UNIVERSITY OF NAPLES
"FEDERICO II"

PhD in Chemical Sciences

XXX Cycle

Novel strategies for the synthetic manipulation of saccharide functional groups

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

* Traboni, S.; Bedini, E.; Giordano, M.; Iadonisi, A. *Adv. Synth. Catal.* **2015**, *357*, 3562-3572.

** Traboni, S.; Bedini, E.; Iadonisi, A. *Beilstein J. Org. Chem*. **2016**, *12*, 2748-2756.

*** Traboni, S.; Bedini, E.; Iadonisi, A. *ChemistrySelect* **2017**, *2*, 4906-4911.

**** Traboni, S.; Liccardo, F.; Bedini, E.; Giordano, M.; Iadonisi, A. *Tetrahedron Lett*. **2017**, *58*, 1762-1764.

***** Buhl, M.; Traboni, S.; Körsgen, M.; Lamping, S.; Arlinghaus, H. F.; Ravoo, B. J. *Chem. Commun*. **2017**, *53*, 6203-6206.

List of Abbreviations

^{13}C NMR = Carbon nuclear magnetic resonance
^{1}H NMR = Proton nuclear magnetic resonance
Ac = Acetyl
All = Allyl
Alloc = Allyloxycarbonyl
AW 300 MS = Acid washed molecular sieves 4Å
Box = Benzoxazoyl
BSA = Bovine serum albumin
Bz = Benzoyl
Bzd = Benzylidene
Cbz = Benzyloxycarbonyl
CIP = Contact ion pair
ConA = Concanavalin A
ConA-FITC = Fluorescein tagged concanavalin A
ConA-Rh = Rhodamine tagged concanavalin A
Cp = Cyclopentenyl
CSA = (±)-Camphor-10-sulfonic acid
CuAAC = Cu(I) azide alkyne cycloaddition
CyHex = Cyclohexane
DAST = (Diethylamino)sulphur trifluoride
DBU = Diazabicyclo[5.4.0]undec-7-ene
DCE = 1,2-Dichloroethane
DCM = Dichloromethane
DIPEA = N-Ethyldiisopropylamine
DMAP = 4-Dimethylaminopyridine
DMDO = Dimethyldioxyrane
DMF = N,N-Dimethylformamide
DMSO = Dimethyl sulfoxide
DMT = 4,4'-Dimethoxytrityl (=4,4'- Dimethoxytriphenylmethyl)
DMTST = Dimethyl(methylthio)sulfonium triflate
DNA = 2'-Deoxyribonucleic acid
Fmoc = 9-Fluorenylmethyl-carbonate
Gal = Galactose
GalNAc = N-Acetyl galactosamine

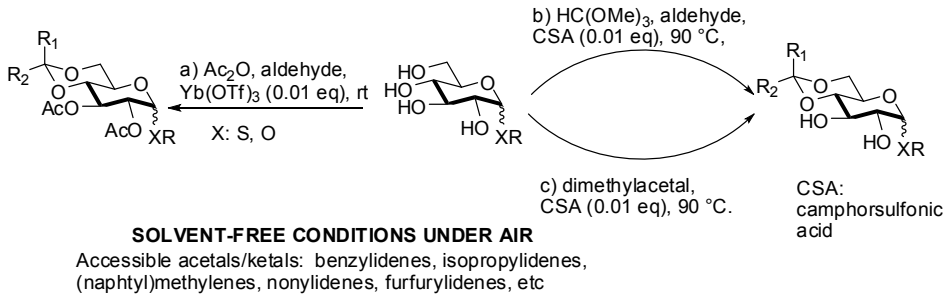
IAD = Intramolecular aglycon delivery
IDCP = Iodonium dicollidine perchlorate
IDCT = Iodonium dicollidine triflate
Lev = Levulinoyl
MALDI = Matrix assisted laser desorption ionization
μCP = Microcontact Printing
NBD = Nitrobenzoxadiazole
NBS = *N*-bromo succinimide
NDPs = Nucleotide 5'-diphosphosugars
NIS = *N*-iodo succinimide
NISac = *N*-Iodosaccharin
PCR = Polymerase chain reaction
PDMS = Polydimethylsiloxane
Pent = Pentenyl
Ph = Phenyl
Phth = Phtaloyl
Piv = Pivaloyl
*p*MBn = *para*-Methoxybenzyl
Py = Pyridine
RT = Room tempreature
SAM = Self-assembled monolayer
S_N1 = Unimolecular nucleophilic substitution
S_N2 = Bimolecular nucleophilic substitution
SPAAC = Strain promoted azide alkyne cycloaddition
SSIP = Solvent separed ion pair
TBAB = Tetrabutylammonium bromide
TBAC = Tetrabutylammonium chloride
TBAI = Tetrabutylammonium iodide
TBDMS = *tert*-Butyldimethylsilyl
TBDPS = *tert*-Butyldiphenylsilyl
TCA = Trichloroacetyl
TES = Triethylsilyl
Tf = Trifluoromethansulfonyl (= Triflyl)
TFA = Trifluoroacetic acid
THF = Tetrahydrofuran
TIPS = Triisopropylsilyl
TLC Thin layer chromatography

TMEDA = *N*,*N*,*N'*- Trimethylethylenediamine
TMS Trimethylsilyl
TMSOTf = Trimethylsilyl triflate
ToF = Time of flight
ToF-SIMS = Time of flight secondary ion mass spectrometry
Tr = Triphenylmethyl (= Trityl)
Troc = Trichloroethoxycarbonyl
Ts = Toluensulfonyl (=Tosyl)
XPS = X-ray photoelectron spectroscopy

Abstract

Carbohydrates are widely available molecules in nature and find multiple applications in several fields such as biochemistry, science of materials, organic synthesis as cheap precursors of multifunctionalized chiral targets and in the pharmacological research for the development of new drugs. Synthetic versatility of these densely functionalized molecules has spurred development of ever more efficient methods for their derivatization, which is often a complex task. Carbohydrates reactive positions are commonly differentiated by installation of a suitable set of protecting groups, a preliminary crucial step in most synthetic elaborations that is often very laborious, due to the high number of similarly reactive functional groups present in the same molecule; other complications arise from the moisture sensitivity of many pivotal reactions in carbohydrate chemistry. This general complexity entails unpractical procedures, often with long multi-step syntheses, reactions requiring strictly controlled conditions and use of toxic and high boiling solvents. The assembly of saccharide targets is therefore highly laborious and time-consuming not only in the non-trivial construction of stereo-defined glycosidic linkages but even in the preliminary steps needed for preparation of building-blocks. Works discussed in the present thesis are related to this context. A broad effort was indeed addressed to the development of innovative methods both aimed at protection/transformation of saccharide functional groups and

at the efficient construction of glycosidic linkages; developed protocols share the common feature of experimental simplicity, in most cases relying on reactions conducted in the absence of solvent, under air and allowing multiple transformations to be performed in a one-pot fashion. The first results of such effort led to the introduction of three simple solvent-free protocols for the acetal functionalization of saccharide diols (**Scheme I**). Generation of acetal or ketal functionalities is indeed an almost ubiquitous step in organic synthesis when polyol substrates have to be chemically manipulated. Nevertheless, the reported protocols for polyol and carbohydrate acetalation are suffering from one or more practical issues such as the use of sensitive or commercially unavailable promoters, adoption of strictly anhydrous conditions with the application of drying agents and inert atmosphere, need for an apparatus aimed at water removal, use of high-boiling solvents, prolonged reaction times.

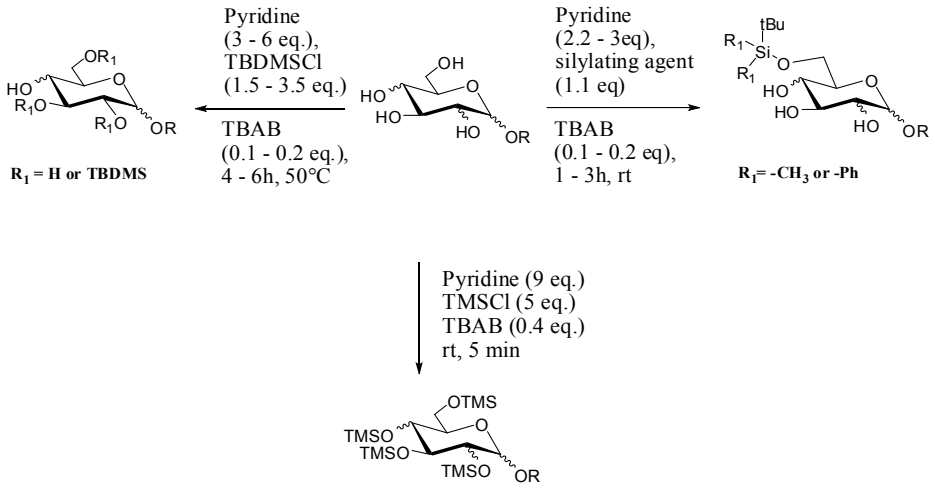


Scheme I. Three solvent-free approaches for the acetal protection of saccharide diols

The first developed strategy (**Scheme I**, path a) is based on an unusual acetolytic activation of the carbonyl compound under very mild conditions at room temperature, and leads to the straightforward generation of an orthogonally fully protected building-block, bearing

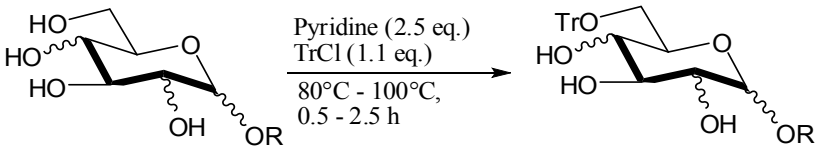
both an acetal group (at positions 4,6) and acetyl groups (at positions 2, 3). In the second approach (**Scheme I**, path b), carbonyl activation is mediated under mild acid conditions by an orthoester co-reagent and yields the acetalation product as a 2,3-diol. The same product can also be accessed by the third procedure (**Scheme I**, path c) where a classical trans-acetalation mechanism is working. The above described strategies proved effective on a wide range of substrates and acetalating agents, avoiding the use of high boiling solvents and special drying systems, usually required when the acetalation of the polyol substrate is achieved through a direct condensation with the aldehyde/ketone. Some of these protocols were also successfully applied to a useful and unprecedented one-pot sequence entailing acetalation of the sugar substrate and concomitant Fischer glycosylation allowing the quick preparation of differentiated building-blocks even from fully unprotected precursors.

The scope of the solvent-free approaches was next extended to the silylation reaction, with introduction of a simplified procedure for the regioselective installation of silyl groups on saccharide polyols. It was based on the simple exposure of the sugar and the requisite silylating agent to a very slight excess of pyridine (3 equivalents or less for carbinol to be protected), and a catalytic amount of tetrabutylammonium bromide (TBAB) under air. This simple protocol, that can be regarded as a solvent-free approach because of the insolubility of the highly polar polyol substrates in the reaction medium, proved effective in the regioselective silylation of both primary and secondary carbinols of many different precursors, and in the fast generation of useful per-O-silylated derivatives (**Scheme II**).



Scheme II. Solvent – Free Silylation of Saccharide Hydroxyls

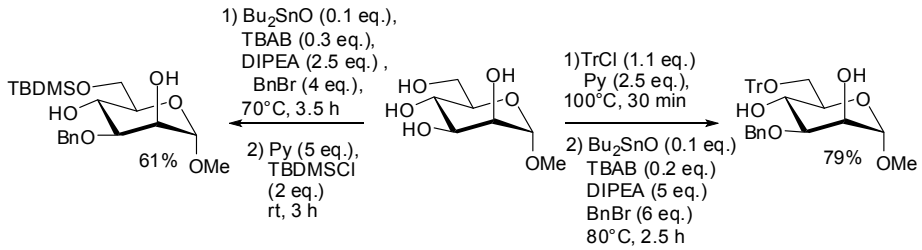
A similar approach, also relying on the use of stoichiometric amounts of pyridine, was addressed to the development of a solvent-free protocol for the quick tritylation of primary positions of carbohydrates (**Scheme III)**; unlike the silylation processes, tritylation reactions were performed at a higher temperature and in the absence of the ammonium salt.



Scheme III. Solvent-Free Tritylation of Primary Saccharide Hydroxyls

The above described procedures are endowed by remarkable advantages over the standard methods for silylation and tritylation of polar substrates, typically requiring a large excess of high-boiling solvents such as pyridine and DMF and very prolonged reaction times. In addition, the feasible incorporation of both procedures into one-pot

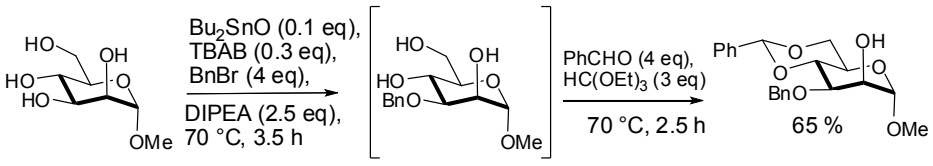
schemes for the alkylation/silylation or alkylation/tritylation of carbohydrates was demonstrated, also taking advantage of a recent protocol developed in our laboratory for the solvent-free alkylation of saccharide polyols mediated by a catalytic tin reagent. Indeed, a wide set of orthogonally differentiated building blocks was accessed in very short times under solvent-free conditions (for some examples see **Scheme IV**).



Scheme IV. Solvent-Free One-Pot Orthogonal Protection of Carbohydrates With Alkyl/Silyl or Trityl Groups

Development of experimentally simplified one-pot procedures for the orthogonal protection of carbohydrates is an important area of investigation, as evidenced by the several sequential procedures designed over last years from several research groups to streamline the access to partially and differentially protected sugars; however, the need for experimentally demanding conditions is a common issue even for the most straightforward one-pot protocols, as reactions are mostly performed under strictly anhydrous atmosphere, in the presence of sensitive acidic promoters and require at least the preliminary activation of the substrate by an additional per-*O*-silylation step. In this frame, a further effort was addressed to test the applicability of solvent-free one-pot methodologies to other combinations of orthogonal protecting groups; thus, it was implemented an innovative fully

solvent-free one-pot strategy involving an initial step of base-promoted regioselective alkylation followed by the acid-catalysed protection of a defined saccharide diol in the same polyol substrate with a cyclic protecting group (acetal or orthoester). An example of such strategy is illustrated in the following synthetic sequence in **Scheme V**.

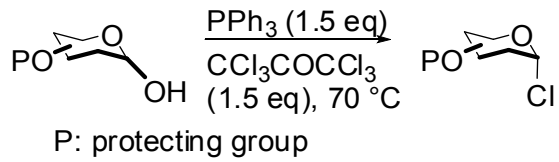


Scheme V. Solvent-Free One-Pot Alkylation and Diol Protection

Besides the experimental advantages associated with the solvent-free approaches and with the feasible installation of orthogonal protecting groups in a one-pot fashion, this strategy is also conceptually original; indeed it relies on the non-trivial occurrence of a base promoted process and an acid catalyzed one sequentially in the same reaction vessel, with the ammonium salt generated as a side product of the alkylation step acting as the promoter of the following acid catalyzed protection.

Another pivotal topic in carbohydrate chemistry is represented by the construction of glycosidic linkages, an essential step in most synthetic applications of carbohydrates but often burdened by several complications, both experimental and conceptual; successful achievement of a glycosylation reaction requires the accurate planning of an effective synthetic strategy and the adoption of several precautions to limit the moisture contamination in the reaction environment. In addition, despite the several strategies described over the years to induce stereoselective glycosylations, this still often represents a non-trivial task, due to the lack of highly reliable methods

of stereocontrol, especially in the synthesis of α-glycosides. In this regard, glycosyl chlorides have been much appreciated as glycosyl donors both for their higher stability in comparison to iodinated or brominated counterparts, and in light of their feasible use in the challenging synthesis of α-glycosides; indeed, an established methodology (known as Lemieux's strategy) to carry out selective α-glycosylations under mild conditions relies on the in situ generation of a reactive β-glycosyl halide from a glycosyl chloride or bromide donor in the presence of an halide salt promoter. Nevertheless, very slow reactions occur under these conditions and this method is traditionally restricted to very reactive donors and acceptors. On the other hand, the use of glycosyl chlorides as donors has drastically decreased over the years, even due to the several drawbacks associated with their preparation, entailing the use of stoichiometric amounts of sensitive reagents and strictly controlled experimental conditions. In light of these issues, an effort was devoted to the search for a more practical entry to this class of glycosyl donors that culminated with development of a very simple protocol (illustrated in **Scheme VI**) allowing quick and high yielding anomeric chlorination of sugar hemiacetals.

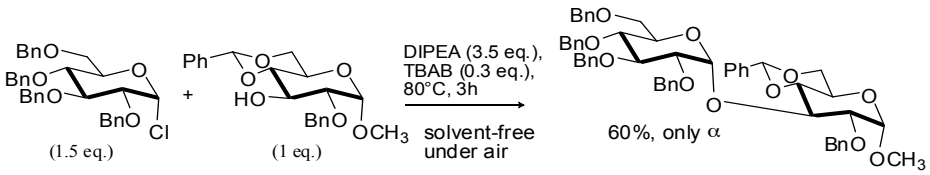


Scheme VI. Solvent-Free Anomeric Chlorination of Sugar Hemiacetals

The introduced method was based on the exposure of the hemiacetal precursor to cheap PPh_3 and hexachloroacetone reagents under air and in the absence of solvent and proved compatible with a wide set of

substrates and protecting groups commonly employed in organic synthesis.

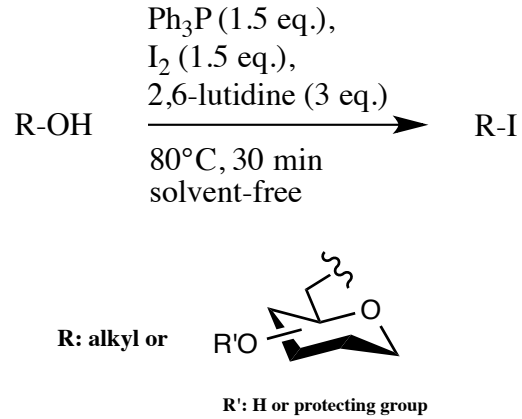
A follow-up investigation was then aimed at clarifying whether thus prepared glycosyl chlorides might find applicability in the development of practical glycosylation protocols. It was indeed demonstrated their feasible use in glycosylation reactions performed under air and in the absence of solvent. It was especially optimized a convenient and versatile protocol for achieving highly stereoselective α-glycosylations, based on an unprecedented solvent-free version of Lemieux's methodology, with a slight stoichiometric excess of a base being the only liquid medium in the reaction. (see example in **Scheme VII**).



Scheme VII. Solvent-Free Approach for Stereoselective α-Glycosylations Under Air

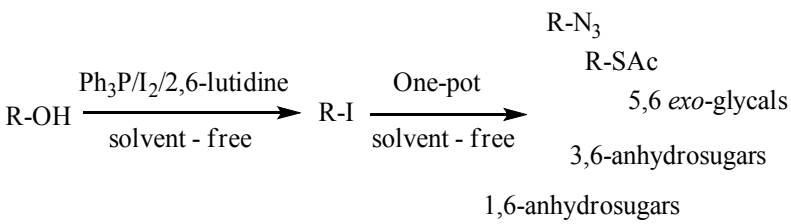
A parallel study was conducted in an attempt to extend the solvent-free approach to further useful elaborations of saccharide functionalities. In light of the broad synthetic versatility of alkyl halides, not only restricted to the field of carbohydrate chemistry, a solvent-free application of the widely employed PPh_3/I_2/base iodination system was investigated and successfully addressed to the conversion of both alcohols and primary saccharide hydroxyls to the corresponding iodides (**Scheme VIII**). The optimized protocol relies on the use of limited stoichiometric amounts of 2,6-lutidine as the base under solvent-free conditions and allows very fast iodination of variously functionalized

substrates and highly polar saccharide precursors, without any additional equipment (e.g. for microwave irradiation or ultrasonication).



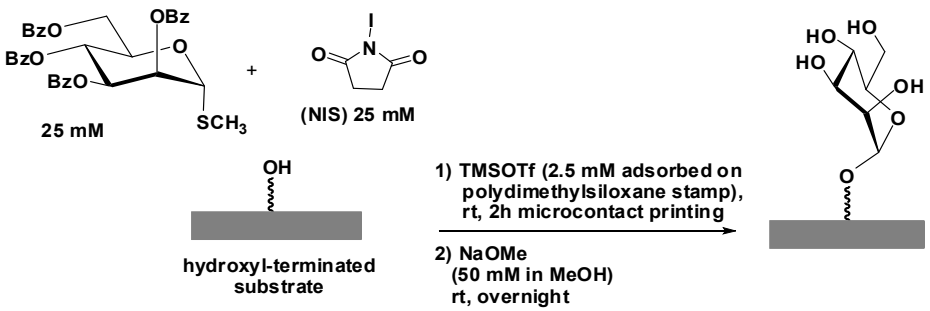
Scheme VIII. Solvent-Free Iodination of Alcohols and Saccharide Substrates

In addition, the application of solvent-free conditions was also usefully exploited in the streamlined one-pot transformation of thus obtained iodides into a wide set of targets of broad synthetic utility (see **Scheme IX**) but traditionally accessed through lengthy and unpractical procedures (for example requiring very prolonged times and the use of toxic and high-boiling solvents).



Scheme IX. One-Pot Elaborations of in situ Generated Iodides via Fully Solvent-Free Synthetic Sequences

Consistently with the aim of the present thesis, an analogously simplified and convenient approach was also extended to an applicative context where carbohydrates play a central role. Indeed, a streamlined method for the immobilization of carbohydrates onto surfaces was developed. Due to the broad application of carbohydrate biochips and arrays in analytical and biological studies, the search for ever more efficient approaches for the attachment and patterning of carbohydrates on surfaces is an important area of research. This is usually achieved through the indirect coupling of the carbohydrate, preliminary derivatized with a functionalized linker, with a proper reactive surface; only few examples of more direct approaches based on enzymatic or chemical glycosylation have instead been reported and however, are not free of drawbacks, owing to the laborious procedures required for preparation of carbohydrate precursors and highly functionalized surfaces, as well as the high cost of materials and chemicals. The developed strategy (see a schematic example in **Scheme X**) allowed the efficient preparation of sugar-modified surfaces, also suitable for ligand-protein recognition, through a direct chemical *O*-glycosylation of easily prepared thioglycoside donors with cheap and readily available hydroxyl terminated glass substrates.



Scheme X. Immobilization of Carbohydrates on Surfaces Through Direct *O*-Glycosylation by Catalytic Microcontact Printing

Besides the efficiency deriving from a streamlined chemistry, the method took advantage of a convenient lithographic technique, known as microcontact printing (μCP), widely emerging nowadays as a valuable alternative to traditional robotic printers for the modification and high resolution patterning of surfaces. It relies on the transfer of reactive "ink" molecules from a microstructured elastomeric stamp onto a surface suitably derivatized with complementary reactive groups and displays a number of advantages in terms of costs, efficiency and patterning resolution.

In light of what herein introduced, it is expected that the several developed methodologies may have a useful application in carbohydrate chemistry to streamline the access to both synthetic saccharide targets and nano-devices of broad utility as analytical tools.

Chapter 1

Introduction

General Introduction: Carbohydrates and Research

Carbohydrates represent a unique family of polyfunctional compounds, widely distributed on Earth in a variety of different forms. They naturally occur as components of many fundamental compounds and materials as monomers, oligomers or polymers of variable complexity. Some examples of widely available carbohydrates are polysaccharides such as cellulose, starch or chitin, playing relevant roles as structural components or energy source. Although these represent fundamental molecules both in the world of animals and plants, the idea of carbohydrates just as energy source or building-blocks for cell walls, is pretty limiting. The high structural complexity and variability of carbohydrates accounts for their multiple roles in biological systems and their huge bio-informative potential, far greater than that of nucleic acids and proteins.[1]Abundant and diverse glycans cover all the cells of all living organisms. Carbohydrate chains are prominent components at the surfaces of mammalian cells and also occur on many secreted and extracellular glycoproteins. 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.[2] Cancer is another area where carbohydrates play a decisive role, cooperating in transmitting the signals that trigger unchecked cell growth.[3] Obviously, the involvement of carbohydrates in so many crucial biological processes suggested their use in medicinal chemistry with development of several carbohydrate-based drugs.[4] 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 and deciphering the "sweet code" still represents an open challenge of current glycomics. This difference relies on the higher structural complexity of carbohydrates; while DNA and proteins have essentially linear sequences composed of few basic building-blocks, 4 and 20 respectively, sugars have more than 30 existing monomers that can form both linear and a variety of branched sequences; even a simple disaccharide composed of two glucose units can be represented by 19 different structures. Clearly, for unravelling the mysteries of sugars and elucidating their biological functions, pure oligosaccharides of defined structure are required in sufficient amounts for biophysical and biochemical studies. The isolation of oligosaccharides in a pure form from natural sources is extremely challenging, when at all possible, since these biomolecules are often found in nature in low concentrations and microheterogeneous forms. 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. Enzymatic or chemo-enzymatic approaches are certainly promising but still expensive, due to the limited availability of glycosyltransferases and their extreme specificity, being able to catalyse the formation of single types of glycosidic linkages. For these reasons, chemical synthesis is still the cheapest and more reliable approach to achieve pure oligosaccharide sequences.

Synthesis of oligosaccharide targets for bio-medical applications is not the only scope of current research in the field of carbohydrate chemistry, though one of the most attractive. Indeed, the structural features, high density and variability of functional groups exhibited by carbohydrates makes these molecules versatile starting materials amenable of multiple chemical transformations; a wide range of sugar – derived functional targets, finding potential applications in several fields can indeed be accessed. An example of this concept is represented by the broad use of carbohydrates in supramolecular chemistry. Their attitude to form multiple hydrogen bonds makes sugars remarkably suitable as building-blocks in the construction of even complex supramolecular architectures. Saccharide – based macrocycles such as cyclodextrins are broadly employed in this regard; these cyclic oligosaccharides, made of 6, 7, or 8 1,4–linked α–D–glucopyranose units, exhibit a hydrophilic surface and a hydrophobic central cavity allowing encapsulation of different guest molecules through the generation of host-guest inclusion complexes; exploiting this structural feature, suitably chemically modified cyclodextrins have been used to construct supramolecular systems that found application in nanotechnology, drug delivery, material sciences and as versatile tools for the study of carbohydrate-proteins or carbohydrate-carbohydrate

interactions.[5] Many other reports demonstrate the applicability of suitably modified sugars in the science of materials; some model examples in this regard are the generation of thermo-reversible polymers,[6] pH-sensitive biodegradable materials[7] or sugar derived gelators with attractive mechanical properties for application in the biomedical field.[8] Furthermore, their instrisically high density of stereocenters supports the frequent use of carbohydrates as cheap "chirality sources" in the enantioselective synthesis of multifunctionalized natural products and as precursors of chiral targets with high applicative potential.[9] The wide range of useful synthetic elaborations and targets accessible from sugars has spurred the development of novel methods in synthetic carbohydrate chemistry. The search for ever more practical, efficient and environmentally friendly protocols aimed both at the preparation of building – blocks and stereoselective glycosylations or, in general, at synthetic derivatizations of carbohydrates, represents a topic of broad interest. Indeed, multifunctional nature of sugars gives not only rise to their great bio-informative features and chemical versatility; it is also responsible for the known difficulty associated with their synthetic manipulation. Installation of a suitable set of protecting groups represents a crucial step, preliminary to most synthetic elaborations of carbohydrates. This derives from the need for differentiating the reactive site that has to be involved in a given transformation, from other functionalities that may in principle compete in the same process. In addition, it is often necessary to differentiate the reactive positions in a given saccharide residue, through the selective installation of different, orthogonal protecting groups, thus allowing saccharide positions with different "synthetic fate" to be deprotected at different stages of the synthesis. It's therefore easily understood that application

of protecting group chemistry to carbohydrates turns out to be a complex issue, given the high number of similarly reactive functional groups present in the same molecule; other complications arise from the moisture sensitivity of many pivotal reactions in carbohydrate chemistry. This general complexity entails inconvenient and unpractical procedures, often involving long multi-step synthetic sequences and strictly controlled conditions; the use of toxic and high boiling solvents, often needed in reactions involving such complex substrates, represents a further drawback to deal with. The assembly of saccharide targets is therefore highly laborious and time-consuming, not only in the non-trivial construction of stereo-defined glycosidic linkages but since the preliminary steps needed for the preparation of building-blocks. In light of such complexity, both experimental and conceptual, synthetic carbohydrate chemistry is still today considered a tricky branch of organic synthesis, usually requiring the know-how of specialized groups and suitably equipped labs.

What is more, synthesis is just an aspect in the overall context of research in this field. Synthesis of a defined saccharide structure is often a preliminary step for wider studies, aimed at investigation of its biological or functional properties. Consequently, development of convenient synthetic approaches to access specific targets strongly supports the parallel search for ever more advanced analytical methods aimed at the study of their functional properties. In this regard, nanotechnology finds a broad application with the use of glyco-nanoparticles and self-assembling aggregates capable of mimicking biological systems or the fabrication of carbohydrate chips, arrays and biosensors, useful tools for the study of carbohydrate-proteins and carbohydrate-carbohydrate interactions.[5,10] Therefore, research aimed at enhancing the potential of these tools is also part of a wider general

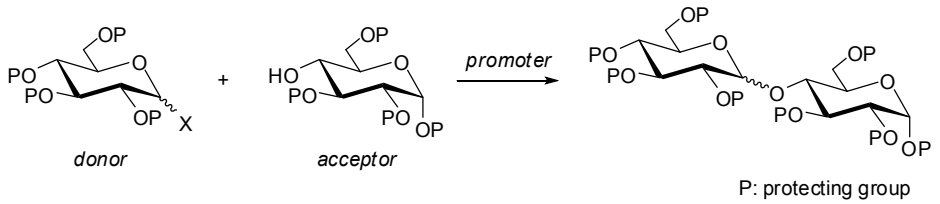
scope, namely exploiting the broad versatility of carbohydrate structures to bring progress in multiple aspects of life on Earth.

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 glycosylation 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, defining the sugar as D or L. 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*. In most cases, an axial orientation of the newly formed glycosidic bond (on the saccharidic backbone of the former glycosyl donor) corresponds to the α-anomer, whereas an equatorial orientation is often associated to the β-anomer.

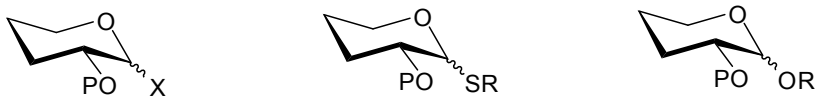
Figure 1 Anomeric Configurations of D-Glucopyranose

Several approaches are used to achieve the desired stereoselectivity. The most effective method involves the use of neighbouring 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**).



Glycosyl halides

(bromides, chlorides, fluorides, iodides)

Thio-derivatives

(thioglycosides, sulfoxides, sulfones, others)

O-derivatives

(imidates, 1,2-anhydro derivatives, phosphates, phosphites, others)

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.

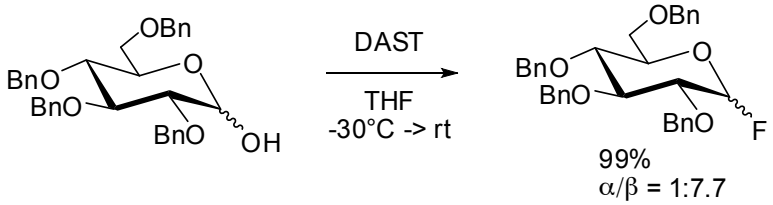
It should be noted that glycosylation reactions of glycosyl halides bearing participating groups at *O*-2 in the presence of excess base lead to 1,2-orthoesters instead of glycosides. Therefore the amount of base in the reaction mixture should be limited. A different type of activation was introduced 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. Traditionally, the scope of this method is limited to reactive glycosyl halides and acceptors.

