeneous mixtures. Hence, chemical synthesis constitutes the only prospect for building strictly homogeneous oligosaccharides of suitable complexity in the required amounts.

Oligosaccharide assembly can be achieved using both automated solid phase synthesis[2] and solution synthesis. The latter approach traditionally requires building of oligosaccharides through the initial preparation of suitable saccharidic precursors properly functionalized and their subsequent assembly through an appropriate sequence of glycosidation reactions alternated to protection/deprotection steps. These latter intermediate steps make the oligosaccharide synthesis more time consuming and increase both the number of chromatographical purifications and the overall cost of the global procedure (**Figure 1**).



X, X' = -F, -Cl, -Br, -I, -O-C(CCl_3)=NH, -O-C(CF_3)=NPh, -SR, -SAr, -SeR, -SeAr, -S(O)Ar, -O-P($OR)_2$, -O-P(O)($OR)_2$
P, P' = protecting groups

Figure 1 Example of a hypothetical linear oligosaccharidic synthesis.

Towards this goal, in the last decade solution synthesis of oligosaccharide has reached a remarkable stage of maturity thanks to the development of sequential one-pot multiglycosidation strategies allowing the construction of more glycosidic bonds in a single synthetic operation[3] (**Figure 2**). In this regard, several approaches have been usefully exploited. An option is represented by the use of the orthogonal strategy which exploits for each coupling the selective activation of one leaving group over another, the two groups being chemically different.[4] Another opportunity is offered by a chemoselective approach, which takes advantage of the feasible reactivity tuning of donors bearing similar anomeric groups by exploiting the arming-disarming[5] effect of the functional groups present on the saccharide scaffold. This latter concept has been broadly elaborated by Wong and co-workers who developed a computer-assisted protocol for choosing the best set of glycosyl donors to assemble a given target sequence.[6,7]

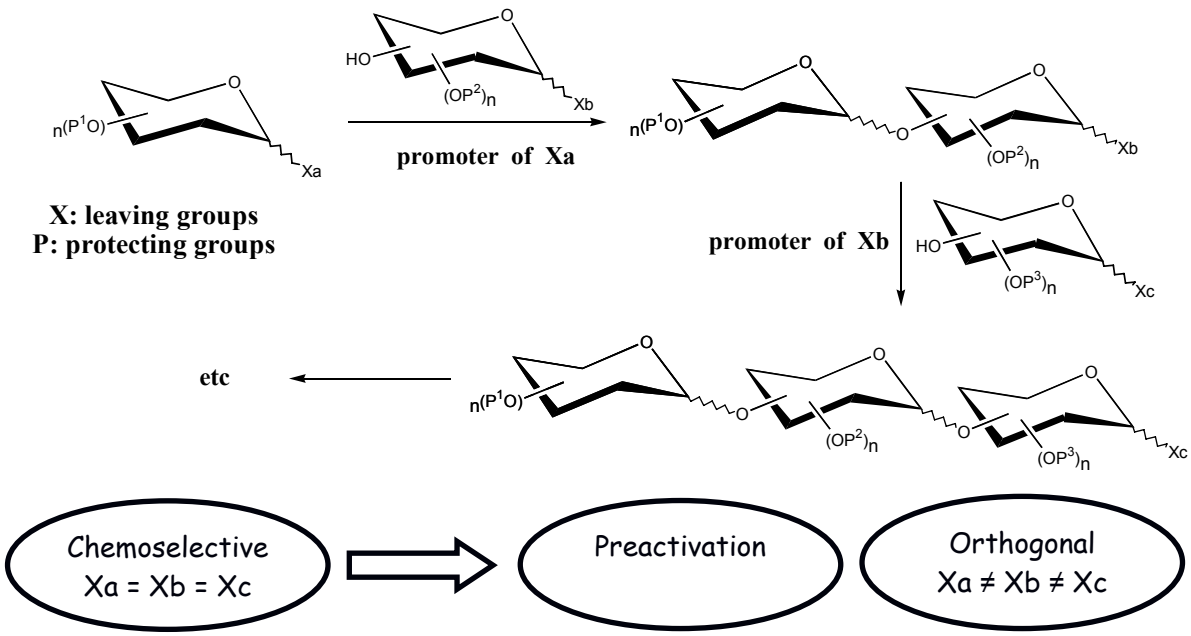


Figure 2 One-pot strategies of sequential multiple glycosydations**.**

Very recently, a special case of the chemoselective scheme has been proposed. It is based on a pre-activation stage for every coupling in which a thioglycoside donor is converted to a highly reactive glycosylating species at low temperature upon exposure to a suitable stochiometric promoter. Subsequent addition of a thioglycoside acceptor yields a glycosidation product which can be "in situ" pre-activated for a further elongation with a further acceptor.[8] This latter strategy is advantageous because it is independent of the relative reactivity of the employed donors (**Figure 3**).

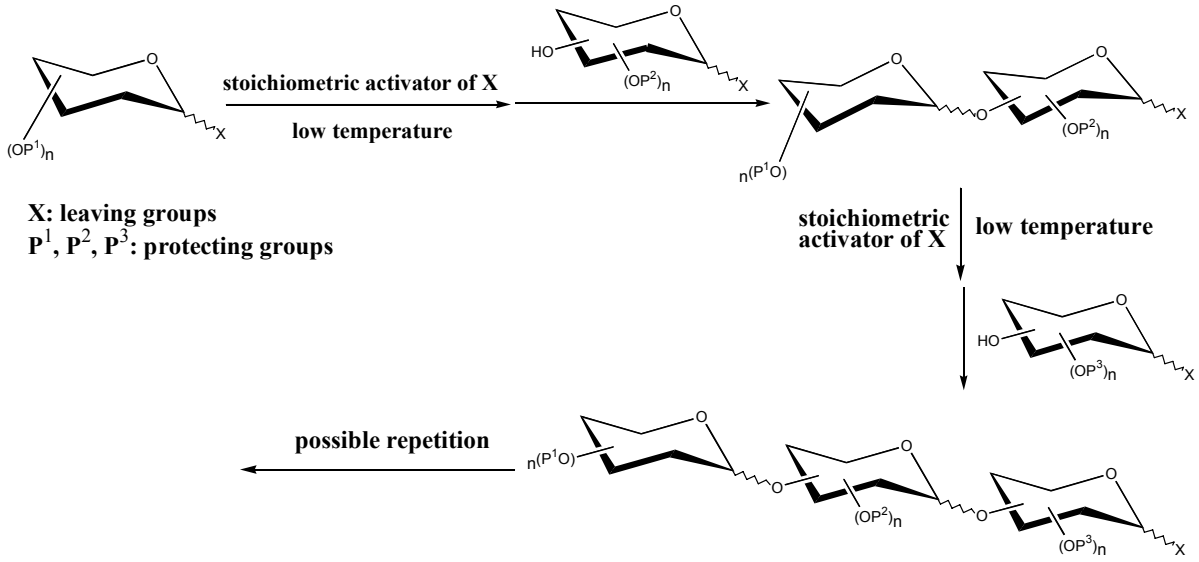


Figure 3 Sequential one-pot multiglycosidation strategy based on the preactivation.

A common drawback of all the one-pot sequential glycosidation procedures so far described is the required activation of glycosyl donors with stoichiometric or excess amounts of costly and/or sensitive reagents such as NIS, triflic anhydride, silver triflate, sterically encumbered pyridines.[3]

Recently, my research group has communicated the first examples of catalytic procedures for the sequential construction of two glycosidic bonds in a one-pot approach.[9] Such protocols were inspired by the recognition of the well differentiated activation conditions of similarly protected glycosyl- trichloroacetimidates[10] and (*N*-phenyl)trifluoroacetimidates[11] under the agency of catalytic ytterbium(III) triflate.[12,13] More recently, my research group has also disclosed that bismuth(III) triflate is a novel activator of glycosyl trihaloacetimidates endowed of exceptional reactivity so that reactions can be performed under relevantly milder conditions in terms of temperature and catalyst loading than when using $Yb(OTf)_3$.[14] The capability of $Bi(OTf)_3$ of promoting high yielding glycosidations in short times appeared well fitting with the attempts to develop ever more efficient catalytic multiglycosidation processes to achieve biologically useful oligosaccharides.

In this chapter, it was reported a work on the sequential one-pot glycosidations performed exclusively under catalytic activation that is a very straightforward and flexible approach for preparing the pentasaccharide component of the anti-tumour agent PI-88 (**Figure 4**). This drug is currently in phase-II clinical trial[15] and is constituted by a mixture of randomly sulfated tri-, tetra-, and penta-mannans bearing a phosphate functionality at the primary site of the non-reducing terminal residue. This phosphate can be replaced by a sulfate group without appreciable loss of biological activity.[16,17] The drug is obtained by the yeast *Pichia (Hansenula) holstii* NRRL Y-2448 as a mixture of phosphorylated mannans that are subsequently randomly sulfated via a chemical approach.[18]

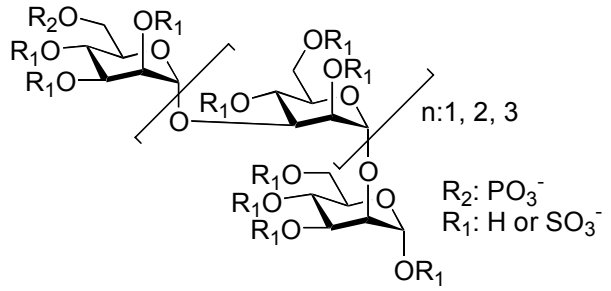


Figure 4 Components of PI-88.

Anti-tumor properties of PI-88 are believed to be connected with its ability to act as inhibitor of both heparanases and angiogenic growth factors[19] (**Figure 5**).

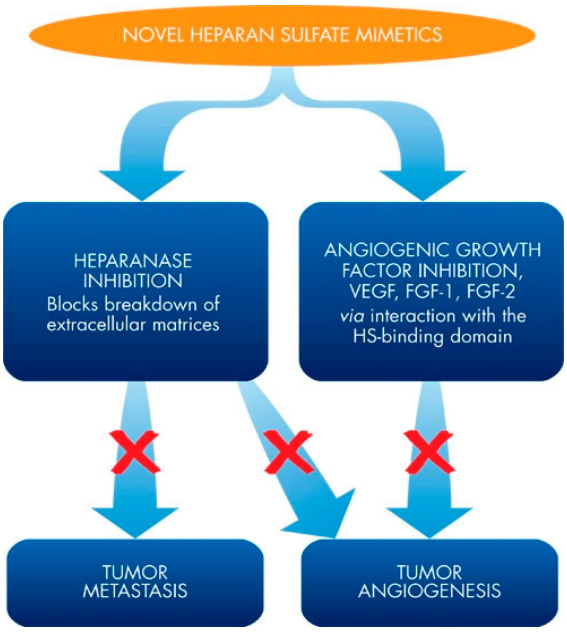


Figure 5

The pentasaccharide fraction is the most abundant and is considered the most active component of the drug. To date, only two examples of chemical syntheses of this pentasaccharide have been reported, including a very recent paper by Ferro and co-workers.[17,20] Both these schemes are providing good overall yields, but a large number of synthetic steps render them rather laborious (**Figure 6a** and **6b**).

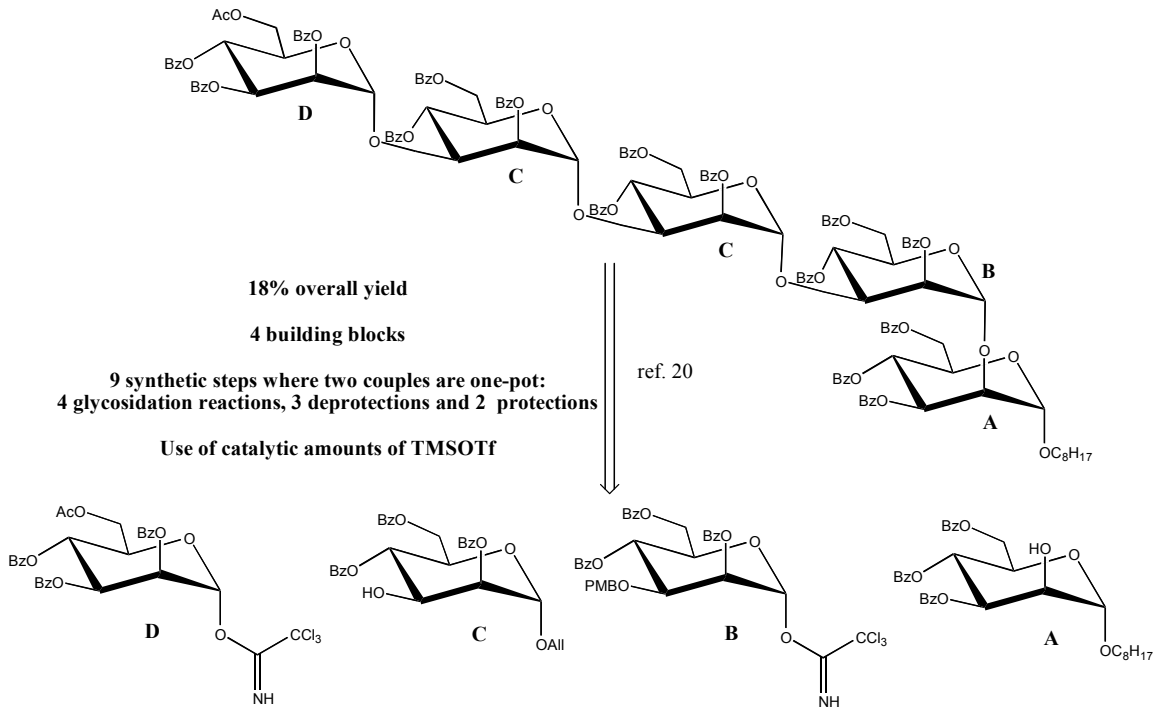


Figure 6a Synthesis of a 6^{V}-sulfated mannopentasaccharide analogue related to PI-88.

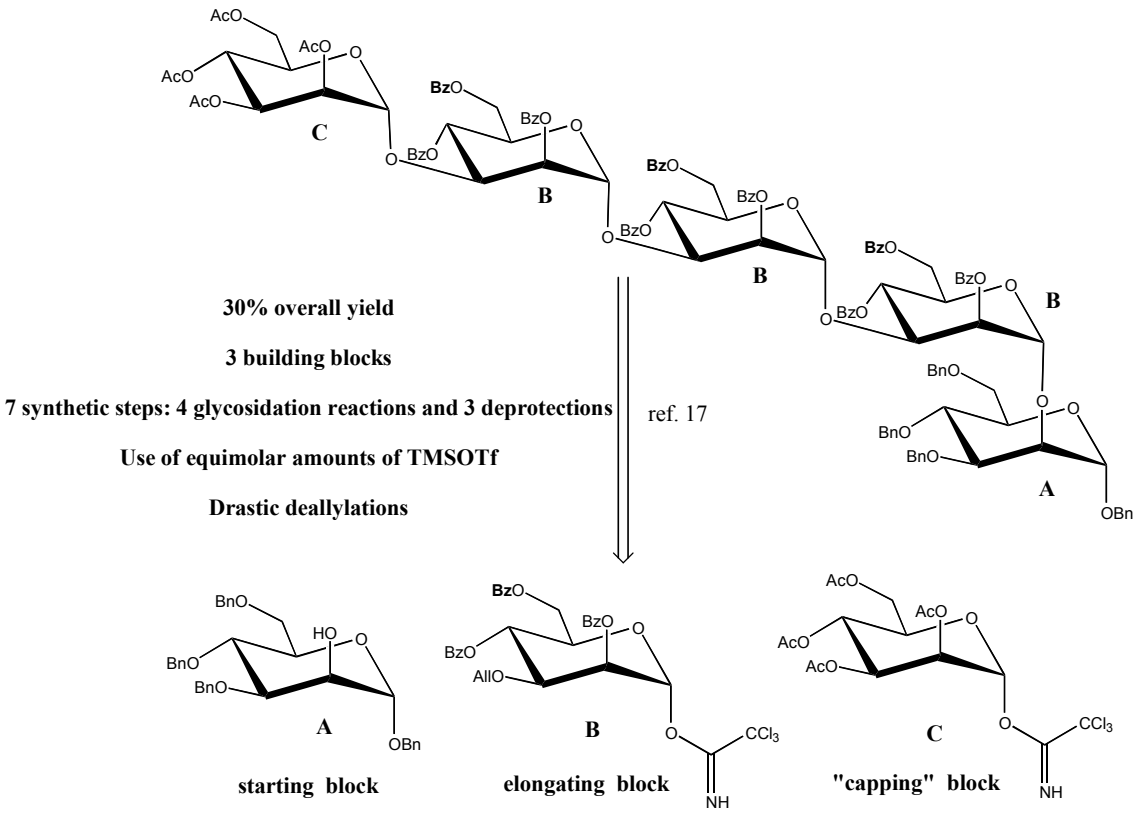
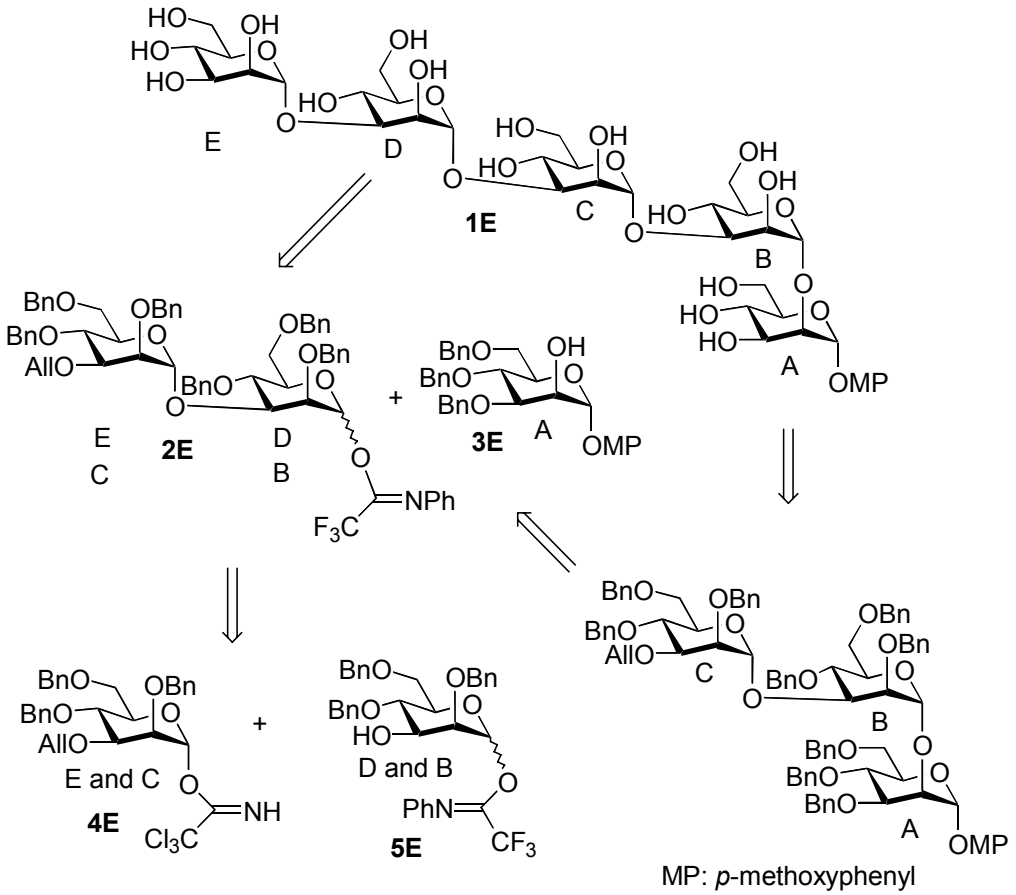


Figure 6b Synthesis and heparanase inhibitory activity of sulfated mannoligosaccharides related to the antiangiogenic agent PI-88.

Here it was reported the straightforward assemblage of the *p*-methoxyphenylpentamannoside of PI-88 **1E** (**Scheme 1**) by an alternative strategy based on only three steps (two one-pot multi-glycosidations and a deallylation intermediate step), and entailing only three monosaccharide building-blocks for the whole task.

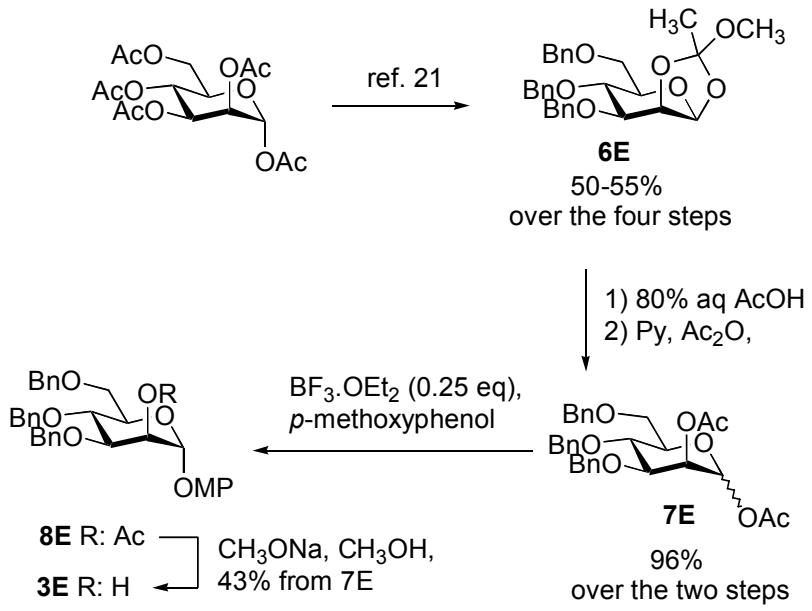
Results and discussion

The proposed strategy (**Scheme 1**) relies on the feasible "in-situ" generation of disaccharide **2E** as the precursor of both BC and DE fragments, whereas readily obtainable acceptor **3E** represents the precursor of the reducing terminus A. Disaccharide **2E** was expected to be accessible by the key chemoselective coupling of trichoroacetimidate donor **4E** and the partially protected trifluoroacetimidate **5E** acting as an acceptor at this stage.



Scheme 1 Retrosynthetic scheme of the PI-88 pentasaccharide.

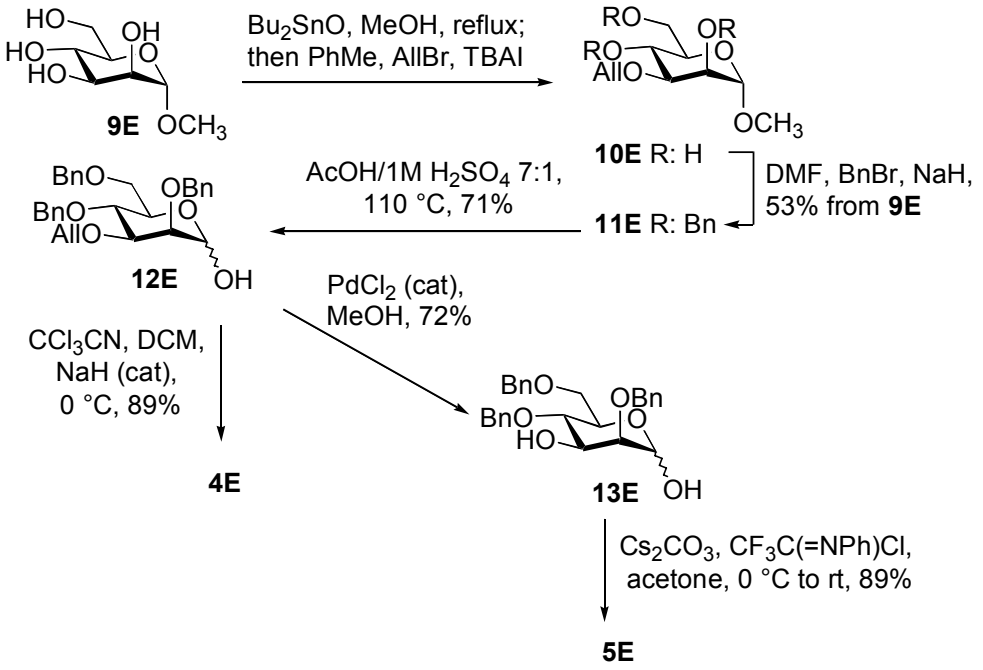
Acceptor **3E** was efficiently obtained starting from penta-*O*-acetyl-D-mannose (**Scheme 2**) which was initially converted into methyl orthoester **6E** through a rapid sequence of four reactions (anomeric iodination, 1,2-orthoesterification, de-*O*-acetylation and per-*O*-benzylation) and without any chromatographical purification of intermediates (50-55 overall yield).[21] Compound **6E** was submitted to sequential acid-mediated cyclic orthoester opening and acetylation to yield almost quantitatively the di-acetylated intermediate **7E**. This latter was in turn directly converted into the corresponding 4-*O*-methoxy phenyl glycoside **8E** under the agency of $BF_3{\cdot}OEt_2$ and then 2-*O*-deacetylated to yield the desired building block **3E**.



Scheme 2

Compounds **4E** and **5E** were prepared through synthetic pathways sharing a large number of steps (**Scheme 3**). Methyl mannoside **9E** was regioselectively 3-*O*-allylated via a stannylidene intermediate[22] and the resulting triol **10E** was then perbenzylated under standard conditions. Derivative **11E** was hydrolyzed under acidic conditions to yield hemiacetal **12E** which was the last common intermediate of the routes leading to **4E** and **5E**. The former was prepared in high yield (ca 90%) with only an additional standard 1-*O*-trichloroacetimidation step. Alternatively, **12E** was deallylated with $PdCl_2$ in methanol in 72% yield and the resulting diol **13E** was then selectively converted into trifluoroacetimidate **5E** (α:β ca 4:1) adopting Cs_2CO_3[13d] as the base.

During the course of this work, with the same sequence reported in **Scheme 3**, mannosyl donors **4E** and **5E** were synthesized starting from allyl α-D-mannopyranoside obtained by Fischer glycosidation of D-mannose under the agency of catalytic amounts (0.03 eq) of $Sc(OT)_3$. After the stage of anomeric hydrolysis of the 1-*O*-allylated analogue of **11E,** hemiacetal **12E** was obtained in lower yield (48% and 78% conversion) than when starting from **11E** thus methyl α-D-mannopyranoside was chosen instead of D-mannose as the starting material for the preparation of **4E** and **5E**. As it will be shown in **Chapter F**, commercially available **9E** will be used also for the synthesis of the precursors of the reducing terminus of other oligosaccharide of biological interest.

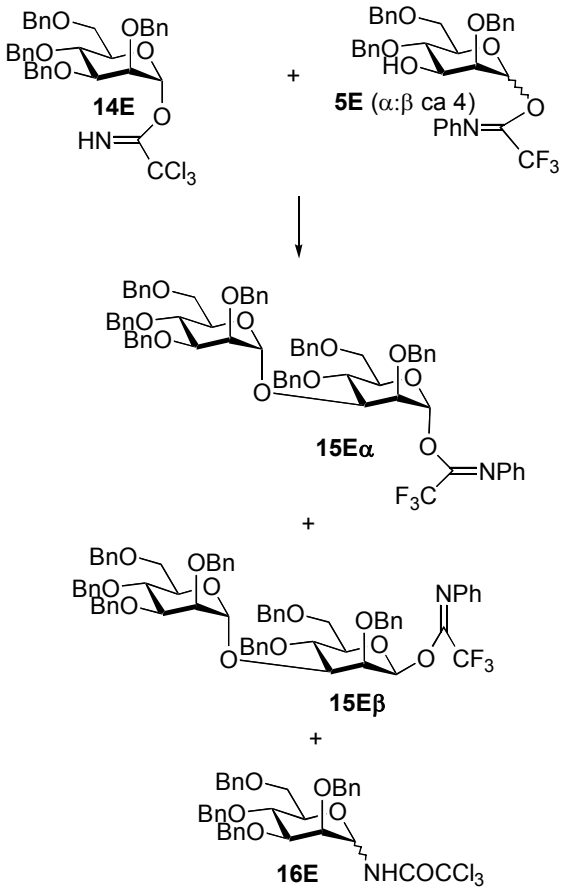


Scheme 3

As shown in the retrosynthetic scheme (**Scheme 1**), the successful assemblage of the target pentasaccharide is critically dependent on the coupling between the fully protected trichloroacetimidate **4E** and the partially protected trifluoroacetimidate **5E**. Indeed, this reaction should provide in high yield and stereocontrol the desired glycosidic bond while leaving intact the activatable trifluoroacetimidate functionality to allow the subsequent glycosidation. To optimize this delicate step, acceptor **5E** and the model trichloroacetimidate **14E**, easier to obtain than **4E**,[10] were coupled under a variety conditions aimed at achieving exclusive activation of the trichloroacetimidate component (**Scheme 4**). The reactions were quenched at low temperature with pyridine to minimize any deterioration of the trifluoroacetimidate functionality. After a preliminary screening, a toluene/diethyl ether mixture was found as the best serving reaction solvent. Reactions conducted under $Bi(OTf)_3$ activation at very low temperature produced the desired disaccharide trifluoroacetimidate **15Eα** in a satisfying isolated yield (**Table 1**, entries 4 and 6) together with minor amounts of the anomer **15Eβ** (equally useful for the purposes in the planned one-pot application). This latter could not be isolated pure being it co-eluted with the by-product **16E** derived from rearrangement of the trichloroacetimidate **14E**. To the best of our knowledge these are the first examples of isolated glycosylation products in which an anomeric (*N*-phenyl)trifluoroacetimidate group is designed to act as a temporary protecting group. With the same amount of $Bi(OTf)_3$ (0.05 eq), the reaction is influenced by variation of the eq ratio between **14E/5E**. In fact, if it decreases then yields of **15Eα** decrease dramatically (**Table 1**,

entry 8). Comparing entry 4 and 6, the yield of **15Eα** is slightly influenced by variation of the eq ratio between **14E/5E** and both the doubling of $Bi(OTf)_3$ amounts and the slight increase of the reaction temperature don't provide better results.

Interestingly, the milder promoter $Yb(OTf)_3$ furnished **15Eα** in a higher yield than $Bi(OTf)_3$ although a remarkably higher temperature (-10 °C vs -60 °C) to accomplish the reactions was required within comparable times (**Table 1**, entry 9).