Glycosyl halides, for a long time the only type of glycosyl donors, have lost over time their predominant role in glycosylations. This is due to attempts to avoid the use of stoichiometric amounts of toxic, expensive and sensitive heavy metal salts for their activation and the multiple problems arising from their low stability that result in tricky preparation and isolation; in the synthesis of glycosyl halides bearing a defined protecting group patterns, the introduction of the halide is usually the last step since 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 center 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; recently, improved methods for both the synthesis and the activation of glycosyl chlorides have been developed in our laboratory; anomeric chlorination of carbohydrates from hemiacetal precursors was efficiently performed through the triphenylphosphine/hexachloroacetone system and several glycosyl chlorides thus prepared were successfully used to develop advantageous glycosylation protocols.[26]

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,[27] and glycosyl fluorides are currently among the most frequently used glycosyl donors. Several methods for the preparation of glycosyl fluorides are known.[28]They are commonly synthesized by the reaction of a protected sugar with a free anomeric hydroxyl group with diethylaminosulfur trifluoride (DAST) (**Scheme 3**).[29]



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[28] using a combination of $SnCl_2$ with $AgClO_4$ (often replaced by AgOTf).[30] Noyori and coworkers introduced the use of SiF_4 and TMSOTf,[31] whereas $BF_3{\cdot}Et_2O$ was introduced independently by Nicolau and Kunz.[32]Additionally, Wessel et al. introduced Tf_2O as a powerful glycosylaton promoter for glycosyl fluoride donors.[33] 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.[34]Glycosyl fluorides have found use in the synthesis of complex natural products.[35]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.[36]

Glycosyl iodides have been known for a long time.[37] However, because of their instability, they have been used only occasionally as glycosyl donors. In general, they can be activated by stoichiometric reagents such as AgOTf and Hg(II) salts;[38] $BiBr_3$ in sub-stoichiometric amounts also proved an effective promoter.[39] Since the introduction of the halide ion-catalysed glycosylation method,[25] a number of glycosylations actually proceeded through *in situ* generated β-glycosyl iodides intermediates by activating glycosyl halides with tetraalkylammonium iodides.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. Several methods have been reported for the preparation of glycosyl iodides, in most cases starting from 1-O-acylated precursors. Some examples are HI 55-58% /Ac_2O,[40] Me_3SiI,[41] I_2/thiolacetic acid or I_2/1,3-propanedithiol,[42] I_2/HMDS.[43] Some improved and very effective methods for the preparation of per-O-acylated glycosyl iodides were developed in our laboratory in last years; according to these procedures, they can be generated in situ in few minutes from per-O-acylated sugars upon a short exposure to either the I_2/Et_3SiH[44] or I_2/PMHS[45] combined system. In addition, glycosyl iodides have been used as crude products, after a simple extractive work-up, to prepare several useful building-blocks such as 1,2-ethylidenes, 1,2-orthoesters, glycals, thio- and selenoglycosides through fast sequential one-pot schemes (**Figure 3**).[44, 46]

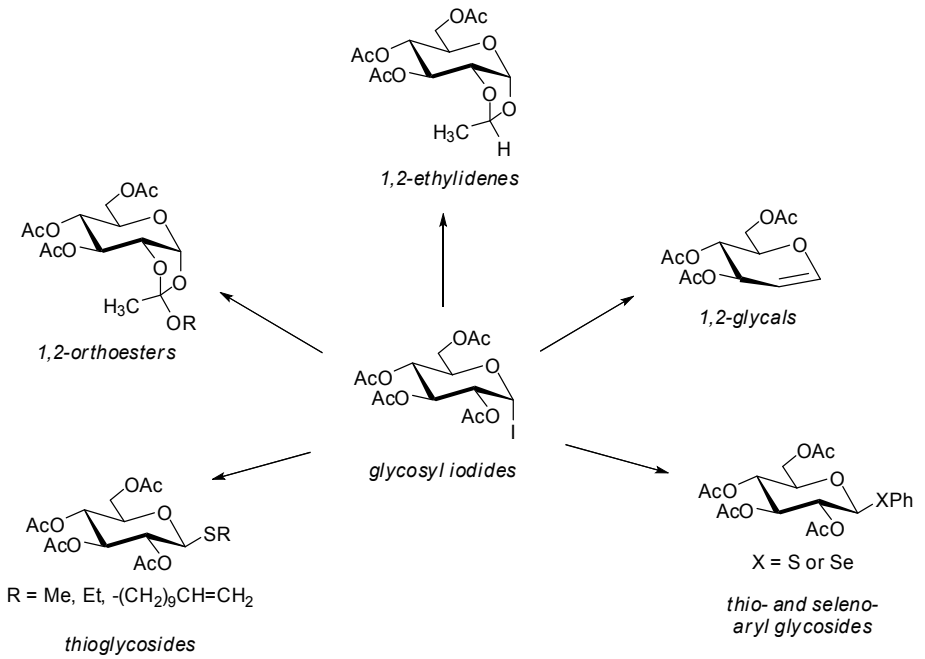


Figure 3 One-Pot Elaborations of Glycosyl Iodides

Thioglycosides are the most used class of donors in oligosaccharide synthesis. The first thioglycoside was synthesized in 1909,[47] 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 4***)*.

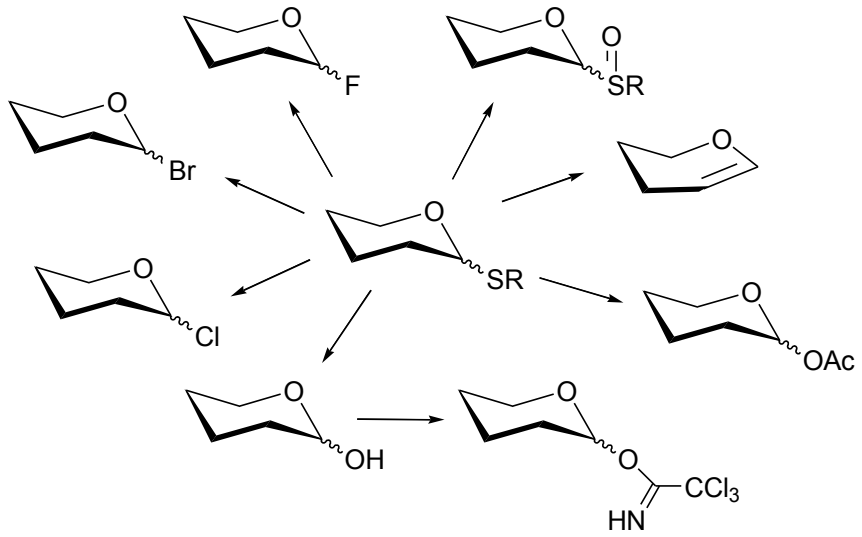
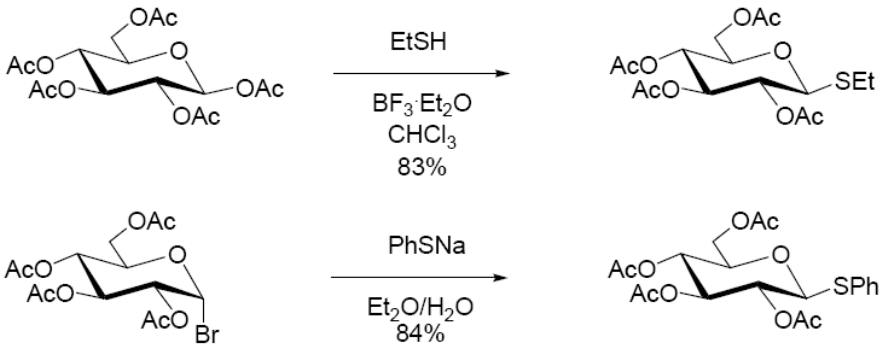


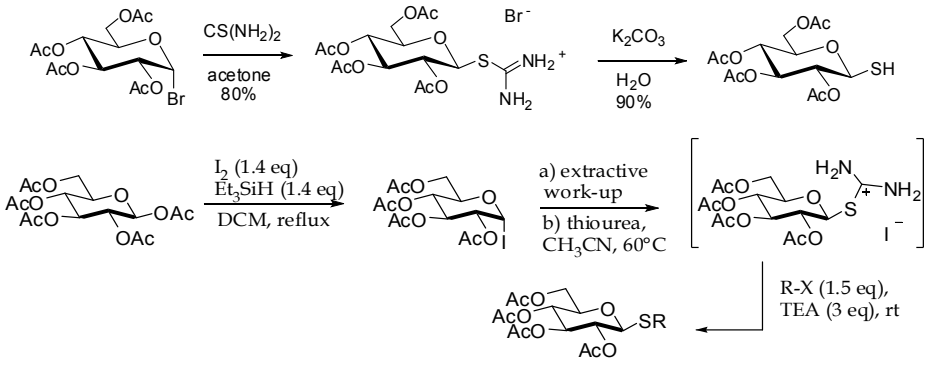
Figure 4 Conversion of Thioglycosides into Other Types of Donors

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,[48] 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[49] and the reaction of an acylated glycosyl halide with a thiolate (**Scheme 4***)*.[47]



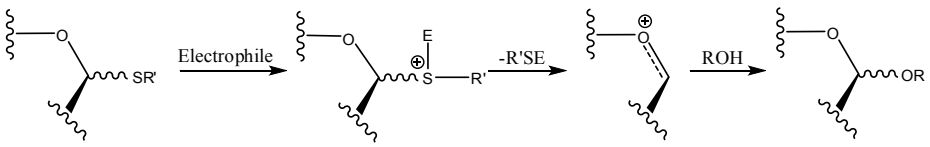
Scheme 4 Synthesis of Thioglycosides

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 5**).[46b, 50]



Scheme 5 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 6**). 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.



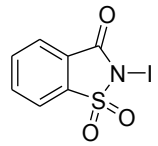
Scheme 6 Activation of Thioglycosides for Glycosylations by Electrophilic Reagents.

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.[51] Other mercury salts, such as $Hg(OAc)_2$, $HgCl_2$, $Hg(OBz)_2$, and PhHgOTf, were tried later.[52] 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,[53] and especially with MeOTf[54] and dimethyl(methylthio)sulfonium triflate (DMTST)[55] a seemingly never-ending spectrum of new promoters has been reported, but also electrochemical and radical activation have been described.[56]

Iodine-containing compounds are also used as promoters. Iodonium dicollidine perchlorate (IDCP) was introduced first as iodonium source,[57] later on the corresponding triflate (IDCT) started to be effectively used.[58] A very efficient promoter system, *N*-iodosuccinimide in the presence of a catalytic amount of triflic acid, was introduced independently by van Boom[59]and Fraser-Reid.[60] 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 $BF_3 \cdot Et_2O$.

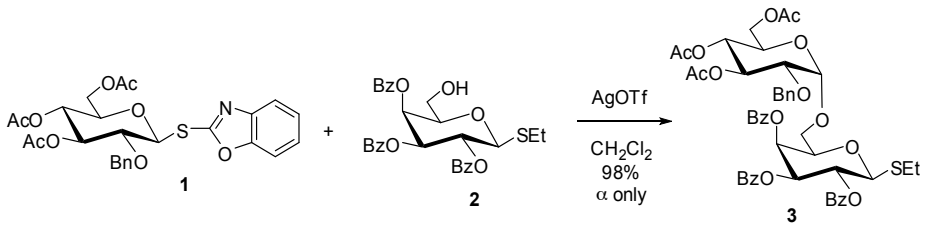
N-iodosaccharin (NISac) (**Figure 5**) was recently proposed as a replacement of NIS to reduce occasional by-products caused by the nucleophilicity of succinimide generally obtained as by- product in NIS promoted reactions.[61]



NISac

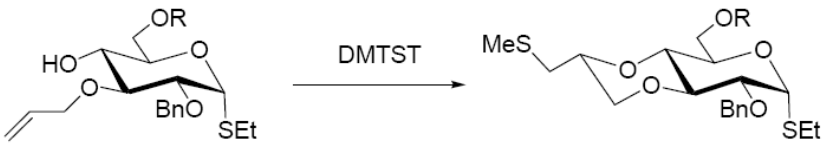
Figure 5 N-iodosaccharin

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.[62] Bulky or electron withdrawing groups on the sulphur decrease the reactivity of thioglycoside donors. Furthermore, several heterocyclic aglycones, such as benzothiazol-2-yl,[63] pyridine-2-yl,[53a] pyrimidin-2-yl[53a] and, most recently, benzoxazol-2-yl[64] 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.[65] AgOTf or $ZrCl_4$-Ag_2CO_3 proved to be effective promoters for the recently introduced benzoxazolyl thioglycosides (SBox glycosides).[64b] As shown in **Scheme 7**, the thioglycoside acceptor **2** could be glycosylated by SBox glycoside **1** in excellent yield as the promoter does not activate the ethylthio-function of the acceptor **2**.[64b]



Scheme 7 Glycosylation with SBox Thioglycoside.

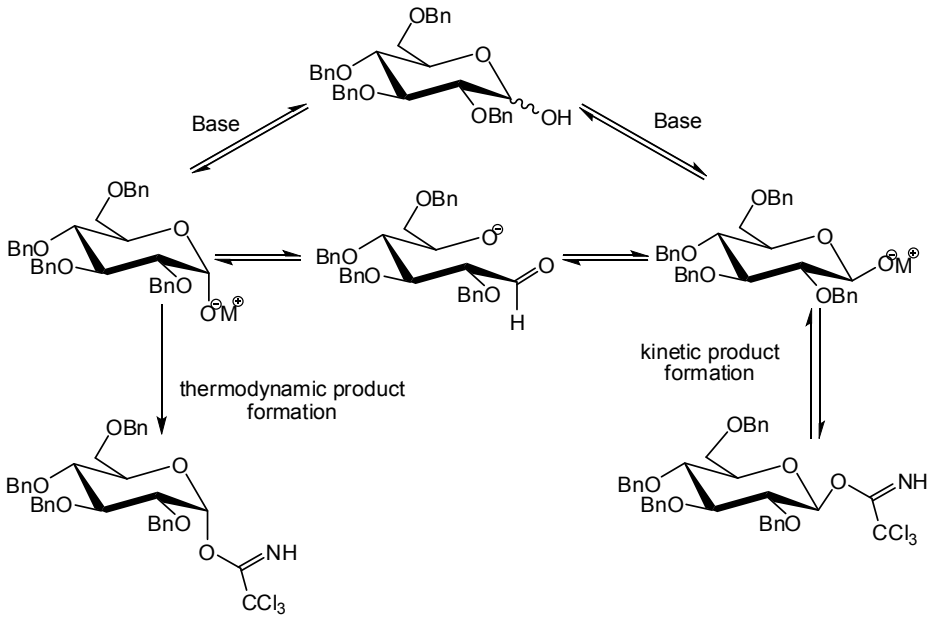
Notwithstanding the efficiency of thioglycosides as donors, problems can, of course, be encountered in various applications. The problems are connected both to the type of thioglycoside used and to the promoter employed. As to the promoter, MeOTf can, if the acceptor is unreactive, give methylation instead of glycosylation of the acceptor hydroxyl group.[66]As previously reported, *N*-succinimide glycosides can be formed as major products in NIS-promoted glycosylations with unreactive acceptors.[67]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.[68] 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 8**).[57a]



Scheme 8 Side-product of Thioglycosides Activation

The use of thioglycosides in glycosylations has been reviewed.[69]

Though thioglycoside donors are 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,[70] 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 9**).[71]



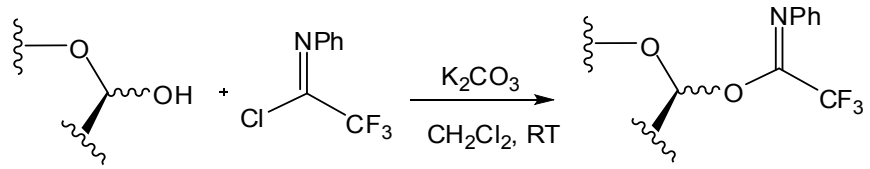
Scheme 9 Anomeric Control in Trichloroacetimidate Syntehsis

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 SN2 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**.[72] 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.[73]

Glycosyl *N*-phenyl trifluoroacetimidates are synthesized in high yield by treatment of the corresponding 1-hydroxyl sugar with *N*-phenyl

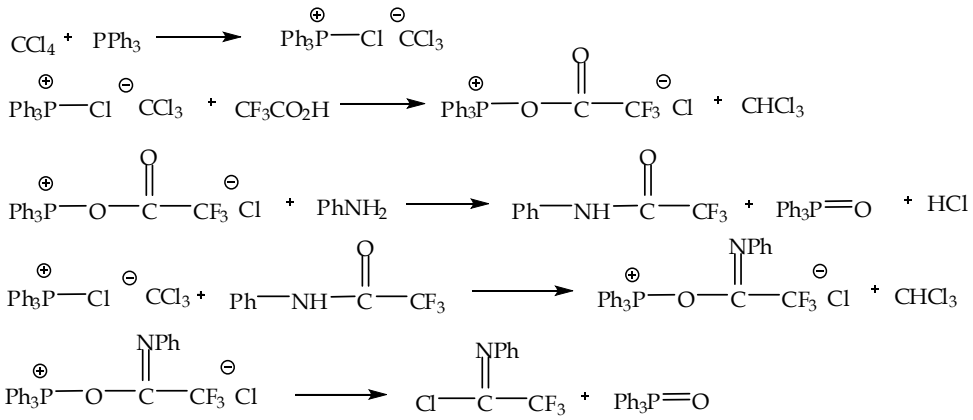
trifluoroacetimidoyl chloride in the presence of Cs_2CO_3 or K_2CO_3 in lab grade non-anhydrous CH_2Cl_2 or acetone at room temperature (**Scheme 10***)*.



Scheme 10 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.[74] 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.[75]

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_4system (**Scheme 11**).[76]



Scheme 11 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.[77] 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,[70]

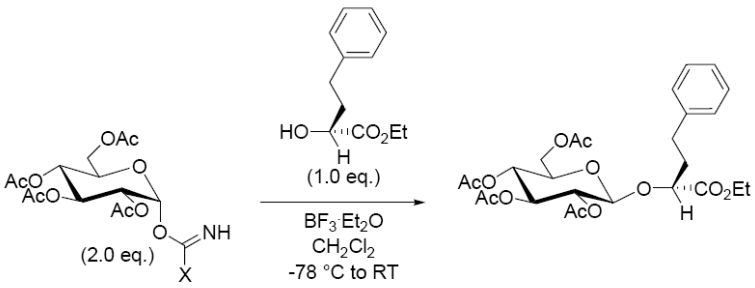
while currently the latter and TMSOTf[78] are the most frequently employed promoters. Glycosylations with these promoters take place at low temperatures and in high yields. Besides the activators mentioned thus far, several additional promoters have been introduced, these include strong protic and Lewis acids.

One of the aims of our lab in last years was the development of new mild, moisture-stable, non-corrosive glycosylation promoting systems for the trihaloacetimidate methods; indeed several mild promoters have been proposed, such as the system I_2/Et_3SiH, as source of *in situ* generated HI,[79] and lanthanide salts such as $Sm(OTf)_3$[80] or $Yb(OTf)_3$.[81] Furthermore, commercially available acid washed molecular sieves (AW 300 MS) proved to effectively activate trihaloacetimidates without any further promoter.[82] The last and very powerful promoting system developed in our lab concerns the use of catalytic amounts of $Bi(OTf)_3$.[83] 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.[84]

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. In recent years these observations were addressed in our lab to 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.[85] 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.[86] 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

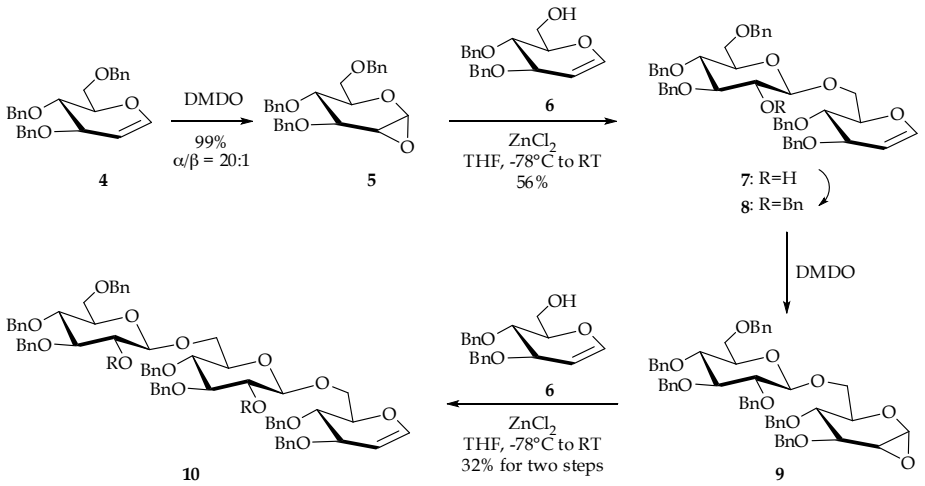
Table 1 $BF_3 \cdot Et_2O$-catalyzed Glycosylation:
Glycosyl Trichloroacetimidates *vs* Trifluoroacetimidates

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[87]or rearrangement to unreactive glycosyl trichloroacetamides.[88]*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*.[89] 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.

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).[90] Reaction of the epoxides **5** and **9**, promoted by $ZnCl_2$ in tetrahydrofuran or dichloromethane, produced 1,2-*trans*-glycosides (**Scheme 12**).



Scheme 12 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.[91]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,[92] or for configurational inversion as in the synthesis of β-mannosides from β-glucosides.[93] 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 6**) are the natural substrates of glycosyl trasferases, that are the enzymes responsible for the biosynthesis of oligosaccharides in living systems.[94]

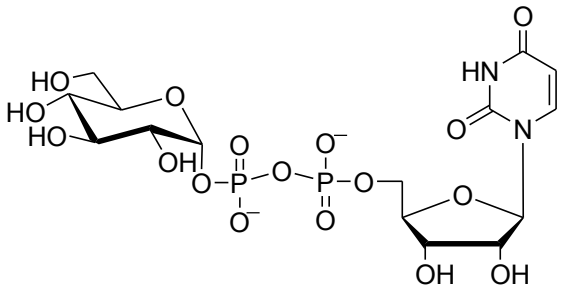


Figure 6 Nucleotide 5'-Diphospho Sugar.

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.[95] 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.[96]

Most frequently, diphenyl and di-*n*-butyl phosphates are used. Recently, Singh and coworkers introduced the cyclic propane-1,3-diyl phosphates (**Figure 7**).[97]

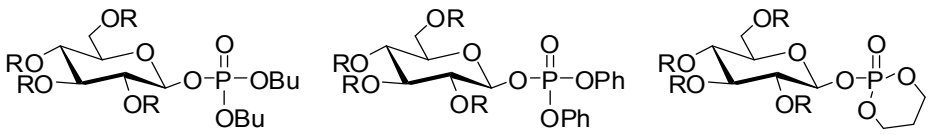


Figure 7 Most Commonly Used Glycosyl Phosphates.

Glycosyl phosphates proved to be very effective glycosylating agents in the syntheses of various biologically relevant oligosaccharides both in solution and on solid-support.[98] Furthermore, their versatility was demonstrated in orthogonal and regioselective glycosylation

strategies.[96] One of the reason for the growing interest toward glycosyl phosphates is their compatibility with the automated solid-phase approach. Seeberger and coworkers developed the first automated solid-phase oligosaccharide synthesizer.[99]A peptide synthesizer was adapted to carbohydrate synthesis. Specific coupling cycles were designed for glycosyl trichloroacetimidate and phosphate methods and successfully addressed to the efficient synthesis of non trivial oligosaccharide structures.

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. 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.[100]

Besides glycosyl phosphates, a variety of other phosphorus containing leaving groups have been designed and proposed. **Glycosyl phosphites** were introduced by Schmidt,[101] Wong[102] and Watanabe.[103] 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 $BiCl_3$.[96,104] Glycosyl thio compounds with phosphorus in the leaving group, such as dithiophosphates[96,105] or **phosphorodiamidimidothioates**,[106] have also been studied (**Figure 8**).

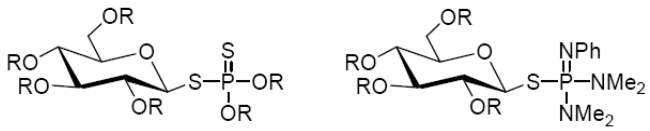
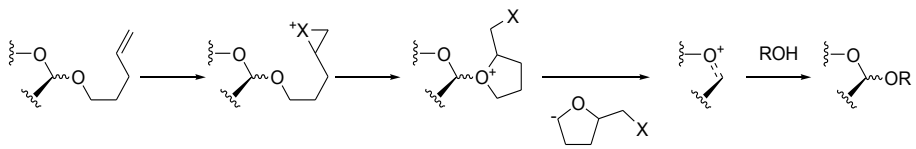


Figure 8 Glycosyl Dithiophosphate and Phosphorodiamidimidothioate Donors

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,[107] 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 13**).



Scheme 13 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[108]or TESOTf,[109]was introduced as a more active catalyst. The *n*- pentenyl glycosylation was used in the synthesis of biologically important molecules.[110]

Glycosyl sulfoxides as glycosyl donors were introduced by Kahne.[111]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.[112]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 $MgBr_2 \cdot Et_2O$.[113]

Stereoselectivity of Glycosylation 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 SN2 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 SN1 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 9**).

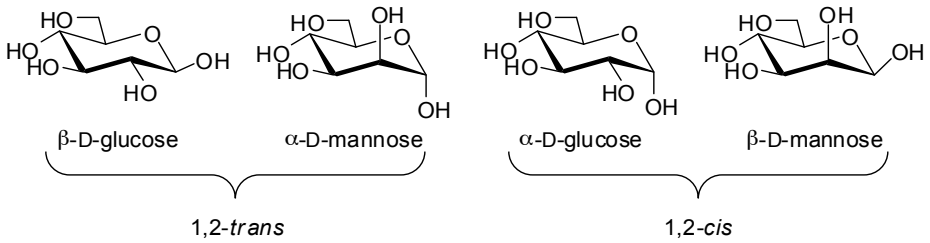
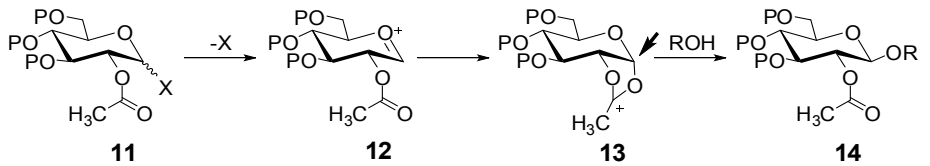


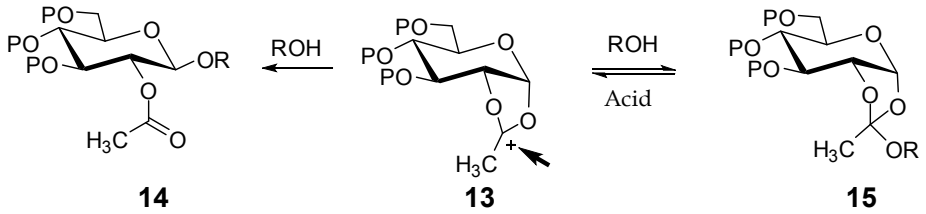
Figure 9 Anomeric Configurations of D-Glucose and D-Mannose.

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 assistedby the carbonyl moiety and the acyloxonium ion **13** is readily formed (**Scheme 14**).



Scheme 14 Neighbouring Group Participation

Reaction of the nucleophile with the acyloxonium ion **13** takes place from the upper face of the ring and therefore resultsin the formation of 1,2-*trans*-glicoside **14** with regeneration of the acyloxy group. The nucleophile might also reactwith the other electrophile carbon, thus forming the undesired orthoester **15** (**Scheme 15**).



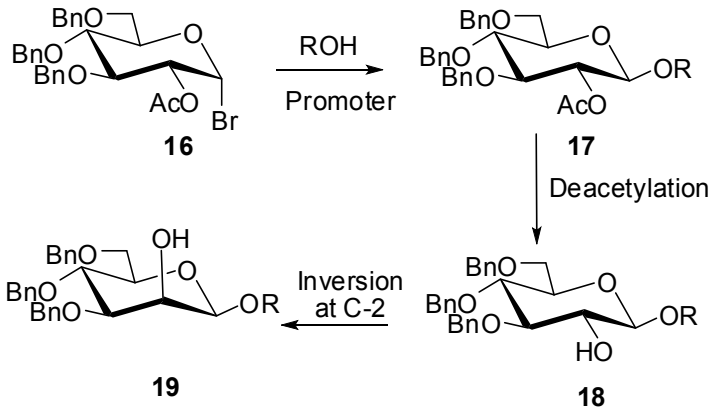
14 **13** **15**

Scheme 15 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,[80,81] 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.[114]

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 ofglycosylation reactions with various glycosyl donors. However the neighbouring group participation is limited to the synthesis of 1,2-*trans*-glycosides, but, since its effectiveness, itis sometimes used for the indirect synthesis of 1,2-*cis*-mannosides (**Scheme 16**). In this approach, the first step takes the advantage of the ready formation of 1,2-*trans*-glucoside **17** by neighbouring group participation from

glucosyl donor **16**, which possesses orthogonally removable acetyl at O-2. After selective removal of this protecting group, the C-2 configuration of the resulting **18** is inverted by nucleophilic displacement or oxidation-reduction type reactions, thus creating the 1,2-*cis*-mannoside **19**.



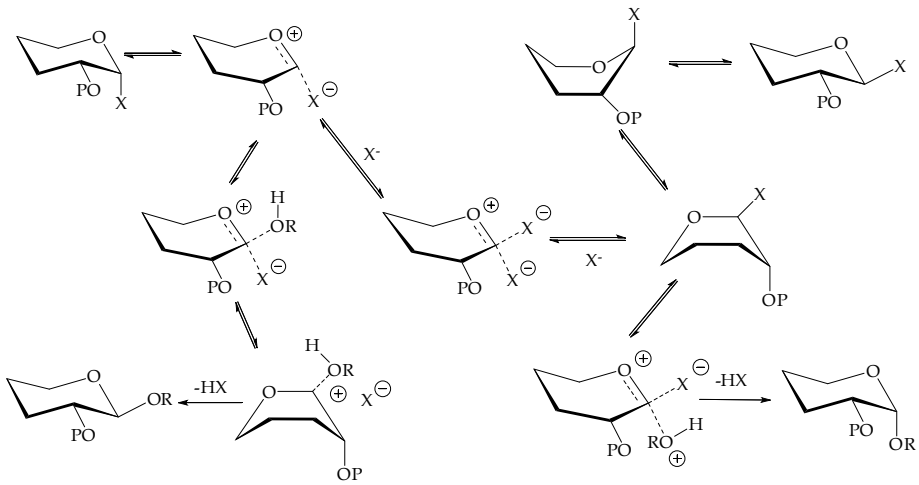
Scheme 16 Synthesis of β-D-Mannopyranosides by Configurational Inversion at C-2

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 glycosyldonor leaving group. Glycosyl donors equipped with electron-withdrawing protecting groups are called *disarmed* and exhibit decreased reactivity.[115] 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

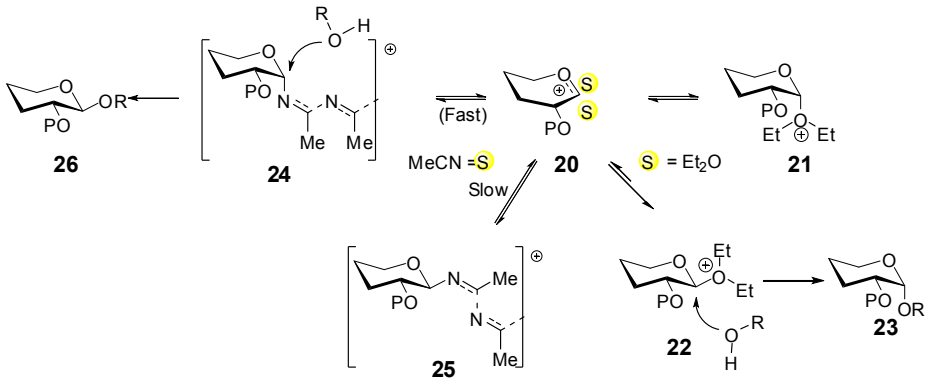
is the avoidance of participating groups at glycosyl donors O-2. Ether-type protecting groups have a low participation tendency and are therefore commonly used for this purpose. In these cases, benzyl ethers are the most frequently used derivatives for hydroxyl groups, whereas for amino sugars, the azido 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 proceed through a tight ion pair, favouring an SN2-like mechanism with inversion of configuration at the anomeric carbon (**Scheme 17**).[116]

The accomplishment of a pure SN2 reaction is very difficult. The ready participation of the endocyclic oxygen in leaving group displacement gives a considerable SN1 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 17 Halide ion catalyzed 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.[117] After the departure of the leaving group from the glycosyl donor, the oxocarbenium ion **20** is solvated by the coordinating solvent (**Scheme 18**).



Scheme 18 Solvent Participation in Glycosylations

In the case of ether-type solvents, the kinetic formation of the α-adduct **21** is rapidly followed by its conversion into the thermodinamically favoured β-oxonium intermediate **22**. The β-adduct **22** is more stable than the axial oxonium **21** 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 10**).

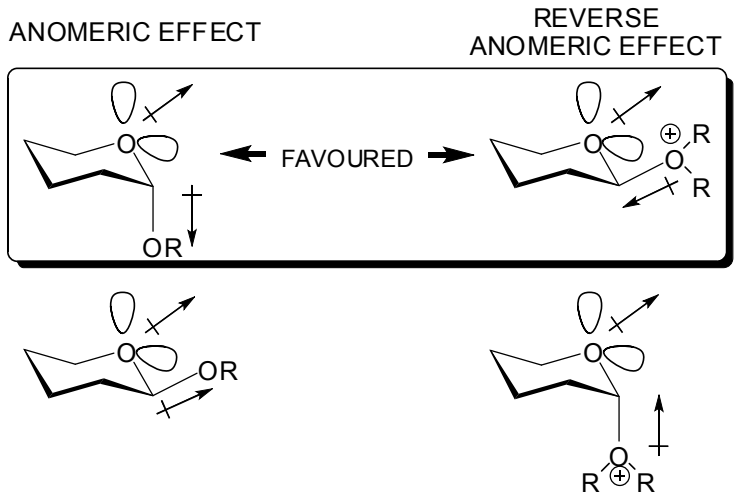
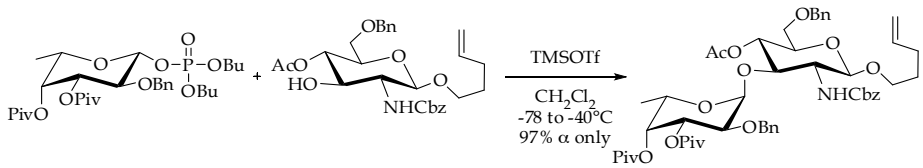


Figure 10 Dipole-Dipole Interaction in Directand Reverse Anomeric Effects.

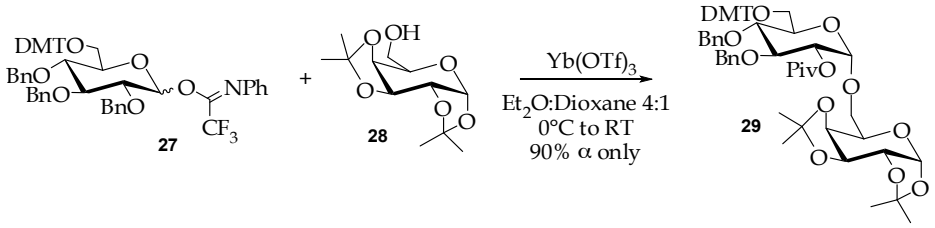
Intermediate **22** then reacts with the nucleophile to form the axial glycoside **23**, thus achieving the desired α-stereoselectivity. When nitrile-type solvents are used, the same model can be applied. In this case, the conversion of the α-adduct **24** into the termodinamically more stable β-nitrilium ion **25** 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 **26**. This model is well established and the solvent effect is widely recognized. It had been supported by several experimental evidences, collected inthe course of the years. Reaction at different temperatures and rates were conducted and the nitrilium ion was also trapped.[118] 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. A broad effort was especially addressed

over the years to improve stereocontrol in the generation of 1,2-*cis*-glycosidic linkages; this kind of glycosylations is still much more challenging than the synthesis of 1,2-*trans*-glycosides due to the lack of a highly reliable strategy for controlling the stereoselectivity, as the neighbouring effect for 1,2-*trans*-glycosylations. 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 19**).[96]



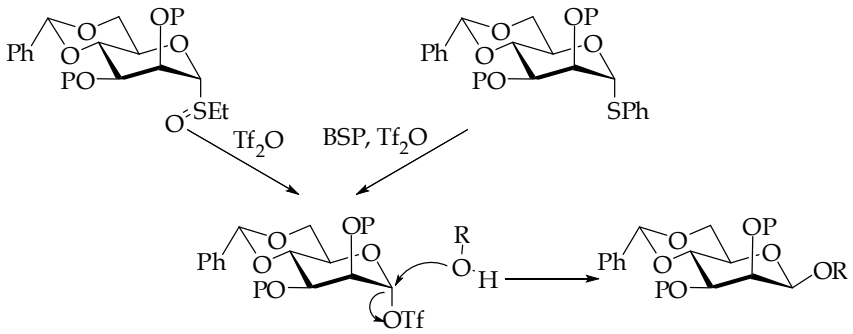
Scheme 19 Long-Range Participation Effect

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 20**, the presence of the bulky dimethoxytrityl group on the O-6 of glucosyl N-phenyl trifluoroacetimidate **27** guaranteed the exclusive formation of the desired α-glycoside **29** in high yield (**Scheme 20**).[84]



Scheme 20 Effect of the Donor 6-O-Substituents on α-Selectivity of Glycosylations.

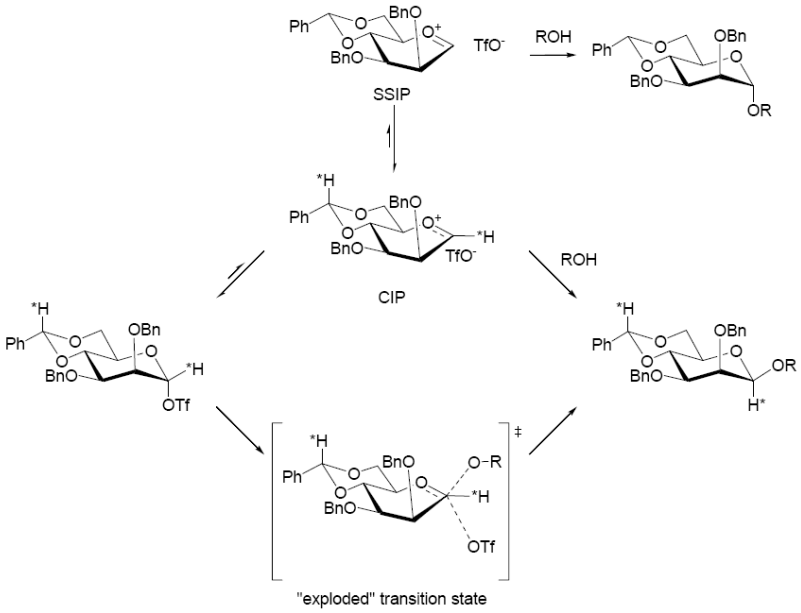
The use of **4,6-O-benzylidene protection** on mannosyl donors is one of the keys to the efficient 1,2-*cis*-selectivity reported by Crich and coworkers in their work.[119] 4,6-O-Benzylidene-protected mannosyl sulfoxides are first activated withtriflic anhydride to give a covalent triflate, that is then 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 21**).[120]



Scheme 21 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 22**).[121] 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. Inthe 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

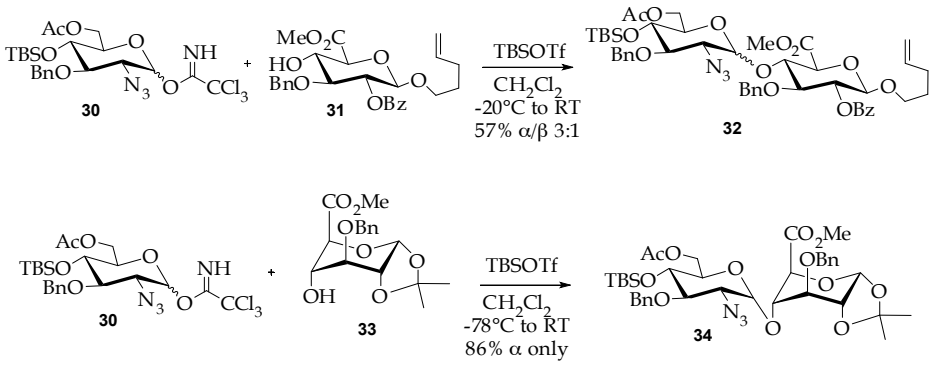
benzylidene group plays an important role in this equilibrium. It opposes to rehybridisation at anomeric carbon because of torsional effect and, so, shifts the complete set of equilibria toward the covalent triflate and away from the SSIP, thereby minimizing α-glycoside formation.



Scheme 22 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)[122] and steric factors, which result in matched/mismatched pairs of glycosyl donors and acceptors.[123]Recently, a new concept for stereochemical control of

glycosylation reaction has been developed by **locking the conformation of the monosaccharide acceptor**.[124] In the synthesis of key disaccharide building blocks for the assembly of the heparin backbone, the reaction of C-2-azido glucose trichloroacetimidate **30** with glucuronic acid acceptor **31** yielded anomeric mixture of disaccharide **32** (**Scheme 23**).



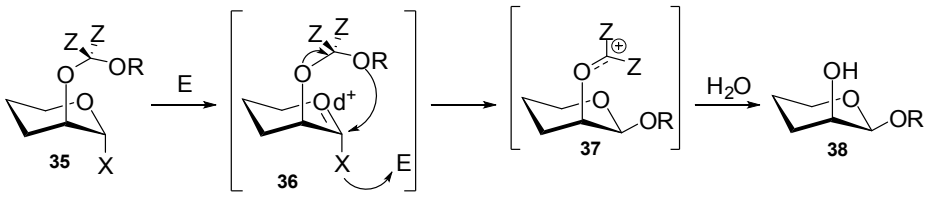
Scheme 23 Improvement of α-Selectivity by Conformational Locking of Glycosyl Acceptor

Glucuronic acid **31** 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 **30** with acceptor **33** resulted exclusively in formation of the α-linked disaccharide **34** 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.[125]

The strategy involves the initial covalent attachment of the glycosyl acceptor to a group on O-2 of the glycosyl donor (**Scheme 24**).

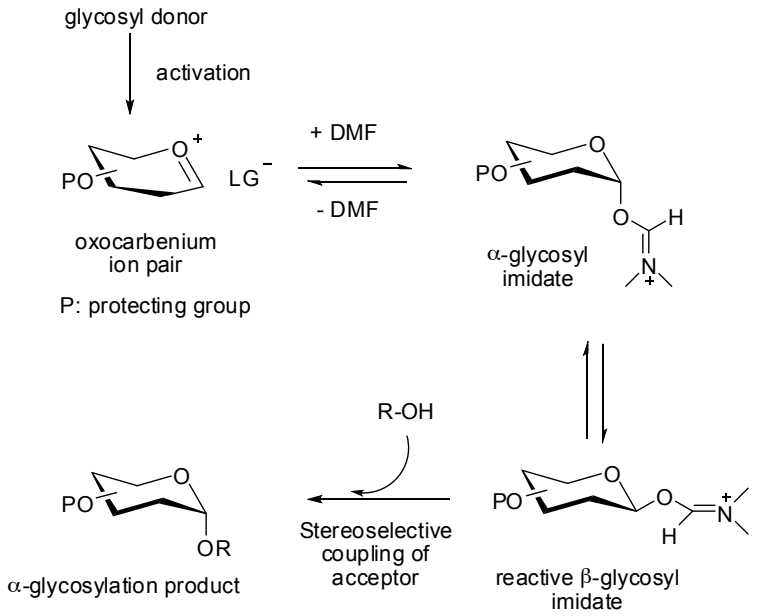
Activation of the anomeric leaving group in the tethered derivative **35**by an electrophile is then expected to proceed intramolecularly via a concerted mechanism. Thus, the derivative **35** results in formation of **37** via **36**. On quenching with water, **37** releases O-2 and yields the glycoside **38**.



Scheme 24 Intramolecular Aglycone Delivery.

The method worked well on simple molecules; however its extension to higher oligosaccharides and complex structures had limited success.[126] Numerous variations of the above described intramolecular glycosylation were studied, including changes in the position of linkers and variations in the length, the type and the rigidity of the linker.[127]

In very recent years new effective methods for selective α–glycosylations have been also introduced; an organocatalytic Koenigs-Knorr glycosylation method, recently reported, exploited urea and thiourea derivatives as hydrogen-bond donors in the non-covalent activation of benzylated glycosyl halides (chlorides or bromides);[128] in another recent report, a nucleophile additive such as DMF was found to act as effective glycosylation modulator, affording α-glycosides through the generation of a reactive β-glycosyl-imidate (**Scheme 25**).[129]



Scheme 25 DMF-modulated α - glycosylation

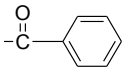
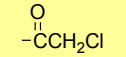
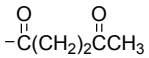
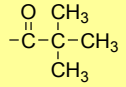
Regioselectivity of Glycosylation Reactions

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 anticipated previously, all the functional groups that could potentially compete with the desired nucleophile in the attack on glycosyl donor are, generally, suitably protected. When a simple disaccharide has to be synthesized, theoretically, only one kind of protecting group can be used for both

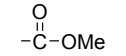
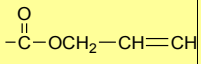
reaction partners. Even in this simple case, however, regioselective protecting group manipulations have to be exerted on both molecules, in order to differentiate the anomeric center from the other hydroxyl groups of glycosyl donor and regioselectively protect all the nucleophilic groups on the acceptor 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.

HYDROXYL PROTECTING GROUPS

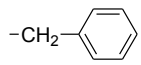
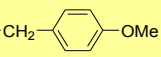
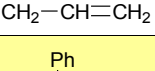
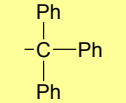
Esters

ACETYL		Ac
BENZOYL		Bz
CHLORO-ACETYL		ClAc
LEVULINOYL		Lev
PIVALOYL		Piv

Carbonates

METHOXY-CARBONYL		
ALLYLOXY-CARBONYL		Alloc

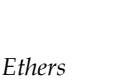
Ethers

BENZYL		Bn
P-METHOXY-BENZYL		*p*MBn
ALLYL		All
TRITYL		Tr

Silyl ethers

*TERT*BUTYL DIMETHYL-SILYL		TBDMS
*TERT*BUTYL DIPHENYL-SILYL		TBDPS
TRIMETHYL-SILYL		TMS
TRIISOPROPYL SILYL		TIPS

Acetals

BENZYLIDENE		Bzd
P-METHOXY-BENZYLIDENE		
ISOPROPYL-IDENE		

AMINO PROTECTING and MASKING GROUPS

Masking Groups

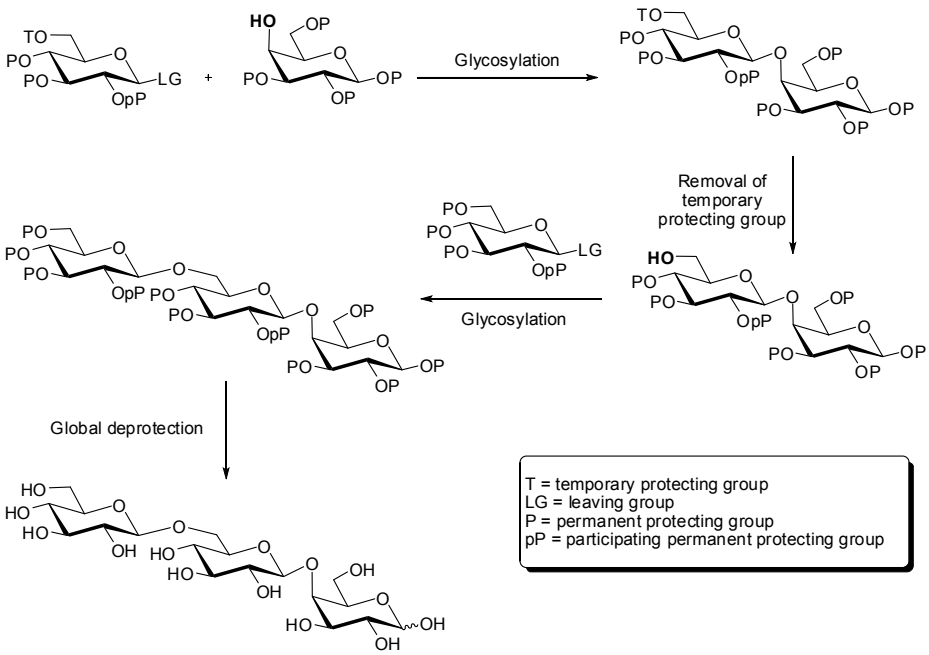
AZIDO		

Protecting Groups

ACETAMIDO		Ac
TRICHLORO-ACETAMIDO		TCA
PHTALIMIDO		NPht
TRICHLORO-ETHYL-CARBAMATE		Troc

Table 2 Protecting Groups Most Commonly Employed in Carbohydrate Chemistry

Amino-protecting groups (for amino-deoxy sugars) and carboxyl protection (for uronic acids) are also of interst. In **Table 2** the protecting groups most frequently used in carbohydrate chemistry are illustrated. Several procedures can be followed for their installation and cleavage also in regioselective fashion.[130] 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 duringthe synthetic sequence will reveal a free hydroxyl group, most often to produce a glycosyl acceptor ready for glycosylation (**Scheme 26**).



Scheme 26 Schematic Synthesis of a Trisaccharide

The two different types of protecting groups require different qualities. It must be possible 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".[131] As summarized in **Figure 11**, when individual hydroxyl groups are protected with A, B, C, and D, respectively, and individual protecting groups can be removed in any order under certain conditions, the protecting groups can be said to be in an orthogonal relationship. A representative set of orthogonal hydroxyl protecting groups successfully used in carbohydrate chemistry is A: chloroacetyl (a: NaHCO3/MeOH/H2O), B: methoxybenzyl (b: TFA/CH2Cl2), C: levulinoyl (c: NH2NH2/AcOH/THF/MeOH), and D: TBDPS (d: HF/Py/AcOH/THF).[132]

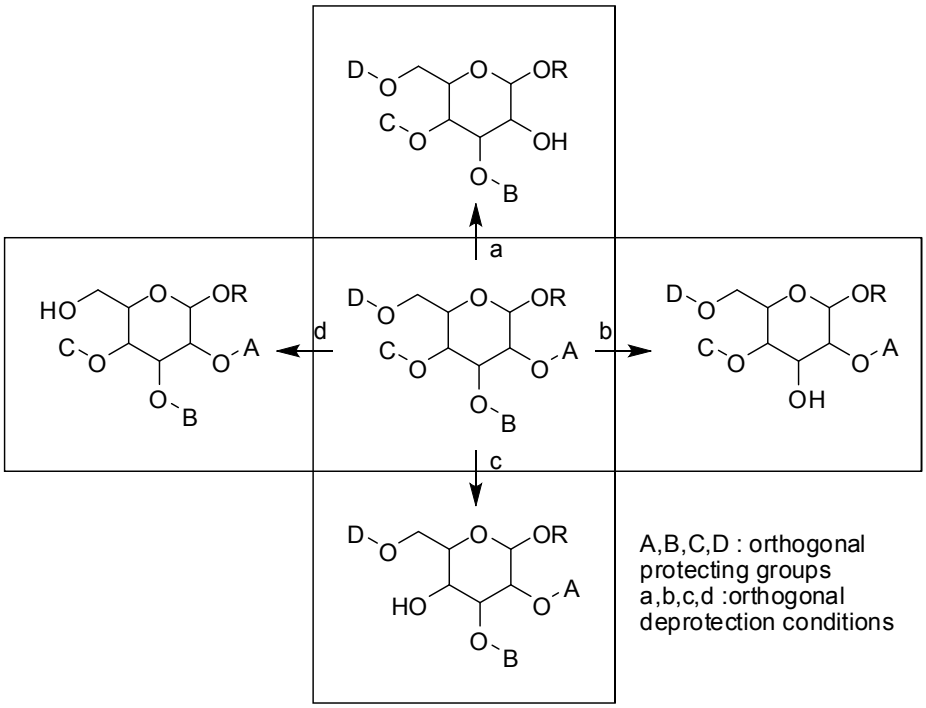


Figure 11 Orthogonal Protecting Group Manipulations.

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. When planning the protection strategy, several issues have to be considered, first of all it has to be taken into account that protecting groups can modify the reactivity of the molecules they are installed on. As examined in details in the previous paragraph, some protecting groups can direct the stereochemical outcome of glycosylations vianeighbouring or long range participation effects or

because of torsional constraints. Furthermore, the intrinsic reactivity of glycosyldonors during glycosylations is strictly dependent on the nature of the protecting groups used for their protection. A major difference in reactivity between perbenzylated and peracylated derivatives was first observed in the case of n-pentenyl glycosides. Specifically, the acylated glycosyl donors react at much slower rates. This observation resulted in the development of the *armed-disarmed* concept, now widely extended alsoto other glycosyl donor classes.[115]A disarmed (acylated) n-pentenyl glycoside with a free hydroxyl group could be glycosylated by an armed (benzylated) n-pentenyl glycoside without self-condensation of the previous one.[133]

A rationalization of this effect can be advanced considering the effects that ether- and acyl-type protecting groups have on the carboxonium intermediates **39** and **40**, that are formed in the glycosylation medium after the departure of the leaving group from the glycosyl donor (**Figure 12**).

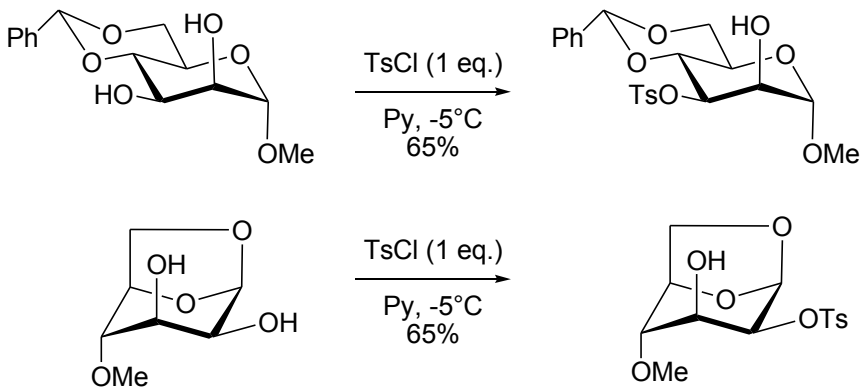
Figure 12 Carboxonium Ion Intermediates

The electron-withdrawing acyl groups destabilize the cationic intermediate **40**. The parent glycosyl donor is, thus, less prone to be activated and converted into **40** with the overall effect of deactivation of the glycosylating capability. In the case of ether-type protecting groups, the destabilizing effect is less strongand the corresponding glycosyl donors are more reactive (armed). The arming-disarming

effect of protecting groups is also used for tuning the reactivity of glycosyl donors. Deoxy sugars, such as fucose or rhamnose, when equipped with a suitable leaving group on the anomeric center, are extremely reactive glycosyl donors. Glycosylations involving these kind of donors generally lead to formation of considerably amounts of lactols as products of hydrolysis side-reaction. In order to decrease their reactivity and, thus, the amount of degradation by-products, acyl protecting groups can be used. So far, it has been described the crucial role played by protecting groups in the synthesis of saccharides and the accurate study required for planning a protection strategy. It's clear that for effectively synthesizing complex oligosaccharide targets 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.[134] 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 hemiacetal 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 hemiacetal OH is clearly different from the others. Unlike the other positions, the anomeric center in acidic conditions undergoes nucleophilc attack and can be thereby easily differentiated. Installation of a temporary protecting group atthe 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 functionalizedwith 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 on 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 as illustrated in **Scheme 27**, which involves two D-mannopyranosyl compounds in the $^{4}C_{1}$ and $^{1}C_{4}$ conformations, whose hydroxyl groups at C-2, C-3 are axial, equatorial and equatorial, axial, respectively.[135]

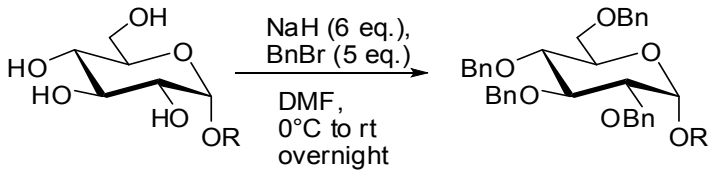
Further generalizations are difficult to make, although it is frequently noted that the hydroxyl group at C-2 of glucopyranosides is the most reactive of the secondary ones while that at C-4 is least so.



Scheme 27 Regioselective Protection of Equatorial Hydroxyl Groups

Clearly, each protecting group requires specific conditions for its installation and removal; however, protecting groups that belong to a given main class usually share similar chemistry. General considerations for some of the most common protecting groups used are examined below.

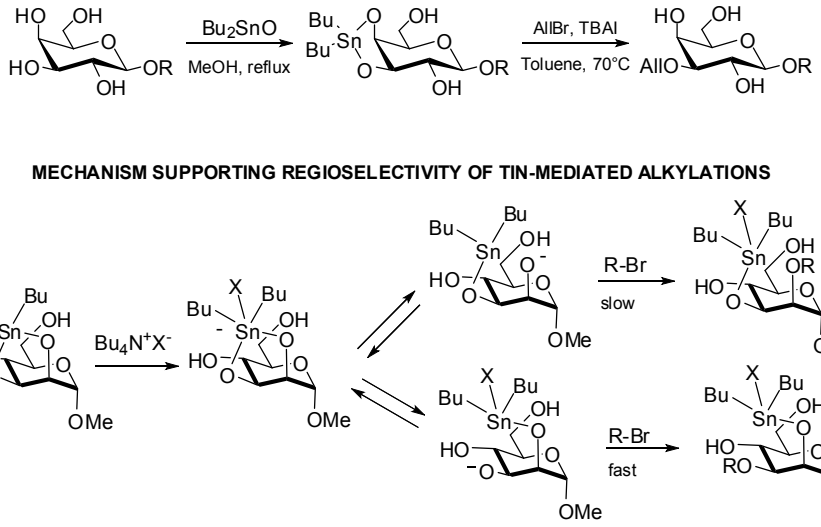
The installation of **ether-type protecting groups**, including alkyl- and silyl- ethers, is commonly performed by reacting a free hydroxyl functionality with the requisite alkyl- or silyl- halide under basic conditions. Benzyl groups are very often employed in carbohydrate chemistry as permanent protecting groups due to their stability to a wide range of conditions. Both the regioselective and the per-O-benzylation of carbohydrates require strong bases, such as sodium hydride or hydroxide (**Scheme 28**).



Scheme 28 General Conditions for the Benzylation of Carbohydrates

Formation of trialkylstannyl ethers or cyclic stannylidene derivarives enhances the nucleophilicity of the oxygen atoms involved and thus activates the hydroxyl groups towards electrophilic reagents.

On the basis of this finding, an alternative approach for the regioselective alkylation of carbohydrates based on tin chemistry was introduced by Hanessian in 1985.[136] Cyclic stannylidene acetals are generally formed by reaction of dibutyltin oxide with a *cis* vicinal diol. The stannylidene generation is followed by the addition, in a subsequent step, of an electrophile (e.g. the alkylating agent) that preferentially reacts with only one of the two oxygen atoms involved in the acetal cycle, after halide ion-promoted stannylidene opening (see mechanism in **Scheme 29**); in most cases the alkylation occurs faster with the equatorial alkoxide, supporting the obtained regioselectivity.



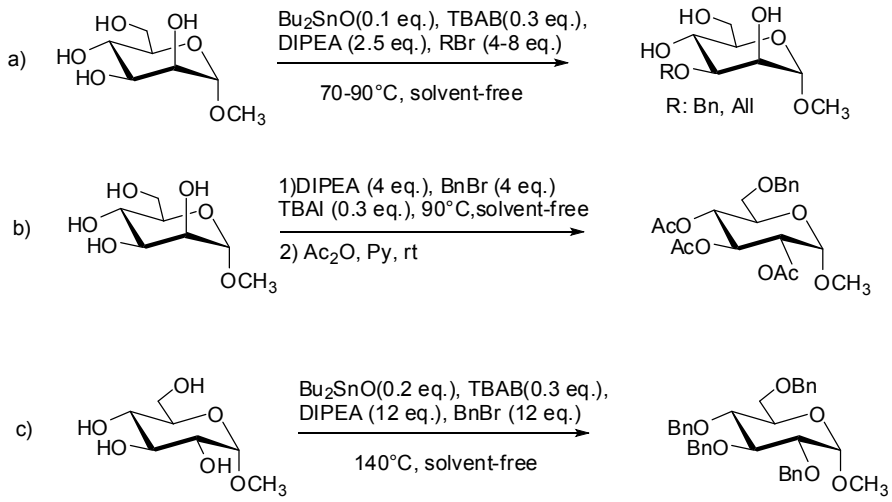
Scheme 29 Generic Regioselective 3-O-Allylation via Stannylidene Acetal Intermediate and Mechanistic Explanation.

The tin chemistry is effectively used for the regioselective protection of the C-3 equatorial hydroxyl groups that are in a *cis* relationship with the axial C-4 and C-2 hydroxyl groups of galacto- and manno-pyranoses, respectively.

The stannylene-mediated strategy has been revisited very recently in our laboratory in the course of some attempts to find more practical conditions for the alkylation of carbohydrates. Thus, the first catalytic approach for the stannylene-mediated benzylation and allylation of secondary saccharide hydroxyls of carbohydrates has been developed and proved very effective in the fast one-step alkylation of several substrates in the presence of very low amounts of the toxic tin reagent and in the absence of solvent.[137]

On the other hand, a novel method for the regioselective benzylation of primary hydroxyls of carbohydrates was also introduced involving very mild basic conditions (DIPEA was used as the base) and the avoided use of the high boiling solvents usually employed;[138] combination of

these innovative methodologies was also applied in the poly- and per-O-benzylation processes (**Scheme 30**).



Scheme 30 Examples of Alkylation of Carbohydrates Through Alternative Solvent-Free Strategies

Benzyl ethers are usually cleaved by hydrogenolysis,[139] though many alternative methods also exist; some examples are acetolysis[140] and oxidative conditions.[141]

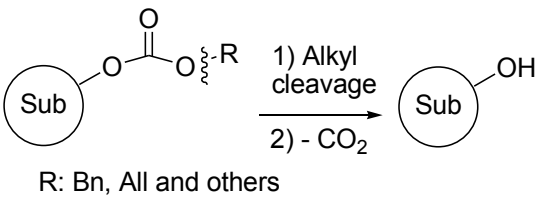
Milder basic conditions are usually needed for the installation of trityl and silyl protecting groups; in most cases weak bases such as pyridine, imidazole, DMAP are used in combination with the requisite halide.[142] Bulky trityl and silyl groups (TBDMS, TBDPS) are of great synthetic utility since they can be easily regioselectively installed at the primary position of polyols in the presence of free secondary hydroxyls and are very often used to this aim in carbohydrate chemistry. Removal of these protecting groups can be performed by acid hydrolysis or, only in the case of silyl ethers, in the presence of fluoride ions (TBAF/THF) due to the generation of a strong fluorine-silicon bond.

Acyl-type protecting groups such as esters, carbonates, amides and

carbamates are most frequently installed through the reaction of a free hydroxyl or amino group with a requisite acylating agent, usually an activated acyl derivative (acyl chlorides, anhydrides, chloroformates etc.) in the presence of a base, in some cases also acting as a nucleophile catalyst. Regioselective acylation of carbohydrates is not as simple as for the alkylation due to the higher reactivity of the acylating agents. Nevertheless, good regioselectivity can be achieved performing the reaction at low temperature with bulky acyl derivatives; for example, especially good regioselectivity can be obtained for the installation of pivaloyl group at the primary position. Besides the widely employed esters, another class of versatile acyl protecting groups is represented by carbonates (e.g. methoxy-, allyloxy- and benzyloxy-carbonyl groups); in general, they can be installed under analogous conditions as for esters. A very effective protocol for their quantitative and quick insertion on saccharide hydroxyls, even in a regioselective fashion, relies on the combination of a given alkyl-chloroformate in the presence of TMEDA.[143]

As mentioned in the previous paragraph, alkoxycarbonyl groups have attracted much interest in the field of glycosylation chemistry due to their good attitude to act as neighbouring protecting groups and much lower tendency to generate undesired orthocarbonate side-products in comparison to esters. This is likely due to the reduced electrophilicity of the carbonyl group that also accounts for their lower reactivity towards the basic solvolysis conditions commonly adopted for the removal of ester groups through an acyl nucleophilic substitution. Despite their low reactivity, alkoxycarbonates can be however cleaved under Zemplen conditions (NaOMe cat. in MeOH) as with esters; on the other hand, especially remarkable is the possibility of an alternative cleavage pathaway entailing an initial alkyl scission followed by

spontaneous loss of CO_2 (**Scheme 31**).[144]



Scheme 31 Common General Mechanism for Removal of Many Alkoxycarbonyl Groups from Alcohols

In this way, several alkoxycarbonyl groups can be selectively removed under specific conditions, compatible with the stability of esters.

It is also worth mentioning in this context that anomeric esters are more labile than other esters and can be removed selectively under mild basic conditions, usually in the presence of a stoichiometric amount of benzylamine or hydrazine acetate. Much harsher conditions are instead required for the removal of amides and carbamates, according to the expected lower electrophilic reactivity at their carbonyl groups.

A very useful approach for the differentiation of the several alcohol moieties of monosaccharides is the use of **cyclic protecting groups for diols**. The main examples are benzylidene and isopropylidene acetals, orthoesters and orthocarbonates, allowing the simultaneous protection of two definite hydroxyl groups. These strategies rely on strict spatial relationships that have to be fulfilled by the hydroxyl groups to be protected. Benzylidene acetals are generally regioselectively installed under acidic conditions in the presence of an aldehyde/acetal reagent, usually leading to a stable six-memberd pyranose ring at C-4 and C-6 position;[145] isopropylidene acetals as well as carbonates require a 1,2-*cis* relationship between the two hydroxyl groups; orthoesters are often formed involving C-1 and C-2 positions. As evident from **Figure 13**, blocking at least two out of five hydroxyl groups enormously simplifies

the further manipulations required for the completion of the synthetic pathway.

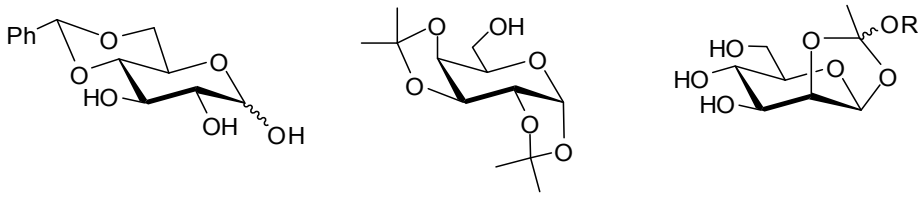
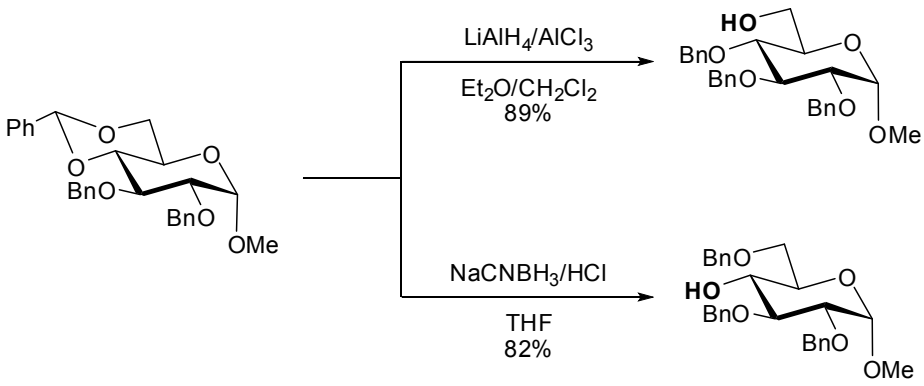


Figure 13 4,6-*O*-Benzylidene-D-Glucopyranose, 1,2:3,4-Di-*O*-Isopropylidene-D-Galactopyranoside and D- Mannopyranose 1,2-Orthoacetate.

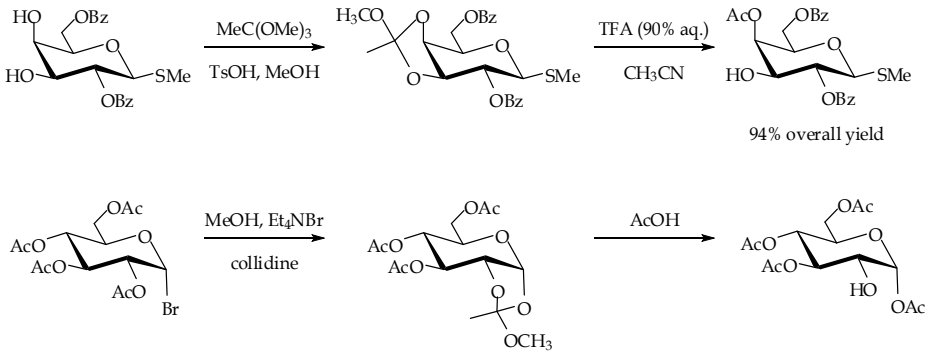
It has also to be considered that the use of benzylidene acetals and orthoesters allows further differentiation of the two oxygen atoms involved in the protection. Indeed, 4,6-*O*-benzylidene acetals can be removed under several conditions; mild acid hydrolysis is commonly employed to obtain the free hydroxyl groups, but many efficient methods have been also developed for the regioselective reductive opening of the acetal yielding benzyl ethers and a free hydroxyl group. The control of the regioselectivity of the reaction is exerted by the choice of the suitable reducing system (**Scheme 32**).