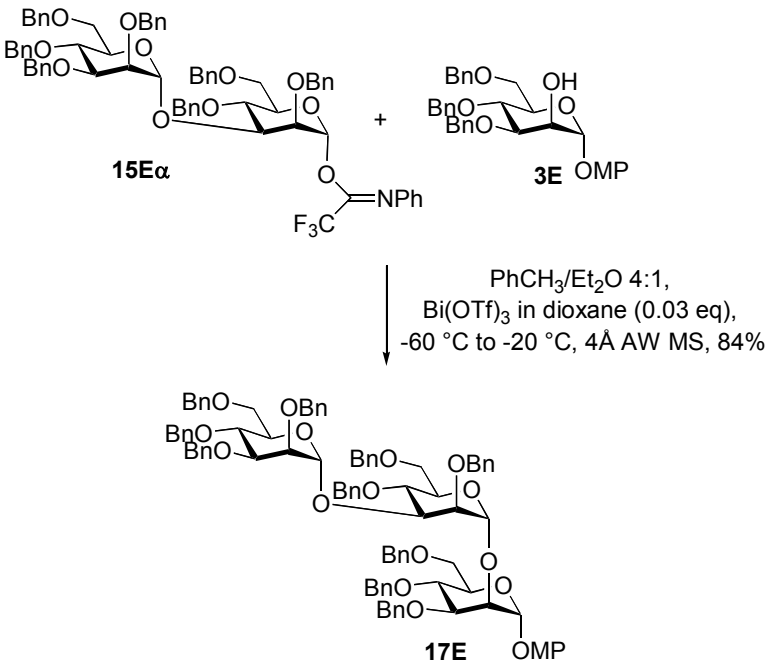
Scheme 4 Chemoselective coupling of **14E** and **5E**.

Table 1

Entry	Eq 14E/Eq 5E	Promoter (eq)	Solvent	T (°C)	Time (h)	Yield (%) of 15Eα[b]
1	1.7	$Bi(OTf)_3$ (0.015)	$PhCH_3$/DME 2:1	-70→0	2.5	25
2	1.5	$Bi(OTf)_3$ (0.015)	$PhCH_3/Et_2O$ 4:1	-70→0	3	28
3	1.6	$Bi(OTf)_3$ (0.035)	$PhCH_3$/DME 2:1	-70→rt	16	21
4	1.5	$Bi(OTf)_3$ (0.10)	$PhCH_3/Et_2O$ 4:1	-60→-55	0.5	42
5	1.5	$Bi(OTf)_3$ (0.10)	$PhCH_3$/DME 2:1	-60→-55	0.3	28
6	1.7	$Bi(OTf)_3$ (0.05)	$PhCH_3/Et_2O$ 4:1	-70→-60	1	47
7	1.4	$Bi(OTf)_3$ (0.05)	$PhCH_3/Et_2O$ 4:1	-60	1.2	27
8	0.7	$Bi(OTf)_3$ (0.05)	$PhCH_3/Et_2O$ 4:1	-70→-55	1.7	n.r.
9	1.4	$Yb(OTf)_3$ (0.03)	$PhCH_3/Et_2O$ 4:1	-10	0.5	58

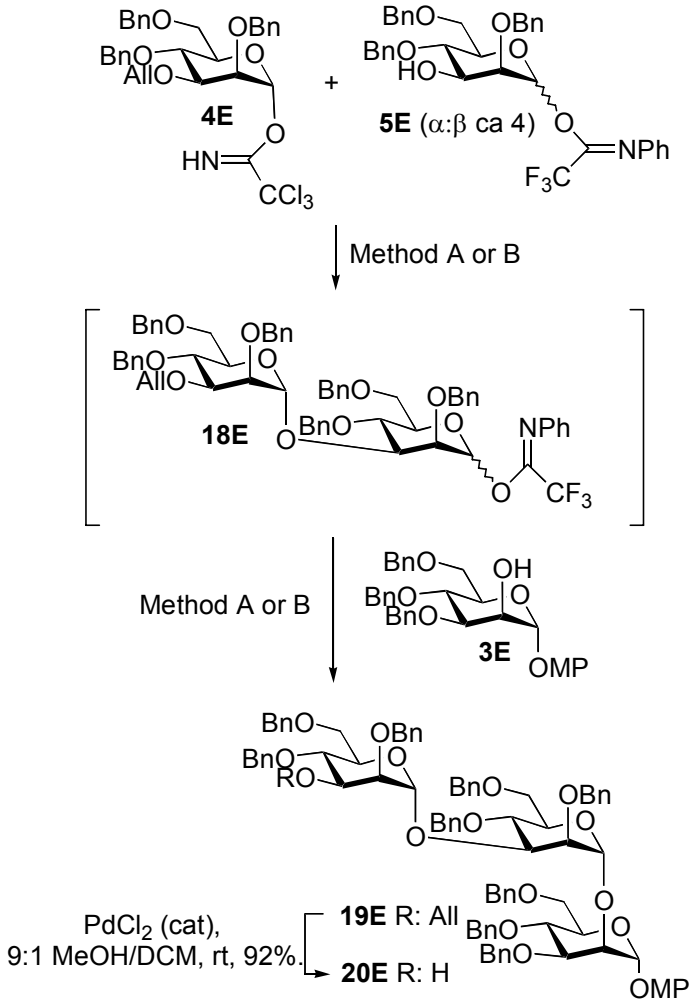
[a]General conditions: **14E** (0.7-1.7 eq), **5E** (1 eq), $PhCH_3$:Et_2O 4/1 or $PhCH_3$/DME 2:1, $Yb(OTf)_3$ or $Bi(OTf)_3$ (16-20 mg/mL in dioxane), 4Å AW MS. [b]Calculated with respect to the overall amount (α and β anomers) of **5E.**

The donor ability of disaccharide **15Eα** under $Bi(OTf)_3$ activation was then examined in the coupling with acceptor **3E**, quickly providing in excellent yield the trisaccharide **17E** (**Scheme 5**), which corresponds to the ABC fragment of the target pentasaccharide and is itself biologically interesting being related to an anti-allergenic sequence.[23]



Scheme 5

Having established the optimized conditions for generating and activating the requisite mannose disaccharide trifluoroacetimidate, their application was targeted towards the assemblage of the desired pentasaccharide via sequences of one-pot double glycosidations.

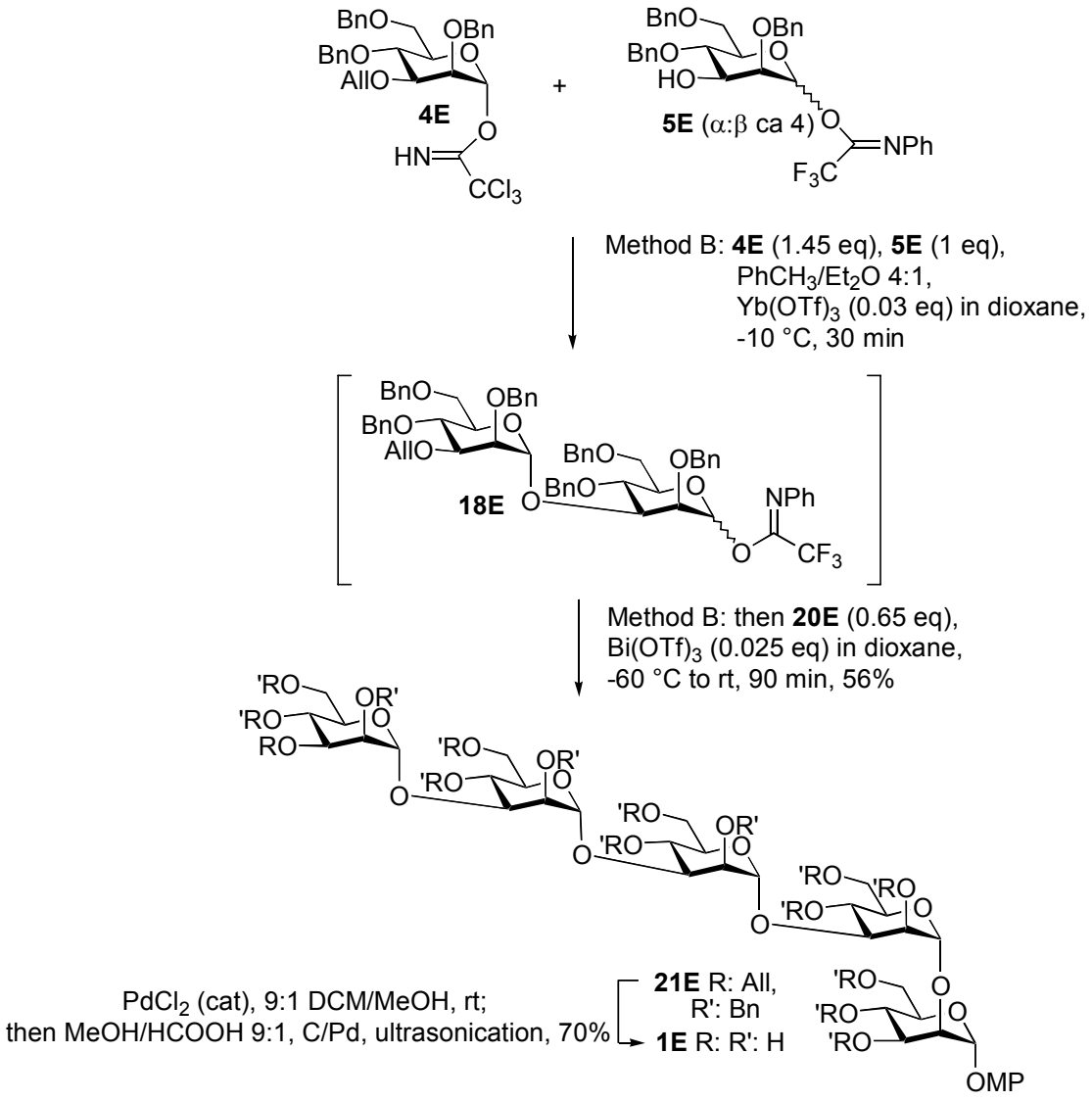


Scheme 6

Method A: **4E** (1.3-1.5 eq), **5E** (1 eq), $PhCH_3/Et_2O$ 4:1, $Bi(OTf)_3$ (0.05 eq) in dioxane, -70 °C to -60 °C, 45 min; then **3E** (1-1.3 eq), -60 °C to 0°C, 90 min, 43-46 %. Method B: **4E** (1.2 eq), **5E** (1 eq), $PhCH_3/Et_2O$ 4:1, $Yb(OTf)_3$ (0.03 eq) in dioxane, -10 °C, 30 min; then **3E** (0.8 eq), $Bi(OTf)_3$ (0.025 eq) in dioxane, -60 °C to 10 °C, 90 min, 60%.

The extensible precursor **19E** of the ABC fragment was prepared by initial coupling of **5E** and the 3-*O*-allylated trichloroacetimidate **4E**, the subsequent addition of acceptor **3E** to the mixture, and the adjustment of the experimental conditions for activating the trifluroacetimidate leaving group (**Scheme 6**). The one-pot synthesis was examined by using either $Bi(OTf)_3$ or $Yb(OTf)_3$ for the initial coupling. In the former case (**Scheme 6**, Method A), the first glycosidation step occurred at a very low temperature (from -70 to -60 °C) and the second coupling was accomplished without any further amount of promoter by the simple addition of acceptor **3E** and the spontaneous warming of the mixture. Alternatively (**Scheme 6**, Method B), $Yb(OTf)_3$ promoted the first coupling between **4E** and **5E** at -10 °C for 30 min

then, after cooling to -60°C, acceptor **3E** and $Bi(OTf)_3$ (0.03 eq) were sequentially added and the mixture was allowed to warm spontaneously. As expected from the results of preliminary experiments shown on **Table 1**, use of a different promoter for each glycosidation (Method B) provided an improved yield, the results being in any way quite satisfying by the means of both methods (yields in the range of 43-60 %). It's worthy of note that in both cases a very low amount of promoter(s) was needed for accomplishing the sequential double glycosidation, and the whole process took less than three hours, with a sensible acceleration in comparison with the previously reported catalytic procedure based on the sole $Yb(OTf)_3$.[8] Trisaccharide **19E** was smoothly deallylated to yield **20E** (**Scheme 6**), the requisite acceptor for the final one-pot sequence leading to pentasaccharide **21E**. Following the procedure that best served for **19E** (Method B, **Scheme 6**), **18E** was transiently formed from **4E** and **5E** under the agency of $Yb(OTf)_3$, and then coupled with **20E** in the presence of $Bi(OTf)_3$ to give **21E** in a gratifying yield of 56% (**Scheme 7**).



Scheme 7

Despite the structural changes in the final acceptor (**20E** rather than **3E**), the yield of this sequence was somewhat similar to that leading to trisaccharide **19E**. Pentasaccharide **21E** was deallylated and debenzylated under standard conditions to yield the free pentasaccharide **1E** which can be submitted to the procedure of random sulfation. On the other hand, the presence in **21E** of differentiated protecting groups (allyl, benzyls and an anomeric 4-methoxy-phenyl group) renders the obtained pentasaccharide amenable of further structural elaborations.

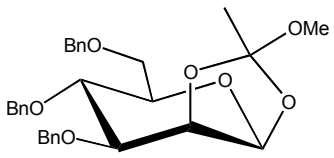
Conclusions

In conclusion, in this chapter it has shown the notable applicative potential of one-pot glycosidation of oligosaccharides conducted under exclusively catalytic conditions of activation, the pentasaccharide component of the drug PI-88 being rapidly accessed through a reduced number of synthetic steps and resorting to only three easily obtained D-mannose building-blocks. Notably, inclusion of $Bi(OTf)_3$ in the activation system allows the one-pot glycosidation sequences to be accomplished in short times and high yields. Additionally, very low amounts of shelf-stable promoter(s) (about 0.10 eq) are sufficient for the assemblage of the overall sequence, which entails the construction of four glycosidic bonds. It's also worthy of note that some model coupling experiments have shown that the trifluoroacetimidate anomeric group can play the role of a temporary anomeric protecting group in sequential multiglycosidation steps. Feasible access to a biological important target establishes a conceptually novel strategy where the catalytic activation of all sequential glycosidation steps allows to overcome important drawbacks of the current strategies such as the use of costly and/or sensitive stoichiometric promoters and the production of higher amounts of side-products.

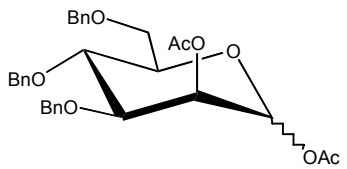
Experimental section

General methods

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (internal standard, for ^{1}H: $CHCl_3$ at δ 7.26; for ^{13}C: $CDCl_3$ at δ 77.0) or D_2O (internal standard, for ^{1}H: HDO at δ 4.80, for ^{13}C CH_3 of acetone at δ 31.5). ^{1}H NMR assignments were based on homo-decoupling experiments. MALDI-MS spectra were recorded in the positive mode: compounds were dissolved in acetonitrile (or water for compound **1E**) at a concentration of 0.1 mg/mL and one microliter of these solutions were mixed with one microliter of a 20 mg/mL solution of 2,5-dihydroxybenzoic acid in 7:3 CH_3CN/H_2O or, in the case of trifluoroacetimidate derivatives, with a 10 mg/mL solution of trihyroxyacetophenone in 1:1 MeOH/H_2O. Analytical thin layer chromatography (TLC) was performed on aluminium plates pre-coated with Silica Gel 60 F_{254} as the adsorbent. The plates were developed with 5% H_2SO_4 ethanolic solution and then heating to 130°C. Column chromatography was performed on silica gel (63-200 mesh). Glycosidations were performed with commercial anhydrous solvents. Ytterbium(III) and bismuth(III) triflate were coevaporated three times in toluene and dried under vacuum for 45-60 minutes before use in glycosidations.

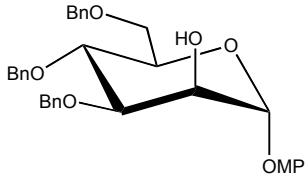


3,4,6-Tri-*O*-benzyl-1,2-*O*-(1-methoxyethylidene)-β-D-mannopyranose (exo-orthoester) (6E). ^{1}H NMR ($CDCl_3$, 200 MHz) δ = 7.50-7.10 (aromatic protons), 5.33 (1H, d, $J_{1,2}$ = 2.4 Hz, H-1), 4.92-4.56 (6H, 3 x AB, 3 x benzyl CH_2), 4.39 (1H, dd, $J_{2,3}$ = 3.8 Hz, H-2), 3.93 (1H, t, J = 9.2 Hz, H-4), 3.82-3.62 (3H, m, H-3, H-6a, H-6b), 3.45-3.34 (1H, m, H-5), 3.28 (3H, s, -OCH_3), 1.74 (3H, s, -CH_3). ^{13}C NMR ($CDCl_3$, 50 MHz) δ 138.0, 137.7, 136.4, 128.3, 128.2, 128.1, 127.8, 127.6, 127.3, 127.2, 126.7, 120.0, 97.4, 78.8, 75.0, 74.0, 73.9, 73.1, 72.1, 68.8, 64.7, 49.5, 24.3.

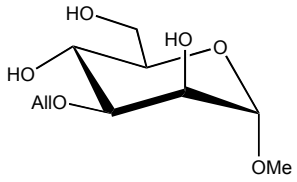


1,2-Di-*O*-acetyl-3,4,6-tri-*O*-benzyl-α,β-D-mannopyranoside (7E). Orthoester **6E** (3.895 g, 7.9 mmol) was dissolved at rt in 80% aq AcOH (20 mL). After 30 minutes, the mixture was diluted with DCM and the organic phase washed with water, and then with aq Na_2CO_3. The aq phases were then re-extracted with DCM and the collected organic phases dried and concentrated under vacuum. The residue was dissolved in pyridine

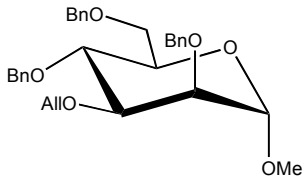
(5 mL) and acetic anhydride (2.5 mL). After 2.5 hours the mixture was treated with MeOH and diluted with DCM. The organic phase was washed with water, dried and concentrated to yield syrupy **7E** in a satisfying purity (3.960 g, α/β ca 4, yield 96%) to be directly submitted to the following step. ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.50-7.00 (aromatic protons), 6.15 (1H, d, $J_{1,2}$ = 2.1 Hz, H-1), 5.39 (1H, bd, H-2), 4.90-4.50 (6H, 3 x AB, 3 x benzyl CH_2), 4.00 (1H, bd, $J_{3,4}$ = 9.3 Hz, H-3), 3.95-3.75 (3H, H-5, H-6a, H-6b), 3.72 (1H, t, $J_{4,5}$ = 9.3 Hz, H-4), 2.17, 2.08 (6H, 2 x s, 2 x –$COCH_3$). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 170.8, 170.0, 138.1 (x2), 137.6, 128.9-127.5, 91.3, 75.3, 73.7, 73.6, 73.5, 71.9, 68.5, 67.5, 20.9. Anal. Calcd. for $C_{31}H_{34}O_8$: C, 69.65, H, 6.41. Found: C, 69.93; H, 6.52.



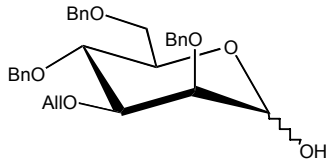
***p*-Methoxyphenyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (3E).** To a solution of compound **7E** (1.234 g, 2.31 mmol), and *p*-methoxyphenol (436 mg, 3.51 mmol) in dry DCM (7 mL) freshly activated 4Å molecular sieves and $BF_3.OEt_2$ (75 μL, 0.59 mmol) were added at 0°C under argon. After removing the ice-bath, the mixture was stirred at room temperature for 3 hours and then pyridine (6 drops) was added to quench the reaction. The mixture was concentrated *in vacuo* and the residue submitted to silica gel flash-chromatography to yield **8E** slightly contaminated with un-reacted *p*-methoxyphenol. To this impure material dissolved in methanol (4 mL), was added drop-wise a solution of MeONa (2M in MeOH) until completion of the reaction (TLC). The mixture was then diluted with DCM, and washed with 0.1 M aq NaOH and water. Aqueous phases were re-extracted with DCM and the collected organic phases were dried and concentrated. The residue was applied to a short silica gel column eluted with petroleum ether/acetone 6:4 to yield **3E** as a yellow oil (556 mg, 43% over two steps). $[\alpha]^{25}_{D}$ + 86.4° (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.44-6.70 (aromatic protons), 5.50 (1H, d, $J_{1,2}$ = 1.8 Hz, H-1), 4.84-4.40 (6H, 3 x AB, 3 x benzyl CH_2), 4.19 (1H, m, H-2), 4.06 (1H, dd, $J_{2,3}$ = 3.3 Hz, H-3), 3.94 (1H, t, $J_{3,4}$ = $J_{4,5}$ = 9.9 Hz, H-4), 3.91-3.84 (1H, m, H-5), 3.74 (1H, dd, $J_{5,6a}$ = 4.2 Hz, $J_{6a,6b}$ = 10.8 Hz, H-6a), 3.73 (3H, s, -OCH_3), 3.63 (1H, dd, $J_{5,6b}$ = 1.5 Hz, H-6b), 2.55 (1H, d, $J_{2,OH}$ = 2.4 Hz, 2-OH). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 154.9, 150.0, 138.3, 138.2, 137.8, 128.4-127.0, 117.7, 114.5, 98.2, 79.9, 75.0, 74.1, 73.2, 72.0, 71.5, 68.8, 68.2, 55.4. MALDI-MS: $[M + Na]^+$ calcd 579.24, found 579.32. Anal. Calcd. for $C_{34}H_{36}O_7$: C, 73.36, H, 6.52. Found: C, 73.25; H, 6.55.



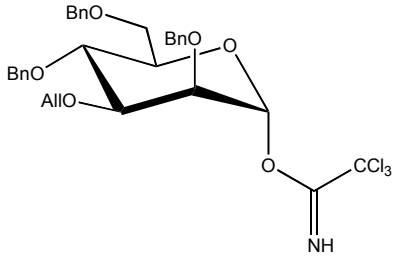
Methyl 3-*O*-allyl-α-D-mannopyranoside (10E). Methyl α-mannopyranoside **9E** (3.118 g, 16.1 mmol) and Bu_2SnO (4.402 g, 17.7 mmol) were refluxed in MeOH (80 mL) for 2 hours. The obtained solution was evaporated under vacuum. To the residue suspended in toluene (100 mL), allyl bromide (14.0 mL, 165 mmol) and TBAI (5.94 g, 16.1 mmol) were sequentially added. The mixture was kept under stirring at 65-70 °C for 20 hours, and concentrated. Silica-gel flash-chromatography of the residue (eluent: ethyl acetate/petroleum ether from 7:3 to 8:2) yielded **10E** slightly contaminated with tetrabutylammonium salts (estimated yield 65-70 % on the base of NMR integrations). The product thus obtained was directly submitted to the subsequent step. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.05-5.85 (1H, m, -C*H*=CH_2), 5.29 (1H, dq, J = 1.4 and 18.8 Hz, -CH=$CH_{cis}H_{trans}$), 5.17 (1H, bd, J = 10.4 Hz, -CH=C$H_{cis}H_{trans}$), 4.73 (1H, bs, H-1), 4.25-3.70 (6H), 3.65-3.40 (2H), 3.31 (3H, s, -OCH_3).



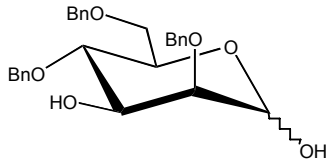
Methyl 3-*O*-allyl-2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (11E). To a solution of compound **10E** (estimated mass ca 2.5 g, ca 11 mmol) in dry DMF (13 mL) were sequentially added at 0°C benzyl bromide (6.4 mL, 54 mmol) and sodium hydride (60% in oil, 1.75 g, 73 mmol). The mixture was allowed to warm to rt, and after 3 hours MeOH (ca 1 mL) was added. The mixture was diluted with DCM and the organic phase washed with water. The aq phase was re-extracted with DCM and the collected organic phases were dried with anhydrous Na_2SO_4 and concentrated *in vacuo* to give a residue which was purified by silica gel flash-chromatography (eluent: petroleum ether/ethyl acetate 85:15) to yield **11E** as an oil (5.465 g, 53% over two steps). $[\alpha]^{25}_D$ + 29.4° (c 1.0, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.05-5.85 (1H, m, -CH_2C*H*=CH_2), 5.34 (1H, dq, J = 1.6 and 17.4 Hz, -CH=$CH_{cis}H_{trans}$), 5.17 (1H, dq, J = 10.2 Hz, -CH=C$H_{cis}H_{trans}$), 4.78 (1H, bs, H-1), 4.93-4.50 (6H, 3 x AB, benzyl CH_2), 4.15-4.05 (2H, m, -OCH_2CH=CH_2), 4.00-3.85 (2H), 3.85-3.70 (4H), 3.34 (3H, s, -OCH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.5, 138.4 (x2), 134.9, 128.2-127.5, 116.5, 99.0, 79.8, 75.0, 74.8, 74.5, 73.3, 72.5, 71.6, 71.0, 69.3, 54.7. MALDI-MS: $[M + Na]^+$ calcd 527.24, found 527.30. Anal. Calcd. for $C_{31}H_{36}O_6$: C, 73.79, H, 7.19. Found: C, 73.65; H, 7.23.



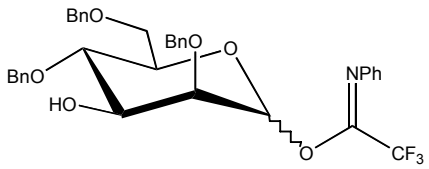
3-*O*-Allyl-2,4,6-tri-*O*-benzyl-D-mannopyranose (12E). A solution of **11E** (446 mg, 0.88 mmol) in 7:1 AcOH/1M H_2SO_4 (5.4 mL) was heated at 110 °C for 70 minutes. The mixture was then diluted with DCM, and the organic phase was washed with water. The aq phase was re-extracted with DCM. Collected organic phases were washed with aq sodium carbonate and concentrated. The residue was purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate from 3:1 to 7:3) to yield **12E** as a yellow oil (434 mg, α/β ca 7:1, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.05-5.85 (1H, m, -C*H*=CH_2), 5.34 (1H, bd, J = 17.4 Hz, CH_2CH=$CH_{cis}H_{trans}$), 5.25 (1H, bs, H-1), 5.19 (1H, bd, J = 10.2 Hz, CH=C$H_{cis}H_{trans}$), 4.91-4.48 (6H, 3 x AB, benzyl CH_2), 4.15-4.00 (3H), 3.95-3.60 (5H), 3.24 (bs, 1-OH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 138.3 (x2), 137.8, 134.8, 128.2-127.5, 116.4, 92.4, 79.3, 75.0, 74.9, 73.0, 72.4, 71.2, 70.9, 70.8, 69.5. MALDI-MS: $[M + Na]^+$ calcd 513.23, found 513.18. Anal. Calcd. for $C_{30}H_{34}O_6$: C, 73.45, H, 6.99. Found: C, 73.28; H, 7.04.



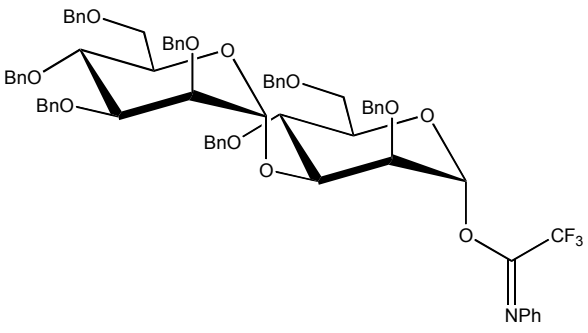
Trichloroacetimidoyl 3-*O*-allyl-2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (4E). To a solution of **12E** (488 mg, 0.99 mmol) in DCM (5 mL) were sequentially added at 0°C trichloroacetonitrile (400 μL, 4 mmol) and sodium hydride (60% in oil, 10 mg, 0.25 mmol). The mixture was allowed to warm to rt and concentrated after 40 minutes. The residue was chromatographed on neutral alumina (Brockman grade 2, eluent: petroleum ether/ethyl acetate 9:1 with two drops of pyridine for every 100 mL of eluent) to yield **4E** as an oil (560 mg, yield 89%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 8.69 (1H, s, -NH), 7.53-7.20 (aromatic protons), 6.52 (1H, s, H-1), 6.04-5.91 (1H, m, -OCH_2-C*H*=CH_2), 5.37 (1H, dd, J = 1.2 and 17.4 Hz, CH=$CH_{cis}H_{trans}$), 5.24 (1H, dd, J = 10.5 Hz, –OCH_2-CH=C$H_{cis}H_{trans}$), 4.99-4.57 (6H, 3 x AB, 3 x benzyl CH_2), 4.23 (1H, t, J = 9.6 Hz, H-4), 4.19-4.07 (3H, m, H-5 and -OCH_2CH=CH_2), 4.06 (1H, dd, $J_{1,2}$ = 1.8 Hz, $J_{2,3}$ = 2.7 Hz, H-2), 3.97 (1H, dd, H-3), 3.91 (1H, dd, $J_{5,6a}$ = 4.5 Hz, $J_{6a,6b}$ = 11.4 Hz, H-6a), 3.81 (1H, bd, H-6b). ^{13} C NMR ($CDCl_3$, 75 MHz) δ = 160.0, 138.0 (x2), 137.6, 134.4, 128.1-127.1, 116.8, 95.9, 90.7, 78.7, 74.9, 74.5, 73.7, 73.0 (x2), 72.3, 70.8, 68.4. Anal. Calcd. for $C_{32}H_{34}Cl_3NO_6$: C, 60.53, H, 5.40. Found: C, 60.41; H, 5.46.