Scheme 32 Reductive Cleavage of Benzylidene Acetals

Benzylidene acetals can be also opened under oxidative, non regioselective conditions obtaining from a 4,6-acetal, both a 4-O- and a 6-O-benzoylated derivative.[141]

Orthoesters undergo ring opening by mild acidic hydrolysis to yield the corresponding ester derivative exposing a hydroxyl for further reactions.[146] Interestingly, the selectivity is opposite to many other methods, since opening of an orthoester protecting a vicinal *cis*- diol gives the ester on the axial hydroxyl group (**Scheme 33**).



Scheme 33 Orthoester Formation and Opening.

Care has to be taken to avoid acyl migration tothe uncovered equatorial hydroxyl group, using, for example, orthobenzoates instead of orthoacetates, since benzoates migrate more slowly than acetates.

All the protection strategies described so far are applied in the syntheses of the variously functionalized building blocks that are then used in the oligosaccharide assembly. Often several consecutive protection-deprotection steps are required to obtain the desired monosaccharidic targets. Generally, preparation of the monomeric precursors represents the most time-consuming and, at the same time,

challenging issue in oligosaccharide syntheses. The excellence of a synthetic plan is strongly dependent on the protection strategies adopted. Of course, the fewer protecting group manipulations, the better the synthesis is valued.

Oligosaccharide Synthesis

For the successful synthesis of oligosaccharides, both chemical reactions and tactics are important concerns. All the methodologies developed for effectively promoting 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 14**). 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.

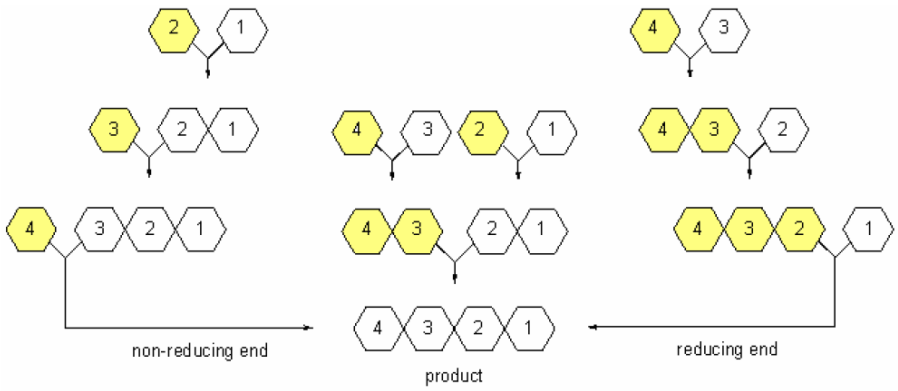
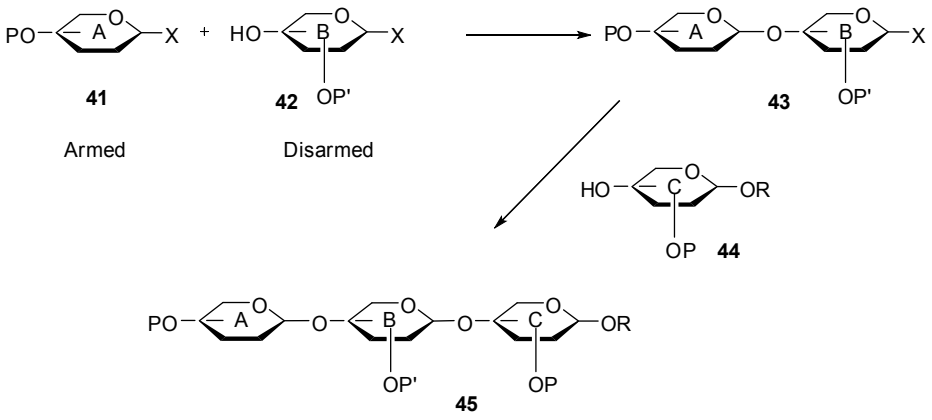


Figure 14 Stepwise and Convergent Methods in the Synthesis of Oligosaccharides.

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 fulfill 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.

A very useful approach used in the block-synthesis relies on the use of *different types of glycosyl donors* in sequential glycosylation steps. In this way, a definite glycosyl donor can be first coupled with a glycosyl acceptor bearing a different leaving group at its anomeric position, that

is stable under the first glycosylation step conditions; the newly generated block can thus be directly used as donor in a subsequent glycosylation step without any replacement of the anomeric substituent. The *armed-disarmed* concept is also worth mentioning among the several glycosylation strategies used in block syntheses. As shown in **Scheme 34**, the armed glycosyl donor **41**can be coupled with the disarmed **42** without self condensation of the latter. The resulting disarmed compound **43** 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.



Scheme 34 Block Armed-Disarmed Glycosylation

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.

In the mentioned strategies (sequential and 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 15**).

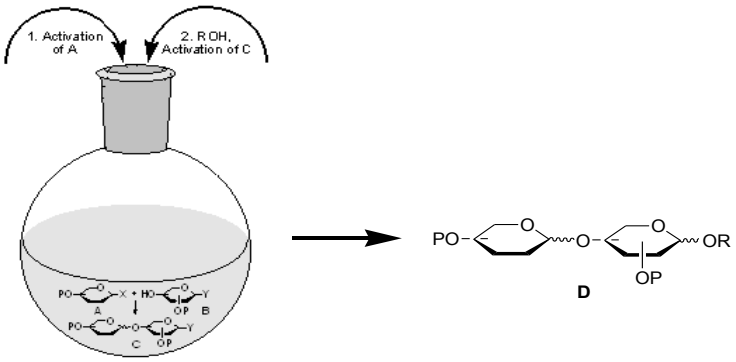
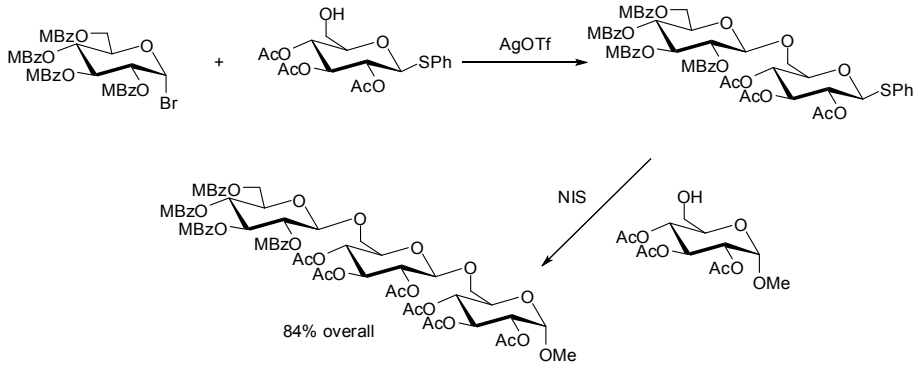


Figure 15 General Scheme of One-Pot Glycosylation.

Several glycosylation strategiescan be performed in a one-potmanner. Often different types of glycosyl donors are employed in one-pot sequential glycosylations. Glycosylations are performed starting from the non reducing end, sequentially activating glycosyl donors with increasing stability. The first one-pot glycosylation sequence using this approach (**Scheme 35**) performed the progressive glycosylation of a thioglycoside acceptor by a glycosyl bromide donor and then of a O-glycoside acceptor by the newly formed thioglycoside donor (glycosyl bromide →thioglycoside →O-glycoside).[147]

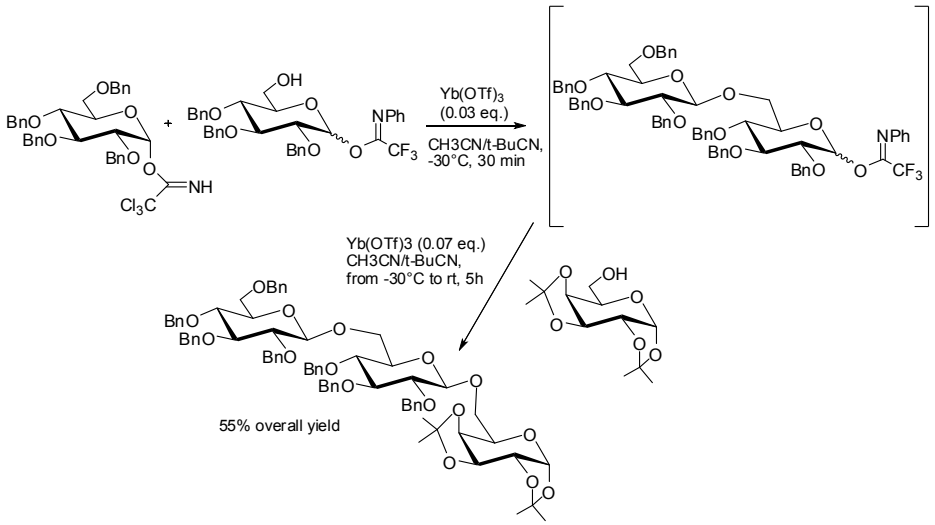


Scheme 35 One-Pot Sequential Glycosylations Using Different Types of Glycosyl Donors

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 ina 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.

As previously anticipated, very effective methods for the one-pot sequential glycosylations have been reported from our laboratory in recent years, relying on the sequential activation of trichloro- and the less reactive N-phenyltrifluoroacetimidate donors with catalytic amounts of lanthanide triflates (**Scheme 36**).[85]



Scheme 36 One-Pot Trisaccharide Synthesis via Sequential Activation of Trichloro- and N-Phenyl Trifluoro acetimidate donors under catalytic conditions.

This approach, representing the first example of catalytic procedure for the sequential one-pot glycosylations, was also successfully applied in the straightforward assembly of a biologically relevant pentasaccharide, related to the anti-tumor agent PI-88, in only 3 steps and entailing only 3 monosaccharides building blocks.[85b]

Glycosylation on Solid Surfaces

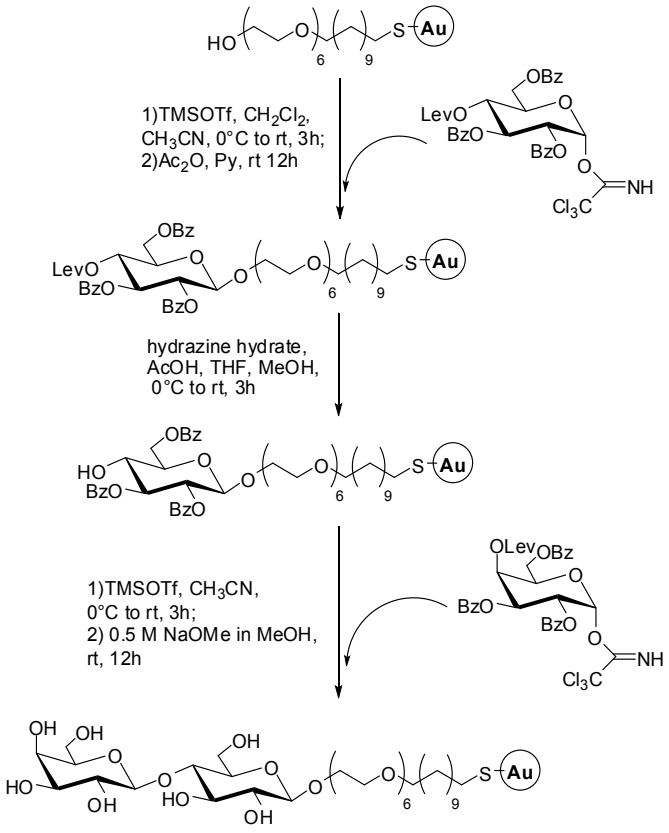
Since the advent of effective glycosylation methods in the 1980s, **solid-phase oligosaccharide synthesis** has been extensively studied and allowed the construction of even complex saccharide sequences.[148] Interest towards this approach was supported by the established effectiveness of solid-phase techniques in several fields of organic synthesis. The advantage of solid-phase reactions is the simple and quick workup process. Since only the growing molecule is attached on

the support, a simple filtration is enough to wash away all the other reagents used in the reaction. Higher reaction yields can generally be achieved by the use of excess amounts of reagents. As support matrices, Merrifield's resin (polystyrene cross-linked with 1% divinylbenzene), controlled pore glass or PEG grafted on polystyrene (TentaGel, ArgoGel) are commonly employed. Various linkers have been applied to attach the carbohydrate to the solid support, including silyl ethers and acid- or base-labile linkers. The recently introduced octanediol linker is very versatile as it provides n-pentenyl glycosides after cleavage by olefin metathesis.[149]

A great variety of glycosyl donors and glycosylation methods have been tried in solid-phase synthesis, including glycals,[150] glycosyl sulfoxides,[151]thioglycosides,[152] glycosyl trichloroacetimidates,[153] n-pentenyl glycosides[154] and glycosyl phosphates.[155] Oligosaccharides up to the size of a dodecamer have been synthesized.[152b] Quite recently solid-phase oligosaccharide synthesis has been automated by the use of a modified peptide synthesizer.[99] The effectiveness of the automated approach has been confirmed by the successful assembly of several biologically relevant oligosaccharides using glycosyl trichloroacetimidate and glycosyl phosphate methods.Automated solid-phase oligosaccharide synthesis shows great promise as a future technology to fuel the growing need for defined oligosaccharide structures.

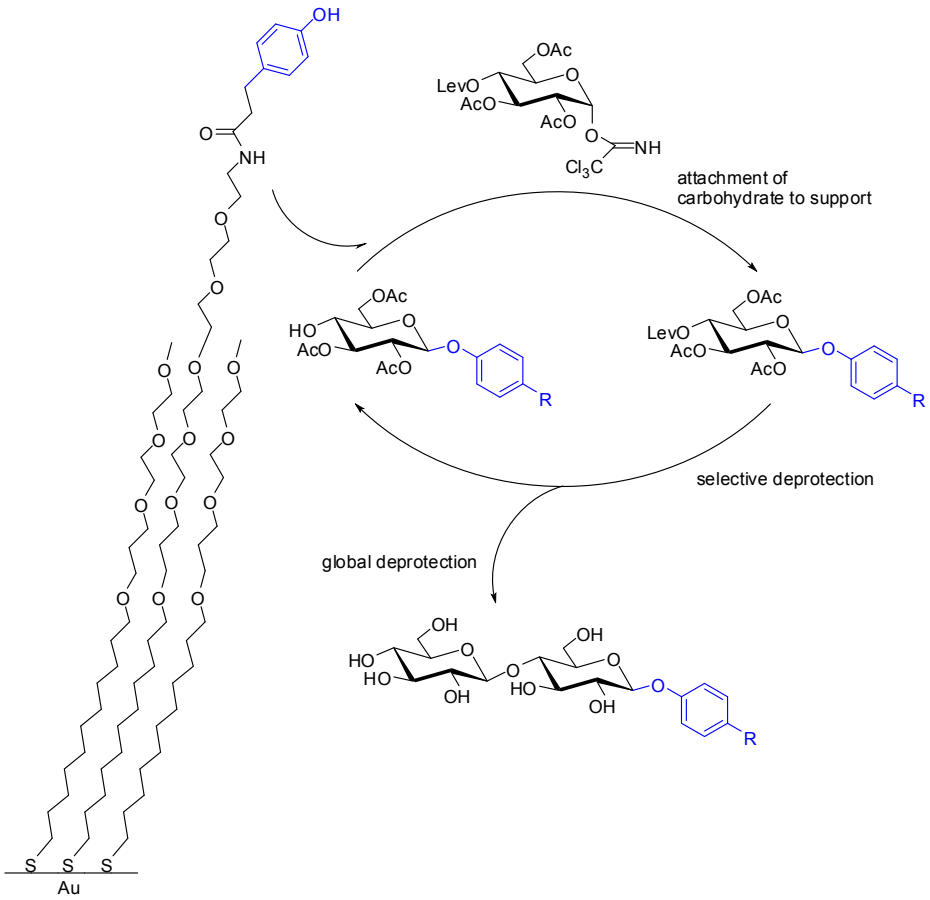
The principle of solid-phase synthesis aimed at construction of target saccharide sequences has also been applied in the field of nanotechnology. For example, solid-phase construction of oligosaccharides on gold **nanoparticles** by trichloroacetimidate method has been reported; [156] as shown in **Scheme 37**, the first glycosylation step provides the attachment of the first saccharide residue on the

nanoparticle, through a oligoethyleneglycol linker; then, according to traditional solid-phase strategies, selective deprotection of the anchored carbohydrate and subsequent glycosylation lead to the chain elongation.



Scheme 37 Carbohydrate Elongation onto Gold Nanoparticle.

An analogous approach hasalso beenused for the construction of oligosaccharide sequences on gold surfaces modified with self-assembled monolayers of alkanethiolates displaying terminal phenol groups (**Scheme 38**).[157]



Scheme 38 SchematicExample of On-Chip Synthesis of Oligosaccharides on Gold Surfaces

This strategy provided effective construction of **carbohydrate chips**, since a long time considered advanced tools for biochemical studies concerning saccharide structures. Indeed, carbohydrate chips, variously prepared through the immobilization of glycans on solid surfaces (mainly gold or glass substrates suitably modified), proved useful in a wide range of analytical applications. Among numerous examples, enzymatic glycosylation of glycans immobilized on surfaces has been used to study the substrate-specificity of glycosyltransferases[158] and the role of ligand density in their enzymatic activity.[159] Biochips of

immobilized glycans have been also used in the investigation of carbohydrate-protein and carbohydrate-carbohydrate interactions and other several applications.[5,160]

Very useful to these purposes is the generation of patterned surfaces, especially for the fabrication of carbohydrate microarrays, made of different glycans immobilized on a surface with a high spatial control, in a well defined order and position. Several methods have been developed over the years for the covalent attachment and patterning of carbohydrates and fabrication of these devices; however, the most part of these methods do not rely on the direct glycosylation of the surface. Most frequently, the carbohydrate is previously chemically modified with a functionalized linker, reactive towards a properly derivatized surface (**Figure16**).

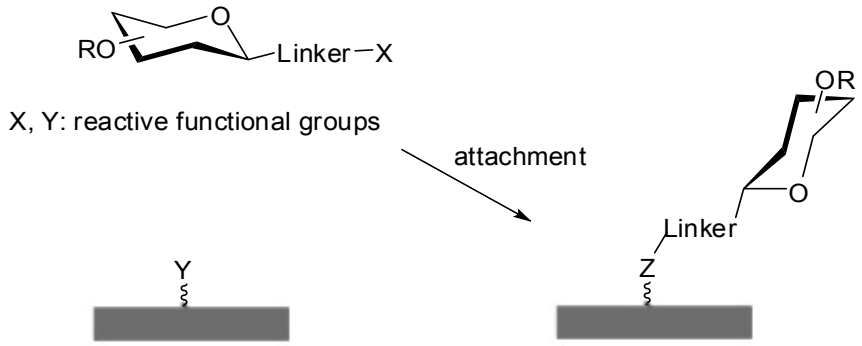


Figure 16 Typical Approach for Carbohydrate Immobilization

Some known examples in this direction are the attachment of maleimide- or thiosulfonate-conjugated carbohydrates to thiol-coated surfaces, attachment of thiol-conjugated glycans to maleimide- or 2-pyridyl disulfide-coated surfaces, reactions between amine-conjugated

sugars and N-hydroxysuccinimide ester-coated surfaces or aminooxy-linked sugars with aldehyde-coated surfaces; further examples are based on azide-alkyne cycloaddition or on Diels-Alder reactions between diene- or dienophile-conjugated sugars to a surface coated with a dienophile/diene counterpart.[161]

Widely used techniques for patterning biomolecules on surfaces are robotic contact printing and ink-jet printing, allowing fabrication of biochips containing a high number of different compounds in a array format.[162] Robotic contact printers dispense small drops of the biomolecule solution from a set of metallic pins onto the surface by physical contact while ink-jet printing methods rely on dispensing the sample solution without a direct contact between the print head and the substrate. Soft lithography methods are strongly emerging alternatives in this field; especially microcontact printing (μCP) is broadly used nowadays for the modification and patterning of surfaces. This technique relies on the transfer of reactive molecules ("ink molecules") from a microstructured elastomeric stamp onto a surface properly modified with complementary reactive groups, by keeping the stamp and the surface in a close contact; selective transfer of the ink molecules occurs exclusively in the area of contact, resulting in a high resolution pattern (**Figure 17**).[163]

Figure 17 Schematic Representation of μCP

Silicon or glass substrates are most used for the surface, while PDMS (polydimethylsiloxane) is the most commonly adopted material to make stamps, since it is cheap, non-toxic, chemically resistant and easily amenable of several useful modifications.

μCP has proved compatible with many different reactions and several compounds have been successfully patterned on surfaces by this technique. Click chemistry (either azide-alkyne cycloaddition or thiol-ene reaction) and Diels-Alder reaction have been especially used to attach carbohydrates via μCP (**Figure 18**) and also for the fabrication of carbohydrate arrays.[164]

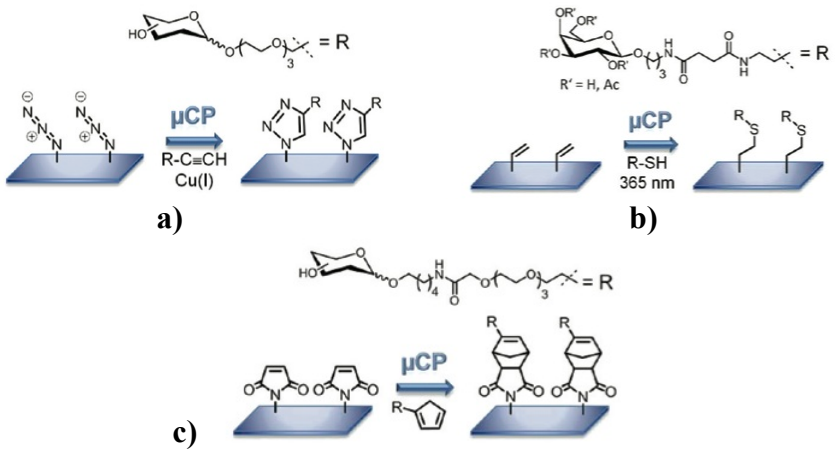


Figure 18 Examples of carbohydrate immobilization via μCP. a) attachment of alkyne-conjugated carbohydrate onto azide coated-surface; b) attachment of thiol-conjugated carbohydrate onto alkene-coated surface; c) attachment of cyclopentadiene-conjugated carbohydrate onto maleimide-coated surface.

Very recently an innovative and unprecedented method for the direct attachment of carbohydrates through chemical glycosylation by μCP has been developed and will be discussed in detail in *Chapter 8*.

Other Relevant Modifications of Carbohydrates

As previously introduced, synthetic versatility of carbohydrates is not only expressed through their use in glycosylation reactions; derivatization of saccharide functional groups can be not only addressed to the preparation of glycosyl donors and acceptors, as demonstrated by the multiple applications of variously protected carbohydrates in several fields of organic chemistry as materials, chiral auxiliaries ororganocatalysts and in total synthesis of natural products. In addition, useful synthetic modifications of carbohydrates are not limited to the "simple" protection of saccharide functionalities but frequently involve conceptually different transformations. Some of these entail deoxygenation of defined hydroxylated positions and **substitution with other heteroatoms.** An example is the replacement of a saccharide hydroxyl with Cl, Br or I, resulting in the generation of synthetically useful halo-deoxysugars.[165] Other useful heteroatoms are nitrogen and chalcogens such as sulfur and selenium; the former is commonly introduced through azidation of a properly activated saccharide position, in most cases followed by reduction and further elaboration of the resulting amino group, while the latter are usually installed by nucleophilic substitution of sulfur/selenium nucleophiles (thiolates, selenolates, thioacetates, thiocyanates, selenobenzoates etc.) to tosylates, halides or under Appel/Mitsunobu conditions. Installation of such heteroatoms plays a key role in the synthesis of hydrolytically stable **oligosaccharide mimics**, often used as valuable inhibitors of specific enzymes and proteins. For example, seleno-derivatives based on selenide or diselenide motifs, have been reported as non-glycosidically linked pseudo-saccharides,[166] while S-linked carbohydrates have been extensively described as oligosaccharide analogues (thio-oligosaccharides).[167]A relevant example in this regard

are synthetic inhibitors of galectins, frequently sharing a thio-di-galactoside framework with an amide functionality at positions 3 and 3', being crucial to enhance the binding affinity with the protein(**Figure19**).[168]

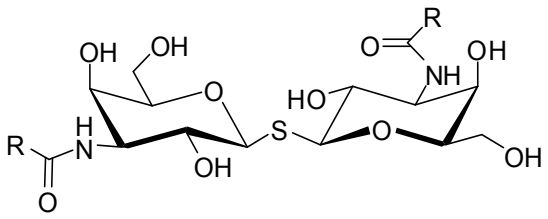


Figure19 General structure of many high-affinity synthtetic inhibitors of human galectins

On the other hand, nitrogen- and sulfur-containing groups are frequently chosen to act as linking functionalities in the conjugation of carbohydrates to other molecules, in the synthesis of different kinds of **glycoconjugates** and macrostructures like dendrimers and glycoclusters, often conveniently accessed by click reactions (azide-alkyne cycloaddition or thiol-ene reaction).[169]

Other useful transformations of carbohydrates other than oxygen substitution, entail **modifications of the saccharide backbone**. For example, several methods have been developed for the generation of anhydrosugars **(Figure 20)** through **intramolecular cycloetherification.** The most common approaches are based on cyclization mechanisms promoted by strong bases; harsh acidic conditions can be also adopted to activate an anomeric leaving group in the synthesis of anhydrosugars involving the anomeric position.[170]

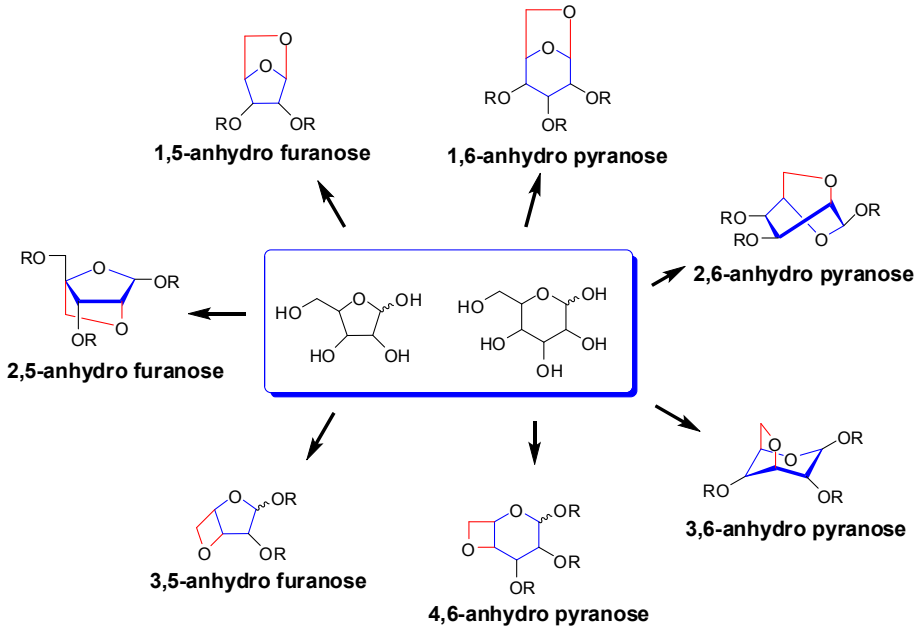
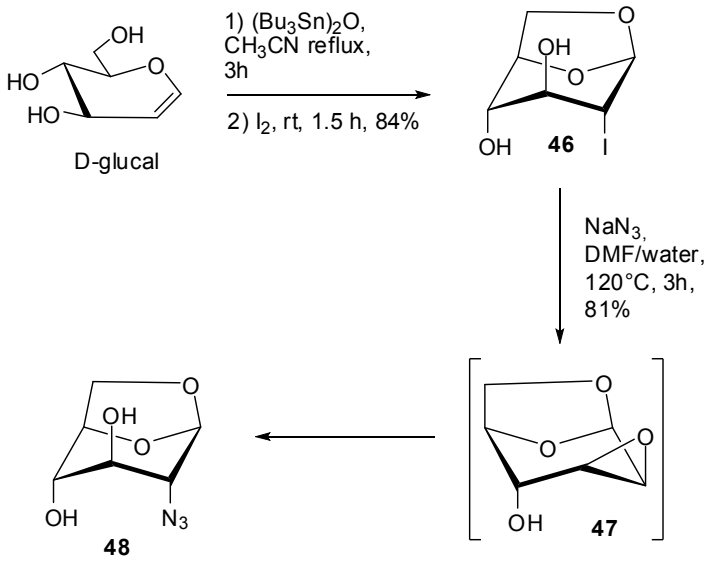


Figure 20 General structures of anhydrosugars

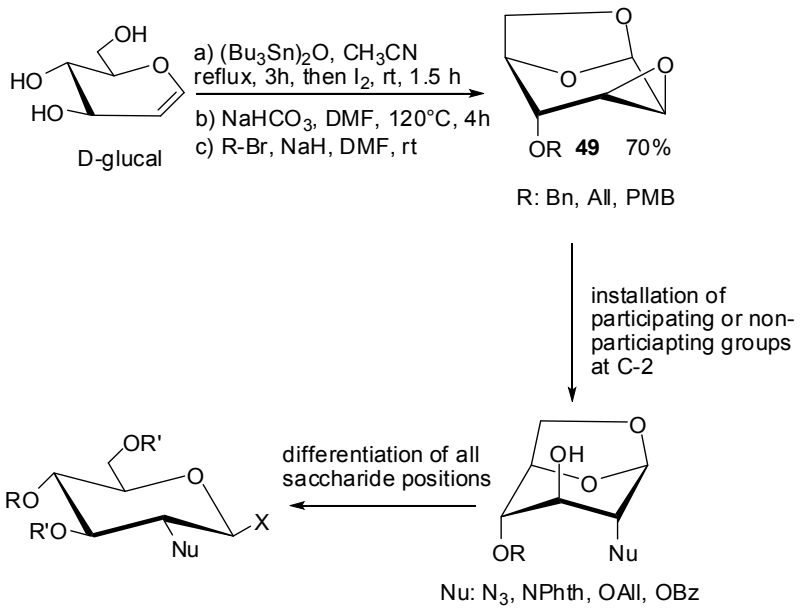
Anhydro-monosaccharides occur in several bioactive saccharide motifs. In the field of organic synthesis, some anhydrosugars are used as common synthons in the construction of different carbohydrate structures; also relevant is their role as useful precursors of aminosugar building blocks, frequently occurring in bioactive oligosaccharide sequences. Indeed, regio- and stereo-selective generation of glucosazide residues can be conveniently accessed through a two-step procedure involving1,6-anhydro-sugar intermediate **46**, readily prepared via 1,6-iodo-cycilzation of D-glucal (**Scheme 39).**[171]



Scheme 39 Preparation of 2-azido-2-deoxy-β-Dglucopyranose derivatives from D-glucal

Reaction of **46** with sodium azide at high temperature, yields selectively glucosazido derivative **48**; retention of configuration in the azidation process is supported by a double inversion mechanism, passing through initial generation of 1,6:2,3-dianhydro intermediate **47** (known as Cerny epoxide), subsequently opened by the azide ion, preferentially in a trans-diaxial fashion.

Since the introduction of this strategy, further applications of the Cerny epoxides chemistry were reported. As shown in **Scheme 40,** alkylated Cerny epoxides **49** could be selectively prepared from D-glucal under basic conditions; subsequent trapping of **49** with nitrogen or oxygen nucleophiles allowed streamlined preparation of several building blocks bearing both participating and non-participating functionalities, that were used in the fast synthesis of glycosaminoglycans fragments.[172]



Scheme 40 Preparation of sugar- and aminosugar- building-blocks through Cerny epoxides

Generation of carbon-carbon double bonds involving the saccharide framework is also worth mentioning as useful modification of carbohydrates. Besides the known class of 1,2-unsaturated sugars, more generally named "glycals", also relevant are compounds bearing a carbon-carbon double bond external to the saccharide ring, the so called *exo*-glycals. The most representative examples of such compounds are shown in **Figure 21**.

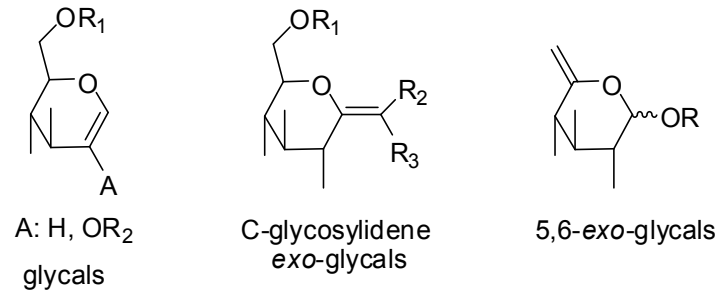


Figure 21 General structures of unsaturated sugar-derived compounds

C-glycosylidene compounds display an exo C-C double bond involving the anomeric position and are useful precursors of C-glycosides. They are frequently prepared from sugar lactones through either a direct olefination strategy (e.g. Wittig-type olefination) or a stepwise method involving generation of an anomeric C-C single bond and subsequent β-elimination. 5,6-unsaturated sugars are instead usually accessed through β-elimination of 6-halo- or 6-O-sulphonyl- precursors[173]and find useful synthetic applications as intermediates for the stereospecific generation of C-C bonds,[174] for thesynthesis of functionalized cyclohexanones through Ferrier carbocyclization[175] and in oligosaccharide synthesis as convenient precursors of L-sugars.[176] Given the high number and variety of hydroxyl groups in a saccharide residue, different **oxidation** processes are also possible, paving the way towards introduction of new functionalities (see **Figure 22** for some examples).

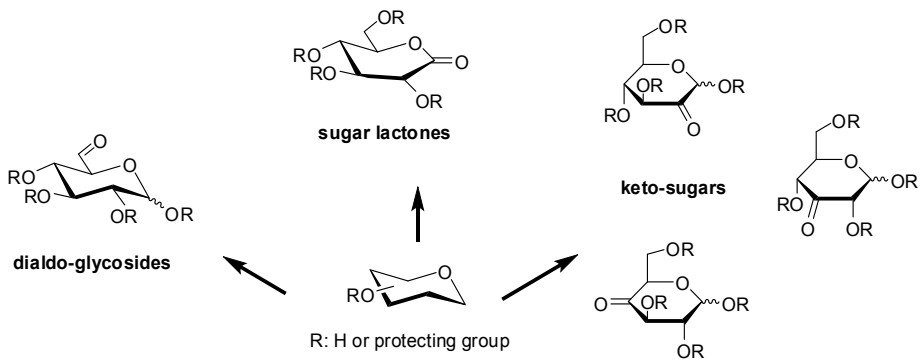


Figure 22 Some Useful Products Derived From Oxidation of Carbohydrates

In this regard, regio- and chemo-selective oxidation of a primary saccharide position in the presence of different oxidizing agents, including pyridinium chlorochromate (PCC) and 2,2,6,6-Tetramethyl-1-piperidinyloxy radical (TEMPO), affordsan aldehyde functionality

that can be exploited for glycoconjugation, for example by reductive amination reactions.[177]

Oxidation of the anomeric hydroxyl group of carbohydratescan be performed under mild conditions, usually through Swern oxidation in the presence of DMSO/oxalyl chloride or DMSO/Ac_2O, leading to the corresponding lactones, useful intermediates in the synthesis of sugar-derived compounds such as azasugars,[178] C-glycosyl conjugated dienes and aldehydes[179]and previously mentioned exo-glycals.

Besides the established oxidation methods based on chromium (VI) oxide and its various salts and complexes, including PCC and chromium trioxide-pyridine complex,[180] other methods have been also developed for the oxidation of secondary saccharide hydroxyls. Some recent and convenient approaches are based on[(neocuproine)PdOAc]$_2$OTf$_2$[181] or organotin catalysis,[182] allowing catalytic and regioselective oxidation of secondary hydroxyls from unprotected carbohydrates; carbonyl group of the resulting keto-sugars can be converted to C-C, C-N, C-O, C-S bonds, thus acting as precursor of many useful derivatives.

Reactions discussed in this paragraph are some selected examples among the variety of synthetic elaborations accessible from carbohydrates, offering a general idea of their wide versatility. Some of these transformations will be further discussed in the following chapters.

Aim and Outline of the Thesis

In this work, several synthetic aspects of carbohydrate chemistry have been explored, with a particular emphasis on the development of experimentally simplified protocols aimed both at protection/transformation of saccharide functional groups and at the

construction of glycosidic linkages. As described in the previous paragraphs, most of the current methods used for the synthetic manipulation of carbohydrates suffer from several drawbacks arising from the inconvenient experimental conditions needed in the reported procedures; these often entail the use of expensive or sensitive reagents, strictly anhydrous conditions, lengthy multi-step synthetic sequences and very often the use of toxic and high boiling solvents, thus making the preparation of building-blocks and the construction of glycosidic linkages highly tricky and time-consuming tasks. In light of these issues, a broad effort has been addressed over the years in our laboratory to the search for more practical methods in synthetic carbohydrate chemistry. Works discussed in this thesis concern the implementation of streamlined methodologies for several synthetic elaborations of saccharide functional groups; a special focus is addressed to solvent-free protocols and their incorporation into synthetic schemes allowing multiple transformations to be performed under air and in a one-pot fashion.

In *Chapter 2* three innovative protocols for the installation of acetal protecting groups on saccharide diols are presented, two of which relying on a condensation mechanism and one based on a trans-acetalation approach. The presented protocols are all endowed with remarkable experimental simplicity all the reactions being performed under air, in the absence of solvent and catalyzed by very reduced amounts of mild acidic promoters ($Yb(OTf)_3$ or CSA). Some of these protocols are also addressed to the one-pot construction of useful 4,6-O-protected glycosides from reducing sugars.

In *Chapter 3* is reported an effective method for the regioselective protection of saccharide polyols with silyl groups (TMS, TBDMS, TBDPS) under solvent- free conditions. The presented methodology

that relies on the use of pyridine as a base in slight stoichiometric excess, in combination with sub-stoichiometric amounts of TBAB, can also be incorporated into one-pot fully solvent-free sequences for the very fast generation of many orthogonally protected building-blocks.

Adjustment of reaction conditions to higher temperature and without the TBAB catalysis, allowed the extension of this approach to the streamlined generation of differentiated building-blocks from saccharide polyols through the initial regioselective tritylation, which is discussed in *Chapter 4*.

An unprecedented solvent-free one-pot entry to saccharide building blocks orthogonally protected with alkyl and acetal (or orthoester) groups is shown in *Chapter 5*. Besides its many experimental advantages, this method displays several elements of originality, since combining a base mediated-alkylation with an acid catalyzed protection, this latter being promoted by the ammonium ions ($DIPEAH^+$) formed as byproduct of the alkylation step.

In *Chapter 6* applicability of a solvent-free approach to the effective preparation of glycosyl chlorides from sugar hemiacetals is demonstrated. The proposed method, that takes advantage of the cheap PPh_3/hexachloroacetone combined system, allows fast and high yielding anomeric chlorination of variously protected precursors.

Several useful transformations of saccharide functionalities, other than protection, are also explored in *Chapter 7*. An improved method for the iodination of hydroxyl groups of both carbohydrates and non-saccharide substrates is proposed, based on the combination of PPh_3, I_2 and 2,6 – lutidine under solvent free conditions. Fast *in situ* transformation of thus obtained alkyl iodides into azides, thioacetates, anhydrosugars and 5-6-*exo*-glycals is also demonstrated through the application of fully solvent-free one-pot sequences.

Chapter 8 introduces the application of an experimentally simplified approach to the immobilization of carbohydrates on surfaces; this novel method relies on the unprecedented direct O-glycosylation between a thioglycoside donor and an hydroxyl terminated glass surface by catalytic microcontact printing and allows effective generation of sugar modified surfaces, suitable for protein recognition.

Chapter 9 describes the feasible use of glycosyl chlorides (readily prepared by the strategy introduced in *Chapter 6*) as donors in an unprecedented solvent-free version of Lemieux's glycosylation method.[25] This novel approach allows fast and highly stereoselective generation of α-glycosides under air from different, not necessarily highly reactive, glycosyl donors and acceptors.

References

1) a) Robyt, J. F. *Essentials of Carbohydrate Chemistry*, Springer Science & Business Media, **2012**; b) Taylor, M. E.; Drickamer, K. *Introduction to Glycobiology*, Oxford University Press: New York, **2006**.
2) a) Rudd, P. M.; Elliott, T.; Cresswell, P.; Wilson, I. A.; Dwek, R. A. *Science***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; h) Miller, D. J.; Macek, M. B.; Schur, B. D. *Nature***1992**, *357*, 589; i) Feizi, T. *Nature***1985**, *314*, 53.
3) 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.
4) *Carbohydrate-based Drug Discovery*, Wong, C.-H., Ed., Wiley-VCH: Weinheim, **2003**.
5) Delbianco, M.; Bharate, P.; Varela-Aramburu, S.; Seeberger, P. H. *Chem. Rev*. **2016**, *116*, 1693.
6) Teramoto, N.; Arai, Y.; Shibata, M. *Carbohydr. Polym.* **2006**, *64*, 78.
7) Bachelder, E. M.; Beaudette, T. T.; Broaders, K. E.; Dashe, J.; Frechet, J. M. J. *J. Am. Chem. Soc.* **2012**, *134*, 15840.

8) Datta, S.; Bhattacharya, S. *Chem. Soc. Rev*. **2015**, *44*, 5596.

9) a) Hanessian, S. “Total Synthesis of Natural Products: The 'Chiron' “Approach”, Pergamon Press, Elmsford. NY, **1983**; b) Boysen, M. M. K. *Chem. Eur. J.***2007**, *13*, 8648; c) Nicolaou, K. C.; Mitchell, H. J. *Angew. Chem. Int. Ed.***2001**, *40*, 1576.

10) a) Voskuhl, J.; Stuart, M. C. A.; Ravoo, B. J. *Chem. Eur. J.* **2010**, *16*, 2790; b) Lim, C. W.; Crespo-Biel, O.; Stuart, M. C.; Reinhoudt, D. N.; Huskens, J.; Ravoo, B. J. *Proc. Natl. Acad. Sci. U.S.A*. **2007**, *104*, 6986; c) Vico, R. V.; Voskuhl, J.; Ravoo, B. J. *Langmuir* **2011**, *27*, 1391.

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**; c) Zhu, X.; Schmidt, R. R. *Angew. Chem. Int. Ed*. **2009**, *48*, 1900.

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

26) More detailed description of these methods for the synthesis of glycosyl chlorides and their innovative use in glycosylation reactions is object of *Chapters 6* and *9* respectively.

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

28) 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.

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

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

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

32) 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.

33) 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.

34) 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.

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

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

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

38) 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.

39) Pastore, A.; Adinolfi, M.; Iadonisi, A. *Eur. J. Org. Chem*. **2008**, 6206.

40) Ness, R. K.; Fletcher, H. G.; Hudrson, C. S. *J. Am. Chem. Soc.* **1950**, *72*, 2200.

41) Gervay, J.; Nguyen, T. N.; Hadd, M. J. *Carbohydr. Res*. **1997**, *300*, 119.

42) Chervin, S. M.; Abada, P.; Koreeda, M. *Org. Lett.* **2000**, *2*, 369.

43) Mukhopadhyay, B.; Ravindranathan Kartha K. P.; Russell D. A.; Field R. A. *J. Org. Chem.* **2004**, *69*, 7758.

44) Adinolfi, M.; Iadonisi, A.; Ravidà, A.; Schiattarella, M. *Tetrahedron Lett*. **2003**, *44*, 7863.

45) Giordano, M.; Iadonisi, A. Eur. J. Org. Chem. **2013**, 125.

46) 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.

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

48) 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.

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

50) Horton, D. *Methods Carbohydr. Chem.* **1963**, *2*, 433.

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

52) 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.

53) 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.

54) 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.

55) 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, NewYork, **2002**, http://www.mrw.interscience.wiley.com/eros/eros_articles_fs.html.

56) 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.

57) 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.

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

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

60) 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.

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

62) 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.

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

64) 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.

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

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

67) 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.

68) 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.

69) 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.

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

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

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

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

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

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

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

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

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

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

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

81) 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.

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

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

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

85) a) Adinolfi, M.; Iadonisi, A.; Ravidà, A. *Synlett* **2006**, 583; b)Valerio, S.; Adinolfi, M.; Iadonisi, A.; Pastore, A. *J. Org. Chem.***2008**, *73*, 4496-4503.

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

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

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

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

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

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

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

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

94) 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.

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

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

97) 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.

98) 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.

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

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

101) 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.

102) 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.

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

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

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

106) 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.

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

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

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

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

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

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

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

114) 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.

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

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

117) 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.

118) 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.

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

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

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

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

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

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

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

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

127) 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.

128) Sun, L.; Wu, X.; Xiong, D.-C.; Ye, X.-S. *Angew. Chem. Int. Ed*. **2016**, *55*, 1.

129) Lu, S.-R.; Lai, Y.-H.; Chen, J. H.; Liu, C. Y.; Mong, K.-K. T. *Angew. Chem. Int. Ed*. **2011**, *50*, 7315.

130) 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**.

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

132) Wong, C. –H.; Ye, X. –S.; Zhang, Z. *J. Am. Chem. Soc*. **1998**, *120*, 7137.

133) Fraser-Reid, B.; Wu, Z.; Udodong, U. E.; Ottoson, H. *J. Org. Chem*. **1990**, *55*, 6068.

134) 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**.

135) Aspinall, G. O.; Zweifel, G. *J. Chem. Soc*.**1957**, 2271.

136) David, S.; Hanessian, S.*Tetrahedron* **1985**, *41*, 643.

137) Giordano, M.; Iadonisi, A. *J. Org. Chem*. **2014**, *79*, 213. Application of this methodology in solvent – free one-pot protection schemes of carbohydrates is discussed in *Chapters 3,4,5* and *7*.

138) Giordano, M.; Iadonisi, A. *Tetrahedron Lett*. **2013**, *54*, 1550.

139) a) Freifelder, M. *Catalytic Hydrogenation in Organic Synthesis*; Wiley: New York, 1978; p.109; b) Pearlman, W. M. *Tetrahedron Lett.* **1967**, *17*, 1663; c) Hanessian, S.; Liak, T. J. Vanasse, B. *Synthesis* **1981**, 396; d) Rao, V. S.; Perlin, A. S. *Carbohydrate Res.* **1980**, *83*, 175.

140) a)Yang, G.; Ding, X.; Kong, F. *Tetrahedron Lett*. **1997**, *38*, 6725; b) Giordano, M.; Iadonisi, A.; Pastore, A. *Eur. J. Org. Chem.* **2013**, 3137.

141) Adinolfi, M.; Barone, G.; Guariniello, L.; Iadonisi, A. *Tetrahedron Lett.* **1999**,*40*, 8439.

142) For a detailed discussion of silyl and trityl groups installation see *Chapters 3* and *4*, respectively.

143) Adinolfi, M.; Barone, G.; Guariniello, L.; Iadonisi, A. *Tetrahedron Lett*. **2000**, *41*, 9305.

144) Adinolfi, M.; Iadonisi, A.; Pastore, A. *Tetrahedron Lett.* **2009**, 50*,* 7051.

145) Acetals/Ketals protecting groups are object of *Chapter 2.*

146) Lemieux, R. U.; Driguez, H. *J. Am. Chem. Soc*. **1975**, *15*, 4069

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

148) a) Osborn, H. M. I.; Khan, T. H. *Tetrahedron***1999**, *55*, 1807; b) Seeberger, P. H.; Haase, W. C. *Chem. Rev*. **2000**, *100*, 4349; c) Seeberger, P. H. J. *Carbohydr. Chem*. **2002**, *21*, 613.

149) Andrade, R. B.; Plante, O. J.; Melean, L. G.; Seebereger, P. H. *Org. Lett*. **1999**, *1*, 1811.

150) Danishefsky, S. J.; McClure, K. F.; Randolph, J. T.; Ruggeri, R. B. *Science***1993**, *260* , 1307.

151) Liang, R.; Yan, L.; Loebach, J.; Ge, M.; Uozumi, Y.; Sekanina, K.; Horan, N.; Gildersleeve, J.; Thompson, C.; Smith, A.; Biswas, K.; Still, W. C.; Kahne, D. *Science***1996**, *274*, 1520.

152) a) Nicolaou, K. C.; Wissinger, N.; Pastor, J.; DeRoose, F. *J. Am. Chem. Soc*. **1997**, *119*, 449; b) Nicolaou, K. C.; Watanabe, N.; Li, J.; Pastor, J.; Wissinger, N. *Angew. Chem. Int. Ed.***1998**, *37*, 1559.

153) Wu, X.; Grathwohl, M.; Schmidt, R. R. *Angew. Chem. Int. Ed***. 2002**, 4489.

154) Rodebaugh, R.; Joshi, S.; Fraser-Reid, B.; Geysen, H. M. *J. Org. Chem*. **1997**, *62*, 5660.

155) Palmacci, E. R.; Plante, O. J.; Seeberger, P. H. *Eur. J. Org. Chem.***2002**, 595.

156) Shimizu, H.; Sakamoto, M.; Nagahori, N.; Nishimura, S.-I.*Tetrahedron***2007**, *63*, 2418.

157) Ban, L.; Mrksich, M. *Angew. Chem. Int. Ed*. **2008**, *47*, 3396.

158) Volgmeir, J.; Sardzik, R.; Weissenborn, M. J.; Flitsch, S. L. *OMICS***2010**, *14*, 437.

159) Houseman, B. T.; Mrksich, M. *Angew. Chem. Int. Ed*. **1999**, *38*, 782.

160) Park, S.; Lee, M.-r.; Pyo, S. J.; Shin, I. *J. Am. Chem. Soc.***2004**, *126*, 4812.

161) Park, S.; Gildersleeve, J. C.; Blixt, O.; Shin, I. *Chem. Soc. Rev*. **2013**, *42*, 4310.

162) Rozkiewizc, D. I.; Ravoo, B. J.; Reinhoudt, D. N. *The Supramolecular Chemistry of Organic-Inorganic Hybrid Materials,* John Wiley & Sons **2010**, Chapter 14*, Immobilization and Patterning of Biomolecules on Surfaces.*

163) Wendeln, C.; Ravoo, B. J. *Langmuir* **2012***, 28,* 5527.

164) a) Wendeln, C.; Heile, A.; Arlinghaus, H. F.; Ravoo, B. J. *Langmuir* **2010***, 26,* 4933; b) Olaf, M.; Ravoo, B. J. *Langmuir* **2008**, *24*, 12116.

165) More details about halogenation of saccharide hydroxyls and substitution with other heteroatoms can be found in *Chapter 7*

166) Fournière, V.; Cumpstey, I. *Tetrahedron Lett*. **2010**, *51*, 2127.

167) a) *Carbohydrates in Chemistry and Biology*, Part I Vol.1, Ernst B., Hart G. W., Sinaÿ P., Eds, Wiley-VCH: Weinheim, **2000**; b) Pachamuthu, K.; Schmidt, R. R. Chem. Rev. 2006, 106, 160.

168) Téllez-Sanz, R.; García-Fuentes, L.; Vargas-Berenguel, A. *Curr. Med. Chem*. **2013**, *20*, 2979.

169) a) Kushwaha, D.; Dwivedi, P.; Kuanar, S. K.; Tiwari, V. K. *Curr Org Synth***2013**, *10*, 90; b) *Click Chemistry in Glycoscience: New Developments and Strategies*, Witczac, Z. J.; Bielski, R., John Wiley & Sons **2013**.

170) For some literature reports and description of novel methods for the preparation of anhydrosugars see *Chapter 7.*

171) Tailler, D.; Jacquinet, J.-C.; Noirot, A.-M.; Beau, J.-M. *J. Chem. Soc. Perkin Trans*. **1992**, 3163.

172) a)Xue, J.; Guo, Z. *Tetrahedron Lett*. **2001**, *42*, 6487; b) Arndt, S.; Hsieh-Wilson, C.-H. *Org. Lett*. **2003**, *5*, 4179.

173) For some literature reports for the preparation of *exo*-glycals and description of an improved method for the preparation of 5,6-*exo*-glycals see *Chapter 7.*

174) Chapleur, Y.; Grapsas, Y. *Carbohydr. Res*. **1985**, *141*, 153.

175) a) Ferrier, R. J.; Middleton, S. *Chem. Rev*. **1993**, *93*, 2779; b) Iimori, T.; Takahashi, H.; Ikegami, S.*Tetrahedron Lett*. **1996**, *37*, 649.

176) Lopatkiewicz, G.; Mlynarski, J. *J. Org. Chem*. **2016**, *81*, 7545.

177) a)Hollenberg, D. H.; Klein, R. S.; Fox, J. J. *Carbohydr. Res*. **1978**, *67*, 491; b) Angelin, M.; Hermansson, M.; Dong, H.; Ramström, O. *Eur. J. Org. Chem*. **2006**, 4323.

178) Overkleeft, H. S.; van Wiltenburg, J.; Pandit, U. K. *Tetrahedron***1994**, *50*, 4215.

179) Yang, W.-B.; Chang, C.-F.; Wang, S.-H.; Teo, C.-F.; Lin, C.-H. *Tetrahedron Lett.* **2001**, *42*, 4657.

180) Garegg, P. J.; Samuelsson , B. *Carbohydr. Res*. **1978**, *67*, 267.

181) Jäger, M.; Hartmann, M.; de Vries, J. G.; Minnaard, A. J. *Angew. Chem. Int. Ed*. **2013**, *52*, 7809.

182) Muramatsu, W. *Org. Lett*. **2014**, *16*, 4846.

Chapter 2

Three Solvent-Free Catalytic Approaches to the Acetal Functionalization of Carbohydrates and Their Applicability to One-Pot Generation of Orthogonally Protected Building-Blocks

Introduction

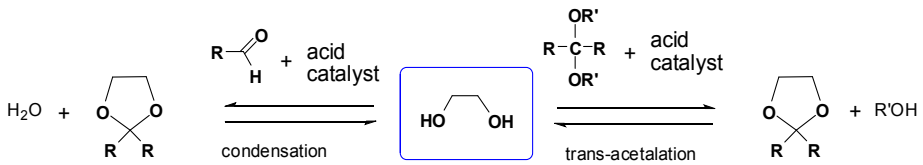
Generation of acetal or ketal functionalities is an almost ubiquitous step in organic synthesis when polyol substrates have to be chemically manipulated. The reaction allows protection of either 1,2- or 1,3-diol motifs, and the selectivity is dependent on several factors such as nature of the polyol substrate, nature of the acetalating agent and experimental conditions applied.[1]

As anticipated in the previous chapter, installation of acetal/ketal groups is a broadly employed strategy in carbohydrate chemistry allowing simultaneous protection of two saccharide positions, most commonly involving the 4,6-diol of pyranoses due to the generation of a stable six-membered cyclic acetal; in addition, installation of this kind of protecting groups allows to further differentiate the two saccharide positions involved, by the choice of either a reductive or oxidative cleavage approach (see *Chapter 1*).

Besides the broad application in the synthesis of highly functionalized targets, the usefulness of this reaction is further demonstrated by the

increasing number of examples of sugar acetals employed as key building-blocks in materials science.[2]

The acetal/ketal functionalization of polyols is more commonly performed through an acid catalyzed transacetalation process committing the polyol substrate and the requisite dimethyl acetal/ketal (**Scheme 1**). For this purpose, sulfonic acids in polar solvents are routinely employed,[1] but a large set of alternative acid catalysts such as HBF_4, $NaHSO_4$-SiO_2, H_2SO_4-SiO_2, $HClO_4$-SiO_2, tetrabutylammonium tribromide, $FeCl_3$, I_2, $In(OTf)_3$, $Cu(OTf)_2$ have also been reported.[3,4] Very recently, feasible use of organic catalysts has been described, too.[5] A more straightforward and atom-economical strategy for acetal/ketal synthesis entails an acid-catalyzed condensation of the polyol with the requisite aldehyde/ketone, but especially demanding experimental conditions are needed for the removal of water in order to shift equilibrium towards desired products, and much slower reactions are generally observed than with the trans-acetalation approaches.[2,6]



Scheme 1 Most Diffused Approaches for the Acetalation of Polyols

Collectively, the reported protocols for polyol acetalation are suffering from one or more practical issues such as the use of sensitive or commercially unavailable promoters, use of sub-stoichiometric or stoichiometric amounts of acidic agents, adoption of strictly anhydrous conditions with the application of drying agents and inert atmosphere, need for an apparatus aimed at water removal, use of high-boiling

solvents, application of *in vacuo* conditions, use of ultrasonication, prolonged reaction times.

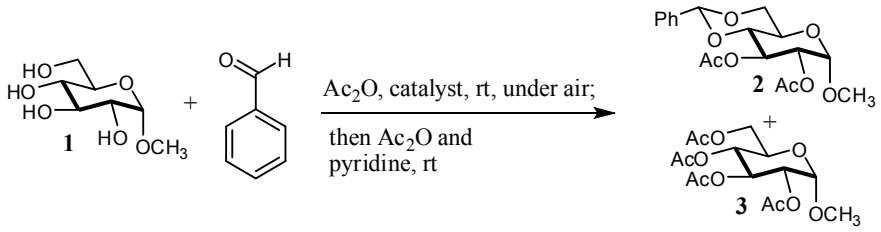
Research in our laboratory has been long focused on the development of practical procedures for the experimentally simple manipulation of carbohydrates; a special effort was addressed over last years to solvent-free protocols aimed at regioselective protection of saccharide polyols, that recently led to the introduction of convenient methods for the regioselective alkylation.[7] On pursuing our interest towards this goal, an effort was targeted to practical acetalation approaches employing experimentally simple procedures in absence of solvents and under air. Herein are reported three alternative strategies aimed at the practical acetal functionalization of saccharide precursors and polyols and their feasible application to the straightforward preparation of useful orthogonally protected building-blocks.

Results and Discussion

Initially, a sugar/aldehyde condensation triggered by the *O*-acetylation of the carbonyl component was examined,[8] a mechanism which would prevent generation of water as the side product (acetic acid should be instead formed). In the first trials, the activation under air of a moderate excess of acetic anhydride (3 eq.) with a catalytic amount of several acid promoters, in the presence of methyl α-glucopyranoside **1** and a moderate excess of benzaldehyde (3 eq.), afforded in some cases 4,6-*O*-benzylidene products in interesting yields (significant examples in **Table 1**). Since the 4,6-*O*-benzylidenation was often accompanied by partial and unselective acetylation of saccharide carbinols, a short per-*O*-acetylation step was performed *in situ* so to simplify the composition

of the final mixtures, invariably containing benzylidene **2** and per-*O*-acetylated **3**.

Table 1. Optimization of the acetolysis-induced synthesis of benzylidenes[a]

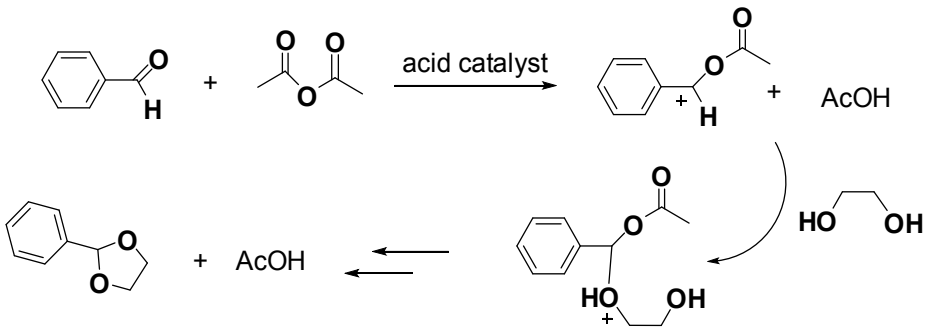


Entry	Catalyst	Time (h)	Yield of **2**
1	$Yb(OTf)_3$	4	60
2	$Cu(OTf)_2$	4	50
3	$Bi(OTf)_3$	4	10
4	CF_3SO_3H	4	55
5	CSA	36	70
6[b)]	$Yb(OTf)_3$	2.5	77
7[b)]	CF_3SO_3H	2.5	71

[a)] General conditions: benzaldehyde (3 eq), Ac_2O (3 eq), catalyst (0.01 eq), rt; addition of pyridine (1.2 mL/mmol) and Ac_2O (3 eq). [b)] benzaldehyde (3 eq), Ac_2O (1.5 eq), catalyst (0.01 eq), rt; after 1.5 h, addition of further Ac_2O (1.5 eq); after total 2.5 h, per-O-acetylation as above described.

In this preliminary screening, $Yb(OTf)_3$,[9] $Cu(OTf)_2$, and triflic acid proved effective at rt within 4 hours, with a loading as low as 1 %, to afford benzylidene **2** as the main product (**Table 1**, entries 1, 2 and 4), whereas per-*O*-acetylation largely prevailed with $Bi(OTf)_3$ (**Table 1**, entry 3). Interestingly, a typical acetalation catalyst such as camphorsulfonic acid (CSA) led to a much slower reaction albeit in a high yield (**Table 1**, entry 5). A remarkable yield improvement was achieved through the portionwise addition of acetic anhydride, that

minimized the undesired competitive acetylation at *O*-4 and *O*-6 (compare entries 6 and 7, with entries 1 and 4, respectively). The reaction was instead unproductive when **1** was added to a premixed mixture of all the other reagents. In addition, the reaction was very sluggish also when performed in absence of acetic anhydride, thus evidencing the key role played by this latter reagent and supporting the mechanistic hypothesis of an acetolytic pathaway (illustrated in **Scheme2**).

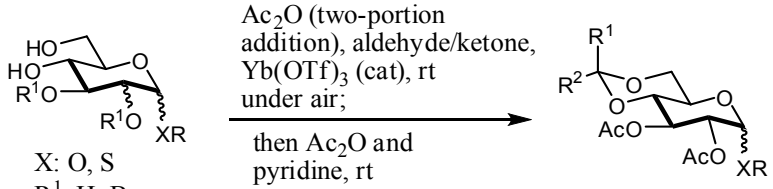


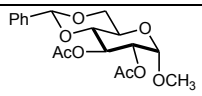
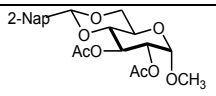
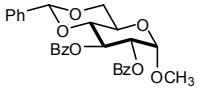
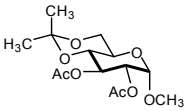
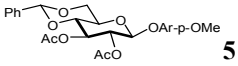
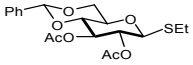
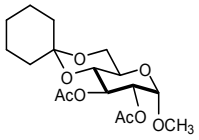
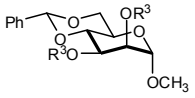
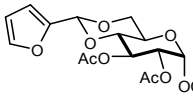
Scheme 2 Acetalation of Diols via a Condensation Mechanism Triggered by Acetolytic Activation of the Carbonyl Compound.

This acetalation approach is mechanistically interesting because the benzaldehyde carbonyl is apparently *O*-acetylated faster than saccharide carbinols with most acid catalysts (**Table 1**).[10]

A critical role for this selectivity might be played by the insolubility of the sugar in the liquid medium, as suggested by the yield decrease observed on applying the $Yb(OTf)_3$-catalyzed procedure in the benzylidenation of glucosides less polar than **1** (**Table 2**, entries 2 and 3). The scope of this really simple procedure was then examined on **1** with alternative aldehydes and ketones and satisfying results were achieved in the synthesis of glucosides **6-8** (**Table 2**, entries 4-6).

Table 2. Synthesis of sugar acetals/ketals via an acetolytic activation of the aldehyde/ketone[a]



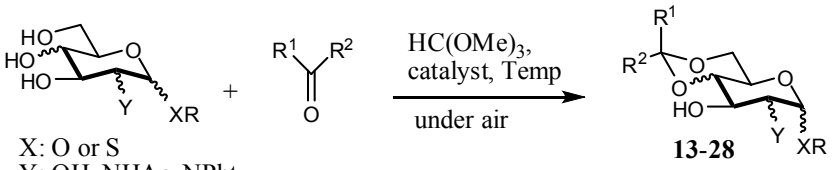
Entry	Product and yield[b]	Entry	Product and yield[b]
1	 **2** 77%	6[c]	 **8** 82%
2	 **4** 41%	7[d]	 **9** 85%
3	 **5** 53%	8	 **10** 24%
4	 **6** 78%	9	 **11** R^3: Ac 40%[e] **12** R^3: >CHPh 40%[e]
5	 **7** 71%		

[a] General conditions: aldehyde or ketone (3 eq), Ac_2O (1.5 eq), $Yb(OTf)_3$ (0.01 eq), rt; after 1.5 h, addition of further Ac_2O (1.5 eq); after total 2-4 h, addition of pyridine (1.2 mL/mmol) and Ac_2O (3 eq). [b] Isolated yield unless otherwise stated. [c] A third aliquot of Ac_2O (1.5 eq) was added prior to the *O*-acetylation step. [d] 2,2-dimethoxypropane was used as the reagent. [e] Yield estimated by NMR analysis of the crude reaction mixture.

The isopropylidenated compound **9** was also prepared in a very good yield (**Table 2**, entry 7), but in this case the reaction was effective only on using 2,2- dimethoxypropane rather than acetone. On the other hand, the method failed in the attempted condensation with anisaldehyde and nonanal, or when assessed on alternative sugar substrates. For example, attempted protection of a β-thio-glucoside tetraol afforded the corresponding benzylidene **10** in a low yield (**Table 2**, entry 8), whereas *galacto*-configured substrates exhibited a very poor reactivity (data not shown). In all these latter cases per-*O*-acetylation of the tetraol was the prevailing route. With methyl α-mannopyranoside (**Table 2**, entry 9), the method gave an approximately equimolar mixture of 4,6-*O*-benzylidene **11** (acetylated at O-2 and O-3) and dibenzylidene **12** (diastereoisomeric mixture).

In an attempt to extend the scope of the solvent-free strategies for acetal protection, alternative synthetic pathways were surveyed. Combination of orthoesters with carbonyl compounds under acid catalysis is occasionally employed under solvent-free conditions for the acetalation of diols,[11] but it is not applied to regioselective functionalization of polyols. This is likely due to the poor solubility of polar polyol substrates in the reaction medium and the possible occurrence of competitive processes arising from direct interaction of the orthoester reagent with sugars (i.e. generation of sugar orthoesters).[5b, 12] Notwithstanding, an extensive screening of conditions evidenced that the aldehyde-orthoester strategy can lead to especially good results in absence of solvents (**Table 3**), adopting methyl orthoformate or orthobenzoate as the orthoesters, and a very low catalytic loading of CSA or $Yb(OTf)_3$ (0.01-0.03 eq in most cases).