2,4,6-Tri-*O*-benzyl-D-mannopyranose (13E). To a solution of **12E** (307 mg, 0.63 mmol) in methanol (2 mL) was added at rt palladium chloride (15 mg, 0.085 mmol). The mixture was stirred overnight and then concentrated under vacuum. The residue was then filtered through a short plug of silica gel (eluent DCM/MeOH 95:5), concentrated, and purified by silica-gel flash chromatography (eluent: petroleum ether/ ethyl acetate from 7:3 to 6:4) to provide diol **13E** as an oil (α:β ca 9:1, 205 mg, yield 72%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.5-7.10 (aromatic protons), 5.31 (1H, s, H-1), 4.89-4.51 (6H, 3 x AB, 3 x benzyl CH_2), 4.10-4.00 (2H, m, H-3, H-5), 3.84-3.64 (3H, m, H-2, H-6a, H-6b), 3.60 (1H, t, $J_{3,4} = J_{4,5} = 9.6$ Hz, H-4), 2.92 (1-OH). ^{13}C NMR ($CDCl_3$, 75 MHz) 138.5, 137.9 (x2), 128.4-127.6, 91.5, 79.0, 78.6, 74.8, 73.4, 72.9, 71.5, 70.6, 69.7. Anal. Calcd. for $C_{27}H_{30}O_6$: C, 71.98, H, 6.71. Found: C, 71.85; H, 6.77.

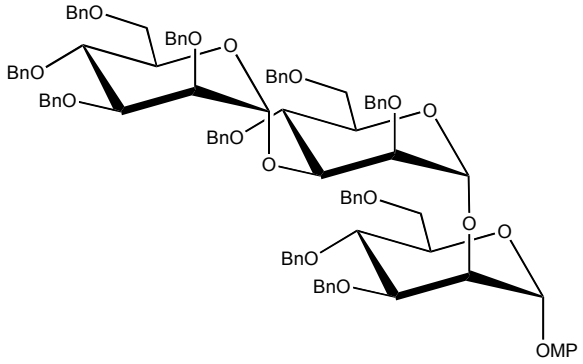


(*N*-Phenyl)trifluoroacetimidoyl 2,4,6-tri-*O*-benzyl-α,β-D-mannopyranoside (5E). To a solution of diol **13E** (399 mg, 0.89 mmol) in acetone (3 mL) were sequentially added at 0 °C Cs_2CO_3 (324 mg, 0.99 mmol) and (*N*-phenyl)trifluoroacetimidoyl chloride (220 μL, 1.8 mmol). The mixture was allowed to warm to rt and after two hours concentrated under vacuum. The residue was purified by chromatography on neutral alumina (Brockman grade 2, eluent: petroleum ether/ethyl acetate 9:1 with two drops of pyridine for every 100 mL of eluent) to yield **5E** as a yellow oil (anomeric mixture α/β ca 4:1, 492 mg, yield 89%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.50-6.81 (aromatic protons), 6.42 (1H, bs, H-1), 4.92-4.56 (6H, 3 x AB, 3 x benzyl CH_2), 4.08 (1H, m, H-3), 4.03-3.77 (5H), 2.75 (1H, d, $J_{3,OH} = 8.4$ Hz, 3-OH). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 143.3, 138.0 (x2), 137.0, 129.0-127.7, 127.4, 124.3, 119.3, 94.5, 75.9, 75.5, 74.9, 73.8, 73.3, 72.7, 71.2, 68.5. Anal. Calcd. for $C_{35}H_{34}F_3NO_6$: C, 67.62, H, 5.51. Found: C, 67.50; H, 5.59.



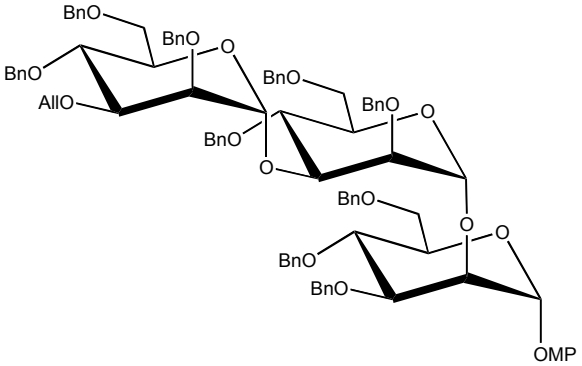
(*N*-Phenyl)trifluoroacetimidoyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (15Eα). Trichloroacetimidate **14E** (26 mg, 0.038 mmol) and trifluoroacetimidate **5E** (17 mg,

0.027 mmol) were coevaporated three times with toluene (3 x 0.5 mL) and dried under vacuum. After adding 4Å AW 300 MS, the mixture was dissolved with 4:1 toluene/Et_2O (1 mL) and cooled to -10 °C. After stirring for ca 15 min, a solution of $Yb(OTf)_3$ in dioxane (20 mg/mL, 25 μL, 8.1 μmol) was added and after 30 min the reaction was quenched at the same temperature with pyridine. The mixture was filtered on a short plug of neutral alumina and concentrated. The residue was chromatographed on neutral alumina (Brockman grade 2, eluent: petroleum ether/ethyl acetate 85:15 with two drops of pyridine for every 100 mL) to yield **15Eα** as an oil (18 mg, yield 58%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ = 7.60-6.75 (aromatic protons), 6.25 (1H, bs, H-1), 5.25 (1H, s, H-1′), 4.90-4.46 (14H, 7 x AB, 7 x benzyl CH_2), 4.15 (1H, dd, H-3), 3.94 (1H, d, $J_{2,3}$ = 3.3 Hz, H-2), 3.77 (1H, bd, H-2′), 4.20-3.60 (9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ = 143.4, 138.7, 138.4, 138.2, 138.1, 138.0, 137.5, 129.3-119.4, 100.1, 94.7, 79.7, 75.8, 75.5, 74.9, 74.7, 74.5, 74.1, 73.39, 73.38, 72.7, 72.4, 72.2, 69.3, 68.6. MALDI-MS: $[M + Na]^+$ calcd 1166.46, found 1166.70. Anal. Calcd. for $C_{69}H_{68}F_3NO_{11}$: C, 72.42, H, 5.99. Found: C, 72.40; H, 6.07.

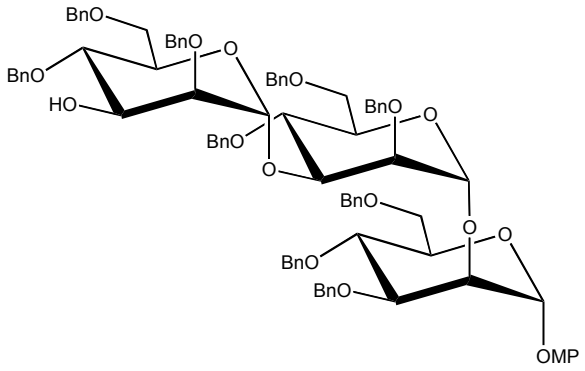


***p*-Methoxyphenyl 2,3,4,6-tetra-*O*-benzyl-α-D-mannopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-mannopyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (17E).** Disaccharide donor **15Eα** (25 mg, 0.022 mmol) and acceptor **3E** (9 mg, 0.017 mmol) were co-evaporated three times with toluene (3 x 0.5 mL) and dried under vacuum. After adding 4Å AW 300 MS, the mixture was dissolved under argon with 4:1 toluene/Et_2O (0.7 mL), cooled to -60 °C, and stirred for 15 min. A solution of $Bi(OTf)_3$ in dioxane (20 mg/mL, 17 μL, 0.5 μmol) was then added, and after stirring for 20 min at -60 °C, the temperature was allowed to raise up to -20 °C over 60 minutes. Pyridine was added to quench the reaction and the mixture was filtered on a short plug of silica gel, concentrated and purified by silica gel flash chromatography (eluent: petroleum ether/ethyl acetate from 8:2 to 7:3) to yield **17E** as an oil (22 mg, 84% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.40-7.00 (benzyl protons), 6.98 and 6.72 (4H, 2 x d, J_{ortho} = 9.2 Hz, aromatic *p*-methoxyphenyl protons), 5.57 (1H, d, J = 1.6 Hz, H-1), 5.23 (1H, bs, anomeric proton), 5.22 (1H, d, J = 1.6 Hz, anomeric proton), 4.90-4.33 (20H, 10 x AB, 10 x benzyl CH_2), 4.26 (1H, t, H-2), 4.21 (1H, dd, J = 3.0 and 8.4 Hz), 4.13-4.06 (2H), 4.00-3.80 (7H), 3.73 (3H, s, -OCH_3), 3.77-3.62 (6H), 3.56 (1H, bd, J = 10.0

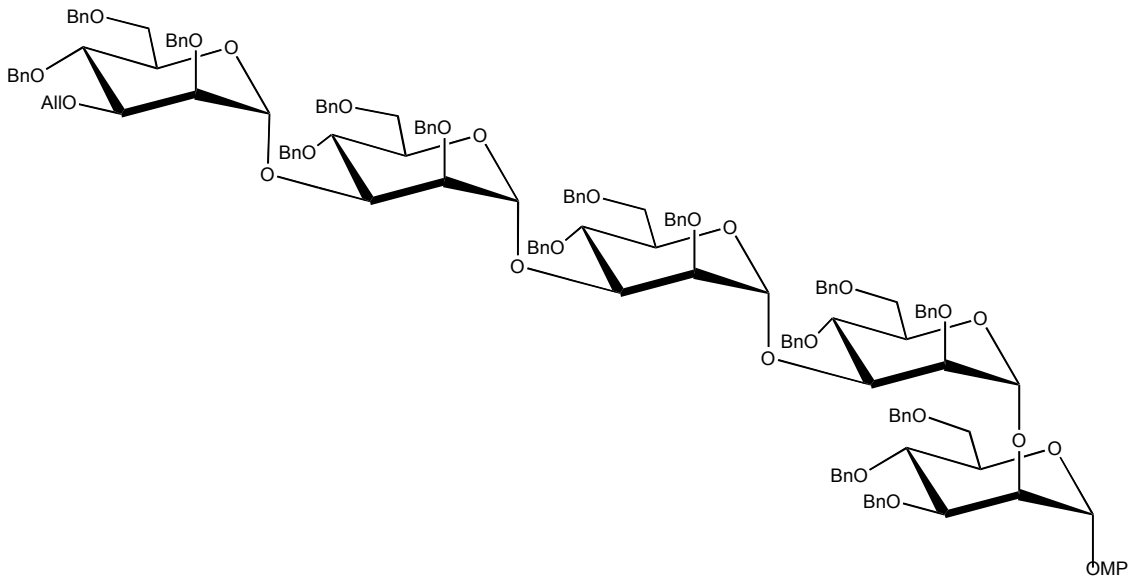
Hz). ^{13} C NMR ($CDCl_3$, 50 MHz) 154.8, 150.1, 138.8, 138.5-138.2, 128.2-127.0, 117.9, 114.5, 99.6, 99.5, 98.0, 80.0, 79.6, 75.5, 75.1, 75.0, 74.7, 74.2, 73.3, 73.2, 72.5, 72.3, 72.2, 72.1, 69.2, 68.9, and 55.6. MALDI-MS: $[M + Na]^+$ calcuId 1533.67, found 1533.56. Anal. Calcd. for $C_{95}H_{98}O_{17}$: C, 75.47, H, 6.53. Found: C, 75.28; H, 6.62.



***p*-Methoxyphenyl 3-*O*-allyl-2,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-mannopyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (19E).** Trichloroacetimidate **4E** (123 mg, 0.194 mmol) and trifluoroacetimidate **5E** (106 mg, 0.170 mmol) were coevaporated three times with anhydrous toluene (3 x 1 mL) and dried under vacuum for 1 hour. The residue was dissolved under argon with 4:1 toluene/Et_2O (4.7 mL) in the presence of freshly activated 4Å AW300 MS. The mixture was then cooled to -10 °C and stirred for 15 minutes. A solution of $Yb(OTf)_3$ in dioxane (25 mg/mL, 125 μL, 0.005 mmol) was added at that temperature, the mixture was stirred for 30 min and then cooled to –60°C. Acceptor **3E** (75 mg, 0.135 mmol) in 4:1 toluene/Et_2O (0.9 mL) and a solution of $Bi(OTf)_3$ in dioxane (16.6 mg/mL, 160 μL, 0.004 mmol) were subsequently added, and the temperature was allowed to warm up to 10 °C over 90 minutes. The reaction was quenched with some drops of pyridine and the mixture was filtered on a short plug of silica gel (eluent: DCM/MeOH/acetonitrile 85:10:5), concentrated, and purified by silica-gel flash-chromatography (eluent: petroleum ether/ethyl acetate from 9:1 to 8:2) to yield trisaccharide **19E** as a yellow oil (118 mg, 60 % overall yield). $[\alpha]^{25}_D$ + 29.7° (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.50-7.10 (aromatic benzyl protons), 7.10 and 6.93 (4H, 2 x d, J_{ortho} = 9.2 Hz, aromatic *p*-methoxyphenyl protons), 5.80-5.95 (1H, m, OCH_2-C*H*=CH_2), 5.58 (1H, d, $J_{1,2}$ = 1.6 Hz, H-1), 5.26 (1H, dd, J_{trans} = 1.2 and 16.8 Hz, -OCH_2-CH=$CH_{cis}H_{trans}$), 5.24 (2H, bs, H-1′ and H-1″), 5.26 (1H, dd, J_{cis} = 10.4 Hz, -OCH_2-CH=C$H_{cis}H_{trans}$), 4.90-4.30 (18H, 9 x AB, 9 x benzyl CH_2), 4.27 (1H, t, H-2), 4.23 (1H, dd, J = 3.2 and 8.4 Hz), 4.15-4.10 (2H), 3.74 (3H, s, -OCH_3), 4.15-3.65 (16 H), 3.56 (1H, bd, J = 9.6 Hz). ^{13} C NMR ($CDCl_3$, 75 MHz) 154.9, 150.1, 138.6-138.2, 135.0, 128.3-127.0, 116.4, 118.0, 114.5, 99.5 (x2), 98.0 (C-1), 79.7, 79.6, 75.3, 75.2, 75.1, 74.8, 74.6, 73.2, 73.1, 71.0, 69.2, 68,8, 55.6. MALDI-MS $[M + Na]^+$ calcld 1483.65, found 1483.85. Anal. Calcd. for $C_{91}H_{96}O_{17}$: C, 74.77, H, 6.62. Found: C, 74.60; H, 6.69.

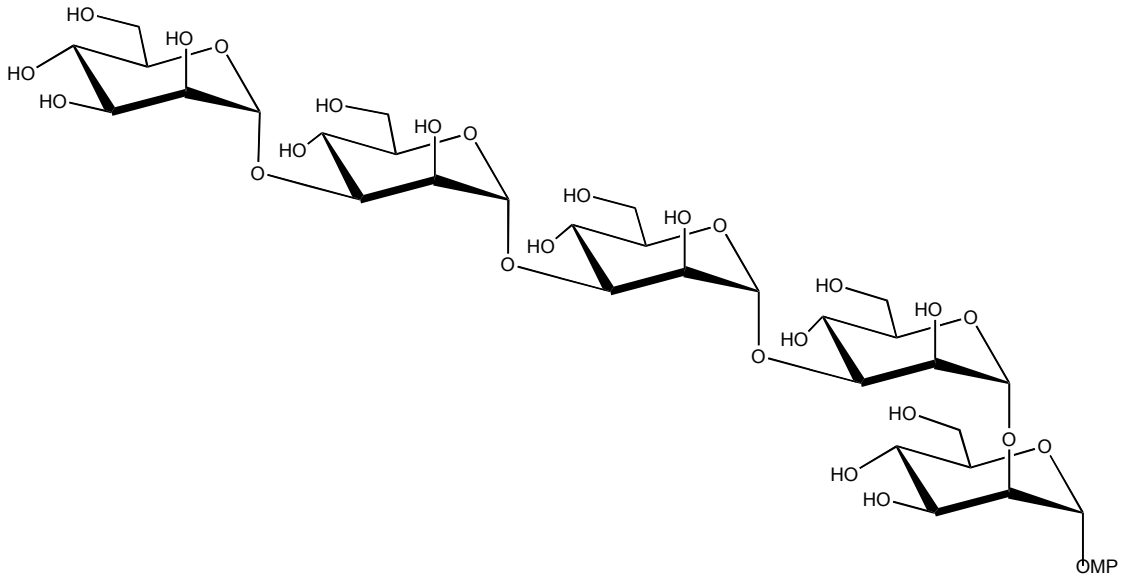


***p*-Methoxyphenyl 2,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-mannopyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (20E).** $PdCl_2$ (2 mg, 0.011 mmol) was added to a solution of trisaccharide **19E** (110 mg, 0.075 mmol) in MeOH/DCM 9:1 (6 mL). After three hours under stirring the mixture was concentrated under vacuum, resuspended with DCM/MeOH 95:5, filtered on a short plug of silica-gel, concentrated and purified by silica-gel flash chromatography (eluent: toluene/acetone 96:4) to yield **20E** as an oil (98 mg, yield 92%). $[\alpha]^{25}_D$ + 35.2° (c 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ = 7.50-7.10 (benzyl aromatic protons), 6.99 and 6.73 (4H, 2 x d, J_{ortho} = 9.2 Hz, p-methoxyphenyl protons), 5.60 (1H, d, J = 1.6 Hz, H-1), 5.27 (1H, bs, anomeric proton), 5.23 (1H, d, J = 1.6 Hz, anomeric proton), 4.85-4.30 (18 H, 9 x AB, 9 x benzyl CH_2), 4.28 (1H, t, H-2), 4.25 (1H, dd, J = 3.2 Hz, 9.6 Hz), 4.20-4.10 (2H), 3.74 (3H, s, -OCH_3), 4.05-3.60 (14 H, m), 3.52 (1H, bd, J = 11.6 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 154.9, 150.2, 138.7, 138.3, 138.2 (x6), 137.7, 128.5-126.9, 117.9, 114.5, 99.6, 98.5, 98.0, 79.6, 78.7, 77.5, 75.1 (x2), 74.9, 74.7, 74.5, 74.2, 73.3, 73.2, 73.1, 72.4, 72.3, 72.1, 72.0, 71.7, 71.6, 69.2, 68.7, 55.6 (-OCH_3). MALDI-MS $[M + Na]^+$ calcld 1443.62, found 1443.78. Anal. Calcd. for $C_{88}H_{92}O_{17}$: C, 74.35, H, 6.52. Found: C, 74.18; H, 6.61.



***p*-Methoxyphenyl 3-*O*-allyl-2,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (21E).** Trichloroacetimidate **4E** (44 mg, 0.069 mmol) and trifluoroacetimidate **5E** (29 mg, 0.047 mmmol) were coevaporated three times with anhydrous toluene (3 x 1 mL) and dried under vacuum for 45 minutes. The residue was dissolved under argon with 4:1 toluene/Et_2O (1.5 mL) in the presence of freshly activated 4Å AW300 MS and the resulting mixture was cooled to -10 °C and stirred for 15 minutes. A solution of $Yb(OTf)_3$ in dioxane (22.5 mg/mL, 40 μL, 1.4 μmol) was added at that temperature, the mixture was stirred for 30 min and then cooled to – 60°C. Acceptor **20E** (44 mg, 0.031 mmol) in 4:1 toluene/Et_2O (0.4 mL) and a solution of $Bi(OTf)_3$ in dioxane (16.6 mg/mL, 49 μL, 1.2 μmol) were subsequently added, and the temperature was allowed to raise up to rt over 2 hours. The reaction was quenched with some drops of pyridine and the mixture was filtered on a short plug of silica gel (eluent: DCM/MeOH/acetonitrile 85:10:5), concentrated, and purified by silica-gel flash-chromatography (eluent: petroleum ether/ethyl acetate from 9:1 to 8:2) to yield pentasaccharide **21E** as an oil (40 mg, yield 56 %). $[\alpha]^{25}_D$ + 25.3° (c 0.8, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.40-7.00 (benzyl protons), 6.98 and 6.73 (4H, 2 x d, J_{ortho} = 9.2 Hz, aromatic p-methoxyphenyl protons), 6.00-5.90 (1H, m, -OCH_2-C*H*=CH_2), 5.60 (1H, bs, H-1), 5.28 (3H, bs, 3x anomeric protons), 5.25 (1H, bs, anomeric proton), 5.23 (1H, bd, J_{trans} = 17.6 Hz, -CH=$CH_{cis}H_{trans}$), 5.08 (1H, bd, J = 10.4 Hz, -CH=C$H_{cis}H_{trans}$), 4.75-4.25 (30H, 15 x AB, 15 x benzyl CH_2), 4.30-4.20 (3H), 4.15-4.10 (2H), 4.05-3.68 (16H), 3.74 (3H, s, -OCH_3), 3.65-3.60 (2H), 3.60-3.55 (3H), 3.55-3.45 (3H), 3.38 (1H, bd, J = 10.4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) 154.9, 150.2, 139.0, 138.7, 138.4 (x4), 138.3 (x4), 138.2 (x4), 138.1, 135.0, 128.5-

126.8, 118.0, 116.4, 114.5, 99.9, 99.6, 99.4, 99.3, 98.0, 76.7, 76.6, 78.9, 78.4, 77.8, 77.3, 77.2, 76.9, 76.8, 75.7, 75.2, 75.1, 75.0, 74.7, 74.5, 74.3, 73.3, 73.2, 73.1, 72.7, 72.6, 72.5, 72.3, 72.2, 72.0, 71.9, 71.0, 69.4, 69.3, 69.2, 69.0, 68.8, 55.6. MALDI-MS $[M + Na]^+$ calcld 2349.05, found 2348.93. Anal. Calcd. for $C_{145}H_{152}O_{27}$: C, 74.85, H, 6.58. Found: C, 74.63; H, 6.66.



***p*-Methoxyphenyl α-D-mannopyranosyl-(1→3)-α-D-mannopyranosyl-(1→3)-α-D-mannopyranosyl-(1→3)-α-D-mannopyranosyl-(1→2)-α-D-mannopyranoside (1E).** $PdCl_2$ (2 mg, 0.011 mmol) was added to a solution of pentasaccharide **21E** (37 mg, 0.014 mmol) in MeOH/DCM 9:1 (3 mL). After ca 60 minutes under stirring the mixture was concentrated under vacuum, resuspended with DCM/MeOH 95:5, filtered on a short plug of silica-gel and concentrated. The residue was dissolved with several aliquots of MeOH/formic acid 9:1 (total volume 4 mL) and added under argon to palladium on charcoal (10 %, 50 mg) previously wet with tha same solution. The mixture was ultra-sonicated for two hours and then filtered on a plug of celite and concentrated under vacuum. The residue was eluted with water and methanol on a short column of mixed-bed ion exchange resin and concentrated to yield pentasaccharide **1E** as a white amorphous solid (9 mg, 70% over two steps). $[\alpha]^{25}_D$ + 43.3° (c 0.6, H_2O). ^1H NMR (D_2O, 400 MHz) δ = 7.08 and 6.93 (4H, 2 x d, J_{ortho} = 10.2 Hz, *p*-methoxyphenyl protons), 5.71 (1H, d, $J_{1,2}$ = 1.6 Hz, H-1), 5.09 (2H, bs, 2 x anomeric protons), 5.07 (1H, d, $J_{1,2}$ = 1.2 Hz, anomeric proton), 5.01 (1H, d, $J_{1,2}$ = 1.8 Hz, anomeric proton), 4.21 (1H, dd, J = 1.8 and 3.0 Hz), 4.18-4.16 (2H), 4.13 (1H, dd, J = 1.8 and 3.4 Hz, H-2), 4.08 (1H, dd, J = 3.0 and 8.8 Hz), 4.03-4.01 (2H), 3.98 (1H, m), 3.96 (1H, m), 3.76 (3H, s, $-OCH_3$), 3.92-3.60 (21H). ^{13}C NMR (D_2O, 50 MHz) 155.9, 151.0, 120.1, 116.3, 103.6 (x2), 103.5,

103.4, 99.1, 80.3, 80.2, 79.3, 74.8, 74.7, 74.6, 71.6, 71.3, 70.9, 68.1, 68.0, 67.5, 67.4, 62.3, 61.9, 57.0. MALDI-MS: $[M + Na]^+$ calculd 957.31, found 957.45. Anal. Calcd. for $C_{37}H_{58}O_{27}$: C, 47.54, H, 6.25. Found: C, 47.38; H, 6.30.

References

1. a) Wong, C.-H. *Carbohydrate-based drug discovery*, WILEY-VCH, Weinheim, **2003**. b) Sinay, P.; Ernst; B.; Hart, G. W. *Carbohydrates in chemistry and biology*, Wiley-Wch, **2000**. c) Seeberger, P. H.; Werz, D. B. *Nature* **2007**, *446*, 1046-1051.

2. Plante, O. J.; Seeberger, P. H.; Palmacci, E. R. *Science* **2001**, *291*, 1523-1527.

3. For recent reviews: a) Wang, Y.; Ye, X-S.; Zhang, L.-H. *Org. Biomol. Chem.* **2007**, *5*, 2189-2200. b) Codee, J. D. C.; Litjens, R. E. J. N.; Van den Bos, L. J.; Overkleeft, H. S.; Van der Marel, G. A. *Chem. Soc. Rev.* **2005**, *34*, 769-782.

4. For some examples: a) Yamada, H.; Harada, T.; Takahashi, T. *J. Am. Chem. Soc.* **1994**, *116*, 7919-7920. b) Grice, P.; Ley, S. V.; Pietuszka, J.; Priepke, H. W. M.; Walther, E. P. E. *Synlett* **1995**, 781-784; c) Cheung, M.-K.; Douglas, N.; Hinzen, B.; Ley, S. V.; Pannecouncke, X. *Synlett* **1997**, 257-260; d) Grice, P.; Ley, S. V.; Pietuszka, J.; Osborn, H. M. I.; Priepke, H. W. M.; Warriner, S. L. *Chem. Eur. J.* **1997**, *3*, 431-440; e) Green, L.; Hinzen, B.; Ince, S. J.; Langer, P.; Ley, S. V.; Warriner, S. L. *Synlett* **1998**, 440-443; f) Langer, P.; Ince, S. J.; Ley, S. V. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3913-3915; g) Yamada, H.; Kato, T.; Takahashi, T. *Tetrahedron Lett.* **1999**, *40*, 4581-4584. h) Tanaka, H.; Adachi, M.; Tsukamoto, H.; Ikeda, T.; Yamada, H.; Takahashi, T. *Org. Lett.* **2002**, *4*, 4213-4216. i) Hashihayata, H.; Ikegai, K.; Takeuchi, K.; Jona, H.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **2003**, *76*, 1829-1848. l) Mukaiyama, T.; Kobashi, Y. *Chem. Lett.* **2004**, *33*, 10-11. m) Tanaka, H.; Adachi, M.; Takahashi, T. *Tetrahedron Lett.* **2004**, *45*, 1433-1436. n) Pornsuriyasak, P. P.; Demchenko, A. V. *Tetrahedron: Asymmetry* **2005**, *16*, 433-439. o) Kim, J.-H.; Yang, H. Boons, G.-J. *J. Am. Chem. Soc.* **2005**, *127*, 12090-12097. p) Wang, P.; Lee, H.; Fukuda, M.; Seeberger, P. H. *Chem. Comm.* **2007**, 1963-1965.

5. Fraser-Reid, B.; Udodong, U. E.; We, Z. F.; Ottosson, H.; Merritt, J. R.; Rao, C. S.; Roberts, C.; Madsen, R. *Synlett*, **1992**, 927-942.

6. Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734-753. For applications to biologically important oligosaccharides: a) Burkhart, F.; Zhang, Z.; Wacowich-Sgarbi, S.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2001***, 40,* 1274-1277. b) Mong, K.-K. T.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2002***, 41,* 4087-4090. c) Lee, J.-C.; Wu, C.-Y.; Apon J. V.; Siudzak, G.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2006***, 45,* 2753-2757. d) Polat, T.; Wong, C.-H. *J. Am. Chem. Soc.* **2007**, *129*, 12795-12800.

7. For examples from other groups: a) Ley, S. V.; Priepke, H. W. M. *Angew. Chem. Int. Ed.* **1994**, *33*, 2292-2294. b) Douglas, N. L.; Ley, S. V.; Lücking, U.; Warriner, S. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 51-65. c) Lahmann, M.; Oscarson, S. *Org. Lett*. **2001**, *3*, 4201-4204. d) Huang, L.; Wang, Z.; Huang, L. *Chem. Comm.* **2004**, 1960-1961. e) Fridman, M.; Solomon, D.; Yogev, S.; Baasov, T. *Org. Lett*. **2002**, *4*, 281-284. f) Wang, Y.; Huang, X.; Zhang, L.-H., Ye, X.-S. *Org. Lett*. **2004**, *6*, 4415-4418.

8. a) Huang, X.; Huang, L.; Wang, H.; Ye, X-S. *Angew. Chem. Int. Ed.* **2004***, 43,* 5221-5224. b) Huang, X.; Huang, L. *Chem. Eur. J.* **2007***, 13,* 529-540. c) Wang, Z.; Zhou L.; El-Boubbou, K.; Ye, X-S.; Huang, X. *J. Org. Chem.* **2007**, *72*, 6409-6420. d) Miermont, A.; Zeng, Y.; Jing, Y.; Ye, X-S.; Huang, X. *J. Org. Chem.* **2007**, *72*, 8958-8961. e) Teumelsan, N.; Huang, X. *J. Org. Chem.* **2007**, *72*, 8976-8979.

9. Adinolfi, M.; Iadonisi, A.; Ravidà, A. *Synlett*, **2006**, 583-586.

10. Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21-123.

11. Yu, B.; Tao, H. *Tetrahedron Lett.* **2001**, *42*, 2405-2407.

12. a) Adinolfi, M.; Barone, G.; Iadonisi, A.; Schiattarella, M. *Tetrahedron Lett.* **2002**, *43*, 5573-5577. b) Adinolfi, M.; Iadonisi, A.; Ravidà, A.; Schiattarella, M. *Tetrahedron Lett.* **2004**, *45*, 4485-4488.

13. For applications of $Yb(OTf)_3$-activated imidates to the synthesis of biologically interesting oligosaccharides: a) Adinolfi, M.; Iadonisi, A.; Ravidà, A.; Schiattarella, M. *Synlett* **2004**, 275-278. b) Jayaprakash, K. N.; Fraser-Reid, B. *Org. Lett.* **2004**, *6*, 4211-4214. c) Adinolfi, M.; Iadonisi, A.; Ravidà, A.; Schiattarella, M. *J. Org. Chem.* **2005**, *70*, 5316-5319. d) Hanashima, S.; Castagner, B.; Esposito, D.; Nokami, T.; Seeberger P. H. *Org. Lett.* **2007**, *9*, 1777-1779. e) Jayaprakash, K. N.; Chauduri, S. R.; Murty, V. S. R.; Fraser-Reid, B. *J. Org. Chem.* **2007**, *72*, 5534-5545.