Table 3. Solvent-free synthesis of sugar acetals mediated by orthoesters[a]



X: O or S
Y: OH, NHAc, NPht

13-28

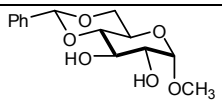
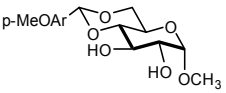
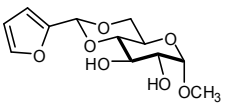
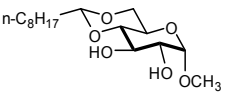
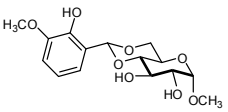
Entry	Catalyst (equiv), time	Additional remarks	Product and isolated yield
1	CSA (0.01), 0.5 h		 **13** 79%
2[b)]	CSA (0.02), 1.5 h		**13** 92%
3[b)]	CSA (0.02), 1.5 h	0.1 equiv H_2O added	**13** 90%
4[b)]	CSA (0.02), 1.5 h	10 g-scale	**13** 85%
5[b,c)]	$Yb(OTf)_3$ (0.02), 1.5 h		**13** 79% (anomeric mixture)
6	CSA (0.01), 1 h		 **14** 84%
7	CSA (0.01), 2.5 h		 **15** 44%
8[d)]	$Yb(OTf)_3$ (0.02), 1 h		 **16** 59%
9	$Yb(OTf)_3$ (0.01), 1.5 h	$PhC(OMe)_3$ in place of $HC(OMe)_3$	**16** 91%
10	CSA (0.01), 1.5 h		 **17** 91%

Table 3. (Continued)

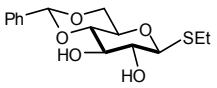
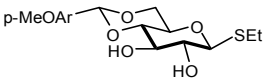
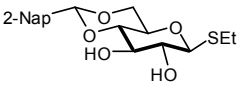
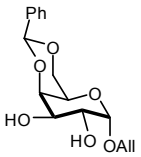
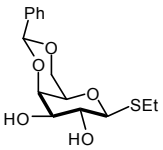
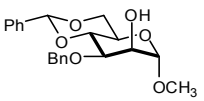
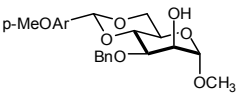
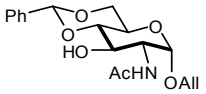
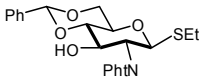
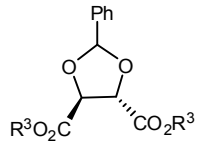
Entry	Catalyst (equiv), time	Additional remarks	Product and isolated yield
11[b)]	$Yb(OTf)_3$ (0.02), 4 h		 **18** 75%
12[d)]	$Yb(OTf)_3$ (0.02), 4 h	Under argon	**18** 82%
13	$Yb(OTf)_3$ (0.01), 2 h		 **19** 90%
14[e)]	CSA (0.01), 4.5 h	Gram-scale, 3 equiv of $HC(OMe)_3$,	 **20** 69%
15	$Yb(OTf)_3$ (0.01), 3.5 h		**20** 73%
16[f)]	CSA (0.05), 3 h	3 equiv of $HC(OMe)_3$	 **21** 81%
17[g)]	$Yb(OTf)_3$ (0.03), 2 h	3 equiv of $HC(OMe)_3$	 **22** 89%
18	CSA (0.01), 3 h		 **23** 74%
19	CSA (0.01), 1 h		 **24** 80%

Table 3. (Continued)

Entry	Catalyst (equiv), time	Additional remarks	Product and isolated yield
20[b)]	CSA (0.02), 1.5 h		 **25** 67%
21[b)]	$Yb(OTf)_3$ (0.02), 2.5 h		 **26** 67%
22	CSA (0.01), 3 h	Diisopropyl tartrate as the substrate	 **27** R^3: *i*Pr 67% **28** R^3: *i*Pr and/or Me 20 %

[a)] General conditions: aldehyde (3 equiv), $HC(OMe)_3$ (2 equiv), CSA or $Yb(OTf)_3$ (0.01 equiv), 90 °C. Further catalyst was added in some cases up to the final amount indicated in the scheme (see footnotes below for details). Times are referred to the overall process (including the eventual pre-activation step, see below). [b)] The second aliquot of the catalyst was added after 1 hour. [c)] Product obtained as an anomeric mixture (α:β ca 8). [d)] The overall amount of the catalyst added from the start. [e)] Aldehyde, orthoester and the catalyst kept at 90 °C for 1 h, then addition of the sugar. [f)] Aldehyde, orthoester and $Yb(OTf)_3$ (0.03 eq) kept at 90 °C for 1.5 h, then addition of the sugar and the second aliquot of the catalyst. [g)]Aldehyde, orthoester and the catalyst kept at 70 °C for 1.5 h, then addition of the sugar and the second aliquot of the catalyst.

Due to the much lower cost of methyl orthoformate than the orthobenzoate counterpart, the former was preferentially assessed in the following applications. As to the acid, CSA was the preferred choice in most cases, although $Yb(OTf)_3$ was found to be the best serving catalyst with thioglycoside substrates (**Table 3**, entries 11-13, 15, 17, 21) and in the synthesis of nonylidene **16** (entries 8 and 9); on the other hand, its application in the benzylidenation of *O*-glycoside substrates

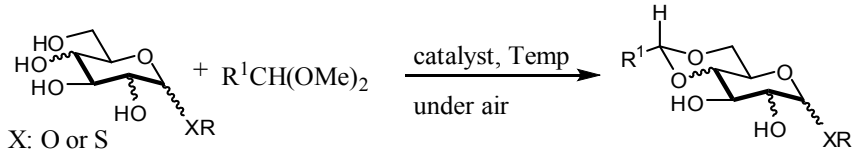
caused partial anomerization (**Table 3**, entry 5). As shown in **Table 3**, high yields were generally achieved within a few hours at 70-90 °C, with a wide range of aldehydes and saccharide precursors. In most cases 1 % catalyst was sufficient for a fast reaction; when necessary, the *in situ* addition of a further aliquot was performed to shorten reaction times. The method was found applicable at a 10 g-scale (entry 4) and effective even in the presence of purportedly added water (entry 3). Notably, the best performing methods described in the literature for the generation of **13** via a condensation with benzaldehyde[2b, 3f, 5b, 6b] gave comparable or slightly lower yields than under solvent free conditions herein reported (**Table 3**, entry 2), but required a higher catalyst loading and often much more prolonged reaction times.

A preliminary exposure of the aldehyde and orthoester to the catalyst in absence of the polyol was occasionally found critical for yield improvement, owing to the minimized generation of undesired sugar orthoesters; this beneficial effect was especially evident in the synthesis of the *galacto*-products **21** and **22** (**Table 3**, entries 16 and 17). Application to mannosides once again was affected by the competitive double acetalation (data not shown), whereas the method served well with a 3-*O*-protected mannoside precursor (**Table 3**, entries 18 and 19), easily obtained in a single regioselective step from a mannoside precursor.[7b,13] Besides the effective installation of benzylidene protecting groups, the strategy worked remarkably well with alternative alkyl or aromatic aldehydes (**Table 3**, entries 6-10, 13, 14, and 19), even when applied to a sterically hindered di-substitued benzaldehyde such as *o*-vanillin (**Table 3**, entry 10). In a test experiment, synthesis of **18** (**Table 3**, entry 11) was also performed under argon, and just a slight increase of yield was recorded (**Table 3**, entry 12) to confirm the tolerance of the method towards adventitious moisture. For a

comparison purpose, synthesis of (2-naphtyl)methylidene **20** (entries 14 and 15) was attempted through a standard protocol by exposing ethyl β-thioglucoside to 2-naphtaldehyde in DMF and in the presence of CSA (0.3-0.5 equiv); under these conditions compound **20** was never obtained in yields exceeding 40% even after prolonged reaction times (48 h) at high temperature. Unlike the method in **Table 2**, this orthoster-based approach was unfruitful for the isopropylidene protection; indeed, neither acetone nor 2,2-dimethoxypropane were successfully activated by this reagent system.

Another result of this investigation lies in the extension of the solvent free strategy to the transacetalation approach that is prevalently exploited to carry out the benzylidene functionalization of carbohydrates; indeed, exposure of the polyol to just a moderate excess of benzylidene dimethyl acetal and a very low loading of CSA (0.01-0.02 eq) at 90 °C proved effective within short times (0.5 – 3.5 hours) on a variety of substrates (**Table 4**). Also in this case, the best performing methods described in the literature for the generation of **13** via a trans-acetalation mechanism[3e, 3h, 5b, 5c, 14] gave comparable or slightly lower yields than under solvent free conditions herein reported (**Table 4**, entry 1), requiring a higher catalyst loading.

Table 4. Solvent-free synthesis of sugar acetals via a transacetalation process[a]



13, **14**, **18**, **19**, **21**, **25**, **26-28**

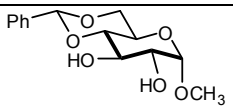
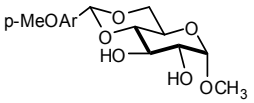
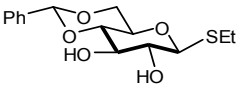
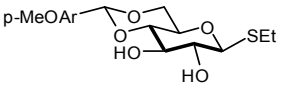
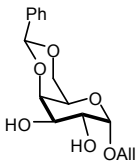
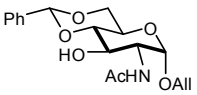
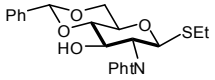
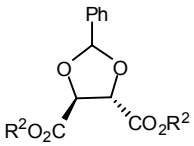
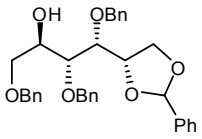
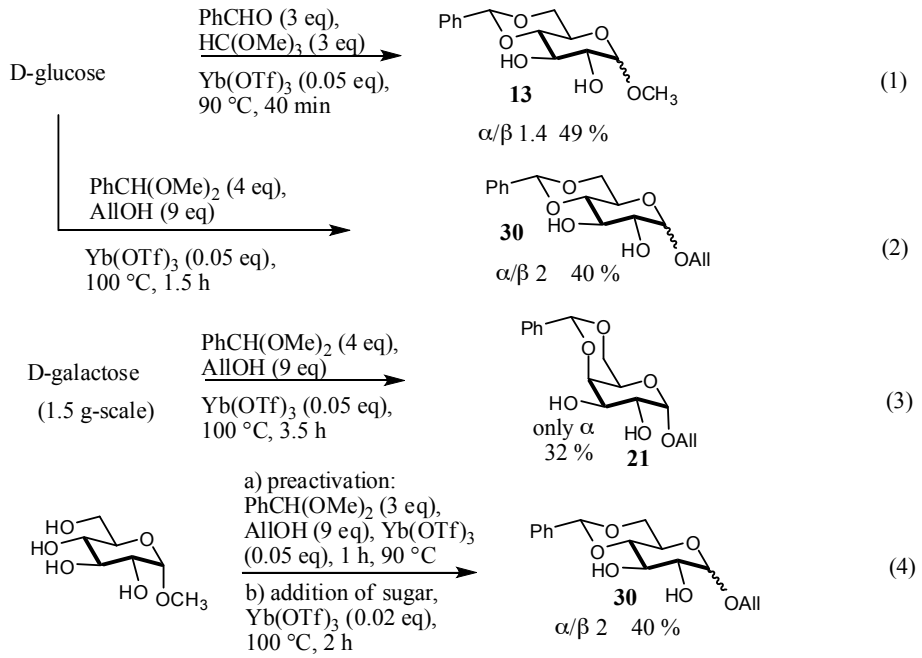
Entry	Catalyst (equiv)	Time (h)	Product and isolated yield
1	CSA (0.01)	1	 **13** 95%
2	$Yb(OTf)_3$ (0.01)	1	**13** 65%
3	CSA (0.01)	1	 **14** 80%
4	CSA (0.01)	3	 **18** 76%
5	CSA (0.01)	1	 **19** 85%
6	CSA (0.03)	1	 **21** 78%
7	CSA (0.01)	0.5	 **25** 78%

Table 4. (Continued)

Entry	Catalyst (equiv)	Time (h)	Product and isolated yield
8	CSA (0.01)	1.5	 **26** 83%
9	CSA (0.01)	3.5	 **27** R^2**:** *i*Pr 65 % **28** R^2: *i*Pr and/or Me 20 %
10	CSA (0.02)	3.5	 **29** 58 % (73 %)[b]

[a] General conditions: dimethyl acetal (2 eq), CSA or $Yb(OTf)_3$ (0.01-0.03 eq), 90 °C; [b] Conversion

The scope of some of the developed approaches was further extended to an unprecedented one-pot process leading to concomitant Fischer glycosidation and acetal protection of glucose and galactose in the reducing form, where $Yb(OTf)_3$ (0.05-0.07 eq) proved to be the best performing catalyst (**Scheme3**); for example, 4,6-*O*-benzylidenated methyl glucoside **13** was directly accessed as an anomeric mixture upon a short exposure at 90 °C of glucose to benzaldehyde, trimethyl ortoformate and the catalyst (**Scheme 3**, reaction 1).



Scheme 3 One pot Fischer glycosidation/acetalation of sugars under solvent-free conditions.

Even more remarkable is the feasible installation of the allyl aglycone (synthetically more versatile than the methyl one) simply performing the transacetalation reaction in the presence of excess allyl alcohol (**Scheme 3**, reactions 2 and 3). It is also worth noting that such conditions also allowed the *O*-1 methyl to be replaced with an allyl group along with the benzylidene installation (**Scheme 3**, reaction 4).

Conclusions

In conclusion, in this chapter three alternative approaches are presented for the selective acetal functionalization of polyols. These procedures are differentiated on the acetalation mechanism, but are endowed with multiple advantages such as a remarkable experimental simplicity, the avoided use of high-boiling solvents, the feasible applicability to a wide

range of carbonyl precursors, reduced reaction times, very low catalyst loadings. In addition, some of the protocols are compatible with an unprecedented Fischer glycosidation/acetal formation one-pot scheme.

Experimental Section

General remarks

All acidic catalysts adopted in this investigation are commercially available and were used as supplied without any pre-treatment. The progress of reactions was monitored by TLC; after elution in the suitable eluent, the plates were soaked in 5 % conc H_2SO_4 in ethanol and heated at 230 °C. NMR spectra were recorded in a 400 MHz device.

Synthesis of sugar acetals/ketals mediated by acetic anhydride

To a mixture of the polyol sugar (1 mmol), the aldehyde (or ketone) (3 mmol) and acetic anhydride (140 μL, 1.5 mmol), ytterbium(III) triflate (6.2 mg, 0.01 mmol) was added under air. The mixture was kept under stirring for 90 minutes at rt, afterthen a further aliquot of acetic anhydride (140 μL, 1.5 mmol) was added. When the starting sugar was totally consumed, pyridine (0.9 mL) and acetic anhydride (190 μL, 2.0 mmol) were added. On completion of the acetylation step (approx. one hour), the mixture was treated with methanol, and diluted with DCM. The organic phase was washed with water, and the aqueous phase re-extracted with DCM. Combined organic phases were dried with anhydrous sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica-gel flash-chromatography to afford acetal derivatives in the yields indicated in Table 2.

Synthesis of sugar acetals mediated by an orthoester

To a mixture of the polyol sugar (1 mmol), the aldehyde (or ketone) (3 mmol) and the orthoester (220 μL, 2 mmol), ytterbium(III) triflate or camphorsulfonic acid (0.01 mmol) was added under air. The mixture was kept under stirring at 90 °C allowing distillation of the volatiles. When necessary a further aliquot of the catalyst was added (see Table 3 for times and amounts). The reaction was quenched with a few drops of pyridine and the mixture was concentrated *in vacuo*. The mixture was submitted to silica-gel flash chromatography (eluents: dichloromethane/methanol or hexane/ethyl acetate mixtures) for purification of acetal products. Unsubstituted benzylidene products obtained by this procedure were generally contaminated with variable amounts of benzoic acid which was removed washing a DCM solution of the benzylidene with 0.1M aq NaOH, and water. The resulting organic phase was dried with sodium sulfate and concentrated *in vacuo* to yield the desired product in a pure form.

In the synthesis of *galacto*-benzylidenes **21** and **22**, best results were obtained by premixing the aldehyde (3 mmol), the orthoester (3 mmol) and ytterbium(III) triflate or camphorsulfonic acid (0.01 mmol) at 90 °C. The sugar was then added with the second aliquot of catalyst (see Table 3 for times and amounts)

Large scale synthesis of 13 mediated by methyl orthoformate

To a mixture of methyl glucoside **1** (10.0 g, 51.5 mmol), methyl orthoformate (11.3 mL. 103 mmol) and benzaldehyde (15.6 mL), camphorsulfonic acid (120 mg, 0.51 mmol) was added. The mixture was kept at 90 °C (oil bath) for 1 h allowing distillation of volatiles, then another aliquot of camphorsulfonic acid (120 mg, 0.51 mmol) was added. Upon completion of the reaction (TLC, approx. 90 minutes), the

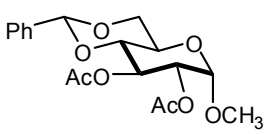
mixture was diluted with dichloromethane and washed with 0.1 M aq NaOH (to remove benzoic acid). The residue of the organic phase was then crystallized with ethyl acetate/hexane mixtures to obtain 8.20 g of **13**. The supernatant was concentrated and submitted to flash-chromatography (eluent: dichloromethane and then dichloromethane/methanol 95:5) to obtain further 4.16 g of **13** (85 % overall yield).

Synthesis of sugar acetals based on a transacetalation mechanism

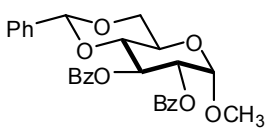
To a mixture of the polyol sugar (1 mmol) and dimethyl acetal (2 mmol), camphorsulfonic acid (0.01 mmol) was added under air (see Table 4). The mixture was kept under stirring at 90 °C, allowing distillation of the volatiles. The reaction was quenched with a few drops of pyridine and the mixture was concentrated *in vacuo*. The mixture was submitted to silica-gel flash chromatography (eluents: dichloromethane/methanol or hexane/ethyl acetate mixtures) for purification of the acetal products.

One-pot Fischer glycosidation/benzylidenation of free sugars

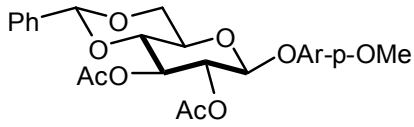
For the relative amounts of reagents and the reaction temperatures see entries in Scheme 1. To a mixture of the free sugar, the acetalating agent, methyl orthoformate (when necessary), and allyl alcohol (when necessary), ytterbium(III) triflate was added under air. The mixture was heated to the reaction temperature and kept under stirring allowing distillation of the volatiles. Upon completion (TLC analysis) the reaction was quenched with a few drops of pyridine and the mixture was concentrated *in vacuo*. The mixture was submitted to silica-gel flash chromatography (eluents: dichloromethane/methanol or hexane/ethyl acetate mixtures) for purification of the acetal products.



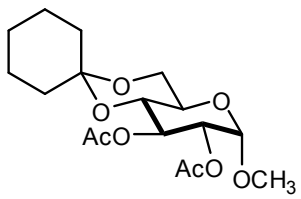
Methyl 2,3-di- *O* -acetyl-4,6-*O*-benzylidene-α-D-glucopyranoside (2).[15] Eluted with hexane/ethyl acetate from 7:3 to 1:1. White solid; m. p. 107-109 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45-7.30 (aromatic H, 5 H), 5.59 (H-3, t, J = 9.6 Hz, 1 H), 5.50 (benzylidene acetal CH, s, 1H), 4.94 (H-1, d, J = 3.2 Hz, 1 H), 4.91 (H-2, dd, J = 3.6, 9.6 Hz, 1 H), 4.29 (H-6eq, dd, J = 4.8, 10.0 Hz, 1H), 3.92 (H-5, m, 1 H), 3.77 (t, J = 10.0 Hz, 1 H), 3.65 (t, J = 10.0 Hz, 1 H), 3.40 (1-OCH_3, s, 3H), 2.09 and 2.05 (2 x –$COCH_3$, 2 x s, 6H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.3 and 169.7 (-*C*OCH_3), 136.8 (aromatic C), 129.1, 128.4, 126.0 (aromatic CH), 101.4 and 97.4 (acetal CH), 79.1, 71.5, 68.9, 68.7, 62.1, 55.2, 20.7, 20.6. MALDI-MS (*m*/*z*): *m*/*z* = 389.35 [M + Na]$^{+}$, calcd. for ($C_{18}H_{22}O_8$) 389.12. Anal. Calcd. for $C_{13}H_{16}O_4$: C, 59.01; H, 6.05. Found: C, 58.94; H, 6.10.



Methyl 2,3-di-*O*-benzoyl-4,6-*O*-benzylidene-α-D-glucopyranoside (4).[16] Eluted with hexane/ethyl acetate from 8:2 to 7:3. White solid; m. p. 152-154 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.00-7.30 (aromatic H, 15H), 6.11 (H-3, t, J = 9.6 Hz, 1 H), 5.60 (s, 1H), 5.31 (H-2, dd, J = 3.6, 9.6 Hz, 1H), 5.21 (H-1, d, J = 3.6 Hz, 1 H), 4.40 (H-6eq, dd, J = 4.8, 10.0 Hz, 1 H), 4.11 (H-5, m, 1H), 3.95 (H-4, t, J = 10.0 Hz, 1 H), 3.89 (H-6ax, t, J = 10.0 Hz, 1 H), 3.45 (3H, s, -OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.9, 165.5 (2 x –*C*OPh); 136.8, 133.3, and 132.9 (aromatic C); 130.0-126.1 (aromatic CH); 101.5 and 97.7 (acetal CH), 79.3, 72.5, 69.4, 68.8, 62.5, 55.4. MALDI-MS (*m*/*z*): *m*/*z* = 513.20 [M + Na]$^{+}$, calcd. for ($C_{28}H_{26}O_8$) 513.15. Anal. Calcd. for $C_{28}H_{26}O_8$: C, 68.56; H, 5.34. Found: C, 68.40; H, 5.40.

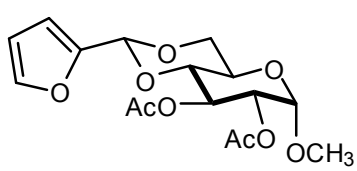


***p*-Methoxyphenyl 2,3-di- *O* -acetyl-4,6- *O* -benzylidene-β- D-glucopyranoside (5)**.[17] Eluted with hexane/ethyl acetate from 8:2 to 3:7. White solid; m. p. 211-212 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45-6.80 (aromatic H, 9H), 5.52 (s, 1H), 5.39 (H-3, t, *J* = 9.6 Hz, 1 H), 5.25 (H-2, dd, *J* = 8.0, 9.6 Hz, 1 H), 5.06 (H-1, d, *J* = 7.6 Hz, 1 H), 4.38 (H-6eq, dd, *J* = 4.8, 10.0 Hz, 1 H), 3.84 (H-4, t, *J* = 10.0 Hz, 1 H), 3.81 (H-6ax, t, *J* = 10.0 Hz, 1 H), 3.77 (3H, s, -OCH_3), 3.60 (1H, m, H-5), 2.08 and 2.07 (2 x –$COCH_3$, 2 x s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.1, 169.5 (2 x –*C*OCH_3); 155.8, 150.8, 136.7 (aromatic C); 130.1, 129.1, 128.4, 126.1, 118.7, 114.7 (aromatic CH); 101.5 and 100.8 (acetal CH), 78.0, 72.2, 71.7, 68.5, 66.4, 55.6, 20.7, 20.6. MALDI-MS (*m*/*z*): *m*/*z* = 481.20 $[M + Na]^+$, calc. for ($C_{24}H_{26}O_9$) 481.15. Anal. Calcd. for $C_{24}H_{26}O_9$: C, 62.88; H, 5.72. Found: C, 62.70; H, 5.75.

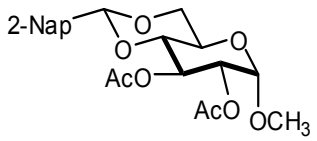


Methyl 2,3-di-*O*-acetyl-4,6-*O*-cyclohexylidene-α-D-glucopyranoside (6). Eluted with hexane/ethyl acetate from 7:3 to 6:4. Oil. $[\alpha]_D^{23}$: +87.8 (*c* 1.8, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.25 (H-3, t, *J* = 9.6 Hz, 1 H), 4.80-4.70 (H-1 and H-2, overlapped signals, 2 H), 3.75 (H-6eq, dd, *J* = 4.0, 10.0 Hz, 1 H), 3.66 (t, *J* = 9.6 Hz, 1 H), 3.61 (H-5, m, 1 H), 3.54 (t, *J* = 9.6 Hz, 1 H), 3.25 (1-OCH_3, s, 3 H), 2.25-2.00 (m, 3 H), 1.95 and 1.92 (2 x –$COCH_3$, 2 x s, 6H), 1.80-1.20 (m, 7 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0 and 169.4 (-*C*OCH_3), 99.4 and 97.3 (acetal CH), 71.2, 71.1, 69.1, 63.0, 61.3, 54.8, 37.4, 27.2, 25.2, 22.4, 22.3, 20.4. MALDI-MS

(*m*/*z*): *m*/*z* = 381.35 $[M + Na]^+$, calcd. for ($C_{17}H_{26}O_8$) 381.15. Anal. Calcd. for $C_{17}H_{26}O_8$: C, 56.97; H, 7.31. Found: C, 56.84; H, 6.35.

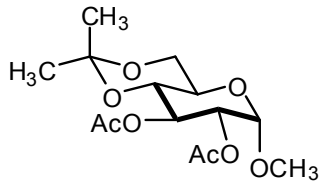


Methyl 2,3-di-*O*-acetyl-4,6-*O*-(2-furyl)methylene-α-D-glucopyranoside (7).[18] Eluted with hexane/ethyl acetate 6:4. Foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (bs, 1 H), 6.40 (bs, 1 H), 6.31 (bs, 1H), 5.51 (s, 1 H), 5.50 (H-3, t, J = 10.0 Hz, 1 H), 4.88 (H-1, d, J = 3.2 Hz, 1 H), 4.84 (H-2, dd, J = 3.2, 10.0 Hz, 1 H), 4.24 (H-6eq, dd, *J* = 4.8, 10.4 Hz, 1 H), 3.88 (H-5, m, 1 H), 3.69 (t, *J* = 10.4 Hz, 1 H), 3.57 (t, *J* = 10.4 Hz, 1 H), 3.35 (1-OCH_3, s, 3 H), 2.08 and 2.03 (2 x –$COCH_3$, 2 x s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2 and 169.6 (-*C*OCH_3), 149.2 (aromatic C); 142.5, 110.0, and 107.9 (aromatic CH); 97.3 and 96.0 (acetal CH), 78.9, 71.3, 68.6, 68.5, 61.9, 55.1, 20.6 and 20.5. MALDI-MS (*m*/*z*): *m*/*z* = 389.30 $[M + Na]^+$, calcd. for ($C_{16}H_{20}O_9$) 389.11. Anal. Calcd. for $C_{16}H_{20}O_9$: C, 56.97; H, 7.31. Found: C, 53.93; H, 5.66.

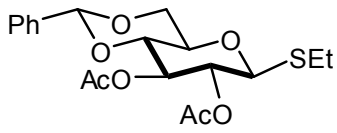


Methyl 2,3-di-*O*-acetyl-4,6-*O*-(2-naphtyl)methylene-α-D-glucopyranoside (8).[6a] Eluted with dichloromethane/hexane from 80:20 to 100:0. Foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.95-7.45 (aromatic H, 7 H), 5.67 (s, 1 H), 5.64 (H-3, t, *J* = 9.6 Hz, 1 H), 4.98 (H-1, d, J = 4.0 Hz, 1 H), 4.95 (H-2, dd, J = 4.0 and 9.6 Hz, 1 H), 4.37 (H-6eq, dd, *J* = 4.8 and 10.0 Hz, 1 H), 4.00 (H-5, m, 1 H), 3.84 (t, *J* = 10.0 Hz, 1 H), 3.72 (t, *J* = 10.0 Hz, 1 H), 3.44 (1-OCH_3, s, 3 H), 2.12 and 2.07 (2 x –$COCH_3$, 2 x s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4 and 169.7 (-*C*OCH_3), 134.2, 133.5, 132.7

(aromatic C); 128.3, 128.0, 127.6, 126.4, 126.0, 125.6, 123.6 (aromatic CH); 101.7 and 97.5 (acetal CH), 79.2, 71.5, 68.9, 62.3, 55.3, 20.7. MALDI-MS (*m*/*z*): *m*/*z* = 439.05 $[M + Na]^+$, calc. for ($C_{22}H_{24}O_8$) 439.14. Anal. Calcd. for $C_{22}H_{24}O_8$: C, 63.45; H, 5.81. Found: C, 63.65; H, 5.75.

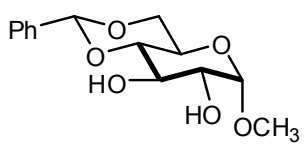


Methyl 2,3-di-*O*-acetyl-4,6-*O*-isopropylidene-α-D-glucopyranoside (9). Eluted with hexane/acetone 8:2. Oil. $[\alpha]_D^{23}$: +85.1 (*c* 1.2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.43 (H-3, t, *J* = 9.6 Hz, 1 H), 4.96 (H-1, d, *J* = 3.6 Hz, 1 H), 4.90 (H-2, dd, *J* = 3.6 and 9.6 Hz, 1 H), 3.95 (m, 1 H), 3.87-3.65 (overlapped signals, 3 H), 3.46 (1-OCH_3, s, 3 H), 2.12 and 2.09 (2 x –$COCH_3$, 2 x s, 6 H), 1.53 and 1.44 (2 x isopropylidene methyls, 2 x s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2 and 169.7 (-*C*OCH_3), 99.6 (-*C*$(CH_3)_2$) and 97.4 (C-1), 71.8, 71.5, 69.2, 63.0, 62.0, 55.0, 28.8, 20.6, 20.5, 18.8. MALDI-MS (*m*/*z*): *m*/*z* = 341.10 $[M + Na]^+$, calc. for ($C_{14}H_{22}O_8$) 341.31. Anal. Calcd. for $C_{14}H_{22}O_4$: C, 52.82; H, 6.97. Found: C, 53.03; H, 6.90.

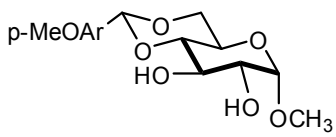


Ethyl 2,3-di-*O*-acetyl-4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (10).[19] Eluted with hexane/ethyl acetate from 8:2 to 7:3. Foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50-7.30 (aromatic H, 5H), 5.50 (s, 1 H), 5.34 (H-3, t, *J* = 10.0 Hz, 1 H), 5.04 (H-2, t, *J* = 10.0 Hz, 1 H), 4.59 (H-1, d, *J* = 10.0 Hz, 1 H), 4.37 (H-6eq, dd, *J* = 4.8 and 10.4 Hz, 1 H), 3.78 (t, *J* = 10.4 Hz, 1 H), 3.66 (t, *J* = 10.4 Hz, 1 H), 3.52 (H-5, m, 1 H), 2.69 (m, -SC*H*$_2$$CH_3$, 2 H), 2.07 and 2.04 (2 x –$COCH_3$, 2 x s,

6 H), 1.26 (-SCH_2CH_3, t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.0 and 169.6 (-$COCH_3$), 136.6 (aromatic C); 129.0, 128.2, 126.6 (aromatic CH); 101.4 (acetal CH), 84.0 (C-1), 79.1, 72.6, 71.3, 70.6, 70.5, 68.4, 24.2, 20.7 and 14.8. MALDI-MS (*m*/*z*): *m*/*z* = 419.20 $[M + Na]^+$, calc. for ($C_{19}H_{24}O_7S$) 419.11. Anal. Calcd. for $C_{19}H_{24}O_7S$: C, 57.56; H, 6.10. Found: C, 57.70; H, 6.05.

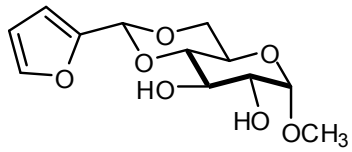


Methyl 4,6-*O*-benzylidene-α-D-glucopyranoside (13).[20] Eluted with dichloromethane/methanol from 100:0 to 95:5. White solid; m. p. 165-167 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60-7.40 (aromatic H, 5 H), 5.65 (s, 1H), 4.92 (H-1, d, *J* = 3.6 Hz, 1 H), 4.41 (H-6eq, dd, *J* = 4.4 and 10.0 Hz, 1 H), 4.04 (t, *J* = 9.6 Hz, 1 H), 3.93 (H-5, m, 1 H), 3.87 (t, *J* = 9.6 Hz, 1 H), 3.76 (H-2, dd, *J* = 3.6, 9.6 Hz, 1 H), 3.60 (t, *J* = 9.6 Hz, 1H), 3.58 (1-OCH_3, s, 3H), 2.82 (-OH, 1 H), 2.36 (-OH, d, *J* = 9.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.0 (aromatic C), 129.1, 128.2, and 126.3 (aromatic CH); 101.7 and 99.8 (acetal CH), 80.8, 72.5, 71.0, 68.8, 62.3, 55.3. MALDI-MS (*m*/*z*): *m*/*z* = 305.00 $[M + Na]^+$,calcd. for ($C_{14}H_{18}O_6$) 305.10. Anal. Calcd. for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.55; H, 6.40.

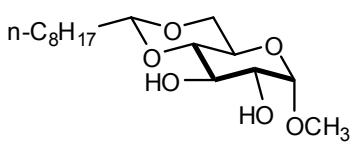


Methyl 4,6-*O*-(p-methoxy)benzylidene-α-D-glucopyranoside (14).[21] Eluted with dichloromethane/methanol from 100:0 to 90:10. Solid; m. p. 193-195 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42 and 6.90 (2 x d, *J* = 8.4 Hz, aromatic H, 4 H), 5.50 (s, 1 H), 4.82 (H-1, d, *J* = 3.2 Hz, 1 H), 4.29 (H-6eq, dd, *J* = 4.4, 10.0 Hz, 1 H), 3.96 (t, *J* = 9.6 Hz, 1 H), 3.81 (aromatic-OCH_3, s, 3 H), 3.80 (H-2, dd, *J* = 3.6, 9.6

Hz, 1 H), 3.78 (t, *J* = 9.6 Hz, 1 H), 3.77 (H-5, m, 1 H), 3.50 (t, *J* = 9.6 Hz, 1 H), 3.48 (1-OCH_3, s, 3H), 2.63 and 2.23 (2 x bs, 2 x OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.2 and 129.4 (aromatic C); 127.5, 113.6 (aromatic CH), 101.8 and 99.6 (acetal CH), 80.7, 72.7, 71.7, 68.8, 62.2, 55.4, 55.2. MALDI-MS (*m*/*z*): *m*/*z* = 335.25 $[M + Na]^+$, calcd. for ($C_{15}H_{20}O_7$): 335.12. Anal. Calcd. for $C_{15}H_{20}O_7$: C, 57.69; H, 6.45. Found: C, 57.80; H, 6.35.

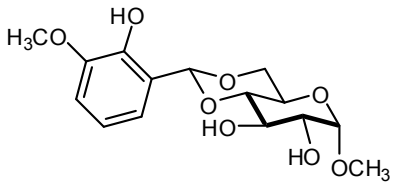


Methyl 4,6-*O*-(2-furyl)methylene-α-D-glucopyranoside (15).[18] Eluted with ethyl acetate/methanol from 100:0 to 80:20. Foam. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37 (bs, 1H), 6.45 (d, *J* = 2.8 Hz, 1 H), 6.32 (bd, *J* = 2.8 Hz, 1 H), 5.54 (s, 1H), 4.69 (H-1, d, *J* = 3.6 Hz, 1 H), 4.19 (H-6eq, dd, *J* = 4.8, 10.0 Hz, 1 H), 3.87 (t, *J* = 9.6 Hz, 1 H), 3.75 (H-5, m, 1 H), 3.65 (t, *J* = 9.6 Hz, 1 H), 3.55 (H-2, dd, *J* = 3.6, 10.0 Hz, 1 H), 3.39 (t, *J* = 9.6 Hz, 1 H), 3.36 (1-OCH_3, s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.4 (aromatic C), 142.6, 110.1, 108.2 (aromatic CH), 99.8 and 95.6 (acetal CH), 80.8, 72.4, 70.7, 68.7, 62.0, 55.2. MALDI-MS (*m*/*z*): *m*/*z* = 295.30 $[M + Na]^+$, calcd. for ($C_{12}H_{16}O_7$): 295.08. Anal. Calcd. for $C_{12}H_{16}O_7$: C, 52.94; H, 5.92. Found: C, 52.75; H, 5.80.

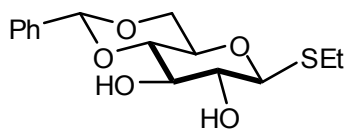


Methyl 4,6-*O*-nonylidene-α-D-glucopyranoside (16).[22] Eluted with ethyl acetate/hexane 7:3. Oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 4.78 (H-1, d, *J* = 3.6 Hz, 1 H), 4.59 (nonylidene acetal CH, t, *J* = 5.2 Hz, 1 H), 4.15 (H-6eq, dd, J = 4.8, 10.0 Hz, 1 H), 3.90 (t, *J* = 9.6 Hz, 1 H), 3.67 (H-5, m, 1 H), 3.62 (H-2, dd, *J* = 3.6 and

9.6 Hz, 1 H), 3.52 (t, J = 9.6 Hz, 1 H), 3.46 (1-OCH_3, s, 3 H), 3.30 (t, J = 9.6 Hz, 1 H), 2.15-2.10 (m, 2 H), 1.80-1.65 (m, 2 H), 1.40-1.20 (m, 10 H), 0.93 (nonylidene -CH_3, s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 102.6 and 99.9 (acetal CH), 80.4, 72.7, 71.1, 68.4, 62.5, 55.2, 34.1, 31.7, 29.4 (x2), 29.1, 24.0, 22.5, 14.0. MALDI-MS (m/z): m/z = 341.10 $[M + Na]^+$, calcd. for ($C_{16}H_{30}O_6$): 341.20. Anal. Calcd. for $C_{16}H_{30}O_6$: C, 60.35; H, 9.50. Found: C, 60.40; H, 9.40.

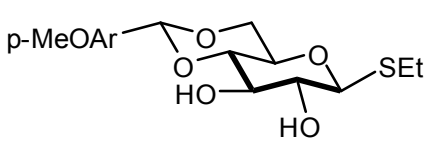


Methyl 4,6-*O*-(o-hydroxy-m-methoxy)benzylidene-α-D-glucopyranoside (17). Eluted with ethyl acetate/methanol from 100:0 to 90:10. Foam. $[\alpha]_D^{23}$: +80.8 (c 1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10-6.80 (aromatic H, 3 H), 6.44 (phenol OH), 5.83 (s, 1 H), 4.73 (H-1, bs, 1 H), 4.26 (H-6eq, dd, J = 3.6, 9.6 Hz, 1 H), 3.90-3.60 (overlapped signals, 3 H), 3.77 (aromatic –OCH_3, s, 3 H), 3.52 (m, 1 H), 3.43 (t, J = 9.6 Hz, 1 H), 3.42 (1-OCH_3, s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 147.0, 143.4, 122.8 (aromatic C); 119.6, 118.9, 111.6 (aromatic CH), 99.9 and 98.4 (acetal CH), 81.0, 72.5, 70.9, 68.9, 62.2, 56.0, 55.4. MALDI-MS (m/z): m/z = 351.00 $[M + Na]^+$ calcd. for ($C_{15}H_{20}O_8$): 351.11. Anal. Calcd. for $C_{15}H_{20}O_8$: C, 54.87; H, 6.14. Found: C, 54.70; H, 6.25.

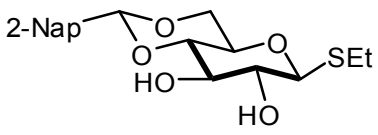


Ethyl 4,6-*O*-benzylidene-1-thio-β-D-glucopyranoside (18).[23] Eluted with dichloromethane/methanol from 100:0 to 90:10. Foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50-7.30 (aromatic H, 5 H), 5.48 (s, 1 H), 4.38 (H-1, d, J = 9.6 Hz, 1H), 4.29 (H-6eq, dd, J =

4.0, 10.0 Hz, 1 H), 3.75-3.60 (overlapped signals, 3 H), 3.50-3.35 (overlapped signals, 2 H), 2.71 (m, -SC*H*$_2$CH$_3$, 2 H), 1.29 (-SCH$_2$C*H*$_3$, t, J = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.8 (aromatic C), 129.2, 128.2, 126.2 (aromatic CH); 101.7 (acetal CH), 86.2 (C-1), 80.2, 74.3, 73.0, 70.3, 68.4, 24.5, and 15.1. MALDI-MS (m/z): m/z = 335.37 $[M + Na]^+$, calc. for ($C_{15}H_{20}O_5S$): 335.09. Anal. Calcd. for $C_{15}H_{20}O_5S$: C, 57.67; H, 6.45. Found: C, 57.45; H, 6.50.

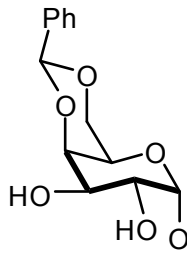


Ethyl 4,6-*O*-(p-methoxy)benzylidene-1-thio-β-D-glucopyranoside (19).[24] Eluted with dichloromethane/methanol from 100:0 to 90:10. Foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40 and 6.84 (2 x d, J = 8.4 Hz, aromatic H, 4 H), 5.42 (s, 1 H), 4.36 (H-1, d, J = 10.0 Hz, 1 H), 4.24 (H-6eq, dd, J = 4.8, 10.4 Hz, 1 H), 3.75 (-OCH$_3$, s, 3 H), 3.75-3.60 (overlapped signals, 2 H), 3.50-3.30 (overlapped signals, 3 H), 2.68 (m, -SC*H*$_2$CH$_3$, 2 H), 1.26 (-SCH$_2$C*H*$_3$, t, J = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.0, 129.3 (aromatic C), 127.8, 113.7 (aromatic CH); 101.6 (acetal CH), 86.2 (C-1), 80.1, 74.3, 73.1, 70.3, 68.4, 55.2, 24.5, and 15.1. MALDI-MS (m/z): m/z = 365.30 $[M + Na]^+$, calc. for ($C_{16}H_{22}O_6S$): 365.40. Anal. Calcd. for $C_{16}H_{22}O_6S$: C, 56.12; H, 6.48. Found: C, 56.35; H, 6.40.

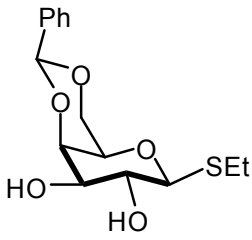


Ethyl 4,6-*O*-(2-naphtyl)methylene-1-thio-β-D-glucopyranoside (20). Eluted with dichloromethane/methanol from 100:0 to 95:5. Foam. $[\alpha]_D^{23}$: -18.0 (c 1.1, $CHCl_3$).^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.96-7.40 (aromatic H, 7 H), 5.62 (s, 1 H), 4.37 (H-1, d, J

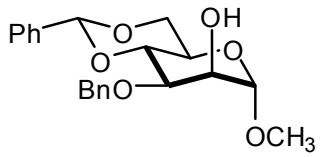
= 9.6 Hz, 1 H), 4.34 (H-6eq, dd, *J* = 4.8, 10.4 Hz, 1 H), 3.80 (t, *J* = 10.0 Hz, 1 H), 3.74 (t, *J* = 10.0 Hz, 1 H), 3.60-3.40 (overlapped signals, 3 H), 2.70 (m, -SC*H*$_2$CH$_3$, 2 H), 1.27 (-SCH$_2$C*H*$_3$, t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.2, 133.6, 132.8 (aromatic C), 128.3, 128.2, 127.6, 16.5, 126.2, 125.9, 123.7 (aromatic CH); 101.8 (acetal CH), 86.3, 80.3, 74.4, 73.2, 70.3, 68.5, 24.5, and 15.1. MALDI-MS (*m*/*z*): *m*/*z* = 385.05 $[M + Na]^+$, calcd. for ($C_{19}H_{22}O_5S$): 385.11. Anal. Calcd. for $C_{19}H_{22}O_5S$: C, 62.96; H, 6.12. Found: C, 62.75; H, 6.25.



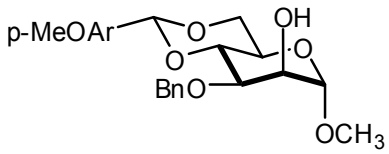
Allyl 4,6-*O*-benzylidene-α-D-galactopyranoside (21).[25] Eluted with ethyl acetate/methanol from 100:0 to 90:10. Foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ = δ 7.60-7.30 (aromatic H, 5 H), 6.02 (CH_2=C*H*CH_2-, m, 1 H), 5.63 (s, 1 H), 5.42 ($CH_{cis}H_{trans}$=CHCH$_2$-, bd, *J* = 17.2 Hz, 1 H), 5.33 (C*H*$_{cis}$H$_{trans}$=CHCH$_2$-, bd, *J* = 10.4 Hz, 1 H), 5.17 (H-1, bs, 1 H), 4.40-4.30 (CH_2=CHC*H*$_a$H$_b$-, H-4, H-6a; overlapped signals, 3 H), 4.20-4.10 (CH_2=CHCH$_a$*H*$_b$-, H-6b; overlapped signals, 2 H), 4.04 (H-2 and H-3, overlapped signals, 2 H), 3.80 (H-5, s, 1 H), 3.02, 2.78 (2 x OH, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.5 (aromatic C), 133.5 (CH_2=*C*HCH_2-), 129.1, 128.1, 126.2 (aromatic CH), 117.9 (*C*H$_2$=CHCH$_2$-), 101.1, 98.2 (acetal CH), 75.9, 69.6, 69.4, 69.2, 68.7, 62.9. MALDI-MS (*m*/*z*): *m*/*z* = 331.35 $[M + Na]^+$, calcd. for ($C_{16}H_{20}O_6$): 331.12. Anal. Calcd. for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 62.20; H, 6.45.



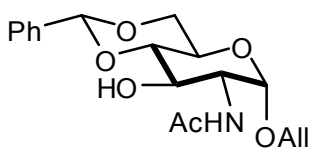
Ethyl 4,6-*O*-benzylidene-1-thio-β-D-galactopyranoside (22).[26] Eluted with hexane/acetone 1:1. Foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50-7.30 (aromatic H, 5 H), 5.47 (s, 1 H), 4.30 (H-1, d, J = 9.6 Hz, 1 H), 4.26 (H-6a, bd, J = 12.0 Hz, 1 H), 4.13 (H-4, J = 2.4 Hz, 1 H), 3.94 (H-6b, bd, J = 12.0 Hz, 1 H), 3.78 (H-2, t, J = 9.6 Hz, 1 H), 3.62 (H-3, dd, J = 2.4, 9.6 Hz, 1 H), 3.37 (H-5, bs, 1 H), 2.80 (m, -SCH_2CH$_3$, 2 H), 1.31 (t, J = 7.2 Hz, -SCH_2CH$_3$, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.4 (aromatic C), 128.9, 128.0, 126.2 (aromatic CH), 101.0 (acetal CH), 84.9 (C-1), 75.4, 73.4, 69.6, 69.2, 68.9, 23.2, and 14.9. MALDI-MS (m/z): m/z = 335.20 [M + Na]$^+$, calcd. for ($C_{15}H_{20}O_5S$): 335.09. Anal. Calcd. for $C_{15}H_{20}O_5S$: C, 57.67; H, 6.45. Found: C, 57.55; H, 6.40.



Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside (23).[27] Eluted with hexane/ethyl acetate from 7:3 to 1:1. Oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60-7.30 (aromatic H, 10 H), 5.63 (s, 1H), 4.86 and 4.72 (-CH_2Ph, AB, J = 12.0 Hz, 2H), 4.76 (H-1, s, 1H), 4.29 (H-3, dd, J = 3.6 and 9.6 Hz, 1H), 4.12 (H-4, t, J = 9.6 Hz, 1H), 4.05 (H-2, bs, 1H), 3.95-3.80 (H-5 and H_2-6, overlapped signals, 3H), 3.38 (1-OCH$_3$, s, 3H), 2.79 (OH-2, s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.8, 137.4 (aromatic C), 133.3-126.0 (aromatic CH), 101.5, 101.0 (acetal CH), 78.7, 75.5, 72.9, 69.7, 68.7, 63.1, 54.8. MALDI-MS (m/z): m/z = 395.20 [M + Na]$^+$, calc. for ($C_{21}H_{24}O_6$): 395.15. Anal. Calcd. for $C_{21}H_{24}O_6$: C, 67.73; H, 6.50. Found: C, 67.50; H, 6.60.

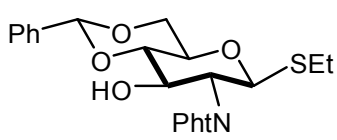


Methyl 3-*O*-benzyl-4,6-*O*-(p-methoxy)benzylidene-α-D-mannopyranoside (24). Eluted with hexane/ethyl acetate from 7:3 to 1:1. Oil. $[\alpha]_D^{23}$: +35.3 (*c* 2, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60-7.00 (aromatic H, 9 H), 5.71 (s, 1 H), 4.97 and 4.82 (-CH_2Ph, AB, *J* = 12.0 Hz, 2 H), 4.86 (H-1, d, *J* = 1.2 Hz, 1 H), 4.40 (H-6eq, dd, J = 3.6 and 9.6 Hz, 1 H), 4.25 (t, J = 9.6 Hz, 1 H), 4.13 (H-2, dd, *J* = 1.2, 9.6 Hz, 1 H), 4.02 (H-3, dd, *J* = 3.6, 9.6 Hz, 1 H), 4.01 (t, *J* = 9.6 Hz, 1 H), 3.97 (H-5, m, 1 H), 3.95 (aromatic –OCH_3, s, 3 H), 3.49 (1–OCH_3, s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8, 137.9, 128.3 (aromatic C), 128.3, 127.7, 127.2, 113.4 (aromatic CH), 101.4, 101.0 (acetal CH), 78.6, 75.5, 72.8, 69.6, 68.6, 63.1, 55.1, 54.7. MALDI-MS (*m*/*z*): *m*/*z* = 425.00 $[M + Na]^+$, calcd. for ($C_{22}H_{26}O_7$) 425.16. Anal. Calcd. for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51. Found: C, 65.40; H, 6.45.

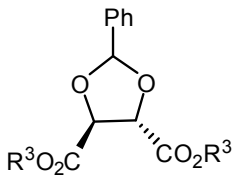


Allyl 4,6-*O*-benzylidene-2-deoxy-2-acetamido-α-D-glucopyranoside (25).[28] Eluted with dichloromethane/methanol from 100:0 to 95:5. Solid; m. p. 207-209 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50-7.30 (aromatic H, 5 H), 6.00-5.80 (CH_2=C*H*CH_2- and NH-2, overlapped signals, 2 H), 5.57 (s, 1 H), 5.31 ($CH_{cis}H_{trans}$=C*H*CH_2-, bd, *J* = 17.2 Hz, 1 H), 5.25 (C$H_{cis}H_{trans}$=C*H*CH_2-, bd, J = 10.8 Hz, 1 H), 4.87 (H-1, d, *J* = 3.6 Hz, 1 H), 4.30-4.20 (CH_2=CHC*Ha*Hb-, H-6eq and H-2; overlapped signals, 3 H), 3.98 (CH_2=CHCHa*Hb*-, m, 1 H), 3.94 (t, *J* = 10.0 Hz, 1 H), 3.85 (m, H-5, 1 H), 3.76 (t, *J* = 10.0 Hz, 1 H), 3.58 (t, *J* = 10.0 Hz, 1 H), 2.07 (-$NHCOCH_3$, s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4 (CO), 137.0 (aromatic C), 133.2 (CH_2=*C*HCH_2-), 129.1,

128.2, 126.2 (aromatic CH), 118.1 (*C*H_2=CHCH$_2$-), 101.7, 96.9 (acetal CH), 81.9, 71.7, 70.3, 70.1, 62.6, 53.9. MALDI-MS (*m*/*z*): *m*/*z* = 372.30 [M + Na]$^+$, calcd. for ($C_{18}H_{23}NO_6$): 372.14. Anal. Calcd. for $C_{18}H_{23}NO_6$: C, 61.88; H, 6.64. Found: C, 61.70; H, 6.70.

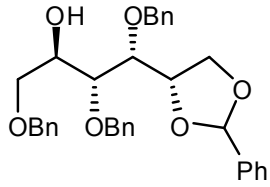


Ethyl 4,6-*O*-benzylidene-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (26).[29] Eluted with hexane/ethyl acetate from 7:3 to 6:4. Foam. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85-7.30 (aromatic H, 9 H), 5.59 (s, 1 H), 5.42 (H-1, d, *J* = 10.4 Hz, 1 H), 4.68 (t, *J* = 9.6 Hz, 1 H), 4.41 (H-6eq, dd, *J* = 4.8, 10.4 Hz, 1 H), 4.35 (t, *J* = 9.6 Hz, 1 H), 3.83 (t, *J* = 9.6 Hz, 1 H), 3.71 (H-5, m, 1 H), 3.62 (t, *J* = 9.6 Hz, 1 H), 2.71 (-SC*H*$_2$CH$_3$, m, 2 H), 1.22 (-SC*H*$_2$CH$_3$, t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.1 and 167.6 (-*C*O), 136.9, 134.0, 131.2, 128.2, 126.2, 123.6, 123.2 (aromatic signals); 101.7 (acetal CH), 81.9, 81.7, 70.2, 69.2, 68.4, 55.4, 24.0, and 14.7. MALDI-MS (*m*/*z*): *m*/*z* = 463.20 [M + Na]$^+$, calcd. for ($C_{23}H_{23}NO_6S$): 463.11. Anal. Calcd. for $C_{23}H_{23}NO_6S$: C, 62.57; H, 5.25. Found: C, 62.75; H, 5.10.

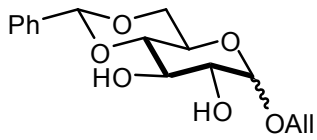


2,3-*O*-benzylidene-diisopropyl-D-tartrate (27).[30] Eluted with hexane/ethyl acetate from 95:5 to 85:15. Oil ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45-7.30 (aromatic H, 5H), 6.15 (-CHPh, s, 1 H), 5.14 (2 x isopropyl CH, hept, *J* = 6.0 Hz, 2 H), 4.85 and 4.75 (H-2 and H-3, 2 x d, J = 3.6 Hz, 2 H), 1.31 (2 x -CH$_3$, d, *J* = 6.0 Hz, 6 H), 1.28 (CH$_3$, d, *J* = 6.0 Hz, 3 H), 1.26 (CH$_3$, d, *J* = 6.0 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.1 and 168.4 (2 x –CO), 135.6 (aromatic C), 129.8, 128.2, 127.1 (aromatic CH), 106.6 (-*C*HPh), 77.6, 77.5, 69.7, 21.6 (x2),

21.5, 21.4. MALDI-MS (*m*/*z*): *m*/*z* = 345.30 $[M + Na]^+$, calc. for ($C_{17}H_{22}O_6$): 345.13. Anal. Calcd. for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 63.55; H, 6.75.



3,4,6-tri-*O*-benzyl-1,2-*O*-benzylidene-D-sorbitole (29). Eluted with hexane/ethyl acetate from 8:2 to 6:4. Foam. $[\alpha]_D^{23}$: -1.0 (*c* 1.8, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.48-7.29 (aromatic H, 20 H), 5.63 (s, 1 H), 4.90-4.33 (3 x $-CH_2Ph$, 3 x AB, *J* = 11.2 Hz, 6 H), 4.15 (d, *J* = 9.6 Hz, 1 H), 4.06 (bd, *J* = 8.0 Hz, 1 H), 4.00 (bd, *J* = 6.4 Hz, 1 H), 3.95 (d, *J* = 11.2 Hz, 1 H), 3.90-3.75 (ovelapped signals, 3 H), 3.58 (dd, *J* = 4.8, 11.2 Hz, 1 H), 1.90 (bs, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.2 (x3), 137.8 (aromatic C); 128.3-126.2 (aromatic CH); 100.9 (acetal CH), 80.5, 78.1, 76.0, 73.9, 73.3, 71.0, 69.9, 67.4, 62.5. MALDI-MS (*m*/*z*): *m*/*z* = 563.35 $[M + Na]^+$, calcd. for ($C_{34}H_{36}O_6$): 563.24. Anal. Calcd. for $C_{34}H_{36}O_6$: C, 75.53; H, 6.71. Found: C, 75.40; H, 6.75.



Allyl 4,6-*O*-benzylidene-α/β-D-glucopyranoside (30). Eluted with dichloromethane/methanol from 100:0 to 95:5. Foam ^1H NMR (400 MHz, $CDCl_3$): significant signals at δ = 7.60-7.30 (aromatic H), 6.00 (CH_2=C*H*CH_2-, m, 1 H), 5.52 (s, 1 H), 5.34 ($CH_{cis}H_{trans}$=C*H*CH_2-, bd, J = 17.2 Hz, 1 H), 5.17 (C$H_{cis}H_{trans}$=C*H*CH_2-, bd, J = 9.6 Hz, 1 H), 4.91 (H-1α, d, J = 3.6 Hz, 1 H), 4.43 (H-1β, d, J = 7.6 Hz, 1 H), 3.95 (t, J = 9.6 Hz, 1 H), 3.85 (m, 1 H), 3.75 (t, J = 9.6 Hz, 1 H), 3.72 (H-2α, dd, J = 3.6, 9.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): significant signals at δ = 137.1 (aromatic C),

133.2 (CH_2=*C*HCH_2-), 129.2, 128.3, 126.3 (aromatic signals); 118.2 (*C*H_2=CHCH_2-), 101.8, 97.9 (acetal CH), 80.9, 72.7, 71.4, 68.8, 62.5. MALDI-MS (*m*/*z*): *m*/*z* = 331.20 $[M + Na]^+$, calc. for ($C_{16}H_{20}O_6$): 331.12. Anal. Calcd. for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54. Found: C, 62.40; H, 6.50.

References

1) Wuts, P. G. M.; Greene, T.W. in *Greene's Protective Groups in Organic Synthesis,* 4th edition, John Wiley and Sons: New York, **2007**.

2) See References 6,7,8 in *Chapter 1*.

3) a) Kartha, K. P. R. *Tetrahedron Lett.* **1986**, *27*, 3415; b) Morimoto, Y.; Mikami, A.; Kuwabe, S.-L.; Shirahama, H. *Tetrahedron Lett.* **1991**, *32*, 2909; c) Mukhopahyay, B.; Russel, D. A.; Field, R. A. *Carbohydr. Res*. **2005**, *340*, 1075; d) Mukhopahyay, B. *Tetrahedron Lett.* **2006**, *47*, 4337; (e) Niu, Y.; Wang, N.; Cao, X.; Ye, X.-S. *Synlett* **2007**, 2116; f) Giri, S. K.; Verma, M.; Kartha, K. P. R. *J. Carb. Chem.* **2008**, *27*, 464; g) Basu, N.; Maity, S. K.; Roy, S.; Singha, S.; Ghosh, R. *Carbohydr. Res*. **2011**, *346*, 534; h) Tran, A.T.; Jones, R. A.; Pastor, J.; Boisson, J.; Smith, N.; Galan, M. C. *Adv. Synth. Cat.* **2011**, *353*, 2593.

4) For applications in one-pot acetalation/acetylation sequences: a) Mukherjee, D.; Ali Shah, B.; Gupta, P.; Taneja, S. C. *J. Org. Chem.* **2007***,* 72*,* 8965; b) Mong, K.-K.; Chao, C. S.; Chen, M.-C.; Lin, C.-W. *Synlett* **2009**, 603; c) Jones, R. A.; Davidson, R.; Tran, A. T.; Smith, N.; Galan, M. C. *Carbohydr. Res.* **2010**, *345*, 1842.

5) a) Khan, A. T.; Khan, M.; Adhikary, A. *Carbohydr. Res*. **2011**, *346*, 673; b) Geng, Y.; Faidallah, H. M.; Albar, H. A.; Mhkalid, I. A.; Schmidt, R. R. *Eur. J. Org. Chem.* **2013**, 7035; c) Tatina, M.; Yousuf, J. K.; Mukherjee, D. *Org. Biomol. Chem.* **2012**, *10*, 5357.

6) a) Liptak, A.; Borbas, A.; Janossy, L.; Szilagyi, L. *Tetrahedron Lett.* **2000**, *41*, 4849; b) Chen, C.-T.; Weng, S.-S.; Kao, J.-Q.; Lin, C.-C.; Jan, M.-D. *Org. Lett.* **2005**, *7*, 3343; c) Lin, C.-C.; Jan, M.-D.; Weng, S.-S.; Lin, C.-C.; Chen, C.-T. *Carbohydr. Res.* **2006**,

341, 1948; d) Giri, S. K.; Verma, M.; Kartha, K. P. R. *J. Carbohydr. Chem.* **2008**, 464.

7) References 137 and 138 in *Chapter 1.*

8) During the preparation of this manuscript, a paper appeared with the description of Knoevenagel condensations where the aldehyde activation was triggered by the combination of acetic anhydride with a Lewis acid: Ogiwara, T.; Takahashi, K.; Kitazawa, T.; Sakai, N. *J. Org. Chem.* **2015**, *80*, 3101.

9) The cheaper hydrated form of $Yb(OTf)_3$ was used in all reported examples in this paper.

10) For examples of alcohol acetylations promoted by metal triflates: a) Saravanan, P.; Singh, P. K.; *Tetrahedron Lett.* **1999**, *40*, 2611; b) Orita, A.; Tanahashi, C.; Kakuda, A.; Otera, J. *Angew. Chem. Int. Eng. Ed.* **2000**, *39*, 2877.

11) a) Gopinath, R.; Hakue, S. J.; Patel, B. K. *J. Org. Chem.* **2002**, *67*, 5842; b) Kotke, M.; Schreiner, P. R. *Tetrahedron* **2006**, *62*, 434.

12) For the generation of sugars orthoesters via transorthoesterification reactions: a) Bouchra, M.; Calinaud, P.; Gelas, J. *Carbohydr. Res.* **1995**, *267*, 227; b) Mukhopadhyay, B.; Field, R. A. *Carbohydr. Res.* **2003**, *338*, 2149. For other reactions of orthoester reactants with saccharide substrates, see: c) Mukherjee, D.; Yousuf, S. K.; Taneja, S. C. *Tetrahedron Lett.* **2008**, *49*, 4944.

13) a) David, S.; Hanessian, S. *Tetrahedron* **1985**, *41*, 643; b) Grindley, T. B. *Adv. Carbohydr. Chem. Biochem.* **1998**, *53*, 17; c) Xu, H.; Lu, Y.; Zhou, Y.; Ren, B.; Pei, Y.; Dong, H.; Pei, Z. *Adv. Synth. Catal.* **2014**, *356*, 1735.

14) For other examples of reports describing a high-yielding synthesis of **13** via a transacetalation process, see: a) Zhang, J.; Ragauskas, A. J. *Carbohydr. Res*. **2005**, *340*, 2812; b) Deng, S.;

Gangadharmath, U.; Tom Chang, C.-W. *J. Org. Chem.* **2006**, *71*, 5179; c) Mandal, P. K.; Misra, A. K. *Synthesis* **2007**, 2660; d) Panchadhayee, R.; Misra, A. K. *J. Carbohydr. Chem.* **2008**, *27*, 148.; e) Sadeghi-Khomami, A.; Forcada, T. J.; Wilson, C.; Sanders, D. A. R.; Thomas, N. R. *Org. Biomol. Chem.* **2010**, *8*, 1596.

15) Procopio, A.; Dalpozzo, R.; De Ninno, A.; Maiuolo, L.; Nardi, M.; Romeo, G. *Org. Biomol. Chem.* **2005**, *3*, 4129.

16) Cheuk, S.; Stevens, E. D.; Wang, G. *Carbohydr. Res.* **2009**, *344*, 41

17) Cox, D. J.; Singh, G. P.; Watson, A. J. A.; Fairbanks, A. *Eur. J. Org. Chem.* **2014**, 4624.

18) Maslinska-Solich, J.; Rudnicka, I. *Carbohydr. Res.* **1984**, *132*, 150.

19) Wang, G.; Lu, Z.; Ding, N.; Zhang, W.; Wang, P.; Li, Y. *Carbohydr. Res.* **2011**, *346*, 2368.

20) a) Evans, M. E. *Carbohydr. Res.* **1972**, *21*, 473; b) Becher, J.; Seidel, I.; Plass, W.; Klemm, D. *Tetrahedron* **2006**, *62*, 5675.

21) a) Chen, C.-T.; Weng, S. S.; Kao, J. Q.; Lin, C. C.; Jan, M. D. *Org. Lett.* **2005**, *7*, 3343; b) Wang, G.; Ella-Menye, J.-R.; Martin, M. S.; Yang, H.; Williams, K. *Org. Lett.* **2008**, *10*, 4203.

22) Dahlhoff, W. V.; Riehl, K.; Zugenmaier, P. *Liebigs Annalen der Chemie* **1993**, 1063.

23) van Steijn, A. M. P.; Kamerling, J. P.; Vliegenthart, J. F. G. *Carbohydr. Res.* **1992**, *225*, 229.

24) Roy, S.; Chakraborty, A.; Ghosh, R. *Carbohydr. Res.* **2008**, *343*, 2523.

25) Nashed, M. A.; Chowdhari, M. S.; Anderson, L. *Carbohydr. Res.* **1982**, *102*, 99.

26) Pornsuriyasak, P.; Yasomanee, J. P.; Balmond, E. I.; De Meo, C.; Demchenko, A. V. *Carbohydrate Chemistry: Proven Synthetic Methods* **2014**, *2*, 189.

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

28) Feng, F.; Okuyama, K.; Niikura, K.; Ohta, T.; Sadamoto, R.; Monde, K.; Noguchi, T.; Nishimura, S.-I. *Org. Biomol. Chem.* **2004** , *2*, 1617.

29) Minuth, T.; Irmak, M.; Groschner, A.; Lehnert, T.; Boysen, M. M. K. *Eur. J. Org. Chem.* **2009**, 997.

30) Sato, H.; Maeba, T.; Yanase, R.; Yamajy-Hasegawa, A.; Kobayashi, T.; Chida, N. *J. Antibiot.* **2005** , *58*, 37.

Chapter 3

Orthogonal Protection of Saccharide Polyols Through Solvent-Free One-Pot Sequences Based on Regioselective Silylations

Introduction

Application of an orthogonal set of protecting groups represents a typical issue in organic synthesis; as widely discussed in the previous chapter, this turns out to be especially challenging when highly functionalized molecules, such as carbohydrates, have to be manipulated since lengthy multistep procedures are often needed to this aim.[1,2] Silyl groups are widely applied in organic chemistry in orthogonal protection strategies owing to their stability to a broad range of conditions and feasible removal under conditions compatible with many other used carbinol protecting groups.[1-3] For this reason, silyl protecting groups are often serving as temporary protecting groups with polyol and saccharide substrates. The most robust and adopted silyl protecting groups are featuring the presence of hindered substituents at silicon such as in *tert*-butyldimethylsilyl (TBDMS) and *tert*-butyldiphenylsilyl (TBDPS) groups. Their bulkiness allows in many cases regioselective silyl protection of primary alcohols. Commonly, *O*-silylation is performed by exposing the carbinol to a suitably substituted silyl chloride in the presence of a base, a catalyst (often

coinciding with the base) and an aprotic solvent.[2-9] Use of more expensive silyl triflates is also reported, especially when poorly reactive alcohols have to be protected.[2, 10-13]

Regioselective silylation of polar saccharide polyols is typically performed with the appropriate silyl chloride in the presence of a high boiling solvent such as DMF or pyridine, often in the presence of a nucleophilic catalyst (more frequently imidazole and DMAP).[14-21] The protection generally takes several hours and the work-up is burdened by necessary removal of the high boiling solvent. A good regioselective control was also reported in an alternative silylation approach based on a dehydrogenative mechanism in which expensive trialkyl silanes were used as silylating agents.[22] Very recently, Vogel and coworkers reported an original strategy based on unusual silylating agents such as silyl methallylsulfinates; this approach proved very high-yielding under neutral conditions, but the preliminary synthesis of the requisite reagent relied on a non-trivial two-step procedure starting from the corresponding silyl chloride.[23]

Regioselective silylation of secondary saccharide carbinols can also be achieved either taking advantage of the inherent difference of reactivity among the hydroxyl functions [24-32] or exploiting the activation effect of boron complexes.[33]

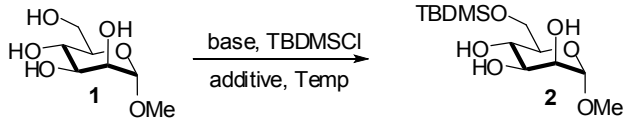
As for the solvent-free methodologies introduced in Chapter 2, the work herein discussed was also spurred by the general goal of developing new practical protocols for carbohydrates derivatization endowed with the experimental ease also characterizing our previously developed methods.[34] Reported here is the extension of the scope of the solvent-free strategies to the silylation reaction, and the feasible incorporation of this step into unprecedented one-pot, fully solvent-free

sequences yielding orthogonally protected saccharide building-blocks in short times under simple experimental conditions.

Results and Discussion

In preliminary experiments, methyl mannopyranoside **1** was selected as the model substrate and exposed to TBDMSCl in the presence of a slight or moderate excess of several bases (**Table 1**).