14. Adinolfi, M.; Iadonisi, A.; Ravidà, A.; Valerio, S. *Tetrahedron Lett.* **2006**, *47*, 2595-2599. For the use with NBS in the activation of thioglycosides: Valerio, S.; Iadonisi, A.; Adinolfi, M.; Ravidà, A. *J. Org. Chem.* **2007**, *72*, 6097-6106.

15. a) Chen, P.-J.; Chang, S.; Lai, C.; Gautam, A.; Wilson, E. *Journal of gastroenterology and epatology* **2006**, A185- A185. b) Basche, M.; Gustafson, D. L.; Holden, S. N.; O'Bryant C. L.; Gore, L.; Witta, S.; Schultz, M. K.; Morrow, M.; Levin, A.; Creese, B. R.; Kangas, M.;

Roberts, K.; Nguyen, T.; Davis, K.; Addison, R. S.; Moore, J. C.; Eckhardt, S. G. *Clin. Cancer. Res* **2006**, *12*, 5471-5480.

16. Karoli, T.; Liu, L. G.; Fairweather, J. K.; Hammond, E.; Cochran, S.; Bergefall, M.; Trybala, E.; Addison, R. S. *J. Med. Chem.* **2005**, *48*, 8229-8236.

17. Fairweather, F J. K.; Hammond, E.; Johnstone, K. D.; Ferro, V. *Biorg. Med. Chem.* **2008**, *16*, 699-709.

18. Ferro, V.; Fewings, K.; Palermo, M. C.; Li, C. P. *Carbohydr. Res.* **2001**, *332*, 183-189.

19. Parish, C. R.; Freeman, C.: Brown, K. J.; Francis, D. J.; Cowden, W. B. *Cancer Research* **1999**, *59*, 3433-3441.

20. Gu, G. F.; Wei, G. H.; Du, Y. G. *Carbohydr. Res.* **2004**, *339*, 1155-1162.

21. Adinolfi, M.; Iadonisi, A.; Schiattarella, M.; Ravidà, A. *Tetrahedron Lett.* **2003**, *44*, 7863-7866.

22. Yang, G. B.; Kong, F.-Z.; Zhou S. H.*Carbohydr. Res.* **1991**, *211*, 179-182.

23. Carpenter, C.; Nepogodiev, S. A. *Eur. J. Org. Chem.* **2005**, 3286-3296.

Chapter F

One-pot catalytic glycosidation-Fmoc removal: an iterable sequence for straightforward assembly of oligosaccharides related to HIV gp120.

Introduction

As it was widely discussed in **Chapter E**, standard strategies of sequential glycosidations contemplate the elongation of the oligomer starting from the non-reducing terminus of the target. However, with the exception of the previously mentioned preactivation strategy, the success of the elongation is critically dependent on the availability of a set of glycosyl donors displaying well differentiated reactivities. Here it was reported the less common approach of sequential glycosidations featuring the opposite elongation direction.[1] In general terms, this can be pursued by first coupling a glycosyl donor with a glycosyl acceptor and then removing in the same reaction vessel a transient protecting group from the in situ generated di- or oligosaccharide. In this way, after a single purification process a potential glycosyl acceptor, ready for a further glycosidation step, is directly obtained. Apart from the reduced overall number of synthetic operations, this strategy is advantageous because it is independent of the anomeric reactivity of the involved components since in each glycosidation step there is no competition between two potential glycosyl donors. So far a few sparse examples of this tactic have been reported.[2] Almost all of them exploit the acidic conditions required in the glycosidation step for performing, upon adjustment of the experimental conditions, the subsequent removal of the transient protecting group (**Figure 1**).

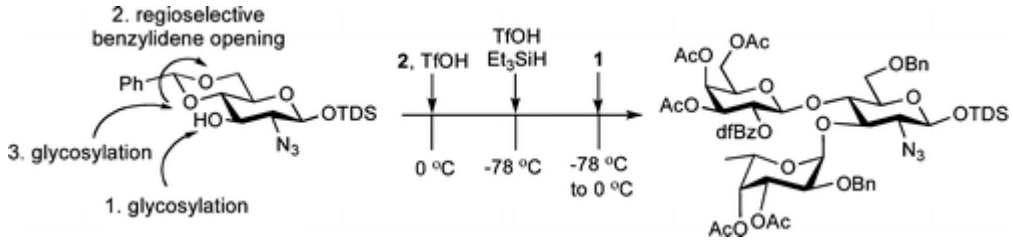


Figure 1

A much less exploited synthetic route is instead the removal of a base labile protecting group immediately after an acid promoted glycosidation. In this regard, Fmoc was recently applied as a transient protecting group[3] in the synthesis of β-(1→6) gluco oligosaccharides conducted in microreactors[4] (**Figure 2**).

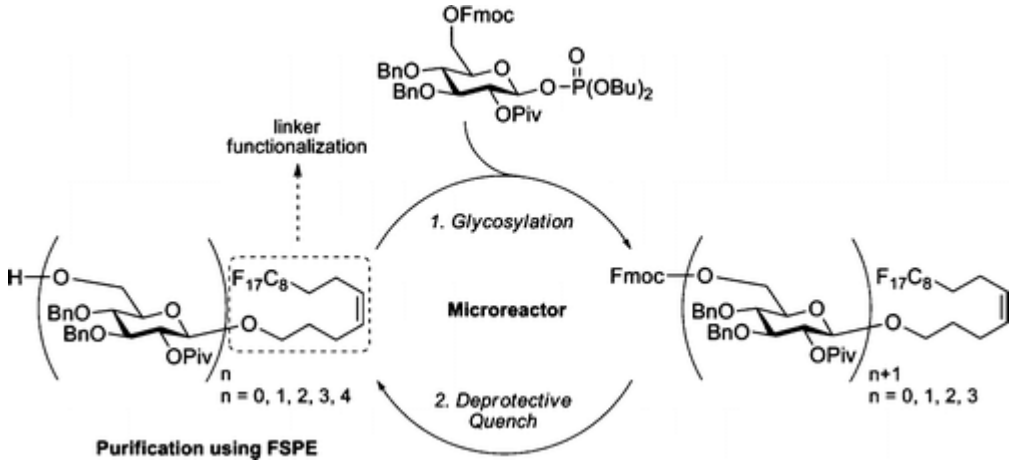


Figure 2

The group survived the acid activation (with 2-3 eq of TMSOTf) of glycosyl phosphate donors and was removed by simple excess addition of a mild base (piperidine/DMF 1:4) to the glycosidation medium. The excess of promoter caused partial trimehtyl silylation of the liberated alcohol, a process which required the addition of desilylation agents in the deprotection mixture. By a similar approach, Fmoc was removed in situ from oligosaccharide intermediates just generated by electrochemical glycosidations.[5]

In this chapter it was described the effective application of Fmoc as a transient group in an iterable sequence for solution oligosaccharide synthesis based on the $Bi(OTf)_3$ catalyzed activation[6,7] of glycosyl trihaloacetimidates. The devised strategy has been targeted to the rapid assembly of two biologically relevant targets, the protected mannose tetrasaccharide **1F** and the branched pentasaccharide **2F**, both corresponding to moieties incorporated into HIV glycoprotein gp120 (**Figure 3**).

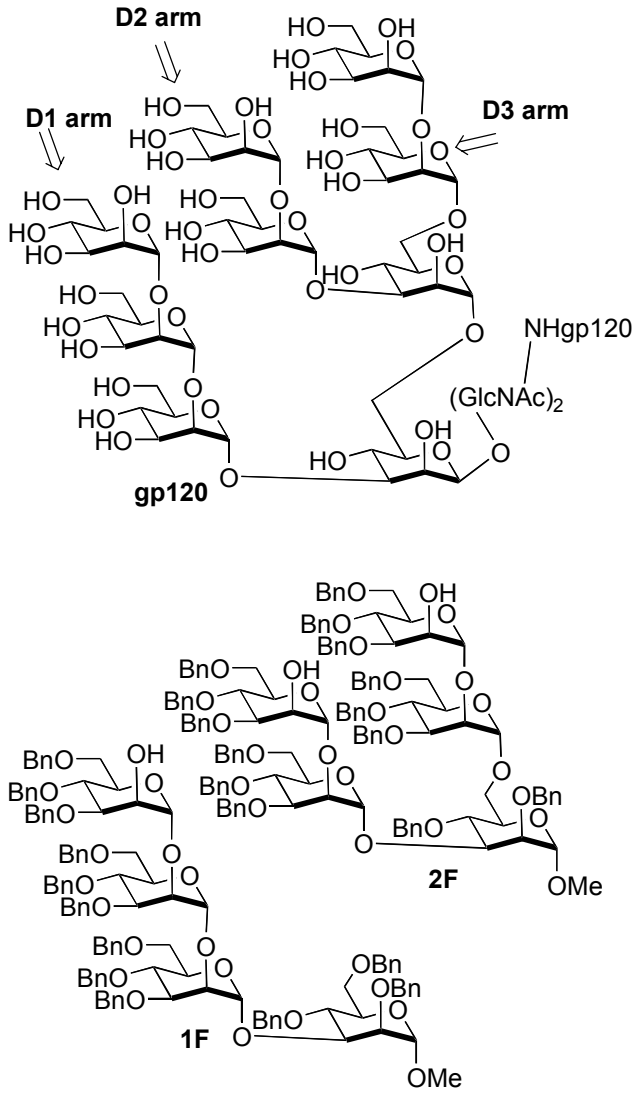


Figure 3 Structures of the gp120 glycan and the synthetic targets of the present work.

In particular, tetrasaccharide **1F** represents the partially protected so-called D1 arm of the highly mannosylated ensemble, whereas compound **2F** embodies both partially protected D2 and D3 arms. Either sequence was found to exhibit high affinity towards human antibody 2G12[8] (**Figure 4, 5** and **6**) so to be currently investigated for immunogenic applications.[9]

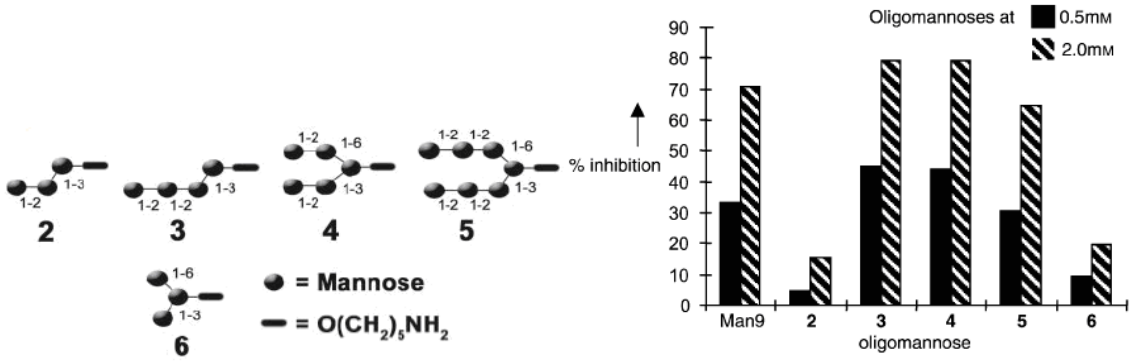


Figure 4 Chemical structures of oligomannosides **2-6** and their inhibition (%) of 2G12 to gp120. Man_9 = $Man_9GlcNAc_2$ (**1**).

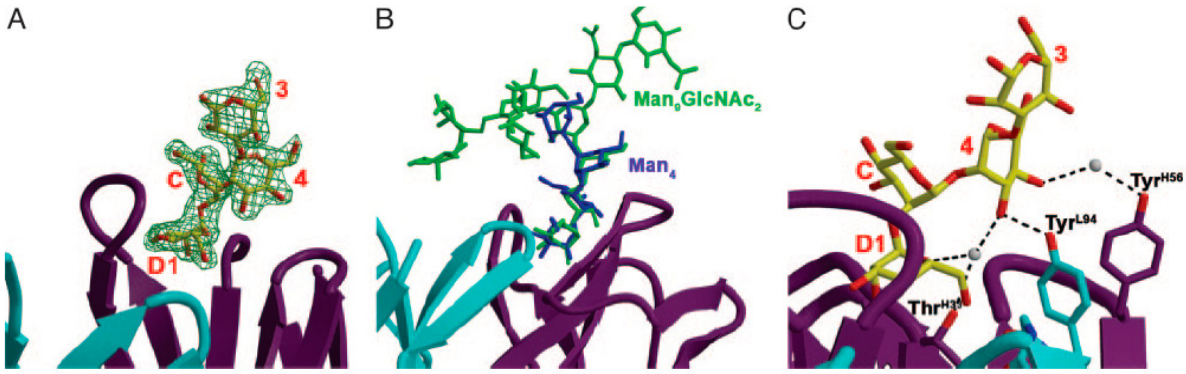


Figure 5 Crystal structure of Fab 2G12 with Man_4. (***A***) 2*F*o – *F*c electron density map of the Man_4 sugar (shown in ball-and-stick) contoured at 1.8σ. Mannose residues are labeled in red. The light and heavy chains of Fab 2G12 are shown in cyan and purple. (***B***) Overlap of the Man_4 sugar (shown in blue) with a previous Fab 2G12 structure[10] bound to $Man_9GlcNAc_2$ (shown in green). The Man_4 clearly adopts a conformation similar to the D1 arm of $Man_9GlcNAc_2$. (***C***) Additional H bonds between Fab 2G12 and mannose 4 of Man_4. Two of the H bonds are water mediated (water molecules shown as gray spheres). These interactions may explain in the preference for D1 arm binding in the context of the full $Man_9GlcNAc_2$ moiety. Figures were made by using MOLSCRIPT[11], BOBSCRIPT[12], and RASTER3D[13].

In the crystal structure of Fab 2G12 in complex with Man_4 (oligomannose **3**), the Man_4 sugar is located in the combining site of the Ab and has extremely well defined electron density (**Fig. 5*A***). As expected, the Manα1–2Man terminus of the sugar (consisting of mannoses D1 and C) binds end-on in a cleft in the binding site. An overlay with a previous structure of Fab 2G12 plus $Man_9GlcNAc_2$[10] shows that Man_4 binds with a similar geometry to the D1 arm of $Man_9GlcNAc_2$ (**Fig. 5*B***) that correlates with the biochemical data that indicate Man_4 binds as well as the entire $Man_9GlcNAc_2$ moiety[8]. The crystal structure of the Fab 2G12–Man_4 complex is of higher resolution and allows better characterization of the interactions between Fab and sugar ligand. A total of 51 van der Waals interactions and 15 H bonds are formed on complex formation; 292 $Å^2$ of molecular surface is buried on Fab 2G12 and 294 $Å^2$ is buried on the sugar in the complex. Although the bulk of the interactions are with Manα1–2Man

(mannoses D1 and C), three H bonds are made between 2G12 and mannose 4, two of which are water-mediated (**Fig. 5*C***). Tyr^{L94} H bonds to the *O*-3 oxygen of mannose 4, whereas water molecules coordinate between the *O*-5 of mannose D1 and the *O*-3 of mannose 4, and between Tyr^{H56} and the *O*-4 of mannose 4.

Man_5 (oligomannose **4**) is instead the structural equivalent of the D2 and D3 arms of $Man_9GlcNAc_2$. 2G12 binds to Man_5 with similar apparent affinity as Man_4 and $Man_9GlcNAc_2$[8]. The Manα1–2Man moieties (mannoses D3 and B), which correspond to the D3 arm of $Man_9GlcNAc_2$, are well ordered in the primary combining site (**Fig. 6**). The other Manα1–2Man (mannoses D2 and A) branch, which corresponds to the D2 arm of $Man_9GlcNAc_2$, points away from the binding site, confirming biochemical studies that suggest 2G12 recognizes the D3 arm in preference to D2. 302 $Å^2$ of molecular surface is buried on Fab 2G12 and 307 $Å^2$ is buried on Man_5 upon complex formation. Unlike Man_4 (D1 arm) binding, no additional H bonds are made to sugars other than with the terminal Manα1–2Man.

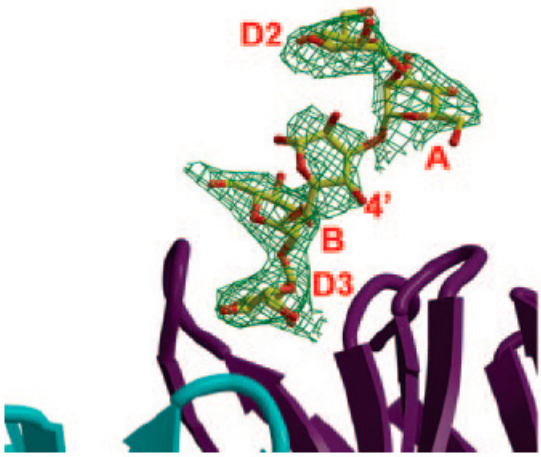
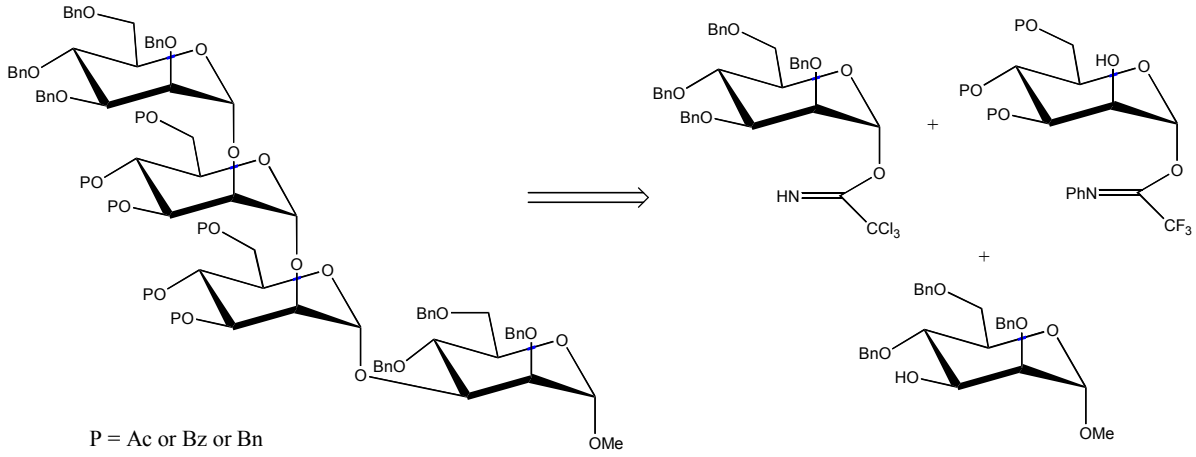


Figure 6

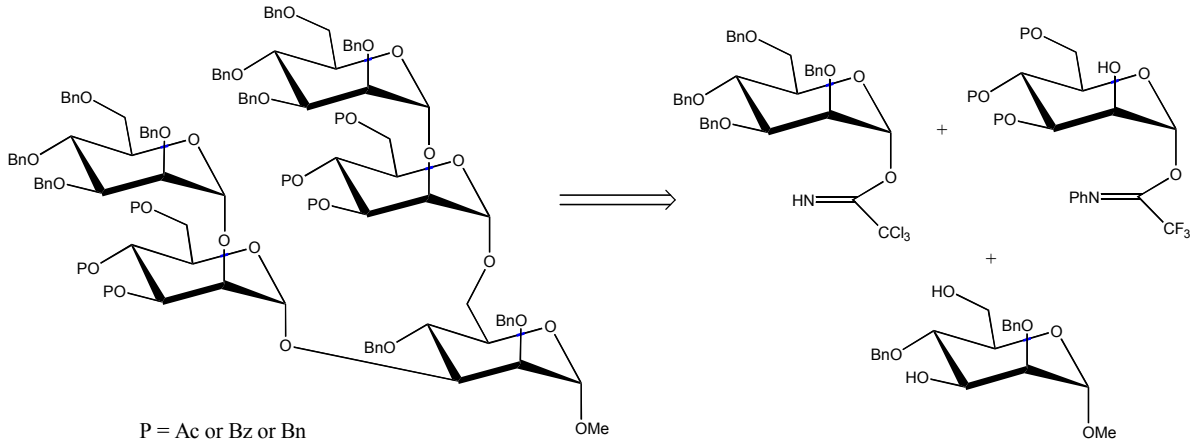
Results and discussion

Before developing the sequential one-pot scheme of $Bi(OTf)_3$ catalyzed multiglicosidation followed by the removal of one or more base labile Fmoc temporary protecting group by simple addition of TEA to the reaction vessel, it was hoped to perform the elaboration of the D1, D2 and D3 arms of the gp120 of the HIV-1 with a sequential one-pot scheme analogous to the straightforward assemblage of the fully protected *p*-methoxyphenyl pentamannoside **21E** of PI-88 as described in **Chapter E**. Both these elaborations potentially would require three building blocks where one of the three is a (*N*-phenyl)trifluoroacetimidate mannosyl

donor deprotected at *O*-2 and also bearing acyl or benzyl groups on the other positions (**Scheme 1** and **2**).

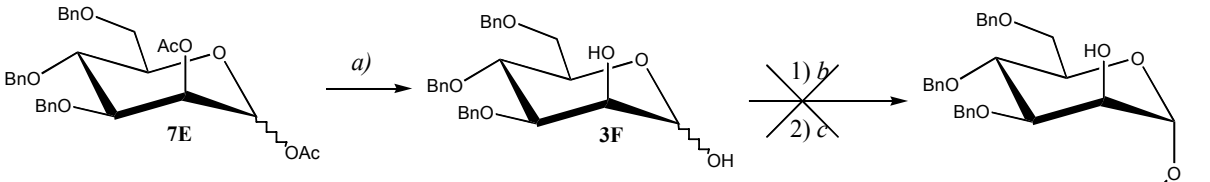


Scheme 1



Scheme 2

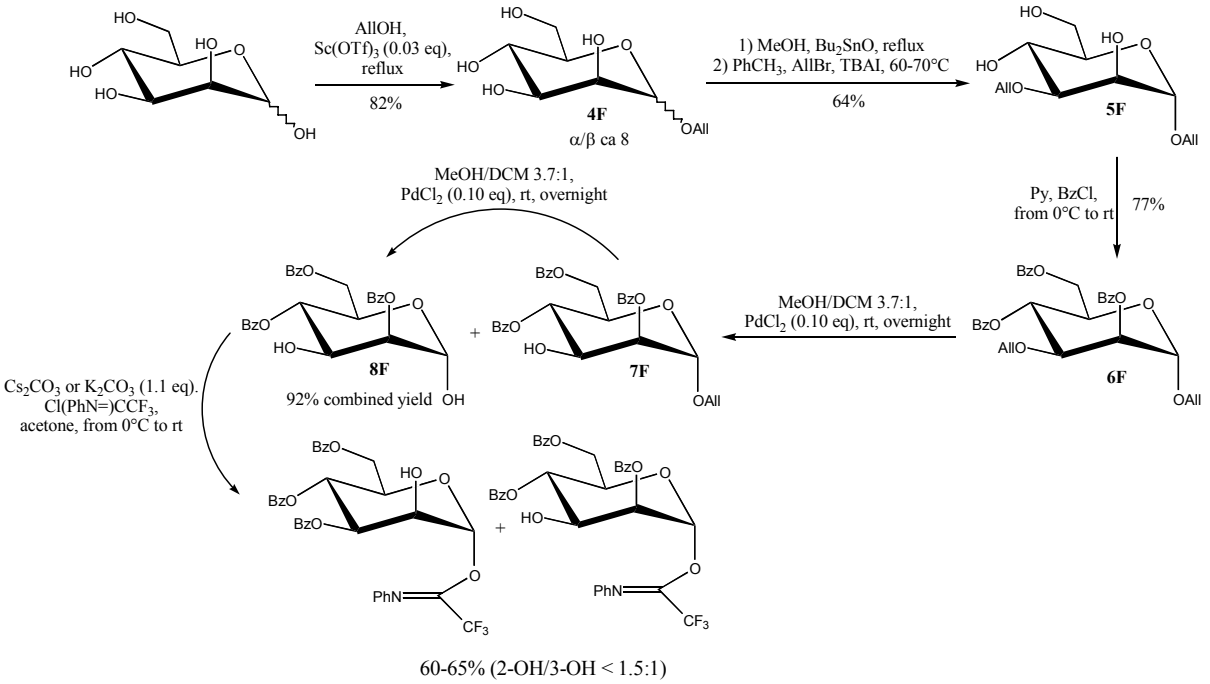
After many experiments of regioselective anomeric trifluoroacetimidoylation of diol **3F** by using different bases (Cs_2CO_3, Cs_2CO_3/TBAI, NaH/TBAI) or by producing in situ an anomeric tri-*n*butylstannyl ether (**Scheme 3**), at the moment I can assert that it is currently impossible to synthesize a 2-OH (*N*-phenyl)trifluoroacetimidate mannosyl donor 3,4,6-tri-*O*-benzylated.



a) MeOH/MeONa 2M, from 0°C to rt
b) $(Bu_3Sn)_2O$, MS 3Å, MeCN, reflux, 3 h
c) $Cl(PhN=)CCF_3$, from 0°C to rt overnight and then from rt to 60°C

Scheme 3

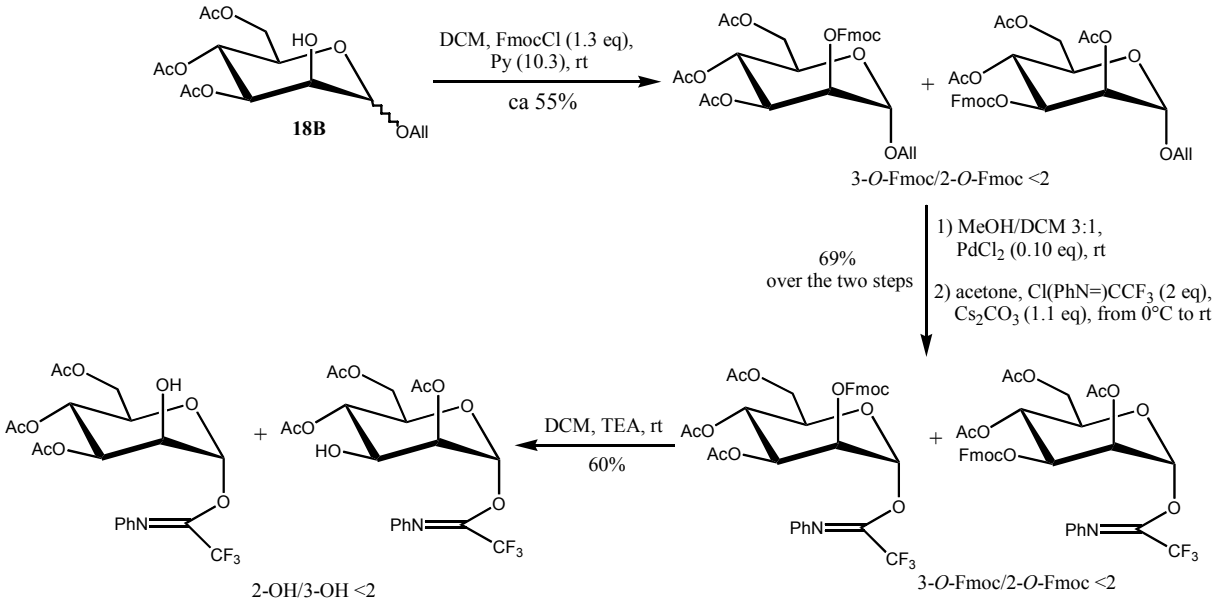
Additionally, it was also tried the synthesis of a a 2-OH (*N*-phenyl)trifluoroacetimidate mannosyl donor 3,4,6-tri-*O*-benzoylated as it has showed in **Scheme 4**. After a standard sequence of reactions it was obtained **6F** that was subsequently deallylated to provide diol **8F**. With this building block, it was hoped that its treatment, with (*N*-phenyl)trifluoroacetimidoyl chloride (2 eq) and a base such as Cs_2CO_3 or K_2CO_3 (1.1 eq) in acetone starting from 0°C and then raising the temperature to rt, would afford the desired mannosyl donor deprotected at *O*-2. Indeed with these experimental conditions and after chromatographic purification of the crude mixture, it was observed the regioselective trifluoroacetimidoylation of the anomeric carbionl but also the simultaneous undesired intramolecular transbenzoylation that afforded a mixture of mannosyl donors deprotected either at *O*-2 or *O*-3. This result was deduced from the ^{1}H NMR spectrum which displayed the presence of these significant signals: two broad singlets at δ 6.48 and 6.42 indicating two α-anomers, two triplets at δ 6.06 and 5.78, a double doublet and a broad doublet in the range of δ 5.74-5.63 denoting the presence of protons (respectively 2x 4-H, 3-H and 2-H) attached to benzoylated carbinols. The heterogeneous sample so obtained was unuseful for the desired synthetic purposes.



Scheme 4

After these frustrating results, the attention was turned to the syntesis of a 2-OH (*N*-phenyl)trifluoroacetimidate mannosyl donor equipped with acetyl groups on the other carbinol positions. In this case it was supposed that access to this kind of mannosyl donor would be possible through an original potential pathway based on the hypotesis of the feasible removal under mild basic conditions of a Fmoc carbonate in the presence of a

trifluoroacetimidate anomeric group. This application would have expand the concept of temporary anomeric protection for this group that was also stated in **Chapter E** in the context of sequential multiglycosidation steps. To verify the validity of this strategy, it was introduced a Fmoc group on the *O*-2 of the previously described allyl mannoside 3,4,6-tri-*O*-acetylated **18B** but in the here reported conditions a mixture of two fully protected building blocks was obtained (**Scheme 5**). Despite this initial unsatisfactory result, the subsequent synthetic steps of deallylation and imidoylation were accomplished and finally it was demonstrated that excess amounts of TEA remove a Fmoc carbonate in the presence of a trifluoroacetimidate anomeric group. This is a very interesting result but once again it was currently impossible to obtain a 2-OH (*N*-phenyl)trifluoroacetimidate mannosyl donor equipped with acyl groups on the other carbinol positions.



Scheme 5

With these poor results in hand, the attention was turned to a different sequential one-pot scheme allowing the synthesis of mannose oligomers starting from the reducing terminus to avoid potential problems associated with the opposite elongation sense such as both availability and use of a set of glycosyl donors featuring a well differentiated decreasing reactivity. As detailed below, catalytic amounts of easy to handle $Bi(OTf)_3$ activate trihaloacetimidate mannosyl donors, equipped with a Fmoc temporary protecting group, to perform one or more glycosidation reactions. The subsequent addition to the reaction vessel of a mild base such as TEA allows both quenching of the promotion system and removal of one or more transient Fmoc groups from the oligosaccharide generated in situ. In this way, after a chromatographic purification an oligosaccharide acceptor is directly obtained and, if

necessary, it is ready for a further elongation step. As it will be widely shown in this chapter, this approach is an especially effective sequential one-pot iterable scheme for constructing the target compounds.

For the target **1F**[14] was planned the following retrosynthetic analysis (**Figure 7**) entailing the availability of only two mannose building blocks, **9F** and **10F**, the latter being the precursor of the reducing terminal residue.

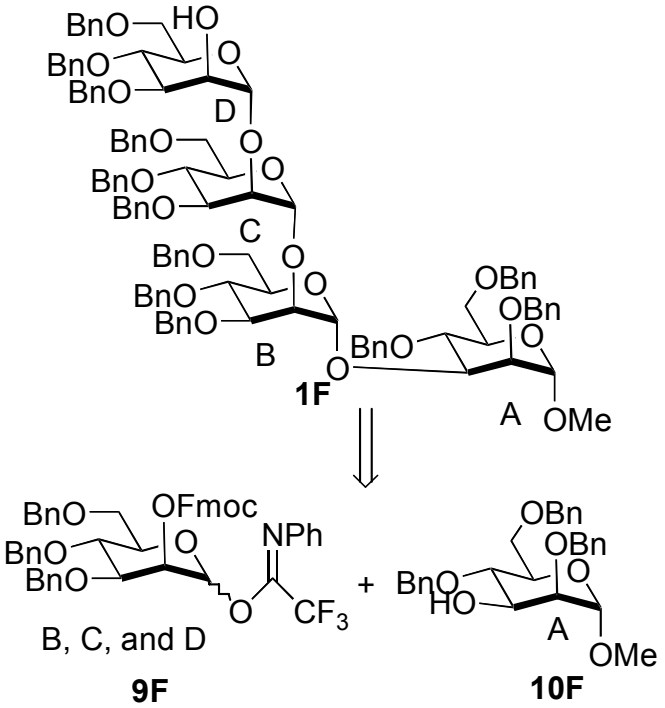
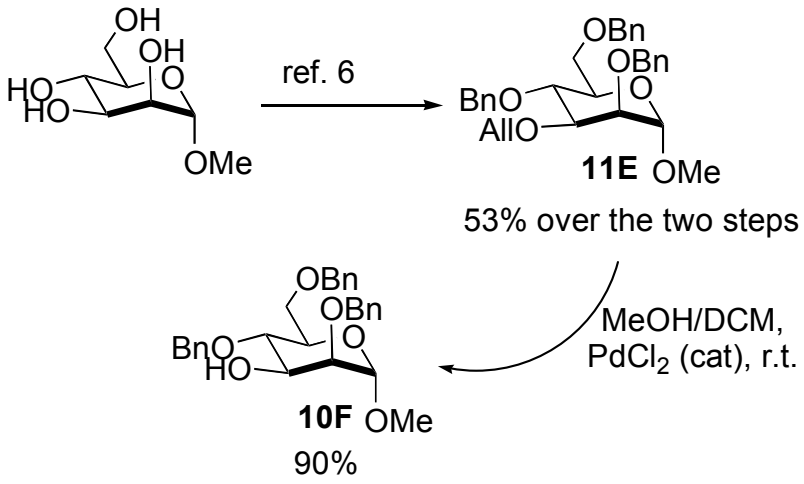


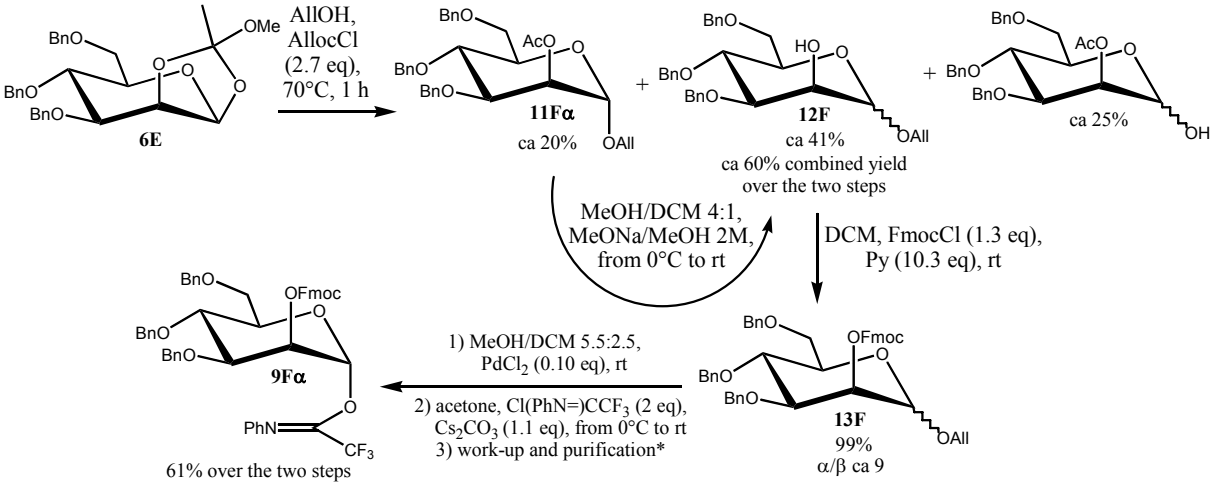
Figure 7 Retrosynthesis of **1F**.

Acceptor **10F** was synthesized (**Scheme 6**) starting from commercially available methyl α-D-mannopyranoside. This was initially allylated at *O*-3 and per-*O*-benzylated to give **11E** as previously reported in **Chapter E**.[6] Deallylation of **11E** smoothly afforded acceptor **10F** (**Scheme 6**).



Scheme 6 Synthesis of acceptor **10F**.

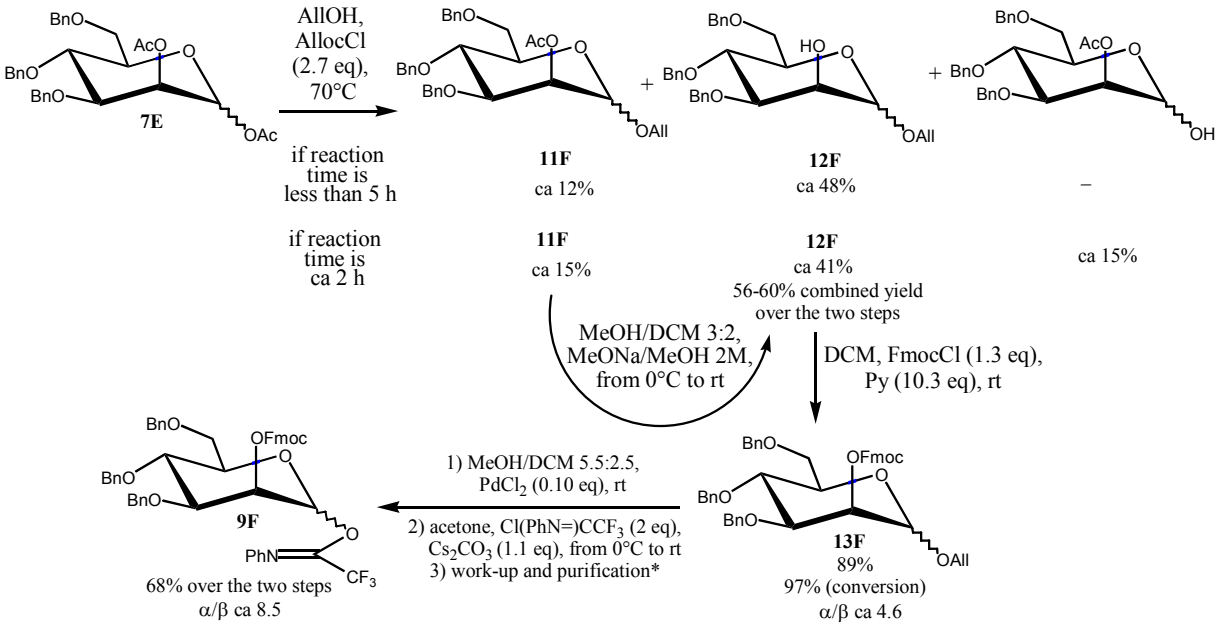
Many experiments were performed to obtain mannosyl donor **9F** with a high yielding approach also requiring a limitated number of purification processes. The synthesis of **9F** generally requires the introduction of the versatile allyl group on the anomeric position followed by the 2-*O*-deacylation step using a 1,2-orthoester or a 1,2-di-*O*-acylated mannosides as precursors. Experiments conducted on methyl orthoester **6E** and **7E**, both previously described in **Chapter E**, in allyl alchol and in the presence of AllocCl (generating HCl *in situ*) afforded intermediate **12F** in similar yields (about 60%, **Schemes 7** and **8**).



* The crude was concentrated and the residue obtained was subsequently purified by chromatography on neutral alumina (Brockman grade 2, eluent: petroleum ether/ethyl acetate from 9:1 to 7:3 with three drops of pyridine for every 200 mL of eluent)

9Fα was synthesized in 36% overall yield over 5 steps and by performing 3 chromatographic purifications

Scheme 7

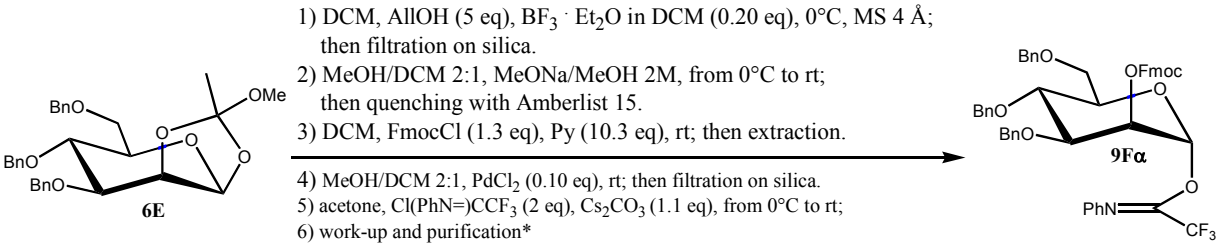


* The crude was concentrated and the residue obtained was subsequently purified by chromatography on neutral alumina (Brockman grade 2, eluent: petroleum ether/ethyl acetate from 9:1 to 7:3 with three drops of pyridine for every 200 mL of eluent)

9F was synthesized in 34-36% overall yield over 5 steps and by performing 3 chromatographic purifications

Scheme 8

So it was necessary the use of a different promotion system, providing a limitated number of by-products during the first step of the synthesis of **9F**, and the attention was turned to substoichiometric amounts of $BF_3 \cdot Et_2O$. When a global one-pot synthesis of **9F** was tried using **6E** as the precursor (**Scheme 9**), the isolated yield of the desired donor was not excellent although a single purification process was performed.



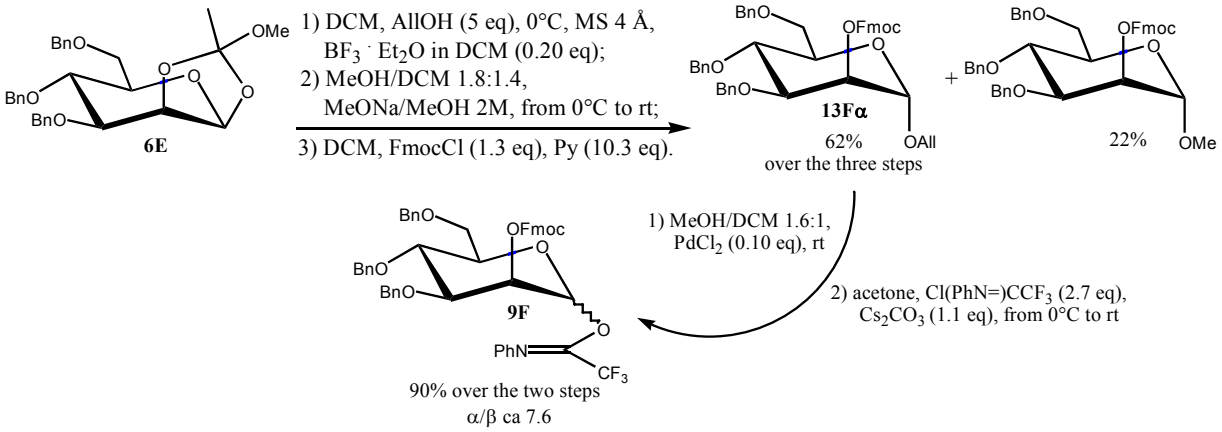
* The crude was concentrated and the residue obtained was subsequently purified by chromatography on neutral alumina (Brockman grade 2, eluent: petroleum ether/ethyl acetate from 9:1 to 7:3 with three drops of pyridine for every 200 mL of eluent)

9Fα was synthesized in 27% overall yield over 5 steps and by performing only one chromatographic purification

Scheme 9

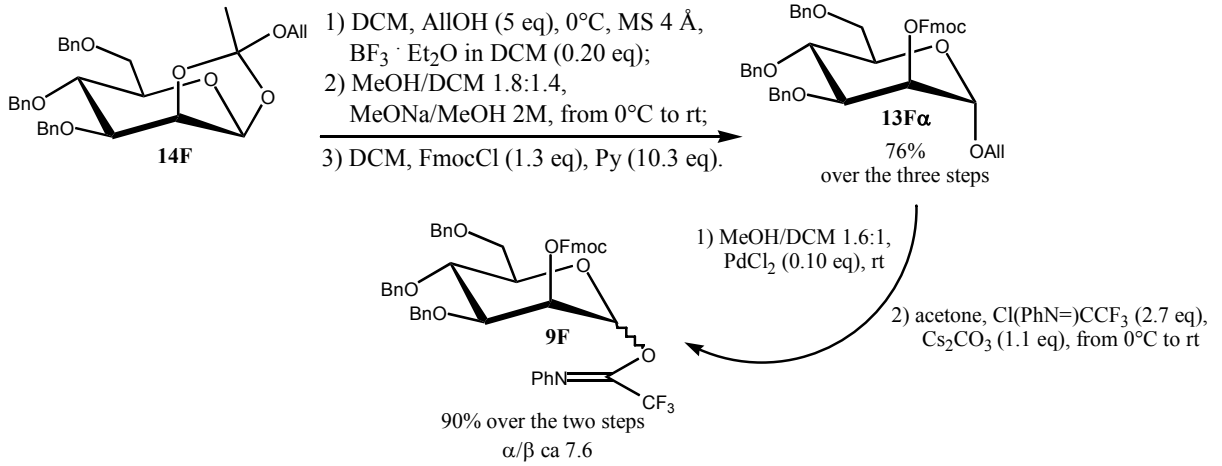
During the first one-pot sequence of the synthesis of **9F** (**Scheme 10**), Methyl 3,4,6-tri-*O*-benzyl-2-*O*-fluorenylmethoxycarbonyl-α-D-mannopyranoside was isolated after chromatographic purification. It derives from the intramolecular rearrangement of the methoxy group belonging to orthoester **6E** and to prevent the production of this by-prodouct,

allyl 1,2-orthoester **14F** was then used. Hence compound **9F** was prepared from intermediate **14F** (**Scheme 11**) obtained via a previously described one-pot sequence.[6,15] Orthoester **14F** was submitted to acid promoted rearrangement in the presence of allyl alcohol to give **11Fα** which was directly submitted to 2-*O*-deacetylation and Fmoc protection to give **13Fα** in 76% yield over three steps. Sequential anomeric deallylation and installation of the trifluoroacetimidate[16] leaving group completed the preparation of **9F** (90% yield over the two steps). Additionally improvements of the isolated yield of **9F** were also obtained by changing both work-up (filtration on a plug of celite instead of solvent removing under vacuum) and chromatographic purification (silica can be used instead of alumina and drops of pyridine aren't necessary in the appropriate eluent of the purification) in the imidoylation step.



9F was synthesized in 56% overall yield over 5 steps and by performing 2 chromatographic purifications

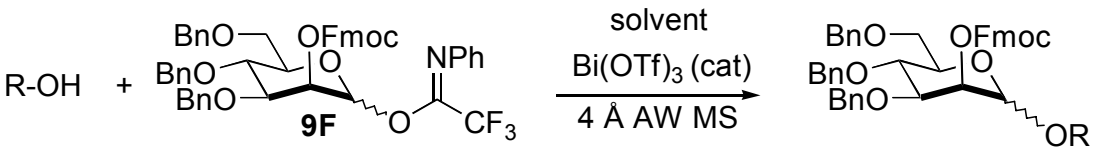
Scheme 10



9F was synthesized in 68% overall yield over 5 steps and by performing 2 chromatographic purifications

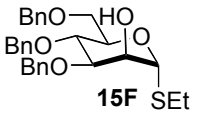
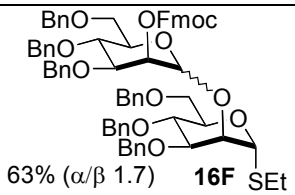
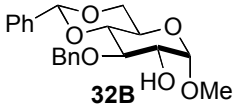
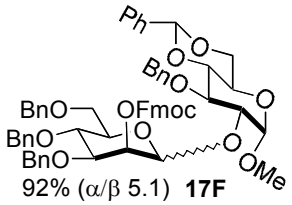
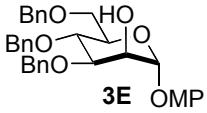
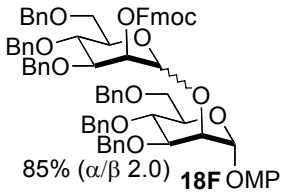
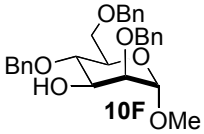
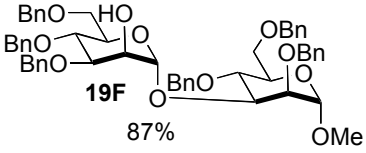
Scheme 11

Before to proceed with the rapid assemblage of the partially protected tetramannoside D1 **1F** of gp120, a significative number of experiments were performed both to understand the reactivity of mannosyl donor **9F** towards a set of glycosyl acceptors in glycosidation reactions promoted by catalytic amounts of $Bi(OTf)_3$ and to find out the optimized conditions for the glycosidations to occur (**Scheme 12**, **Table 1**). Fmoc in 2-*O*-Fmoc trihaloacetimidate donors is expected to behave initially as a participating group to guarantee α-selectivity and then as a transient group removable by simple addition of excess TEA.



Scheme 12

Table 1 Optimization of catalytic α-mannosylations with trifluoroacetimidate donor **9F**.

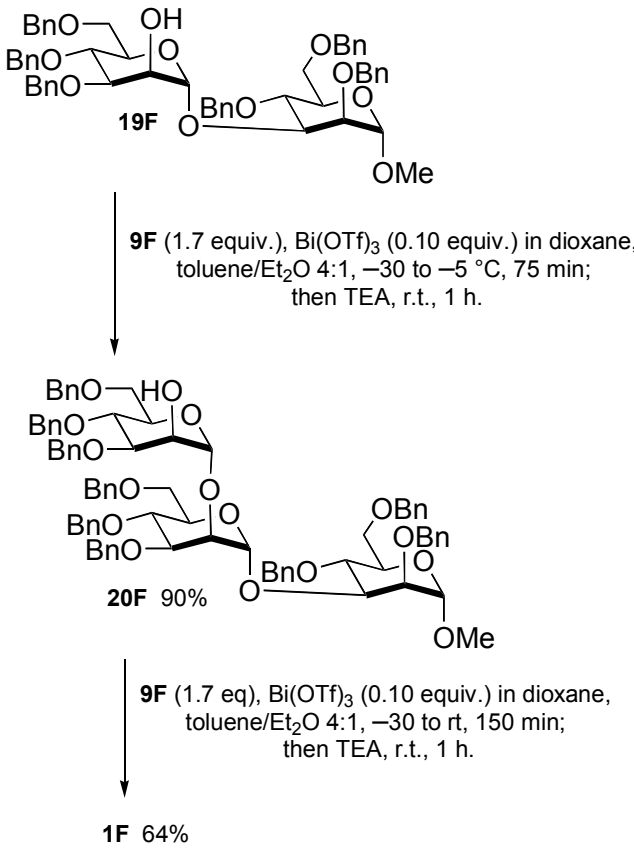
Entry	R-OH	Solvent	Products and yield
1	 **15F** SEt	DCE	 63% (α/β 1.7) **16F** SEt
2	 **32B**	DCE	 92% (α/β 5.1) **17F**
3	 **3E** OMP MP: *p*-methoxyphenyl	DCE	 85% (α/β 2.0) **18F** OMP
4	**3E**	DCM/Et_2O 4:1	**18F** 82% (α/β 2.5)
5	**3E**	$PhCH_3$/DME 2:1	sluggish reaction
6	**3E**	$PhCH_3/Et_2O$ 4:1	**18F** 85% (α only)
7	 **10F** OMe	$PhCH_3/Et_2O$ 4:1	 **19F** 87%

General conditions: **9F** (1.3-1.6 eq), acceptor, solvent, $Bi(OTf)_3$ (0.10 eq) added as a solution in dioxane, -30 °C to rt, 15-180 minutes. For the final solvent composition see experimental section. In entry 7, 0.08 eq of $Bi(OTf)_3$ were used and TEA was added to the glycosidation vessel just after accomplishment of the coupling (see experimental section for details).

The shown results indicate that the reaction outcome was strongly dependent on the solvent mixture. Although Fmoc was expected to act as a reliable participating group, in a DCE/dioxane solvent mixture the reaction provided not negligible amounts of beta-mannosides with different acceptors (entries 1-3), and in the case of the thioglycosyl acceptor **15F** (entry 1) the partial aglycon transfer (with formation of thioethyl 2-*O*-Fmoc mannoside) was also observed as an additional undesired event. To the best of our knowledge, in the literature are lacking examples of glycosidations where Fmoc group fails to act as a participant functionality.[17]

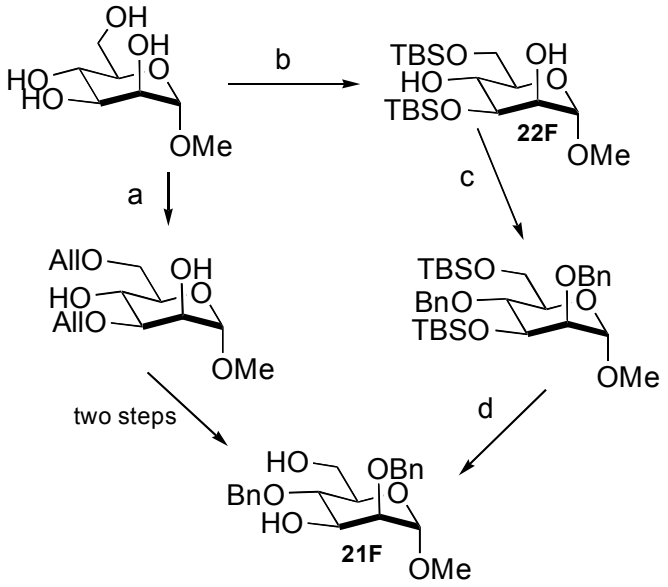
Further experimentation was devoted to the screening of alternative solvent mixtures. Use of a 1,2-dimethoxyethane (DME) containing solvent mixture (entry 5), previously found to be highly α-selective with perbenzylated donors,[18] gave disappointing results due to the sluggish activation of the more disarmed 2-*O*-Fmoc donor. This behaviour might be rationalized by considering the ability of 1,2-dimethoxyethane to chelate the Lewis acid. A mixture of DCM/diethyl ether gave **18F** in high yield (entry 4) but the stereoselectivity was still poor. More rewarding results were eventually gained by using a toluene/diethyl ether/dioxane solvent mixture (entries 6-7), which in previous studies had been applied only to carry out α-selective glycosidations with donors devoid of 2-*O*-participating groups.[6,19,20] Under these conditions, no β-mannosides could be detected in the reaction mixtures. In entry 7 the result refers to the glycosidation reaction/Fmoc removal sequence conducted by simple addition of TEA[21] on completion of the coupling. As anticipated, the desired base-promoted deprotection occurred uneventfully. The deprotected disaccharide **19F** obtained in entry 7, represents the reducing disaccharide terminus of the target sequence **1F** and it was obtained, after chromatographic purification, in very good 87% overall yield in less than two hours.

Once established the best glycosidation solvent, elongation of the acceptor disaccharide **19F** was attempted through the glycosidation of the sterically encumbered axial 2-OH (**Scheme 13**). Slight modifications of the optimized protocol gave acceptor trisaccharide **20F** in an excellent overall yield (90 %), comparable with that of the previous one-pot sequence (**Table 1**, entry 7). Further coupling of this latter with donor **9F** under analogous conditions gave tetrasaccharide **1F** in a rewarding, albeit lower overall yield (64 %). The whole sequence of the three synthetic operations gave the D1 tetrasaccharide **1F** in about 50% overall yield for six steps, corresponding to almost 90% average yield for each step, and required only three chromatographic purifications. Comparison of NMR data with those reported in for a differently synthesized tetrasaccharide **1F**[14a] confirms the identity of the obtained product, with the anomeric linkages all being alpha-configured.



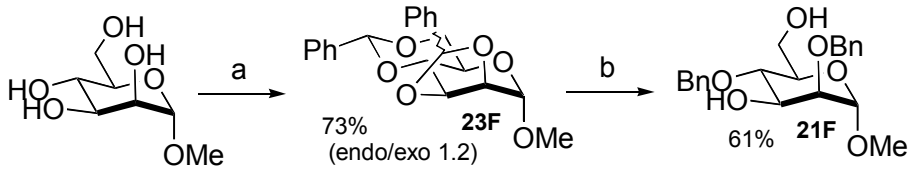
Scheme 13 Assembly of tetrasaccharide **1F**.

The here proposed strategy was then applied to the more demanding target mannan pentasaccharide **2F** (**Figure 3**). This sequence requires an efficient access to diol **21F** that was the reducing terminus precursor of **2F**. For this purpose the synthetic scheme described by Ogawa was applied (**Scheme 14**),[22] but the initial 3,6-di-*O*-allylation via stannylidene chemistry was found too sluggish and not satisfying in terms of yield (ca 30%) due to the prevalent formation of the mono 3-*O*-allylated derivative. Thus the attention turned to an alternative scheme, such as that described by Huang a coworkers on a mannosyl derivative bearing a propylazido aglycon. This entails (**Scheme 14**) regioselective 3,6-di-*O*-silylation with TBSCl of methyl α-D-mannopyranoside affording **22F**, its subsequent 2,4-di-*O*-benzylation and final removal of TBS.[23] The overall sequence proceeded smoothly but afforded the desired diol in 42% overall yield.



Scheme 14 Attempted three-steps routes to diol **21F**. Reaction conditions: a) Bu_2SnO (2.2 eq), MeOH reflux, 3 hours; solvent removal then toluene, TBAI (2 eq), AllBr (20 eq), 70 °C, 72 h; b) TBSCl, DMF, imidazole, 66% yield; c) NaH, BnBr, DMF; d) excess Pyr·HF, 64% yield over two steps.

After having tested known three steps procedures, a more convenient access to the target was attempted by resorting to an original two-steps approach (**Scheme 15**).

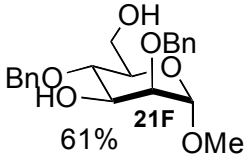
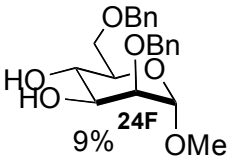
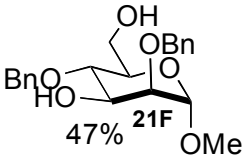
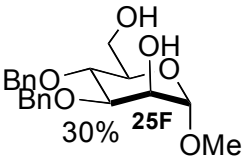
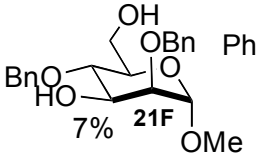
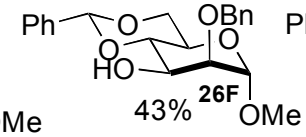
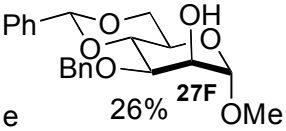


Scheme 15 A two-steps route to diol **21F.** Reaction conditions: a) $PhCH(OMe)_2$, DMF, CSA, 70 °C, 250 mbar; b) BH_3·THF, $Cu(OTf)_2$, 0 °C to rt.

In the first step methyl mannopyranoside was submitted to a double benzylidenation by slightly modifying a previously reported procedure described by Liptak and coworkers.[24] Product **23F** was obtained after chromatographic purification as an almost equimolar diasteroisomeric mixture (*endo*/*exo* 1.2:1). It's well established by several precedents[25,26] that the reductive opening of five-membered benzylidenes displays complementary regioselectivity according to the configuration of the starting material. However, I have observed that when the *exo*/*endo* mixture of **23F** was directly submitted to reductive opening conditions reported by Hung and co-workers (excess BH_3·THF and 0.3 eq of copper(II) triflate)[27] the desired 3,6-diol **21F** largely prevailed (**Scheme 15** and **Table 2**, entry 1). Minor amounts (ca 10 %) of the unexpected 3,4-diol **24F** were also isolated and characterized in its

acetylated form (**Table 2**, entry 1). Other experiments displayed that the outcome of the benzylidene reductive opening was critically dependent on the experimental procedure. As shown on **Table 2**, the reaction was much more sluggish and much less regioselective when it was conducted in the presence of molecular sieves (entries 2 and 3). Preliminary coevaporation of copper(II) triflate in toluene also strongly influenced the final composition of the reaction mixture (compare entry 2 and 3).

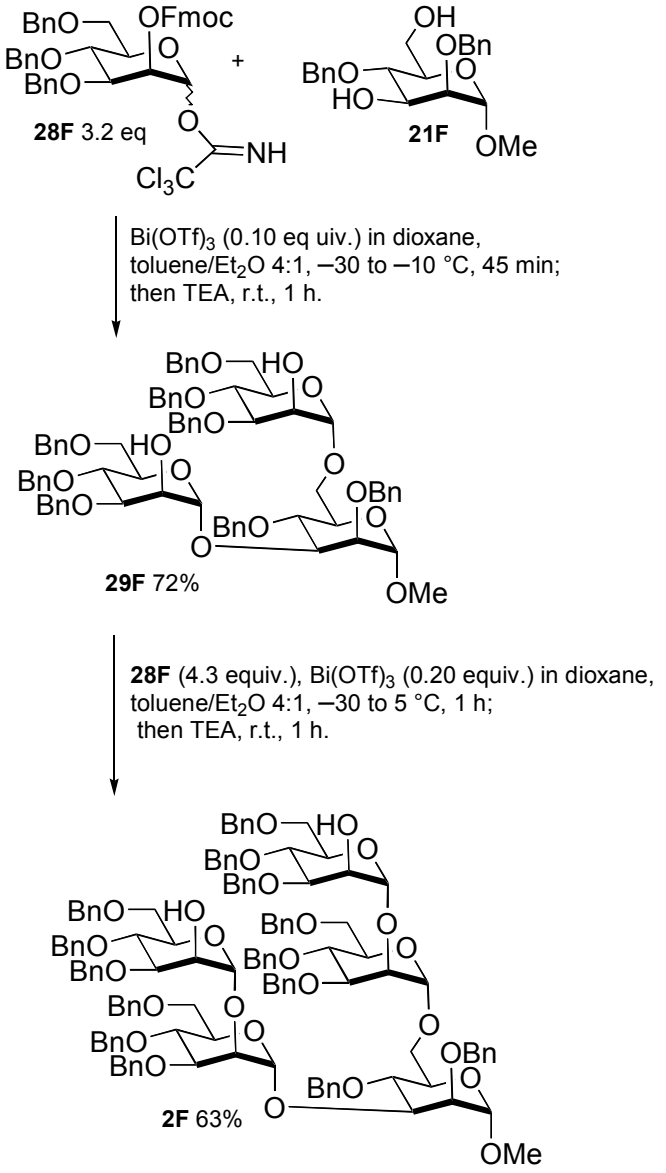
Table 2. Optimization of double reductive opening of **23F.**

Entry	Conditions	Time (h)	Products and yields
1	A	1.7	 61% **21F**  9% **24F**
2	B	48	 47% **21F**  30% **25F**
3	C	48	 7% **21F**  43% **26F**  26% **27F**

General conditions: **23F**, BH_3.THF (1M in THF, 10 eq), then $Cu(OTf)_2$ (sol in THF, 0.3 eq), 0 °C to rt. Condition A: neither use of molecular sieves, nor coevaporation in toluene of $Cu(OTf)_2$ prior to its use. Condition B: use of 4Å molecular sieves and coevaporation in toluene of $Cu(OTf)_2$ prior to its use. Condition C: use of 4Å molecular sieves and no coevaporation in toluene of $Cu(OTf)_2$ prior to its use.

Having established a straightforward access to the reducing terminus precursor of **2F**, its direct double glycosidation was attempted. Simultaneous attachment of two mannose residues to acceptor diol **21F** is not a trivial task (**Scheme 16**). As a matter of fact in some cases the assembly of this trisaccharide structure entails long sequences in which the mannose residues are added to the branching unit at different stages.[28] Additionally, a literature survey[29] reveals that the removal of poorly accessible 2-*O*-transient protecting groups from the inserted mannoses not frequently proceeds in yields higher than 90%. After a preliminary screening, for this application (**Scheme 16**) trichloroacetimidate **28F**[30] proved more efficient than the

trifluoro counterpart (**9F**) at providing trisaccharide **29F**. Indeed, with the latter donor higher amounts of intermediate dimannosides were detected; with donor **28F** the sequence of bis-glycosylation and bis-deprotection was instead satisfyingly carried out under very mild conditions, in short times, and in a very high overall yield (72% for four synthetic steps, **Scheme 16**). Trisaccharide diol **29F** was then exposed to trichloroacetimidate **28F** under $Bi(OTf)_3$ activation to afford pentasaccharide **2F** in 63 % overall yield. The whole synthesis was performed in only two synthetic operations and the overall yield (ca 45%) of its eight synthetic steps corresponded once again to a ca 90% average yield for each step.



Scheme 16 Assembly of pentasaccharide **2F**.

Comparison of NMR data of the obtained pentasaccharide with those of close analogues of **2F** (differentiated exclusively for the aglycon)[23,25] confirm the identity of the structure and the lack of β-mannosidic linkages.[23] It's noteworthy that oligosaccharides **1F** and **2F** were obtained in a partially protected form which can be exploited for further elaborations.

Conclusions

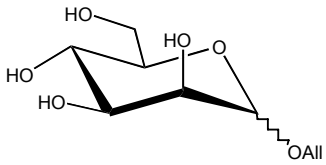
In conclusion, in this chapter it was shown that Fmoc protecting group can be simply removed in the same vessel where a $Bi(OTf)_3$ promoted glycosidation is conducted. Despite the expected participating effect of Fmoc group, it was found that the nature of the solvent is decisive for obtaining highly selective α-mannosylations. Iteration of this one-pot sequence leads to biologically useful mannose oligosaccharides related to HIV gp120 by performing a smaller number of synthetic operations than in other reported procedures towards similar sequences. As to yields, the effectiveness of the present approach often compares favourably with most of the synthetic schemes so far described,[8,9a,14,22,23,28,29] with exceptions being found in a few examples of especially high-yielding synthetic routes.[25,29h,29p-r] Anyway the actual merit of the strategy resides in the combination, rather unusual in other schemes, of simultaneous advantages such as the reduced experimental work (also because of the minimal number of required precursors), the attainment of high yields, and the exclusive use of a catalytic and moisture stable glycosidation promoter. Furthermore, the present iterable one-pot scheme is anticipated to be of broad applicability, thus adding a further useful complement to the recent strategical advances in oligosaccharide synthesis. As an additional result, it was disclosed a rapid approach for accessing a mannose building-block to be incorporated in branched structures that relies on a regioselective double reductive opening of a di-*O*-benzylidene mannose intermediate.

Experimental Section

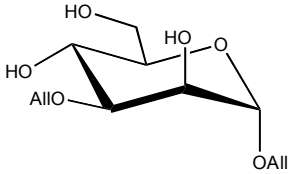
General methods and Material

Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded in $CDCl_3$ (internal standard, for ^{1}H: $CHCl_3$ at δ 7.26; for ^{13}C: $CDCl_3$ at δ 77.0) on Varian spectrometers at 200 or 500 MHz and 50 or 125 MHz, respectively, or on a Bruker Avance 400 spectrometer at 400 MHz. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. ^{1}H NMR assignments were based on homo-decoupling experiments. MALDI-MS spectra were recorded in the positive mode: compounds were dissolved in acetonitrile at a concentration of 0.1 mg/mL and one microliter of these solutions were mixed with one microliter of a 20 mg/mL solution of 2,5-dihydroxybenzoic acid in 7:3 CH_3CN/H_2O or, in the case of trifluoroacetimidate derivatives, with a 10 mg/mL solution of trihyroxyacetophenone in 1:1 $MeOH/H_2O$. Analytical thin layer chromatography (TLC) was performed on aluminium plates precoated with Silica Gel 60 F_{254} as the adsorbent. The plates were developed with 5% H_2SO_4 ethanolic solution and then heating to 130°C. Column chromatography was performed on Kieselgel 60 (63-200 mesh). When specified, anhydrous solvents stored over molecular sieves (purchased from Aldrich) were used. Bismuth(III) triflate was coevaporated three times in toluene and dried under vacuum for 30-45 minutes before being dissolved in the presence of freshly activated 4Å in dioxane.

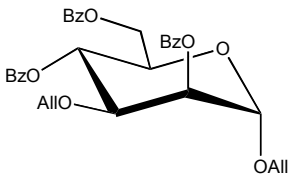
General procedure of glycosidation with donor 9F. A mixture of donor **9F** (0.13-0.16 mmol) and an acceptor (0.10 mmol) was coevaporated three times with anhydrous toluene (3 x 2 mL), and then dried in vacuo for 30 minutes. After adding 4Å AW 300 MS, the mixture was dissolved under argon with 4:1 toluene/Et_2O (4.1 mL), cooled to -30 °C, and stirred for 15 minutes. A solution of $Bi(OTf)_3$ in dioxane (14.5 mg/mL, 10 μmol, 0.45 mL) was then added, and the temperature was allowed to slowly raise to room temperature. On completion of the glycosidation (TLC analysis, 15-180 minutes for entries in **Table 1**), a few drops of pyridine were added and the reaction mixture was filtered on a short plug of silica gel repeatedly washed with DCM/MeOH/acetonitrile 85:10:5. The filtrate was concentrated, and the residue purified by silica-gel flash-chromatography (eluent: *n*-hexane/ethyl acetate or toluene/ethyl acetate).



Allyl α,β-D-mannopyranoside (4F). D-(+)-mannose (560 mg, 3.1 mmol) was suspended in allyl alcohol (2 mL) and then $Sc(OTf)_3$ (4 mg, 0.09 mol) was added. The reaction mixture was heated to reflux for 6 h and after the disappearance of the starting material (TLC 85:15 CH_2Cl_2/MeOH), a few frops of pyridine were added at room temperature. The reaction mixture was concentrated to dryness and flushed through a silica gel column under reduced pressure (9:1 CH_2Cl_2/MeOH), to yield allyl mannopyranoside **4F** (560 mg, 82%, α/β ca 8:1). Data for the α-anomer, ^{1}H NMR (D_2O, 300 MHz) δ 6.30-6.10 (1H, m, -OCH_2CH=CH_2), 5.58 (1H, dq, J_{trans} = 17.1 Hz, J_{gem} = 1.8 Hz, -OCH_2CH=$CH_{cis}H_{trans}$), 5.49 (1H, dq, J_{cis} = 10.2 Hz, -OCH_2CH=$CH_{cis}H_{trans}$), 5.14 (1H, d, $J_{1,2}$ = 1.8 Hz, H-1), 4.44 (1H, m, J_{gem} = 12.3 Hz, -OCH_aH_bCH=CH_2), 4.29 (1H, m, -OCH_aH_b-CH=CH_2), 4.18 (1H, dd, $J_{2,3}$ = 3.6 Hz, H-2), 4.09 (1H, dd, $J_{5,6a}$ = 0.9 Hz, $J_{6a,6b}$ = 11.7 Hz, H-6_a), 4.05-3.95 (2H, m, H-5 e H-6_b), 3.89 (1H, t, $J_{3,4}$ = $J_{4,5}$ = 9.6 Hz, H-4). ^{13}C NMR (D_2O, 75 MHz) δ 133.0 (-OCH_2CH=CH_2),, 118.3 (-OCH_2CH=CH_2), 98.5 (C-1), 72.1, 70.0, 69.5, 67.8, 66.2, 60.4.

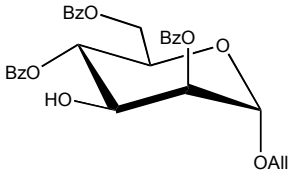


Allyl 3-*O*-allyl-α-D-mannopyranoside (5F). Allyl α,β-mannopyranoside **4F** (328 mg, 1.5 mmol) and Bu_2SnO (410 mg, 1.6 mmol) were refluxed in MeOH (7.4 mL) for 2 hours. The obtained solution was evaporated under vacuum. To the residue suspended in toluene (9 mL), allyl bromide (1.26 mL, 15 mmol) and TBAI (557 mg, 1.5 mmol) were sequentially added. The mixture was kept under stirring at 65-70 °C for 20 hours, and concentrated. Silica-gel flash-chromatography of the residue (eluent: ethyl acetate/petroleum ether from 7:3 to AcOEt) yielded **5F** slightly contaminated with tetrabutylammonium salts (estimated yield 64 % on the base of NMR integrations). The product thus obtained was directly submitted to the subsequent step. ^{1}H NMR ($CDCl_3$, 200 MHz) significative signals δ 6.05-5.70 (2H, m, 2x -OCH_2CH=CH_2), 5.34-5.11 (4H, m, 2x –OCH_2CH=CH_2), 4.86 (1H, s, H-1). ^{13} C NMR ($CDCl_3$, 50 MHz) δ 134.3, 133.5 (2x -OCH_2CH=CH_2), 117.9, 117.2 (2x -OCH_2CH=CH_2), 98.8 (C-1), 79.0, 72.3, 70.8, 67.9, 67.8, 64.7, 60.9.



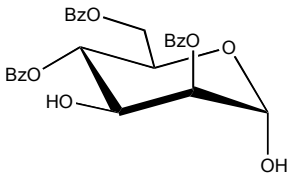
Allyl 3-*O*-allyl-2,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (6F). To a solution of compound **5F** (estimated mass ca 248 mg, ca 0.9 mmol) in dry pyridine (4.4 mL) was added at 0°C benzoyl chloride (442 μL, 4 mmol). The mixture was allowed to warm to rt, and after 2 hours a few drops of MeOH (ca 1 mL) were added. The mixture was diluted with DCM and

the organic phase washed with water. The aq phase was re-extracted with DCM and the collected organic phases were dried with anhydrous Na_2SO_4 and concentrated *in vacuo* to give a residue which was purified by silica gel flash-chromatography (eluent: petroleum ether/ethyl acetate from 9:1 to 8:2) to yield **6F** as an oil (421 mg, 77%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.30-7.10 (Ar), 6.08-5.92 (1H, m, -OCH_2CH=CH_2), 5.89 (1H, t, 4-H, J = 9.9 Hz), 5.80-5.65 (1H, m, -OCH_2CH=CH_2), 5.64 (1H, dd, $J_{1,2}$ = 2.1 Hz, $J_{2,3}$ = 3.0 Hz, 2-H), 5.33 (1H, dd, J_{trans} = 17.1 Hz, J_{gem} = 1.5 Hz, -OCH_2CH=$CH_{cis}H_{trans}$), 5.24 (1H, dd, J_{cis} = 10.5 Hz, J_{gem} = 1.5 Hz, -OCH_2CH=$CH_{cis}H_{trans}$), 5.17 (1H, dd, J_{trans} = 17.1 Hz, J_{gem} = 1.5 Hz, -OCH_2CH=$CH_{cis}H_{trans}$), 5.09 (1H, d, 1-H), 5.04 (1H, dd, J_{cis} = 10.5 Hz, J_{gem} = 1.2 Hz, -OCH_2-CH=$CH_{cis}H_{trans}$), 4.70 (1H, dd, $J_{5,6a}$ = 2.5 Hz, H-6_a), 4.45 (1H, dd, $J_{5,6b}$ = 4.3 Hz, $J_{6a,6b}$ = 12.3 Hz, H-6_b), 4.35-4.26 (2H, m, 5-H, –OCH_2CH=CH_2), 4.21 (1H, dd, 3-H), 4.16-3.98 (3H, m, 3x –OCH_2CH=CH_2). ^{13} C NMR ($CDCl_3$, 75 MHz) δ 165.9, 165.4, 165.2 (3x -*C*OPh), 134.0, 133.1 (x3), 133.0, 132.8, (aromatic C e 2x -OCH_2CH=CH_2), 129.7-129.4, 128.2 (aromatic CH), 118.0, 117.2 (2x -OCH_2CH=CH_2), 96.8 (C-1), 74.3, 70.5, 69.0, 68.8, 68.5, 68.2, 62.9 (C-6).

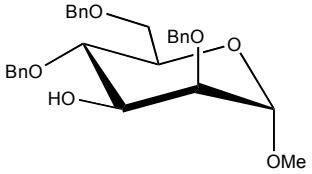


Allyl 2,4,6-tri-*O*-benzoyl-α-D-mannopyranoside (7F). Compuond **6F** (421 mg, 0.73 mmol) was dissolved in the solvent mixture MeOH/DCM 3.7:1 (4.7 mL) and then to the solution was added at rt palladium chloride (14 mg, 0.079 mmol). The mixture was stirred overnight and after the disappearance of **6F** (TLC petroleum ether/ethyl acetate 4:6) we observed two products with different chromatographic mobility, one with R_f = 0.77 and the other with R_f = 0.43. The reaction mixture was then concentrated under vacuum, the obtained residue was then filtered through a short plug of silica gel (eluent DCM/MeOH 95:5), concentrated, and purified by silica-gel flash chromatography (eluent: petroleum ether/ ethyl acetate 7:3) to provide **7F** as an oil (49 mg, yield 12%, R_f = 0.77) and diol **8F** as an oil (286 mg, yield 79%, R_f = 0.43). Compound **7F** was subsequently deallylated under analogous conditions to provide **8F** in 92% combined yield. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.10-7.27 (Ar), 6.04-5.89 (1H, m, -OCH_2CH=CH_2), 5.72 (1H, t, J = 9.9 Hz, 4-H), 5.45 (1H, dd, $J_{2,3}$ = 3.6 Hz, 2-H), 5.34 (1H, dd, J_{trans} = 17.1 Hz, J_{gem} = 1.5 Hz, -OCH_2CH=$CH_{cis}H_{trans}$), 5.26 (1H, dd, J_{cis} = 10.5 Hz, J_{gem} = 1.5 Hz, -OCH_2CH=$CH_{cis}H_{trans}$), 5.11 (1H, d, $J_{1,2}$ = 1.5 Hz, 1-H), 4.68 (1H, dd, $J_{5,6a}$ = 2.4 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6_a), 4.50-4.43 (2H, m, 3-H and H-6_b), 4.36-4.25 (2H, m, 5-H and -OCH_aH_bCH=CH_2), 4.15-4.08 (1H, m, -OCH_aH_bCH=CH_2). ^{13} C NMR ($CDCl_3$, 75 MHz) δ 166.7, 166.1, 165.8 (3x *C*OPh), 133.5, 133.4 (x2), 133.1 (aromatic C and

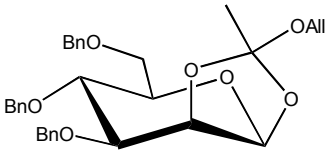
-$OCH_2CH{=}CH_2$), 129.9-128.3 (aromatic CH), 118.1 (-$OCH_2CH{=}CH_2$), 96.6 (C-1), 72.8, 70.3, 69.0, 68.8, 68.5, 63.0.



2,4,6-Tri-*O*-benzoyl-α-D-mannopyranose (8F). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 8.20-7.10 (Ar), 5.75 (1H, t, J = 10.0 Hz, 4-H), 5.49-5.32 (2H, m, 1-H and 2-H), 4.68 (1H, dd, $J_{5,6a}$ = 2.2 Hz, $J_{6a,6b}$ = 12.0 Hz, H-6_a), 4.53-4.42 (2H, m, 3-H and 5-H), 4.36 (1H, dd, $J_{5,6b}$ = 3.4 Hz, H-6_b), 3.34 (1H, d, J = 2.2 Hz), 3.00 (1H, bs). ^{13} C NMR ($CDCl_3$, 50 MHz) δ 166.6, 166.4, 166.1 (3x *C*OPh), 133.4, 133.3, 133.0 (aromatic C), 129.8-128.3 (aromatic CH), 91.9 (C-1), 73.4, 70.2, 68.2 (x2), 62.9.

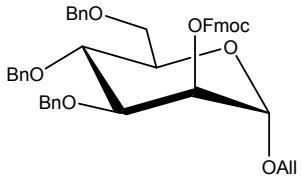


Methyl 2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (10F). To a solution of **11E**[6] (260 mg, 0.515 mmol) in 2.5:1 MeOH/DCM (3.5 mL) was added at rt palladium chloride (10 mg, 0.056 mmol). The mixture was stirred overnight and then concentrated under vacuum. The residue was then filtered through a short plug of silica gel (eluent: DCM/MeOH 95:5), concentrated and purified by silica-gel flash chromatography (eluent: petroleum ether/ethyl acetate from 8:2 to 7:3) to provide **10F** as an oil (215 mg, 90%); $[\alpha]_D^{29}$ +15.6 (*c* 1.0 in $CHCl_3$), (lit.,[31] $[\alpha]^{29}_D$ +14.5 (c 1.0, $CHCl_3$));^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.40–7.15 (Ar), 4.87 (bs, 1 H, 1-H), 4.90-4.50 (3x AB, 6 H, 3x –CH_2Ph), 4.05-3.95 (m, 1 H, 5-H), 3.85-3.70 (overlapped signals, 4 H, 2-H, 4-H and 6-H_2), 3.37 (s, 3 H, 1-OCH_3), 2.50 (br s, 1 H, 3-OH) ppm. ^{13} C NMR (50 MHz; $CDCl_3$): δ = 138.3, 138.1, 137.6 (aromatic C), 128.4-127.4 (aromatic CH), 97.7 (C-1), 78.1, 76.4, 74.6, 73.2, 72.6, 71.6, 70.6, 69.0, 54.7 ppm. MALDI-TOF MS: calcd. for $[M+Na]^+$ 487.21; found 487.45. Calcd. for $C_{28}H_{32}O_6$ (487.21): C, 72.39; H, 6.94; found: C, 72.20; H, 6.85.



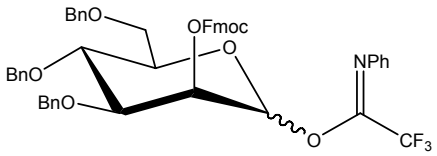
3,4,6-Tri-*O*-benzyl-1,2-*O*-(1-allyloxyethylidene)-β-D-mannopyranose (exo-orthoester) (14F). Allyl orthoester **14F** was syntesized, starting from D-mannose in 55% overall yield, with the same protocol affording methyl orthoester **6E**[15] by using AllOH rather MeOH in the 1,2-orthoesterification step. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.43-7.20 (aromatic protons), 6.00-5.90 (1H, m, -C*H*=CH_2), 5.35 (1H, d, $J_{1,2}$ = 2.5 Hz, H-1), 5.30 (1H, dd, J_{trans} = 17.5 Hz, J_{gem} = 1.5 Hz,-$CH_2CH{=}CH_{cis}H_{trans}$), 5.18 (1H, dd, J_{cis} = 11.0 Hz, -$CH_2CH{=}CH_{cis}H_{trans}$), 4.95-4.53 (6H, 3 x AB, 3 x benzyl CH_2), 4.40 (1H, dd, $J_{2,3}$ = 4.0 Hz, H-

2), 4.10-4.00 (2H, m, -C*H*$_2$CH=CH$_2$), 3.92 (1H, t, J = 9.5 Hz, H-4), 3.80-3.68 (3H, m, H-3, H-6a, H-6b), 3.47-3.40 (1H, m, H-5), 1.77 (3H, s, -CH$_3$). ^{13}C NMR (CDCl$_3$, 50 MHz) δ 138.2 (x2), 137.8 (aromatic C), 134.4 (-*C*H=CH$_2$), 128.5, 128.4, 128.3, 128.0, 127.7, 127.6, 127.5, 126.9 (aromatic CH), 123.8 (quaternary orthoester C), 116.5 (-CH=*C*H$_2$), 97.4 (C-1), 78.9, 76.9, 75.2, 74.1 (x2), 73.3, 72.3, 68.9, 63.6, 24.8 (orthoester -*C*H$_3$).



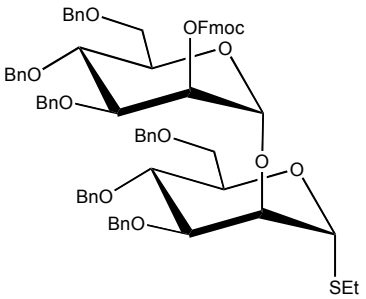
Allyl 3,4,6-tri-*O*-benzyl-2-*O*-fluorenylmethoxycarbonyl-α-D-mannopyranoside (13Fα). Allyl orthoester **14F** (3.69 g, 6.93 mmol) was coevaporated three times with toluene (3 x 5 mL) and dried under vacuum. After adding freshly activated 4Å molecular sieves, **14F** was dissolved at rt in dry DCM (47 mL) and allyl alcohol (2.36 μL, 34.6 mmol) was subsequently added. The mixture was then cooled to 0 °C and stirred for ca 10 minutes. A solution of $BF_3{\cdot}OEt_2$ (0.3 M in DCM, 4.7 mL, 1.41 mmol) was then added at 0°C under argon. The mixture was allowed to warm to rt, stirred overnight and then was quenched at rt with pyridine (112 μl) after the disappearance of **14F** (TLC toluene/ethyl acetate 10:1). The mixture was filtered through a short plug of silica gel (eluent: DCM/MeOH/acetonitrile 85:10:5) and concentrated *in vacuo* to obtain crude **11Fα** as an oil that was directly submitted to the following step. ^{1}H NMR (200 MHz; $CDCl_3$): δ = 7.60–7.15 (Ar), 6.05-5.90 (m, 1 H, -C*H*=CH$_2$), 5.50 (br s, 1 H, 2-H), 5.36 (br d, 1 H, J_{trans} = 17.4, -CH$_2$CH=CH$_{cis}$*H*$_{trans}$), 5.28 (br d, J_{cis} = 10.2 Hz, 1 H, -CH$_2$CH=C*H*$_{cis}$H$_{trans}$), 5.00 (br s, 1 H, 1-H), 4.98-4.55 (6 H, 3x –CH$_2$Ph), 4.26 (m, 1 H, -C*H*$_a$H$_b$CH=CH$_2$), 4.15-3.98 (3 H), 3.95-3.79 (3 H), 2.23 (3 H, s, -COCH$_3$) ppm. ^{13}C NMR (75 MHz; $CDCl_3$): δ = 170.1 (-*C*OCH$_3$), 138.2, 138.0, 137.8 (aromatic C), 133.2 (-*C*H=CH$_2$); 128.2-127.4 (aromatic CH), 117.5 (-CH=*C*H$_2$), 96.7 (C-1), 78.0, 74.9, 74.2, 73.2, 71.6, 71.3, 68.7, 68.6, 67.9 ppm. Crude **11Fα** was dissolved in 4:1 MeOH/DCM (10 mL) and the mixture was then cooled to 0 °C. At this temperature some drops of a solution of MeONa (2M in MeOH) were added, the mixture was allowed to warm to rt and stirred overnight. After adding Amberlist 15, the supernatant was removed and concentrated *in vacuo* to obtain an oil in a satisfying purity to be directly submitted to the last step of this one-pot sequence. Spectroscopic data of the 2-*O*-deacetylated intermediate **12Fα**:[29m] ^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.40–7.10 (Ar), 6.00-5.80 (m, 1 H, -C*H*=CH$_2$), 5.30-5.15 (2 H, -CH=C*H*$_2$), 5.02 (d, $J_{1,2}$ = 1.6 Hz, 1 H, 1-H), 4.90-4.45 (6 H, 3x –CH$_2$Ph), 4.25-4.10 (m, 1 H, -C*H*$_a$H$_b$CH=CH$_2$), 4.08-3.95 (2 H, -C*H*$_a$H$_b$CH=CH$_2$ and H-2), 3.90-3.65 (4 H, 3-H, 4-H, 5-H and 6-H$_2$), 2.44 (d, $J_{2,OH}$ = 2.2 Hz, 1 H, 2-OH) ppm.

The product from the previous step was dissolved at rt in dry DCM (68 mL) and pyridine (5.75 mL, 71.5 mmol) and FmocCl (2.33 g, 9.0 mmol) were sequentially added under argon to the solution. The mixture was stirred for 25 minutes and was then diluted with EtOAc, washed three times with an aqueous saturated solution of $CuSO_4$ and the organic phase was dried with anhydrous Na_2SO_4 and concentrated *in vacuo* to give a residue which was purified by silica gel flash-chromatography (eluent: petroleum ether/ethyl acetate from 9:1 to 85:15) to yield **13Fα** as a yellow oil (3.73 mg, 76% over three steps). $[\alpha]_D^{29}$ +19.9 (*c* 0.6 in $CHCl_3$); ^{1}H NMR (200 MHz; $CDCl_3$): δ 7.80–7.10 (Ar), 6.00-5.80 (m, 1 H, -C*H*=CH_2), 5.35-5.18 (3 H, -CH=C*H*$_2$ and 2-H), 5.02 (d, $J_{1,2}$ = 1.6 Hz, 1 H, 1-H), 4.95-4.25 (9 H, 3x –CH_2Ph and Fmoc –OCH_2CH-), 4.25-4.15 (1 H, m, -C$H_a$$H_b$CH=$CH_2$), 4.10-3.70 (6H, -C$H_a$$H_b$CH=$CH_2$, 3-H, 4-H, 5-H, 6-$H_2$) ppm. ^{13}C NMR (50 MHz; $CDCl_3$): δ 154.5 (Fmoc-CO_2), 143.2, 142.9, 141.0, 140.9, 138.0, 137.9, 137.7 (aromatic C), 133.1 (-*C*H=CH_2); 128.0-126.9, 122.1, 124.9, 119.7 (aromatic CH), 117.5 (-CH=*C*H_2), 96.3 (C-1), 78.0, 75.0, 74.1, 73.1, 72.4, 71.5, 71.3, 69.9, 68.6, 67.8, 46.3 ppm. MALDI-TOF MS: calcd. for $[M + Na]^+$ 735.30, found 735.25. Calcd. for $C_{45}H_{44}O_8$ (712.84): C, 75.82; H, 6.22. Found: C, 75.53; H, 6.15.

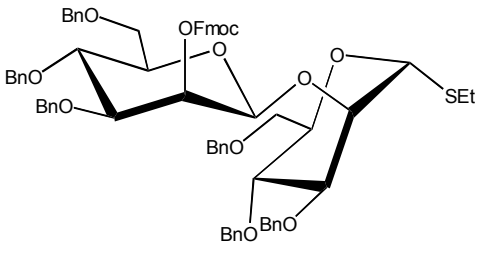


3,4,6-Tri-*O*-benzyl-2-*O*-fluorenylmethoxycarbonyl-α,β-D-mannopyranosyl (N-phenyl)trifluoroacetimidate (9F). To a solution of **13Fα** (474 mg, 0.67 mmol) in 1.6:1 MeOH/DCM (6.7 mL) was added at rt palladium chloride (12 mg, 0.068 mmol). The mixture was stirred overnight and then concentrated under vacuum. The residue was then filtered through a short plug of silica gel (eluent DCM/MeOH 95:5) and concentrated to yield the hemiacetal intermediate in a satisfying purity to be directly submitted to the following step. Spectroscopic data: ^{1}H NMR (200 MHz; $CDCl_3$): significant signals at δ = 7.90–7.20 (Ar), 5.41 (br s, 1 H, 1-H), 5.30 (br d, 1 H, 2-H), 4.14 (dd, $J_{2,3}$ = 2.4 Hz, $J_{3,4}$ = 9.0 Hz, 1 H, 3-H), 3.90-3.70 (m, 2 H, 6-H_2) ppm. ^{13}C NMR (50 MHz; $CDCl_3$): δ = 154.6 (Fmoc-CO_2), 143.3, 143.1, 141.0, 138.1, 137.8, 137.6 (aromatic C), 128.2-127.0, 125.2, 125.0, 119.8 (aromatic CH), 91.9 (C-1), 77.6, 74.9, 74.5, 73.2, 73.0, 71.6, 70.7, 70.0, 69.4 ppm. To a solution of the hemiacetal in acetone (6 mL) were sequentially added at 0 °C Cs_2CO_3 (239 mg, 0.733 mmol) and (*N*-phenyl)trifluoroacetimidoyl chloride (230 μL, 1.82 mmol). The mixture was allowed to warm to rt and after three hours was diluted with DCM, filtered through Celite (eluent: ethyl acetate) and concentrated under vacuum. The residue was purified by silica gel flash-chromatography (eluent: petroleum ether/ethyl acetate from 9:1 to 8.5:1.5) to yield **9F** as a

yellow oil (anomeric mixture α/β ca 7.6:1, 506 mg, 90% over two steps). ^{1}H NMR (400 MHz; $CDCl_3$); signals of α-anomer at δ = 7.90–7.00 (Ar), 6.61 (br s, 1 H, 1-H), 5.55 (bs, 1 H, 2-H), 5.12-4.70 (6 H, 3x –CH_2Ph), 4.63-4.48 (3 H, Fmoc –OCH_2CH-), 4.42-4.10 (3 H, 3-H, 4-H and 5-H), 4.05-3.90 (2 H, 6 H_2) ppm. ^{13}C NMR (50 MHz; $CDCl_3$): δ = 154.3 (Fmoc-CO_2), 143.1, 142.9, 142.8, 141.3, 141.0, 137.8 (x2), 137.3 (aromatic C); 128.8-125.7, 120.4, 119.8, 119.1 (aromatic CH), 93.9 (C-1), 77.3, 75.2, 74.0, 73.4, 73.2, 72.1, 71.1, 70.2, 68.3 ppm. MALDI-TOF MS: calcd. for $[M + Na]^+$ 866.30, found 866.15. Calcd. for $C_{50}H_{44}F_3NO_8$ (866.30): C, 71.16; H, 5.26. Found: C, 71.00; H, 5.35.

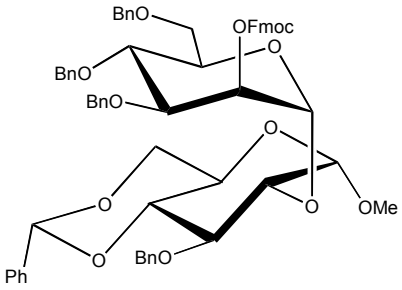


Ethyl 3,4,6-tri-*O*-benzyl-2-*O*-fluorenylmethoxycarbonyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (16α). ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.91-7.00 (Ar), 5.45 (s, 1H, H-1), 5.40 (bd, 1H, H-2'), 5.21 (s, 1H, H-1'), 5.00-4.41 (m, 6 x AB, 12H, 6 x -C*H*$_2$Ph), 4.40-4.23 (m, 3H, -C*H*$_2$O and H-9 Fmoc), 4.20-4.01 (m, 4H, H-2, H-5, H-3' and H-5'), 4.00-3.78 (m, 6H), 3.72 (d, $J_{6a, 6b}$ = 11.1 Hz, 1H, H-6b), 2.64-2.49 (m, 2H, -SC*H*$_2$CH$_3$), 1.24 (t, 3H, *J* 7.2 Hz, -SCH$_2$C*H*$_3$). ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 154.7 (-O*C*O$_2$-), 143.7, 143.4, 141.3, 141.2 (Fmoc aromatic C), 138.6 (x 2), 138.5, 138.4, 138.2, 138.1 (aromatic C), 128.3-120.0 (aromatic CH), 99.4 (C-1'), 80.2 (C-1), 78.2, 75.9, 75.6, 75.2, 75.1, 75.0, 74.6, 73.4, 73.3, 72.8, 72.3 (x 3), 72.0, 70.3, 69.3 (x 2), 46.7 (Fmoc -*C*HCH$_2$), 25.5 (-S*C*H$_2$CH$_3$), 15.0 (-SCH$_2$*C*H$_3$). MALDI-TOF MS: calcd. for $[M + Na]^+$ 1171.47. found 1171.4. Calcd. for $C_{71}H_{72}O_{12}S$: C, 74.19; H, 6.31. Found: C, 74.45; H, 6.25.

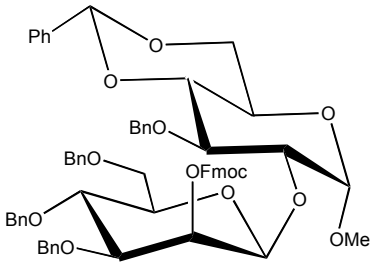


Ethyl 3,4,6-tri-*O*-benzyl-2-*O*-fluorenylmethoxycarbonyl-β-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-1-thio-α-D-mannopyranoside (16β). ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.80-6.90 (Ar), 5.57 (d, $J_{1,2}$ = 2.7 Hz, 1H, H-1), 5.43 (d, $J_{2,3}$ = 1.5 Hz, 1H, H-2'), 5.07-4.77 (m, 4H, -C*H*$_2$Ph and H-1'), 4.76-4.43 (m, 4 x AB, 8H, 4 x -C*H*$_2$Ph), 4.42-4.19 (m, 4H), 4.18-4.05 (m, 2H), 3.94 (t, *J* = 9.4 Hz, 1H), 3.93-3.58 (m, 7H), 3.57-3.48 (m, 1H, H-5'), 2.77-2.43 (m, 2H, -SC*H*$_2$CH$_3$), 1.26 (t, 3H, *J* 7.5 Hz, -SCH$_2$C*H*$_3$). ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 155.1 (-O*C*O$_2$-), 143.9, 143.4, 141.2, 141.1 (Fmoc aromatic C), 138.6, 138.5, 138.4, 138.3 (x 2), 137.6 (aromatic C), 128.4-119.8 (aromatic CH), 95.8 (C-1'), 81.1 (C-1), 80.1, 78.2, 75.9, 75.2, 75.1,

74.5, 74.4, 73.6, 73.4, 73.1, 72.3, 71.8, 71.4, 70.6, 70.3, 69.6, 69.4, 46.8 (Fmoc -*C*HCH$_2$), 25.5 (-S*C*H$_2$CH$_3$), 15.0 (-SCH$_2$*C*H$_3$). MALDI-TOF MS: calcd. for [M + Na]$^+$ 1171.47. found 1171.7. Calcd. for $C_{71}H_{72}O_{12}S$: C, 74.19; H, 6.31. Found: C, 74.40; H, 6.20.

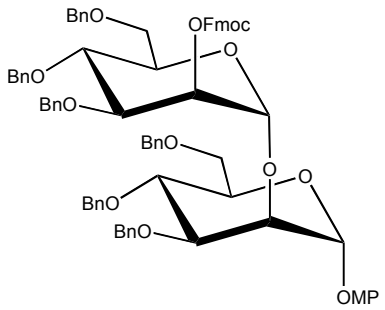


Methyl 3,4,6-tri-*O*-benzyl-2-*O*-fluorenylmethoxycarbonyl-α-D-mannopyranosyl-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (17α). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.03 (m, Ar), 5.58 (s, 1H, benzylidene -CHPh), 5.37 (br d, 1H, H-2'), 5.17 (s, 1H, H-1'), 4.96 (d, $J_{1,2}$ = 3.2, 1H, H-1), 5.00-4.38 (m, 4 x AB, 8H, 4 x -C*H*$_2$Ph), 4.50-4.45 (m, 1H, Fmoc –CHCH$_2$O-), 4.40 (d, J = 12.0 Hz,1H, Fmoc -CHCH$_a$*H*$_b$O-), 4.35-4.28 (m, 3H, H-6a, and Fmoc –CHCH$_2$O-), 4.25-4.20 (m, 1H, H-5'), 4.14 (dd, $J_{2,3}$ = 2.8 Hz, $J_{3,4}$ = 9.6 Hz, 1H, H-3'), 4.07 (t, $J_{3,4}$ = 9.6 Hz, 1H, H-4'), 4.00-3.95 (m, 2H, H-2 and H-3), 3.88 (td, $J_{5,6a}$ = 4.6 Hz, $J_{5,6b}$ = 9.8 Hz, 1H, H-5), 3.76 (t, $J_{5,6b}$ = $J_{6a,6b}$ = 10.0 Hz ,1H, H-6b), 3.73 (dd, $J_{5,6b}$ = 4.0 Hz, $J_{6a,6b}$ = 10.2 Hz, 1H, H-6'a), 3.67-3.57 (m, 2H, H-4 and H-6'b), 3.49 (s, 3H, -OMe). ^{13}C NMR (50 MHz, $CDCl_3$) δ 154.8 (-O*C*O$_2$-), 143.5, 143.1, 141.25, 141.20 (Fmoc aromatic C), 138.6, 138.3, 137.9, 137.8, 137.3 (aromatic C), 129.0-119.9 (aromatic CH), 101.2 (benzylidene -CHPh), 97.0, 94.3 (anomeric CH), 82.1, 79.1, 78.0, 75.6, 75.2, 74.1, 73.6, 73.0, 72.7, 71.8, 71.2, 70.2, 68.9, 68.5, 62.2, 55.4 (-OMe), 46.5 (Fmoc -*C*HCH$_2$). MALDI-TOF MS: calcd. for [M + Na]$^+$ 1049.41. found 1049.3. Calcd. for $C_{63}H_{62}O_{13}$: C, 73.67; H, 6.08. Found: C, 73.45; H, 6.15.

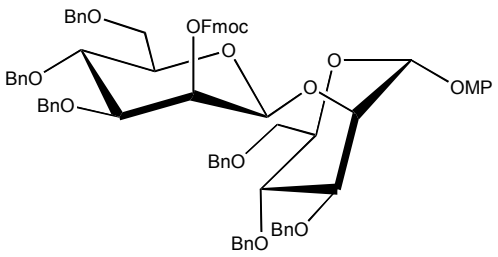


Methyl 3,4,6-tri-*O*-benzyl-2-*O*-fluorenylmethoxycarbonyl-β-D-mannopyranosyl-(1→2)-3-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside (17β). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.06 (Ar), 5.59 (s, 1H, benzylidene H), 5.35 (d, 1H, $J_{2,3}$ = 2.8 Hz, H-2'), 5.01-4.37 (4 x -C*H*$_2$Ph, 8H), 4.94 (d, 1H, $J_{1,2}$ = 3.9 Hz, H-1), 4.78 (s, 1H, H-1'), 4.50-4.35 (m, 2H, Fmoc -CHC*H*$_2$O-), 4.36-4.28 (m, 2H, H-6a and Fmoc -C*H*CH$_2$O-), 4.08 (t, $J_{2,3}$ = $J_{3,4}$ = 9.6 Hz 1H, H-3), 3.91-3.71 (m, 6H), 3.64 (t, $J_{4,5}$ = 9.6 Hz, 1H, H-4), 3.49 (dd, 1H, $J_{3,4}$ = 9.2 Hz, H-3'), 3.47-3.43 (m, 1H, H-5'), 3.30 (s, 3H, -OMe). ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.0 (-OCO$_2$-), 143.6, 143.5, 141.2, 141.1 (Fmoc aromatic C), 138.8, 138.2, 138.0, 137.5, 137.3 (aromatic C), 128.9-119.9 (aromatic CH), 101.3 (benzylidene CH), 100.2, 100.1 (anomeric CH), 82.4, 80.5, 79.5, 78.5, 75.5, 75.3, 74.1, 73.5, 72.1, 71.5, 70.2, 69.3, 69.1, 67.0, 62.3, 55.3

(-OMe), 46.7 (Fmoc -*C*HCH$_2$). [M + Na]$^+$ 1049.41. found 1049.3. Calcd. for $C_{63}H_{62}O_{13}$: C, 73.67; H, 6.08. Found: C, 73.50; H, 6.15.

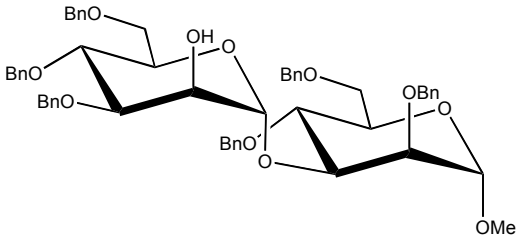


***p*-Methoxyphenyl 3,4,6-tri-*O*-benzyl-2-*O*-fluorenylmethoxycarbonyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (18α).** ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90-7.12 (Ar), 6.97 (d, J = 9.1 Hz, 2H, Ar-H$_{PMP}$), 6.74 (d, J = 9.1 Hz, 2H, Ar-H$_{PMP}$), 5.59 (d, $J_{1,2}$ = 2.0 Hz, 1H, H-1), 5.41 (dd, $J_{2,3}$ = 3.0 Hz, H-2'), 5.25 (d, $J_{1,2}$ = 1.6 Hz,1H, H-1'), 4.97-4.43 (m, 6 x AB, 12H, 6 x -CH_2Ph), 4.32 (d, J = 8.0 Hz, 1H, Fmoc -CHCH_aCH$_a$O-), 4.30 (d, J = 7.9 Hz, 1H, - Fmoc -CHCH$_a$CH_bO-), 4.25 (t, 1H, Fmoc -C*H*CH$_a$CH$_b$O-), 4.21 (t, $J_{2,3}$ = 2.5 Hz, 1H, H-2), 4.14 (dd, 1H, $J_{2,3}$ = 3.0 Hz, $J_{3,4}$ = 8.8 Hz, H-3), 4.11-4.02 (m, 2H, H-5' and H-3'), 3.97 (t, 1H, J = 9.3 Hz), 3.94-3.86 (m, 2H), 3.84-3.72 (m, 3H), 3.74 (s, 3H, -OMe), 3.69 (dd, $J_{5,6}$ = 1.6 Hz, $J_{6a,6b}$ = 11.2 Hz, 1H, H-6). ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.0 (*p*-methoxyphenyl aromatic C), 154.7 (-OCO$_2$), 150.1 (*p*-methoxyphenyl aromatic C), 143.6, 143.3, 141.3, 141.2 (Fmoc aromatic C), 138.5, 138.4, 138.3(3), 138.3(0), 138.2, 138.0 (aromatic C), 128.4-120.0 (aromatic CH), 117.9, 114.6 (*p*-methoxyphenyl aromatic CH), 99.3, 97.7 (C-1' and C-1), 79.5, 78.2, 75.24, 75.20, 75.0, 74.6, 74.5, 73.3, 73.2, 72.7, 72.5, 72.4, 72.2, 72.0, 70.2, 69.2 (x 2), 55.6 (-OMe), 46.7 (Fmoc -*C*HCH$_2$). [M + Na]$^+$ 1233.50. found 1233.6. Calcd. for $C_{76}H_{74}O_{14}$: C, 75.35; H, 6.16. Found: C, 75.20; H, 6.05.

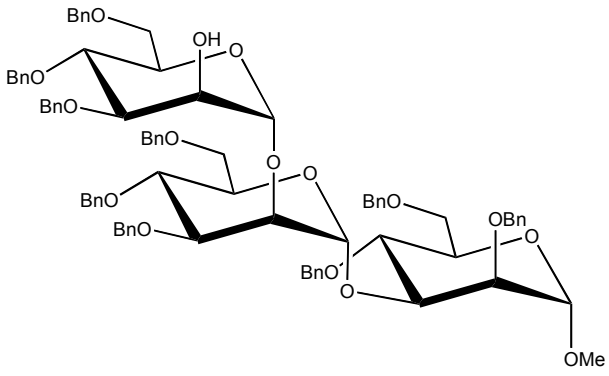


***p*-Methoxyphenyl 3,4,6-tri-*O*-benzyl-2-*O*-fluorenylmethoxycarbonyl-β-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranoside (18β)**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94-6.94 (Ar), 6.77 (d, J = 9.1 Hz, 2H, Ar-H$_{PMP}$), 5.57 (d, $J_{2,3}$ = 3.0 Hz, 1H, H-2'), 5.54 (d, $J_{1,2}$ = 2.4 Hz, 1H, H-1), 4.84 (s, 1H, H-1'), 4.52 (t, $J_{2,3}$ = 2.4 Hz, 1H, H-2), 4.94-4.46 (m, 12H, 6x -CH_2Ph), 4.34 (d, J = 8.0 Hz, 2H, Fmoc -CHCH_2O-), 4.24 (t, 1H, Fmoc -C*H*CH$_2$O-), 4.17-4.07 (m, 2H, H-3 and H-4'), 3.96-3.88 (m, 2H, H-4 and H-5), 3.85-3.70 (m, 3H, H-6a', H-6b', H-3'), 3.74 (s, 3H, -OMe), 3.66 (dd, $J_{5,6b}$ = 5.1 Hz, $J_{6a,6b}$ = 10.9 Hz, 1H, H-6b), 3.62 (dd, $J_{5,6a}$ = 2.3 Hz, 1H, H-6a), 3.58-3.61 (m, $J_{5,6a}$ = 1.7 Hz, $J_{5,6b}$ = 4.8 Hz, $J_{4,5}$ = 9.7 Hz, 1H, H-5'). ^{13}C NMR (50 MHz, $CDCl_3$) δ 155.0 (*p*-methoxyphenyl aromatic C and –OCO$_2$-), 150.5 (*p*-mMethoxyphenyl aromatic C),

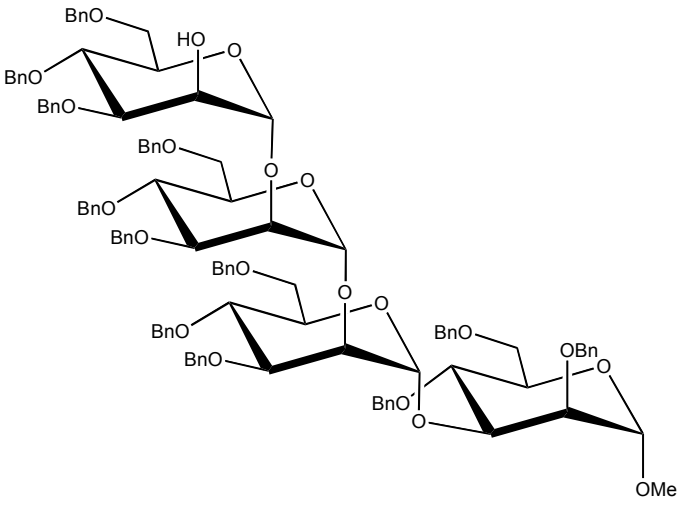
143.8, 143.4, 141.2, 141.1 (Fmoc aromatic C), 138.8, 138.4 (x 2), 138.2 (x 2), 137.6 (aromatic C), 128.4-119.8 (aromatic CH), 118.0, 114.6 (*p*-methoxyphenyl aromatic CH), 96.8, 96.7 (anomeric CH), 80.1, 78.5, 75.8, 75.3, 74.9, 74.5, 74.2, 73.6, 73.1, 72.4, 72.2, 72.1, 71.4, 71.0, 70.3, 69.6, 69.3, 55.6 (-OMe), 46.7 (Fmoc -*C*HCH$_2$). [M + Na]$^+$ 1233.50. found 1233.5. Calcd. for $C_{76}H_{74}O_{14}$: C, 75.35; H, 6.16. Found: C, 75.15; H, 6.10.



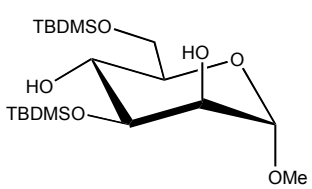
Methyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (19F). A mixture of donor **9F** (147 mg, 0.174 mmol) and acceptor **10F** (49 mg, 0.105 mmol) was coevaporated three times with anhydrous toluene (3 x 2 mL), and then dried in vacuo for 30 minutes. After adding 4Å AW 300 MS, the mixture was dissolved under argon with 4:1 toluene/Et_2O (3.3 mL), cooled to -30 °C, and stirred for 15 minutes. A solution of $Bi(OTf)_3$ in dioxane (14.5 mg/mL, 0.38 mL, 8.4 μmol) was then added, and the temperature was allowed to slowly raise. After 50 minutes (temperature at -20 °C), having realized the completion of the glycosidation step (TLC analysis, eluent: *n*-hexane/ethyl acetate 7:3), TEA (0.8 mL) was added and the reaction vessel was immediately warmed to rt. After one hour the reaction mixture was filtered on a short plug of silica gel repeatedly washed with DCM/MeOH/acetonitrile 85:10:5. The filtrate was concentrated, and the residue purified by silica-gel flash-chromatography (eluent: *n*-hexane/ethyl acetate from 3:1 to 2:1) to yield disaccharide **19F** as an oil (84 mg, 87% overall yield); $[\alpha]_D^{28}$ +29.1 (*c* 1.0 in $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$) δ = 7.40–7.10 (Ar), 5.22 (d, $J_{1,2}$ = 1.2 Hz, 1 H, 1′-H), 4.72 (d, $J_{1,2}$ = 1.6 Hz, 1 H, 1-H), 4.85-4.46 (12 H, 6x-CH_2Ph), 4.13 (dd, J = 3.2 and 10.6 Hz, 1 H), 4.02-3.60 (11 H), 3.29 (s, 3 H, -OCH_3), 2.31 (d, = 2.4 Hz, 1 H, OH-2) ppm. ^{13}C NMR (50 MHz; $CDCl_3$): δ = 138.6, 138.3 (x3), 138.1, 137.9 (aromatic C); 128.5-127.5 (aromatic CH); 101.2 and 98.2 (anomeric CH), 80.0, 78.4, 75.2, 75.0, 74.9, 74.4, 72.1, 72.0, 71.9, 71.7, 69.2, 69.0, 68.6, 54.8 ppm. MALDI-TOF MS: calcd. for [M + Na]$^+$ 919.40, found 919.27. Calcd. for $C_{55}H_{60}O_{11}$ (919.40): C, 73.64; H, 6.74. Found: C, 73.50; H, 6.65.



Methyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (20F). A mixture of donor **9F** (74 mg, 88 μmol) and acceptor **19F** (45 mg, 49 μmol) was coevaporated three times with anhydrous toluene (3 x 1 mL), and then dried in vacuo for 30 minutes. After adding 4Å AW 300 MS, the mixture was dissolved under argon with 4:1 toluene/Et_2O (3.3 mL), cooled to -30 °C, and stirred for 15 minutes. A solution of $Bi(OTf)_3$ in dioxane 14.5 mg/mL, 0.22 mL, 4.9 μmol) was then added, and the temperature was allowed to raise up to -5 °C over 75 minutes. Having realized the completion of the glycosidation step (TLC analysis, eluent *n*-hexane/ethyl acetate 7:3), TEA (0.83 mL) was added and the reaction vessel was immediately warmed to rt. After one hour the reaction mixture was filtered through a short plug of silica gel repeatedly washed with DCM/MeOH/acetonitrile 85:10:5. The filtrate was concentrated, and the residue purified by silica-gel flash-chromatography (eluent: *n*-hexane/ethyl acetate from 3:1 to 2:1) to yield trisaccharide **20F** as an oil (59 mg, 90 % overall yield); $[\alpha]_D^{28}$ +34.2 (*c* 1.3 in $CHCl_3$); ^1H NMR (400 MHz; $CDCl_3$): δ = 7.45–7.10 (Ar), 5.31 ($J_{1,2}$ = 1.6 Hz, 1 H, d, 1″-H), 5.13 (d, $J_{1,2}$ = 1.6 Hz, 1 H, 1′-H), 4.85 (d, $J_{1,2}$ = 1.6 Hz, 1 H, 1-H), 4.92-4.41 (18 H, 9 x-CH_2Ph), 4.18-4.12 (2 H), 4.10-3.80 (9 H), 3.80-3.65 (6 H), 3.55 (bd, *J* = 10.0 Hz, 1 H,), 3.33 (s, 3 H, -OCH_3), 2.48 (bs, 1 H, 2.OH) ppm. ^{13}C NMR (100 MHz; $CDCl_3$): δ = 138.8, 138.6, 138.55, 138.48 (x2), 138.41 (x2), 138.2, 138.1 (aromatic C); 128.5-127.3 (aromatic CH); 101.0 (x2), 98.2 (anomeric CH), 79.9, 79.5, 77.7, 75.4, 75.0, 74.9, 74.7, 74.3, 73.4, 73.3, 73.2, 72.7, 72.2, 72.1, 72.0, 71.8, 69.7, 69.3, 68.6, 68.5 54.8 ppm. MALDI-TOF MS: calcd. for $[M + Na]^+$ 1351.60, found 1351.48. Calcd. for $C_{82}H_{88}O_{16}$ (1351.60): C, 74.18; H, 6.67. Found: C, 73.95; H, 6.71.

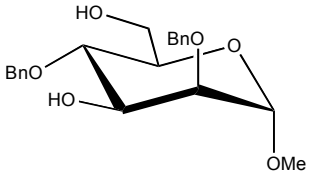


Methyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→3)-2,4,6-tri-*O*-benzyl-α-D-mannopyranoside (1F). A mixture of donor **9F** (11 mg, 13 μmol) and acceptor **20F** (10 mg, 7.5 μmol) was coevaporated three times with anhydrous toluene (3 x 1 mL), and then dried in vacuo for 30 minutes. After adding 4Å AW 300 MS, the mixture was dissolved under argon with 4:1 toluene/Et_2O (0.51 mL), cooled to -30 °C, and stirred for 15 minutes. A solution of $Bi(OTf)_3$ in dioxane (14.3 mg/mL, 34 μL, 0. 75 μmol) was then added, and the temperature was allowed to raise up to rt over 2.5 hours. Having realized the completion of the glycosidation step (TLC analysis, eluent: *n*-hexane/ethyl acetate 7:3), TEA (0.13 mL) was added. After one hour from the addition, the reaction mixture was filtered on a short plug of silica gel repeatedly washed with DCM/MeOH/acetonitrile 85:10:5. The filtrate was concentrated, and the residue purified by silica-gel flash-chromatography (eluent: toluene/ethyl acetate from 100:0 to 85:15) to yield tetrasaccharide **1F** as an oil (8 mg, 64 % overall yield); $[\alpha]^{28}_D$ +28.5 (*c* 0.8 in $CHCl_3$); ^{1}H NMR (500 MHz; $CDCl_3$): δ = 7.40–7.05 (Ar), 5.25 (1 H, br s, 1‴-H), 5.18 (1 H, br s, 1″-H), 5.14 (1 H, bs, 1′-H), 4.70 (1 H, d, $J_{1,2}$ = 1.5 Hz, 1-H), 4.85-4.22 (24 H, 12 x-CH_2Ph), 4.12-4.08 (2 H), 4.00 (1 H, *J* = 1.5 Hz), 3.98-3.60 (18 H), 3.55 (1H, dd, *J* = 3.0 and 11.5), 3.47 (1H, bd, *J* = 11.5), 3.43 (1H, bd, *J* = 10.0), 3.26 (3 H, s, -OCH_3), 2.39 (1 H, br s, 2-OH) ppm. ^{13}C NMR (100 MHz; $CDCl_3$): δ = 138.8–138.1 (aromatic C); 128.5-127.2 (aromatic CH); 101.0, 100.9, 100.8 and 98.2 (anomeric CH), 80.0, 79.6, 79.4, 79.2, 79.0, 77.6, 77.2, 75.6, 75.1, 74.9, 74.7, 74.2, 73.4, 73.3, 73.0, 72.6, 72.5, 72.4, 72.1, 72.0, 71.9, 71.7, 71.6, 69.7, 69.3, 69.0, 68.7, 68.5, 54.7 ppm. MALDI-TOF MS: calcd. for $[M + Na]^+$ 1784.79, found 1784.45. Calc. for $C_{109}H_{116}O_{21}$ (1784.79): C, 74.30; H, 6.64. Found: C, 73.95; H, 6.50.



Methyl 3,6-di-*O*-*tert*-butyldimethylsilyl-α-D-mannopyranoside (22F). Compound **22F** was prepared and elaborated to diol **21F** by reproducing the procedures described in reference[23]. ^{1}H NMR (300

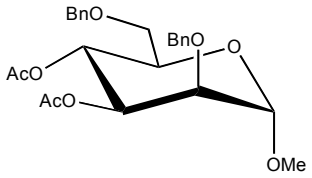
MHz, $CDCl_3$) δ 4.69 (d, $J_{1,2}$ = 0.9 Hz, 1H, H-1), 3.83 (d, 2H, H-6a and H-6b), 3.80 (dd, 1H, H-3), 3.72 (br d, $J_{2,3}$ = 3.6 Hz, 1H, H-2), 3.66 (td, $J_{3,4}$ = 9.1 Hz, 1H, H-4), 3.52 (dt, $J_{5,6a}$ = 4.5 Hz, $J_{5,6b}$ = 5.2 Hz, 1H, H-5), 3.33 (s, 3H, -OMe), 2.78 (d, $J_{4,OH}$ = 2.1 Hz, 1H, 4-O*H*), 2.59 (br s, 1H, 2-O*H*), 0.88 (s, 9H, -C(CH_3)$_3$), 0.87 (s, 9H, -C(CH_3)$_3$), 0.12 (s, 3H, -Si(CH_3)$_2$), 0.10 (s, 3H, -Si(CH_3)$_2$), 0.06 (s, 6H, -Si(CH_3)$_2$). ^{13}C NMR (75 MHz, $CDCl_3$) δ 100.1 (anomeric CH), 73.0, 71.0, 70.6, 70.3, 64.8, 54.6 (-OMe), 25.8 and 25.7 (2 x -C(*C*H$_3$)$_3$), 18.2, 18.0 (2 x -*C*(CH$_3$)$_3$), -5.3, -4.6 (2 x -Si(*C*H$_3$)$_2$), -4.3 (2 x -Si(*C*H$_3$)$_2$).



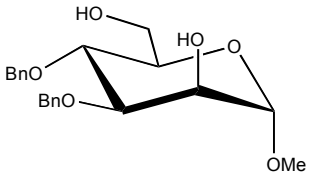
Methyl 2,4-di-*O*-benzyl-α-D-mannopyranoside (21F). Compound **23F**[24,26a] (*endo*/*exo* 1.2:1, 55 mg, 0.15 mmol) was dissolved at 0 °C under argon with 1 M BH_3 in THF (1.5 mL, 1.5 mmol). To the resulting solution was added at 0 °C a solution of copper(II) triflate in THF (0. 069 M prepared dissolving the salt under argon in the presence of 4Å MS, 0.65 mL, 0.045 mmol). After 30 minutes, the ice-bath was removed and the reaction vessel was allowed to warm to rt. After a few minutes a black precipitate appeared. After 1 hour and 40 minutes from the start, the reaction was quenched with TEA (25 μL) and MeOH (0.2 mL). The mixture was concentrated in vacuo and the residue was purified by silica-gel flash chromatography (eluent: *n*-hexane/ethyl acetate from 32:18 to 55:45) to yield diol **21F** as a colourless oil (34 mg, 61% yield). Acetylation of a sample confirmed the presence of free hydroxyls at *O*-3 and *O*-6 as indicated by ^{1}H NMR (200 MHz; $CDCl_3$): signals at δ 5.16 (dd, $J_{2,3}$ = 3.3 Hz, $J_{3,4}$ = 9.0 Hz, 1H, 3-H), 4.30 (dd, $J_{5,6a}$ = 3.0 Hz, $J_{6a,6b}$ = 12.4 Hz, 1H, 6a-H), 4.22 (dd, $J_{5,6b}$ = 4.2 Hz, 1H, 6b-H). Compound **21F**: $[\alpha]_D^{28}$ +21.5 (*c* 1.1 in $CHCl_3$), lit.:[24] $[\alpha]_D$ +23.5 (*c* 0.77 in $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.40–7.25 (Ar), 4.75 (d, $J_{1,2}$ = 1.6 Hz, 1H, anomeric proton), 4.92-4.59 (4H, 2x-CH_2Ph), 3.99 (dd, $J_{2,3}$ = 3.2 Hz, $J_{3,4}$ = 9.6 Hz, 1H, 3-H), 3.86 (dd, $J_{5,6a}$ = 3.2 Hz, $J_{6a,6b}$ = 11.6 Hz, 1H, 6a-H), 3.77 (dd, $J_{5,6b}$ = 4.4 Hz, 1H, 6b-H), 3.73 (dd, 1H, 2-H), 3.68 (t, $J_{4,5}$ = 9.6 Hz, 1H, 4-H), 3.60-3.55 (m, 1H, 5-H), 3.32 (s, 3 H, -OCH_3). ^{13}C NMR (50 MHz; $CDCl_3$) δ 138.3, 137.6 (aromatic C); 128.6-127.8 (aromatic CH); 98.1 (C-1), 78.3, 74.8, 73.1, 71.7, 71.1, 62.3, 54.8 (-OCH_3). MALDI-TOF MS: calcd. for $[M + Na]^+$ 397.17, found 397.25. Calcd. for $C_{21}H_{26}O_6$: C, 67.36; H, 7.00. Found: C, 67.05; H, 7.10.

Other reductive opening procedures (conditions B and **C** of **Table 2)**. The reductive openings were essentially accomplished as illustrated above for preparation of **21F** (condition A of **Table 2**). Only differences were the addition of molecular sieves to the reaction vessel

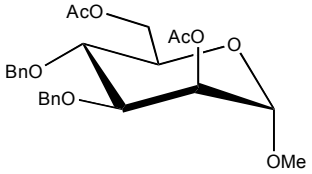
and coevaporation of $Cu(OTf)_2$ with toluene prior to be dissolved in THF, according to the indications on **Table 2** (conditions B and C). Listed below are the NMR data of all products obtained from the reductive openings. In several cases acetylation was exploited for structural confirmation.



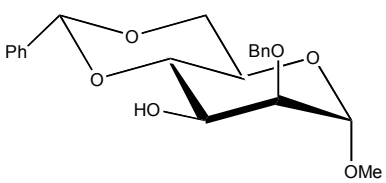
Methyl 3,4-di-*O*-acetyl-2,6-di-*O*-benzyl-α-D-mannopyranoside (acetylated 24F). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42-7.29 (m, 10H, ArH), 5.39 (t, $J_{3,4} = J_{4,5} = 9.9$ Hz, 1H, H-4), 5.21 (dd, 1H, $J_{2,3} = 3.4$ Hz, H-3), 4.75 (d, $J_{1,2} = 1.7$ Hz, 1H, H-1), 4.66-4.54 (2x AB, 4H, 2x -CH_2Ph), 3.88 (ddd, 1H, $J_{5,6a} = 2.3$ Hz, $J_{5,6b} = 3.5$ Hz, H-5), 3.82 (dd, 1H, H-2), 3.61 (dd, 1H, H-6a), 3.56 (dd, 1H, $J_{6a,6b}$ 10.9 Hz, H-6b), 3.38 (s, 3H, -OMe), 1.98 and 1.91 (2xs, 6H, 2x -COCH_3).



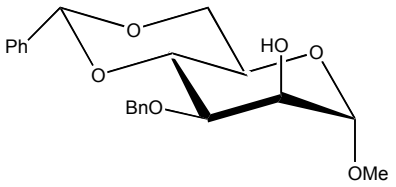
Methyl 3,4-di-*O*-benzyl-α-D-mannopyranoside (25F). ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.49-7.28 (Ar), 4.94-4.60 (m, 5H, 2 x -CH_2Ph and H-1), 4.06-4.00 (br d, 1H, H-2), 3.94-3.72 (m, 4H, H-3, H-4, H-6a and H-6b), 3.70-3.60 (m, 1H, H-5), 3.36 (s, 3H, -OMe). ^{13}C NMR (50 MHz, $CDCl_3$) δ 138.3, 137.8 (aromatic C), 128.5-127.8 (aromatic CH), 100.2 (anomeric CH), 80.0, 75.1, 74.1, 72.1, 71.3, 68.3, 62.1, 54.9 (-OMe).



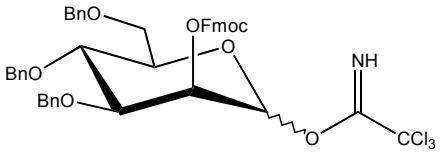
Methyl 2,6-di-*O*-acetyl-3,4-di-*O*-benzyl-α-D-mannopyranoside (acetylated 25F). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43-7.28 (m, 10H, ArH), 5.37 (dd, 1H, $J_{1,2} = 1.8$ Hz, $J_{2,3} = 3.3$ Hz, H-2), 4.92-4.50 (m, 5H, 2 x -CH_2Ph and H-1), 4.38-4.32 (d, 2H, H-6a and H-6b), 4.00 (dd, $J_{4,5} = 9.9$ Hz, 1H, H-3), 3.84 (dt, 1H, $J_{5,6a} = 2.7$ Hz, $J_{5,6b} = 3.6$ Hz, H-5), 3.74 (t, 1H, H-4), 3.36 (s, 3H, -OMe), 2.16 and 2.08 (2x s, 6H, 2x -COCH_3).



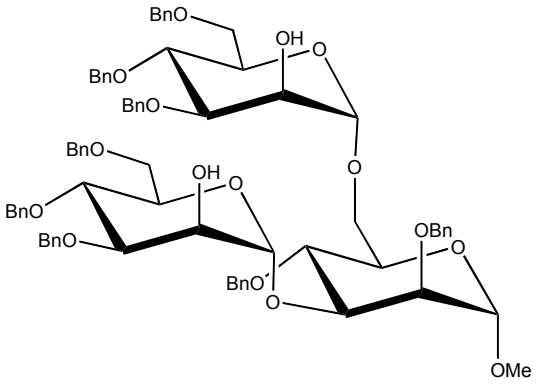
Methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (26F). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53-7.28 (Ar), 5.54 (s, 1H, benzylidene PhCH), 4.72 (s, 1H, H-1), 4.71 (d, 1H, $J_{gem} = 11.5$ Hz, -CH_aH$_b$Ph), 4.67 (d, 1H, -CH$_a$$H_b$Ph), 4.23 (dd, 1H, $J_{5,6a} = 4.2$ Hz, $J_{6a,6b} = 9.7$ Hz, H-6a), 4.05 (dd, 1H, $J_{2,3} = 3.7$ Hz, $J_{3,4} = 9.7$ Hz, H-3), 3.88 (t, 1H, H-4), 3.84-3.70 (m, 3H, H-2, H-5 and H-6b), 3.33 (s, 3H, -OMe), 2.43 (br s, 1H, 3-O*H*).



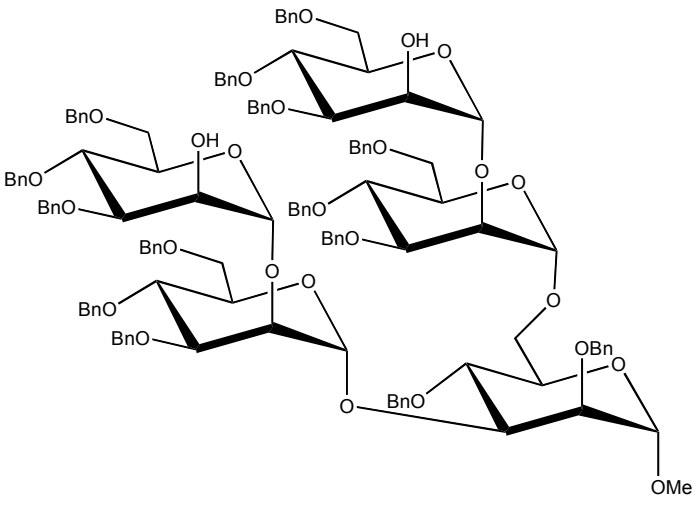
Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (27F). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53-7.28 (Ar), 5.61 (s, 1H, benzylidene PhCH), 4.84 (d, 1H, J_{gem} = 12.0 Hz, -CH_aH$_b$Ph), 4.76 (d, $J_{1,2}$ = 1.0 Hz, 1H, H-1), 4.70 (d, 1H, J_{gem} = 12.0 Hz, -CH$_a$$H_b$Ph), 4.27 (dd, 1H, $J_{5,6a}$ = 4.2 Hz, $J_{6a,6b}$ = 9.7 Hz, H-6a), 4.09 (t, 1H, H-4), 4.04 (dd, 1H, H-2), 3.90 (dd, 1H, $J_{2,3}$ = 3.7 Hz, $J_{3,4}$ = 9.7 Hz, H-3), 3.88-3.77 (m, 2H, H-5 and H-6b), 3.37 (s, 3H, -OMe). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 170.2 (2 x -*C*OCH$_3$), 138.1, 137.8 (aromatic C), 128.4-127.8 (aromatic CH), 98.8 (anomeric CH), 78.1, 75.1, 74.1, 71.7, 69.6, 68.5, 63.4, 54.9 (-OMe), 21.0, 20.8 (2 x -CO*C*H$_3$).



3,4,6-Tri-*O*-benzyl-2-*O*-fluorenylmethoxycarbonyl-α,β-D-mannopyranosyl trichloracetimidate (28F). To a solution of **13Fα** (318 mg, 0.447 mmol) in 1.6:1 MeOH/DCM (4.5 mL) was added at rt palladium chloride (8 mg, 0.045 mmol). The mixture was stirred overnight and then concentrated under vacuum. The residue was then filtered through a short plug of silica gel (eluent DCM/MeOH 95:5) and concentrated to yield the hemiacetal as a foam. The obtained hemiacetal was dissolved in trichloroacetonitrile (6.7 mL) and the solution was added drop-wise to a reaction vessel containing sodium hydride (60% in oil, 1.9 mg) at 0°C under magnetic stirring. After 15 min at the same temperature the mixture was neutralized by portion-wise addition of silica gel and the residue was purified by silica gel flash-chromatography (eluent: toluene/acetone 20:1) to yield **28F** as a foam (anomeric mixture α/β ca 8.3:1, 348 mg, 95% over two steps). ^{1}H NMR (400 MHz; $CDCl_3$): signals of α anomer at δ = 8.83 (s, 1 H, –NH), 8.00–7.15 (Ar), 6.57 (d, $J_{1,2}$ = 1.6 Hz, 1 H, 1-H), 5.47 (t, $J_{2,3}$ = 1.6 Hz, 1 H, 2-H), 4.55-4.35 (3 H, Fmoc –CHCH$_2$O), 4.26 (t, $J_{3,4}$ = $J_{4,5}$ = 9.6 Hz,1 H, 4-H), 4.20 (dd, 1 H, 3-H), 4.20-4.13 (m, 1 H, 5-H), 3.98 (dd, $J_{5,6a}$ = 4.4, $J_{6a,6b}$ = 11.2 Hz, 1 H, 6$_a$-H), 3.87 (dd, $J_{5,6b}$ = 1.6 Hz, 1H, 6$_b$-H) ppm. Significant signals of the β-anomer at δ = 8.78 (1H, s, –NH), 6.05 (1H, s, H-1) ppm. ^{13}C NMR (100 MHz; $CDCl_3$): signals of α anomer at δ = 160.0 (C=NH), 154.6 (-OCO$_2$-); 143.4, 143.2, 141.3 (x2) (Fmoc aromatic C), 138.1, 137.9, 137.4 (benzyl aromatic C); 128.4-127.3, 125.4, 125.3, 120.1 (aromatic CH), 95.3 (C-1), 77.5, 75.6, 74.6, 73.8, 73.5, 72.2, 71.4, 70.6, 68.6, 46.6 ppm.



Methyl (3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→3))-(3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→6))-2,4-di-*O*-benzyl-α-D-mannopyranoside (29F). A mixture of donor **28F** (78 mg, 95 μmol) and diol **21F** (12 mg, 29 μmol) was coevaporated three times with anhydrous toluene (3 x 2 mL), and then dried in vacuo for 30 minutes. After adding 4Å AW 300 MS, the mixture was dissolved under argon with 4:1 toluene/Et_2O (2.8 mL), cooled to -30 °C, and stirred for 15 minutes. A solution of $Bi(OTf)_3$ in dioxane (14.5 mg/mL, 135 μL, 0.29 μmol) was then added, and the temperature was allowed to raise up to – 10 °C over 45 minutes. Having realized the completion of the glycosidation step (TLC analysis, eluent: petroleum ether/ethyl acetate 7:3), TEA (0.70 mL) was added and the reaction vessel was immediately warmed to rt. After one hour the reaction mixture was filtered through a short plug of silica gel repeatedly washed with DCM/MeOH/acetonitrile 85:10:5. The filtrate was concentrated, and the residue purified by silica-gel flash-chromatography (eluent: *n*-hexane/acetone/dichloromethane from 3:1:0.5 to 2:1:0.5) to yield trisaccharide **29F** as an oil (26 mg, 72 % overall yield). $[\alpha]_D^{26}$ +25.9 (*c* 0.77 in $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.40–7.10 (Ar), 5.23 (d, $J_{1,2}$ = 1.2 Hz, 1 H, $1'^3$-H), 5.09 (d, $J_{1,2}$ = 1.2 Hz, 1 H, $1'^6$-H), 4.66 (d, $J_{1,2}$ = 1.6 Hz, 1 H, 1-H), 4.87-4.46 (16 H, 8x-CH_2Ph), 4.15-4.10 (2 H), 4.05-3.95 (2 H), 3.95-3.80 (8 H), 3.80-3.60 (6H), 3.25 (3 H, s, -OCH_3) ppm. ^{13}C NMR (100 MHz; $CDCl_3$): δ = 138.5, 138.4, 138.3 (x2), 138.2, 138.1, 137.9 (x2) (aromatic C); 128.6-127.5 (aromatic CH); 101.4, 98.7, and 98.2 (anomeric CH), 80.1, 79.5, 78.9, 77.7, 75.0, 74.9, 74.8, 74.4, 74.2, 73.6, 73.3, 72.3, 72.0, 71.9, 71.4, 71.1, 69.4, 68.8, 68.7, 68.0, 66.1, 54.7 ppm. MALDI-TOF MS: calcd. for $[M + Na]^+$ 1261.55. found 1261.15. Calcd. for $C_{75}H_{82}O_{16}$ (1261.55): C, 72.68; H, 6.67. Found: C, 72.35; H, 6.50.



Methyl (3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α- D-mannopyranosyl-(1→3))-(3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→2)-3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl-(1→6))-2,4-di-*O*-benzyl-α-D-mannopyranoside (2F). A mixture of donor **28F** (40 mg, 49 μmol) and diol **29F** (14 mg, 11 μmol) was coevaporated three times with anhydrous toluene (3 x 1 mL), and then dried in vacuo for 30 minutes. After adding 4Å AW 300 MS, the mixture was dissolved under argon with 4:1 toluene/Et_2O (2.1 mL), cooled to -30 °C, and stirred for 15 minutes. A solution of $Bi(OTf)_3$ in dioxane (14.5 mg/mL, 100 μL, 2.2 μmol) was then added, and the temperature was allowed to raise up to + 5 °C over one hour. Having realized the completion of the glycosidation step (TLC analysis, eluent petroleum ether/ethyl acetate 7:3), TEA (0.35 mL) was added and the reaction mixture immediately warmed to rt. The reaction mixture was then filtered through a short plug of silica gel repeatedly washed with DCM/MeOH/acetonitrile 85:10:5. The filtrate was concentrated, and the residue purified by silica-gel flash-chromatography (eluent: *n*-hexane/acetone/dichloromethane 3:1:0.5) to yield pentasaccharide **2F** as an oil (15 mg, 63% overall yield); $[\alpha]_D^{28}$ +34.7 (*c* 0.7 in $CHCl_3$); ^{1}H NMR (400 MHz; $CDCl_3$): δ = 7.40–7.10 (Ar), 5.25, 5.11 and 5.05 (3 x d, $J_{1,2}$ = 1.6 Hz, 3 H, 2 x 1″-H and 1′^{3}-H), 4.97 (d, $J_{1,2}$ = 1.6 Hz, 1 H, 1′^{6}-H), 4.64 (d, $J_{1,2}$ = 1.6 Hz, 1 H, 1-H), 4.98-4.30 (28 H, 14 x-CH_2Ph), 4.15-4.05 (4 H), 4.05-3.95 (3 H), 3.95-3.75 (13 H), 3.75-3.63 (6 H), 3.60-3.40 (4 H), 3.16 (s, 3 H, -OCH_3) ppm. ^{13}C NMR (100 MHz; $CDCl_3$): δ = 138.7-138.0 (aromatic C); 128.6-127.0 (aromatic CH); 101.1 (x3), 99.1, and 97.9 (anomeric CH), 80.3, 80.0, 79.9, 79.6, 78.9, 77.8, 75.3, 75.0, 74.9, 74.8, 74.7, 74.6, 74.5, 74.3, 74.2, 73.4, 73.3, 72.7, 72.1, 72.0, 71.8, 71.6, 71.5, 71.0, 69.7, 69.1, 68.9, 68.6, 68.5, 66.5, 54.6 ppm. MALDI-TOF MS: calcd. for $[M + Na]^+$ 2126.94, found 2126.11. Calcd. for $C_{129}H_{138}O_{26}$ (2126.94): C, 73.62; H, 6.61. Found: C, 73.35; H, 6.70.

References

1. For some examples of this unusual elongation strategy: (a) T. Zhu, G.-J. Boons, *Synlett* **1997**, 809-811; (b) T. Zhu, G.-J. Boons, *Tetrahedron Lett.* **1998**, *39*, 2187-2190; (c) T. Zhu, G.-J. Boons, *Angew. Chem. Int. Ed.* **1998**, *37*, 1898-1900; (d) T. Zhu, G.-J. Boons, *J. Chem. Soc., Perkin Trans. 1,* **1998**, 857-861; (e) T. Zhu, G.-J. Boons, *Angew. Chem. Int. Ed.* **1999**, *38*, 3495-3497.

2. (a) Y. Du, M. Zhang, F. Kong, *Org. Lett.* **2000**, *2*, 3797-3800; (b) S. Bhattacharyya, B. G. Magnusson, U. Wellmar, U. J. Nilsson, *J. Chem. Soc., Perkin Trans. 1* **2001**, 886-890; (c) Y. Vohra, M. Vasan, A. Venot, G-J. Boons, *Org. Lett.*, **2008**, *10*, 3247-3250.

3. For examples on the use of Fmoc in oligosaccharide solid phase synthesis: (a) F. Roussel, L. Knerr, M. Grathwohl, R. R. Schmidt, *Org. Lett.*, **2000**, *2*, 3043-3046; (b) D. B. Werz, B. Castagner, P. H. Seeberger, *J. Am. Chem. Soc.* **2007**, *129*, 2770-2771. Examples in solution synthesis: (c) A. Prabhu, A. Venot, G.-J. Boons, *Org. Lett.* **2003**, *5*, 4975-4978; (d) D. B. Werz, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2005**, *44*, 6315-6318; (e) M. A. Oberli, P. Bindschafler, D. B. Werz, P. H. Seeberger, *Org. Lett.* **2008**, *10*, 905-908.

4. F. R. Carrel, K. Geyer, J. D. C. Codèe, P. H. Seeberger, *Org. Lett.* **2007**, *9*, 2285-2288.

5. T. Nokami, H. Tsuyama, A. Shibuya, T. Nakatsutsumi, J. Yoshida, *Chem. Lett.* **2008**, *37*, 942-943.

6. S. Valerio, M. Adinolfi, A. Iadonisi, A. Pastore, *J. Org. Chem.* **2008**, *73*, 4496-4503.

7. (a) M. Adinolfi, A. Iadonisi, A. Ravidà, S. Valerio, *Tetrahedron Lett.* **2006**, *47*, 2595-2599; (b) M. Adinolfi, D. Giacomini, A. Iadonisi, A. Quintavalla, S. Valerio, *Eur. J. Org. Chem.* **2008**, 2895-2899.

8. H.-K. Lee, C. N. Scanlan, C.-Y. Huang, A. Y. Chang, D. A Calarese, R. A.Dwek, P. M.Rudd, D. R. Burton, I. A. Wilson, C.-H. Wong, *Angew. Chem. Int. Ed.* **2004**, *43*, 1000-1003.

9. (a) J. Wang, H. Li, Z. Guozhang, L.-X. Wang, *Org. Biomol. Chem.* **2007**, *5*, 1529-1540; (b) D. A. Calarese, H.-K. Lee, C.-Y. Huang, M. D. Best, R. D. Astronomo, R. L. Stanfield, H. Katinger, D. R. Burton, C.-H. Wong, I. A. Wilson, *Proc. Natl. Acad. Sci. USA* **2005**, *102*, 13372-13377; (c) S.-K. Wang, P.-H. Liang, R. D. Astronomo, T.-L. Hsu, S.-L. Hsieh, D. R. Burton, C.-H. Wong, *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 3690-3695.

10. Calarese, D. A., Scanlan, C. N., Zwick, M. B., Deechongkit, S., Mimura, Y., Kunert, R., Zhu, P.,

Wormald, M. R., Stanfield, R. L., Roux, K. H., *et al.* (2003) *Science* **300,** 2065–2071.

11. Kraulis, P. J. (1991) *J. Appl. Crystallogr.* **24,** 946–950.

12. Esnouf, R. M. (1999) *Acta Crystallogr. D* **55,** 938–940.

13. Merritt, E. A. & Bacon, D. J. (1997) *Methods Enzymol.* **277,** 505–524.

14. For other synthetic approaches to the D1 sequence: ref. 5, ref. 7a. For further references: (a) R. K. Jain, X.-G. Liu, S. R. Oruganti, E. V. Chandrasekaran, K. L. Matta, *Carbohydr. Res.* **1995**, *271*, 185-196: (b) P. Grice, S. V. Ley, J. Pietruzska, H. W. M. Priepke, *Angew. Chem. Int. Ed.* **1996**, *35*, 197-200; (c) A. Düffels, S. V. Ley, *J. Chem. Soc., Perkin Trans. 1* **1999**, 375-378; (d) M. Takatani, Y. Ito, *Chem. Asian J.* **2006**, *1-2*, 64-75.

15. M. Adinolfi, A. Iadonisi, M. Schiattarella, A. Ravidà, *Tetrahedron Lett.* **2003**, *44*, 7863-7866.

16. B. Yu, H. Tao, *Tetrahedron Lett.* **2001**, *42*, 2405-2407.

17. For examples on the use of Fmoc as a participating group for selective 1,2-*trans* glycosidations:

(a) Werz, D. B.; Castagner, B.; Seeberger, P. H. *J. Am. Chem. Soc.* **2007**, *129*, 2770-2771; (b)

Oberli, M. A.; Bindschafler, P.; Werz, D. B.; Seeberger, P. H. *Org. Lett.* **2008**, *10*, 905-908; (c)

Pastore, A.; Adinolfi, M.; Iadonisi, A. *Eur. J. Org. Chem* **2008**, 6206-6212.

18. Adinolfi, M.; Iadonisi, A.; Schiattarella, M.; Ravidà, A. *Tetrahedron Lett.* **2004**, *45*, 4485-4488.

19. Adinolfi, M.; Barone, G.; Iadonisi, A.; Schiattarella, M. *Tetrahedron Lett*. **2002**, *43*, 5573-5577.

20. Adinolfi, M.; Iadonisi, A.; Ravidà, A. *Synlett*, **2006**, 583-586.

21. (a) K. C. Nicolaou, N. Watanabe, J. Li, J. Pastor, N Winssinger, A*ngew. Chem. Int. Ed.* **1998**, *37*, 1559-1561; (b) T. Zhu, G.-J. Boons, *Tetrahedron*: *Asymmetry* **2000**, *11*, 199–205.

22. T. Ogawa, K. Sasajima, *Tetrahedron* **1981**, *37*, 2779-2786.

23. N. Teumelsan, X. Huang, *J. Org. Chem.* **2007**, *72*, 8976-8979.

24. Z.Szurmai, L. Balatoni, A. Liptak, *Carbohydr. Res.* **1994**, *254*, 301-309.

25. S. N. Lam, J. Gervay-Hague, *J. Org. Chem.* **2005**, *70*, 8772-8779.

26. (a) S. C. Ennis, I. Cumpstey, A. J. Fairbanks, T. D. Butters, M.Mackeenb, M. R. Wormaldb, *Tetrahedron* **2002**, *58*, 9403-9411; (b) Jiang, L.; Chan, T. H. *Tetrahedron Lett.* **1998**, *39*, 355-358; (c) Daragics, K.; Fugedi, P. *Tetrahedron Lett.* **2009**, *50*, 2914-2916.

27. C.-R. Shie, Z.-H. Tzeng, S. S. Kulkarni, B.-J. Uang, C.-Y. Hsu, S.-C. Hung, *Angew. Chem. Int. Ed.* **2005**, *44*, 1665-1668.

28. J. R. Merritt, E. Naisang, B. Fraser-Reid, *J. Org. Chem.* **1994**, *59*, 4443-4449.

29. For other approaches towards branched mannose tri- and pentasaccharides related to **14** and **2** see ref. 15, 17b, 20, 21, 23. Further references: (a) O. P. Srivastava, O. Hindsgaul, *J. Org. Chem.* **1987**, *52*, 2869-2875; (b) S. J. Danishefsky, S. Hu, P. F. Cirillo, M. Eckardt, P. H. Seeberger, *Chem. Eur.* J. **1997**, *3*, 1617-1628; (c) J. Rademann, A. Geyer, R. R.Schmidt, *Angew. Chem. Int. Ed.* **1998**, *37*, 1241-1245; (d) Du, Y.; Zhang, M.; Kong, F. *Tetrahedron* **2001**, *57*, 1757-1763; (e) Y. Zhu, F. Kong, *Synlett* **2001**, 1217-1220; (f) J. Zhang, F. Kong, *Tetrahedron: Asymmetry* **2002**, *13*, 243-252; (g) B. Fraser-Reid, J. C. Lopez, K. V. Radhakrishnan, M. V. Nandakumar, A. M. Gomez, C. Uriel, *Chem. Commun.* **2002**, 2104-2105; (h) D. M. Ratner, O. J. Plante, P. H. Seeberger, *Eur. J. Org. Chem.* **2002**, 826-833; (i) L. V. Backinowsky, P. I. Abronina, A. S. Shaskov, A. A. Grachev, N. K. Kochetkov, S. A. Nepogodiev, J. F. Stoddart, *Chem.-Eur. J.* **2002**, *8*, 4412-4423; (j) I. Matsuo, M. Wada, S. Manabe, Y. Yamaguguchi, K. Otake, K. Kato, Y. Ito, *J. Am. Chem. Soc.* **2003**, *125*, 3402-3403; (k) M. Mandal, V. Y. Dudkin, X. Geng, S. J. Danishefsky, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 2557-2561; (l) M. Dowlut, D. G. Hall, O. Hindsgaul, *J. Org. Chem.* **2005**, *70*, 9809-9813; (m) R. Blattner, R. H.Furneaux, M. Ludewig, *Carbohydr. Res.* **2006**, *341*, 299-321; (n) Z.-G. Wang, J. D. Warren, V. Y. Dudkin, X. Zhang, U. Iserloh, M. Visser, M. Eckhardt, P. H. Seeberger, S. J.Danishefsky, *Tetrahedron* **2006**, *62*, 4954-4978; (o) K. N. Jayaprakash, S. R. Chaudhuri, C. V. S. R. Murty, B. Fraser-Reid, *J. Org. Chem.* **2007**, *72*, 5534-5545; (p) F. A. Jaipuri, N. L. Pohl, *Org. Biomol. Chem.* **2008**, *6*, 2686-2691; (q) I. Imagawa, A. Kinoshita, Y. Yamamoto, K. Namba, M. Nishizawa, *Synlett*, **2008**, 1981-1984; (r) C. T. Tanifum, C.-W. T.Chang, *J. Org. Chem.* **2009**, *74*, 634-644.

30. S. Jonke, K. Liu, R. R. Schmidt, *Chem.-Eur. J.* **2006**, *12*, 1274-1290.

31. T. G. George, P. Szolcsanyi, S. G.Koenig, D. E. Paterson, Y. Isshiki, A. Vasella *Helv. Chem. Acta* **2004**, *87*, 1287-1298.