Table 1. Regioselective silylation of **1** under solvent-free conditions[a]



Entry	Base (eq.)	Additive (eq.)	Temperature, Time	Isolated yield
1	DIPEA (5)	-	50 °C, 5 h	< 15
2	DIPEA (5)	TBAB (0.3)	50 °C, 5.5 h	49
3	DIPEA (5)	TBAB (0.3), Bu_2SnO (0.1)	50 °C, 5.5 h	52
4	DIPEA (5)	TBAI (0.3), Bu_2SnO (0.1)	50 °C, 5.5 h	48
5	TEA (5)	TBAB (0.3)	50 °C, 5.5 h	53
6	Pyridine (5)	TBAB (0.3)	50 °C, 1 h	89
7	Pyridine (2.5)	TBAB (0.3)	rt, 1 h	80
8	Pyridine (2.2)	TBAB (0.1)	rt, 1.5 h	84
9	Pyridine (2.2)	-	rt, 1.5 h	70

[a)]General conditions: substrate, base, additive, TBDMSCl (1.2 eq for entries 1-6, 1.1 eq for entries 7-9).

In all cases 6-*O*-silylated derivative **2** was obtained as the main product, but yields and rates were strongly dependent on the adopted base; pyridine (**Table 1**, entries 6-9) gave much better results than tertiary amines (**Table 1**, entries 1-5) that, on the other hand, had previously performed better than pyridine in the tin-catalyzed solvent-free regioselective benzylation or allylation of sugars.[34a]

The silylation rate was not appreciably influenced by tin catalysis (compare entries 2 and 3 in **Table 1**), although a previous report described the stoichiometric use of stannylene acetals in the regioselective silylation of saccharide primary alcohols.[35] At this stage, it should be noted that pyridine is frequently employed as the solvent for silylations, but the conditions herein described can be referred to as "solvent-free" because of the very limited amount of pyridine used, that is by far not sufficient for dissolution of the polar polyol substrates. Interestingly, reactions with pyridine were found to give slightly improved yields (within comparable times) on using a catalytic amount of TBAB (compare in **Table 1** entries 7-9 with entry 10), which may be accounted for by a possible role of bromide ion in the activation of the silylating agent as also suggested by literature.[36]

Taking into account several parameters such as the used amount of pyridine and TBAB, the reaction yield and its length, conditions of entry 8 were elected as the optimized conditions; notably, the conversion of **1** to **2** under these conditions took a much shorter time than previously reported by using the same silylating agent.[14, 15, 18]

With optimized conditions in hand, the TBDMS regioselective installation was tested on a range of saccharide building-blocks, and good yields were achieved in short times with several polyols (**Table 2**, entries 1-3, 5 and 8).

Table 2. Regioselective silylation of saccharide primary carbinols under solvent-free conditions[a]

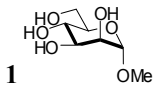
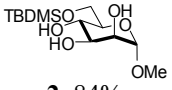
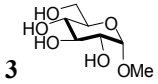
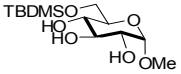
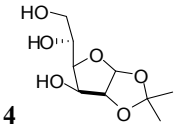
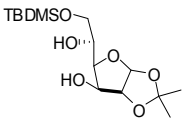
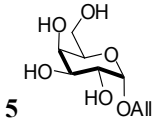
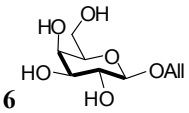
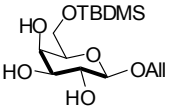
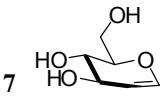
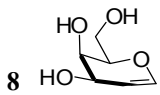
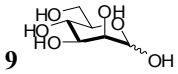
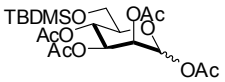
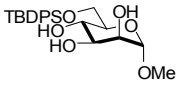
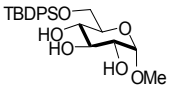
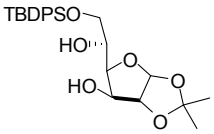
Entry	Substrate	Pyridine/silylating agent/TBAB (eq.)[b]	Time (h)	Product, yield
1	 **1**	pyridine/TBDMSCl/ TBAB (2.2:1.1: 0.1)	1.5	 **2**, 84%
2	 **3**	pyridine/TBDMSCl/ TBAB (2.2:1.1: 0.1)	1.5	 **10**, 83%
3	 **4**	pyridine/TBDMSCl/ TBAB (2.2:1.1: 0.1)	1.5	 **11**, 86%
4	 **5**	pyridine/TBDMSCl/ TBAB (2.2:1.1: 0.1)	1.5	low conversion
5	 **6**	pyridine/TBDMSCl/ TBAB (3.0:2.0: 0.1)	2.5	 **12**, 82%
6	 **7**	pyridine/TBDMSCl/ TBAB (2.2:1.1: 0.1)	1.5	complex mixture
7	 **8**	pyridine/TBDMSCl/ TBAB (2.2:1.1: 0.1)	1.5	complex mixture

Table 2. (Continued)

Entry	Substrate	Pyridine/silylating agent/TBAB (eq.)[b]	Time (h)	Product, yield
8[c]	**9** 	pyridine/TBDMSCl /TBAB (2.2:1.1: 0.1)	2	 **13**, 73% (α/β 1:2)
9	**1**	pyridine/TBDPSCl/ TBAB (2.2:1.1: 0.2)	3	 **14**, 68%
10	**1**	pyridine/TBDPSCl/ TBAB (3.0:1.1: 0.2)	3	**14**, 92%
11	**3**	pyridine/TBDPSCl/ TBAB (3.0:1.1: 0.2)	3	 **15**, 84%
12	**4**	pyridine/TBDPSCl/ TBAB (3.0:1.1: 0.2)	2	 **16**, 98%
13	**7**	pyridine/TBDPSCl/ TBAB (3.0:1.1: 0.2)	5	very sluggish

[a)]General conditions: polyol substrate, pyridine, silylating agent (TBDMSCl or TBDPSCl) and TBAB at rt. See pertinent entries for stoichiometric ratios. [b)]With respect to the polyol substrate. [c)]The crude silylation mixture was acetylated in situ (direct addition of pyridine and acetic anhydride), prior to the purification of the product.

Interestingly, *galacto*-configured substrates exhibited a peculiar reactivity with the reaction outcome depending on their anomeric configuration; in accordance with yields obtained by Lee and Taylor with similar substrates under standard conditions,[14] only β-allylgalactoside **6** was silylated in a good yield (entry 5), whereas the corresponding α-anomer was almost quantitatively recovered (entry 4). As will be shown below, partial protection of allyl α-galactoside *in itinere* can render this substrate much more reactive towards these silylation conditions. High yielding silylation of β-allylgalactoside **6** required the employment of a higher stoichiometric excess of both pyridine and TBDMSCl (entry 5), exhibiting an extent of conversion apparently ruled by an equilibrium-like control.

Among the screened polyols in **Table 2**, glycals **7** and **8** were the only substrates to exhibit a lower regioselectivity, the silylation occurring at comparable rates at the primary (*O*-6) and the allylic (*O*-3) position, to provide a mixture of products (**Table 2**, entries 6 and 7). A similar competitive reactivity was very recently described also with the above mentioned method based on silyl methallylsulfinates.[23] On the other hand, the method herein proposed was found compatible with a reducing sugar such as D-mannose, which was converted in a good yield into the corresponding 6-*O*-silylated product **13**, isolated after *in situ* peracetylation (entry 8).

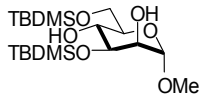
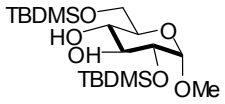
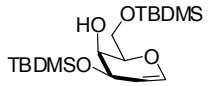
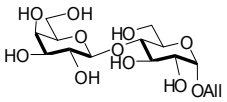
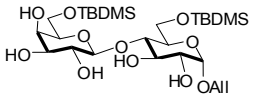
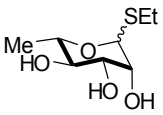
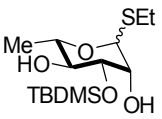
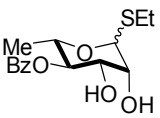
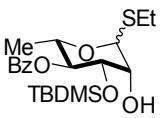
The scope of the TBAB-catalyzed silyl protection under solvent-free conditions was next examined for the regioselective attachment of TBDPS (**Table 2**, entries 9-13), a commonly used silyl protecting group bulkier than TBDMS and more resistant to acidic conditions. Optimization on mannoside **1** indicated that in this case a moderate increase of the pyridine excess (3.0 instead of 2.2 equivalents) is beneficial for the achievement of a higher yield while maintaining the

use of a minimal excess of the silylating agent (**Table 2**, entries 9 and 10); as with TBDMS protection of **6** (entry 5), in this case a sort of steady state was observed when adopting less than three equivalents of pyridine, with coexistence of the reagent and the product.

TBDPS selective protection of polyols **3** and **4** proceeded in high yields (entries 11 and 12), and expectedly the reactions took slightly longer times than for TBDMS protection. The only disappointing result observed in attempted TPDPS protections was the poor yield recorded with glucal **7** (entry 13), a surprising outcome which is somehow consistent with the very slow rate observed for the same reaction under standard conditions.[37,38] As already observed for the synthesis of **2**, the herein described conditions for regioselective TBDMS and TBDPS protections entail shorter reaction times than most of the reported protocols in the literature on monosaccharide polyols;[14-18, 20, 39-51] comparable silylation rates were indeed be found in a few examples, often involving relatively less polar thioaryl glycosides as the substrates and DMF as the solvent.[19, 52-57]

Having established the scope of TBAB-catalyzed mono-silylations with a minimal excess of pyridine, some effort was devoted to ascertain the feasible exploitation of a similar strategy to either regioselective di-*O*-silylations or the protection of secondary carbinols in absence of primary ones (**Table 3**). As a matter of fact, upon doubling the stoichiometric amount of TBAB, pyridine and TBDMSCl, the regioselective synthesis of di-*O*-TBDMS derivatives was achieved at 50 °C in satisfying yields from glycosides **1** and **3** (**Table 3**, entries 1-2), and glycal **8** (entry 3).

Table 3. Solvent-free regioselective silylations committing secondary alcohols[a]

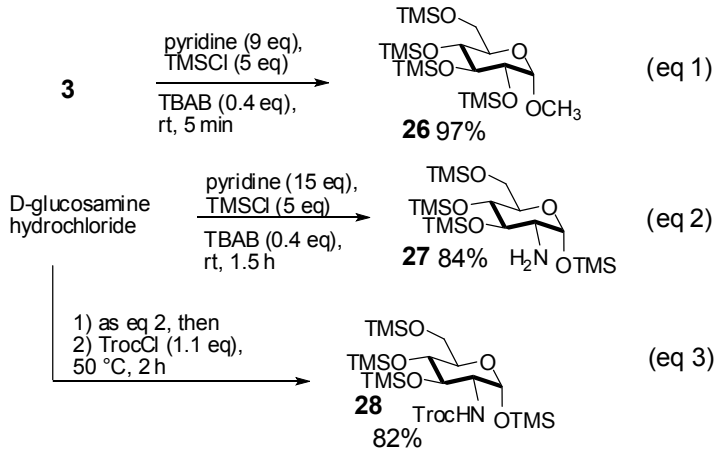
Entry	Substrate	Time (h)	Product, isolated yield
1	**1**	4	 **17**, 72%
2	**3**	4.5	 **18**, 60%
3	**8**	5	 **19**, 56%
4	 **20**	1	 **21**,56%
5	 **22**(α:β ca 2.5)	6	 **23**(α:β ca 4), 75 %
6	 **24**(α:β ca 2.5)	6	 **25**(α:β ca 4), 50% (95 %)[b]

[a)]General conditions (entries 1-3): pyridine (5 eq.), TBDMSCl (2.5 eq.), TBAB (0.3 eq.), 50°C. For entry 4: pyridine (6 eq.), TBDMSCl (3.5 eq.), TBAB (0.3 eq.), rt. For entries 5 and 6: pyridine (3 eq.), TBDMSCl (1.5 eq.), TBAB (0.15 eq.), 50°C. [b)]In parenthesis is indicated the conversion yield.

Double silylation at primary positions of the disaccharide lactoside **20**[58] also proved feasible at room temperature within short times (entry 4). Model substrates devoid of a primary carbinol were also examined; thioethyl rhamnoside **22** (as an anomeric mixture) was 3-*O*-silylated in a good yield, and the anomeric composition of the products revealed the higher reactivity of the α-anomer (entry 5). The same regioselectivity was also found starting from the corresponding 4-*O*-benzoylated precursor **24**[59] (entry 6) and a satisfying yield and an excellent conversion were observed in spite of the increased hindrance and deactivation of the *O*-3 hydroxyl carbinol due to the adjacent electron withdrawing benzoyl group. As already described above in **Table 1** for mono-silylations, tin catalysis did not affect the double silylation processes as evidenced by the reaction of entry 1 that in the presence of 0.1 eq of Bu_2SnO gave **17** in the same yield within the same time. Not unexpectedly, secondary carbinols exhibited a recalcitrant reactivity towards TBDPSCl under these solvent-free conditions, and the di-*O*-silylation process resulted of limited synthetic usefulness (data not shown).

The scope of the solvent-free conditions was further examined in the synthesis of per-*O*-trimethylsilylated derivatives (**Scheme 1**), widely used precursors in one-pot strategies for orthogonal protection of carbohydrates.[60-65] Application of the TBAB catalyzed protocol on glucoside **3** gave product **26** in high yield within a few minutes (**Scheme 1**, eq 1). The method proved also applicable to glucosamine hydrochloride, although in this case a higher excess of pyridine was needed for the conversion to occur (**Scheme 1**, eq 2). Consistent with previous literature reports,[66-70] silylation left unaltered the amino functionality which could be protected *in situ* with a Troc group

without isolation of **27,**[67] as shown in the one-pot, two-step sequence in eq. 3.



Scheme 1 Multiple O-trimethylsilylations of saccharide compounds

Owing to the importance of the one-pot functional diversification of carbohydrates in modern organic synthesis,[60-65, 71-74] the scope of the solvent-free silylation approaches herein introduced was next extended to the development of fully solvent-free one-pot sequences leading to the sequential alkylation/silylation of saccharide polyols with high regiocontrol. For this purpose, combination of the present protocol for silylation of primary alcohols with the tin-catalyzed procedure for benzylation/allylation of saccharide secondary carbinols,[75] previously reported in our laboratory, was explored.

Some experiments were carried out on methyl mannoside **1** in order to establish which order of steps (alkylation/silylation or the reverse sequence) might be higher yielding. Initial experiments indicated that the silylation step was not apparently effective when performed after the tin-catalyzed 3-*O*-benzylation of mannoside **1** (**Table 4**, entry 1). A

competitive reaction of residual benzyl bromide from the first step with pyridine may account for this result; indeed, on repeating the experiment suitably increasing the amount of pyridine in the second step (from 2.2 to 5 equivalents), desired product **29** was obtained in a satisfying 61% yield within a few hours (**Table 4**, entry 2). It should be outlined that this result is especially relevant taking into account that the solvent-free 3-*O*-benzylation alone (the first step of the sequence) occurs in a comparable yield under tin catalysis[34a]. The reverse protection sequence (6-*O*-silylation/3-*O*-benzylation) was found to be less effective in terms of yields, apparently because of the partial loss of the TBDMS group in the second step where relatively forced thermal conditions are needed (entry 3). This latter one-pot sequence was instead much more rewarding when more robust TBDPS group was installed first (entries 5-6). Interestingly, this latter group was satisfyingly stable under the especially forced conditions (a reaction temperature of 90 °C) required to carry out the tin-mediated 2-*O*-benzylation of a *gluco*-substrate (entry 6). In addition, TBDPS installation also proceeded in satisfying yields after a preliminary allylation (entry 4) or benzylation step (entry 8).

In the case of glycal **8**, the application of a benzylation/silylation sequence resulted in very good yields with both silylating agents (**Table 4**, entries 7 and 8), although the 6-*O*-silylation alone had been low yielding in the initial set of experiments (**Table 2**, entries 6, 7 and 13). Comparison of these data seems to indicate that the silylation step is much more effective on less polar, partially protected polyols. As a further evidence of this trend, the 3-*O*-benzylation/6-*O*-silylation sequence was succesfully applied to access α-galactoside **35** (entry 9), although, as shown earlier in **Table 2** (entry 4), direct silylation of the same precursor was quite unfruitful.

Table 4. One-pot regioselective protection of sugar polyols with silyl and alkyl groups[a]

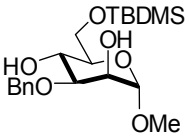
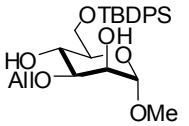
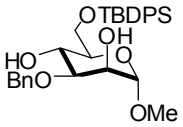
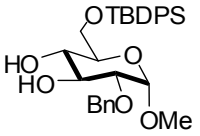
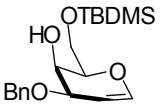
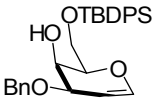
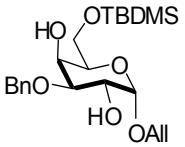
Entry	Substrate	First step conditions (eq.)	Second step conditions (eq.)	Product, isolated yield
1	**1**	DIPEA (2.5), Bu_2SnO (0.1), TBAB (0.3), BnBr (4), 70 °C, 3.5 h	pyridine (2.2), TBDMSCl (2.0), rt, 3 h	low silylation yields
2	**1**	DIPEA (2.5), Bu_2SnO (0.1), TBAB (0.3), BnBr (4), 70 °C, 3.5 h	Pyridine(5.0), TBDMSCl (2.0), rt, 3 h	 **29**, 61%
3	**1**	pyridine (2.2), TBDMSCl (1.1), TBAB (0.3), rt, 1.5 h	DIPEA (3.5), Bu_2SnO (0.1), BnBr (5.5), 70 °C, 4.5 h	**29**, 39%
4	**1**	DIPEA (4), Bu_2SnO (0.1), TBAB (0.3), AllBr (8), 90 °C, 3.5 h	pyridine (5.0), TBDPSCl (1.5), rt, 3.5 h	 **30**, 59%
5	**1**	pyridine (3.0), TBDPSCl (1.1), TBAB (0.3), rt, 3 h	DIPEA (2.5), Bu_2SnO (0.1), BnBr (6), 80 °C, 4 h	 **31**, 62 %

Table 4. (Continued)

Entry	Substrate	First step conditions (eq.)	Second step conditions (eq.)	Product, Isolated yield
6	**3**	pyridine (3.0), TBDPSCl (1.1), TBAB (0.3), rt, 3 h	DIPEA (2.5), Bu_2SnO (0.2), BnBr (7), 90°C, 4h	 **32**, 42%
7	**8**	DIPEA (2.5), Bu_2SnO (0.1), BnBr (2), TBAB (0.3eq) 70 °C, 2.5 h	pyridine (3.5), TBDMSCl (2.0), TBAB (0.3), rt, 1 h	 **33**, 69%
8	**8**	DIPEA (2.5), Bu_2SnO (0.1), BnBr (2), TBAB (0.3), 70 °C, 2.5 h	pyridine (3.5), TBDPSCl (1.5), rt, 2.5 h	 **34**, 75%
9	**5**	DIPEA (2.5), Bu_2SnO (0.1), BnBr (4), TBAB (0.3), 70 °C, 2 h	pyridine (6), TBDMSCl (2), rt, 1.5 h	 **35**, 57%

[a)]General conditions: upon completion of the first step (see times in pertinent entries), the temperature was modified according to conditions of the second step, and the requisite reagents added.

Conclusions

In the first part of this chapter is introduced a very simple approach to carry out the selective TBDMS or TBDPS protection of carbohydrate polyols taking advantage of reactions performed in the presence of a very limited amount of pyridine (3 equivalents or less for carbinol to be protected). The method can indeed be regarded as a solvent-free

approach because of the limited stoichiometric amount of the base that is not sufficient to dissolve the highly polar saccharide substrates. Under these conditions, a catalytic role played by TBAB was also evidenced. Besides the limited amount of the used base, the proposed method is endowed with further practical advantages such as the experimental ease (all reaction herein reported were conducted in air by simply mixing the reagents), and high reaction rates, often comparing favourably with literature examples, in spite of the poor solubility of the starting substrates in the reaction medium. Extension of the scope of the silylation method to secondary carbinols and to the per-*O*-trimethylsilylation of saccharides is also demonstrated.

In the second part of this chapter is shown that combination of the silylation approach here introduced with a previously developed tin-catalyzed methodology for regioselective alkylation of carbohydrates can be addressed to unprecedented one-pot and fully solvent-free synthetic sequences; indeed, it is herein demonstrated that the merging of both methods provides a straightforward and experimentally simple access to saccharide building-blocks orthogonally protected with a silyl at the primary position and a benzyl (or an allyl) group at well defined and predicatable secondary positions.

Experimental Section

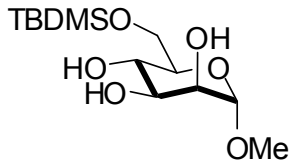
Typical procedure for theregioselective mono-O-silylation: To a mixture of the polyol substrate (0.5 – 1 mmol), TBAB and the silylating agent, pyridine was added under air (see Tables 1 and 2 for stoichiometric proportions). The mixture was kept under stirring at room temperature until consumption of the starting material as revealed by TLC analysis (1.5 – 3 hours). The mixture was concentrated under

vacuum and then submitted to silica-gel flash cromatography (eluents: ethyl acetate or ethyl acetate/hexane mixtures) to afford the mono-*O*-silylated products in the yields indicated in Tables 1 and 2.

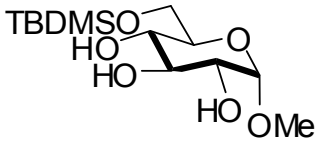
Regioselective double silylation of monosaccharide polyols or silylation of secondary carbinols: To a mixture of the polyol substrate (0.5 – 1 mmol), TBAB and the silylating agent, pyridine was added under air (see Table 3 for stoichiometric proportions). The mixture was kept under stirring at 50°C. Upon completion of the reaction (1 – 6 hours), the mixture was concentrated under vacuum and then submitted to silica-gel flash cromatography (eluents: hexane/ethyl acetate mixtures) to afford the di-*O*-silylated products in the yields indicated in Table 3. The regiochemistry of the double silylation was determined by acetylation of the isolated products (2:1v/v pyridine/acetic anhydride, overnight, rt) and subsequent NMR analysis.

One-pot synthesis of orthogonally protected building-blocks (silylation-alkylation sequence): Upon completion of the mono-O-silylation step (see above for the procedure), to the mixture were sequentially added under air DIPEA, benzyl bromide,and Bu_2SnO,and the vessel placed on an oil bath at the suitable temperature (see Table 4 for stoichiometric proportions and the temperature of the second step). The mixture was kept under stirring until TLC analysis indicated optimal conversion. The flask was cooled to rt and the mixture was diluted with DCM. The organic phase was washed with aqueous NaOH and the aqueous phase re-extracted with DCM. Combined organic phases were dried with anhydrous sodium sulfate and concentrated under vacuum. Flash chromatography (eluents:hexane/ethyl acetate mixtures) provided pure products in the yields indicated in Table 4.

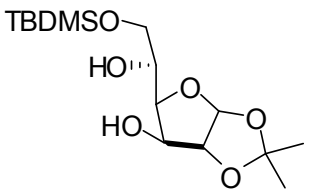
One-pot synthesis of orthogonally protected building-blocks (alkylation-silylation sequence): To a mixture of the substrate (0.5 – 1mmol), Bu_2SnO and TBAB, were sequentially added under air DIPEA and benzyl (or allyl) bromide (see Table 4 for stoichiometric proportions). The mixture was kept under stirring at 70°C (or 90°C for regioselective allylation) until TLC analysis indicated optimal conversion. The flask was cooled to rt and then pyridine and the silylating agent were sequentially added. On completion of the reaction, the mixture was diluted with DCM. The organic phase was washed with aqueous NaOH and the aqueous phase was re-extracted with DCM. Combined organic phases were dried with anhydrous sodium sulfate and concentrated under vacuum. Flash chromatography (eluents:hexane/ethyl acetate mixtures) provided pure products in the yields indicated in Table 4.



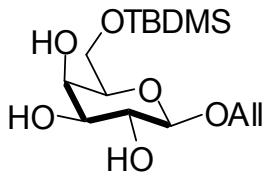
Methyl 6-*O*-*tert*-butyldimethylsilyl-α-D-manno-pyranoside (2).[14,15] ^{1}H NMR (400 MHz, $CDCl_3$):δ = 4.67 (s, 1 H, 1-H), 4.25 (bs, exchangeable, 1H), 4.02(bs, exchangeable, 1H), 3.90-3.80 (overlapped signals, 3 H), 3.76 (bdd, *J* = 2.8 and 9.6 Hz, 1H, 3-H), 3.69 (t, *J* = 9.6 Hz, 1H, 4-H), 3.53 (m, 1H, 5-H), 3.34 (s, 3H, -OCH_3), 0.89 (s, 9H, *t*-butyl protons), 0.09 (s, 6H, -$Si(CH_3)_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ = 100.7, 71.7, 71.4, 69.5, 64.3, 54.7, 25.8, 18.2, - 5.46 ppm. Anal. Calcd. for $C_{13}H_{28}O_6Si$: C, 50.62; H, 9.15. Found: C, 50.75; H, 9.10.MALDI-MS $[M + Na]^+$ calcd. for ($C_{13}H_{28}O_6Si$)331.16, found 331.30.



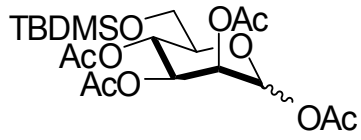
Methyl 6-*O*-*tert*-butyldimethylsilyl-α-D-gluco-pyranoside (10).[4a] ^{1}H NMR (400 MHz, $CDCl_3$):δ = 5.32 (bs, exchangeable, 1H), 4.69 (d, *J* = 3.6 Hz, 1 H, 1-H),4.61 (bs, exchangeable, 1 H), 4.55 (bs, exchangeable, 1 H), 3.87 (bd, *J* = 10.2 Hz, 1 H, 6a-H), 3.75 (dd, *J* = 5.6 and 10.2 Hz, 1 H, 6b-H), 3.71 (t, *J* = 9.6 Hz, 1 H, 3-H), 3.55-3.45 (overlapped signals, 2H), 3.37 (s, 3 H, -OCH_3), 3.49 (t, *J* = 9.6 Hz, 1 H, 4-H), 0.88 (s, 9 H, *t*-butyl protons), 0.06 (s, 6 H, -$Si(CH_3)_2$) ppm.^{13}C NMR (100 MHz, $CDCl_3$):δ = 99.3, 74.1, 71.9, 71.7, 70.8, 63.3, 54.9, 25.9, 18.3, -5.3 ppm.Anal. Calcd. for $C_{13}H_{28}O_6Si$: C, 50.62; H, 9.15. Found: C, 50.55; H, 9.15.MALDI-MS $[M + Na]^+$ calcd. for ($C_{13}H_{28}O_6Si$) 331.16, found 331.05.



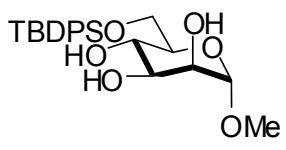
1,2-*O*-isopropylidene-6-*O*-*tert*-butyldimethylsilyl-α-D-gluco-furanose (11).[56] ^{1}H NMR (400 MHz, $CDCl_3$):δ = 5.90 (d, *J* = 3.2 Hz, 1 H, 1-H),4.49 (d, *J* = 3.2 Hz, 1H, 2-H), 4.30 (d, *J* = 2.0Hz, 1H, 3-H), 4.04 (dd, *J* = 2.0 and 6.8 Hz, 1H, 4-H), 3.97 (m, 1 H, 5-H), 3.82 (dd, *J* = 3.6 and 10.0 Hz, 1 H, 6a-H), 3.71 (dd, *J* = 4.8 and 10.0 Hz, 1 H, 6b-H), 3.19 (bs, exchangeable), 1.49 and 1.32 (2 x s, 6H, isopropylidene methyls), 1.09 (s, 9H, t-butyl protons), 0.06 (s, 6 H, -$Si(CH_3)_2$) ppm.^{13}C NMR (100 MHz, $CDCl_3$):δ = 135.5, 132.7, 129.9, 127.9, 111.6, 104.9, 85.1, 79.3, 75.5, 70.3, 64.9, 26.8, 26.2, 19.2, -5.5 ppm. Anal. Calcd. for $C_{15}H_{30}O_6Si$: C, 53.86; H, 9.04. Found: C, 53.80; H, 9.15. MALDI-MS $[M + Na]^+$ calcd. for ($C_{15}H_{30}O_6Si$)357.40, found 357.30.



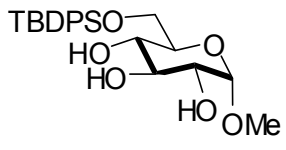
Allyl 6-*O-tert*-butyldimethylsilyl-β-D-galacto-pyranoside (12).[57] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.00-5.90 (m, 1 H, -C*H*=CH_2), 5.28 (bd, *J* = 17.2 Hz, 1 H, -C*H*=C$H_a$$H_b$), 5.17 (bd, *J* = 10.4 Hz, 1 H, -C*H*=$CH_a$$H_b$), 4.34 (dd, *J* = 5.2 and 12.4 Hz, 1 H, 6a-H), 4.24 (d, *J* = 7.6 Hz, 1 H, 1-H), 4.11 (dd, *J* = 6.4and 12.4 Hz , 1 H, 6b-H), 3.94 (bs, 1 H, 4-H), 3.80-3.60 (m, 2 H, -CH_2CH=CH_2), 3.70 (bt, *J* = 8.8 Hz, 1 H, 2-H), 3.56 (m, 1 H, 3-H), 3.43 (m, 1 H, 5-H), 0.87 (s, 9 H, t-butyl protons), 0.06(s, 6 H, -Si(CH_3)$_2$) ppm.^{13}C NMR (100 MHz, $CDCl_3$):δ = 134.0, 117.9, 101.9, 75.0, 73.7, 71.2, 70.0, 68.7, 62.2, 25.8, 18.2, - 5.4 ppm.Anal. Calcd. for $C_{15}H_{30}O_6Si$: C, 53.86; H, 9.04. Found: C, 53.70; H, 9.10. MALDI-MS $[M + Na]^+$ calcd. for ($C_{15}H_{30}O_6Si$) 357.40, found 357.50.



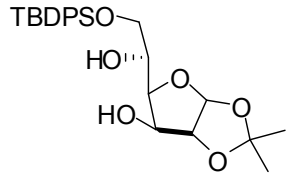
6-*O-tert*-butyldimethylsilyl-1,2,3,4-tetra-*O*-acetyl-α/β-D-manno-pyranose (13).(α/β 1:2.1): ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.03 (d, *J* = 1.6 Hz , 1 H, 1-H α), 5.80 (bs, 1 H, 1-Hβ), 5.40 (d, *J* = 2.4 Hz, 1 H, 2-H β), 5.35 (t, *J* = 9.6 Hz , 1 H, 4-H α), 5.29 (dd, *J* = 1.6 and 2.4 Hz, 1H, 2-H α), 5.28 (t, *J* = 10.0 Hz, 1 H, 4-H β), 5.18 (dd, *J* = 2.4 and 10.0 Hz, 1 H, 3-H β), 3.72 (m, 1 H, 5-H α), 3.80-3-65 (m, 4 H), 3.57 (m, 1 H, 5-Hβ); 2.13, 2.10, 2.04, 1.99 (x3), 1.96 (x2) (5 x s, 24 H, acetyl methyls), 0.85 (s, 18 H, *t*-butyl protons), 0.01 and – 0.01 (2 x s, 12 H, 2 x -Si(CH_3)$_2$) ppm.^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.4, 169.8, 169.3, 168.3, 90.5, 90.2, 75.7, 73.2, 70.9, 69.0, 68.4, 68.3, 65.8, 65.7, 62.1, 61.8, 25.6, 20.6, - 5.5ppm. Anal. Calcd. for $C_{20}H_{34}O_{10}Si$: C, 51.93; H, 7.41. Found: C, 51.80; H, 7.45. MALDI-MS $[M + Na]^+$ calc. for ($C_{20}H_{34}O_{10}Si$) 485.18, found 485.45.



Methyl 6-*O-tert*-butyldiphenylsilyl-α-D-manno-pyranoside (14).[76] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80-7.30 (aromatic H), 4.65 (s, 1 H, 1-H), 3.93 (dd, *J* = 2.8 and 8.8 Hz, 1 H, 3-H), 3.90-3.80 (overlapped signals, 2H), 3.80-3.70 (overlapped signals, 2 H), 3.61 (m, 1 H), 3.29 (s, 3H, OCH_3), 1.05 (s, 6 H, -Si$(CH_3)_2$) ppm.^{13}C NMR (100 MHz, $CDCl_3$):δ = 135.7, 132.9, 129.9, 127.6, 100.6, 71.7, 71.1, 70.3, 69.8, 65.0, 54.7, 26.7, 19.1ppm. Anal. Calcd. for $C_{23}H_{32}O_6Si$: C, 63.86; H, 7.46. Found: C, 63.95; H, 7.45. MALDI-MS $[M + Na]^+$ calcd. for ($C_{23}H_{32}O_6Si$) 455.19, found 455.05.

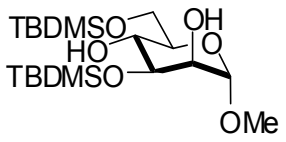


Methyl 6-*O-tert*-butyldiphenylsilyl-α-D-gluco-pyranoside (15).[19] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80-7.30 (aromatic H), 4.80 (bs, exchangeable, 1H), 4.70 (d, *J* = 3.6 Hz, 1 H, 1-H), 4.00-3.85 (overlapped signals, 2 H), 3.82 (dd, *J* = 5.4 and 10.8 Hz, 1 H, 6b-H), 3.76 (t, *J* = 9.2 Hz, 1H, 3-H), 3.64 (m, 1 H, 5-H), 3.55-3.43 (overlapped signals, 2 H), 3.34 (s, 3 H), 1.04 (s, 9 H, -Si$(CH_3)_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$):δ = 135.7, 133.2, 129.6, 127.7, 99.1, 74.3, 72.0, 71.5, 71.1, 64.0, 54.8, 26.8, 19.1 ppm. Anal. Calcd. for $C_{23}H_{32}O_6Si$: C, 63.86; H, 7.46. Found: C, 63.75; H, 7.50. MALDI-MS $[M + Na]^+$ calcd. for ($C_{23}H_{32}O_6Si$) 455.19, found 455.40.

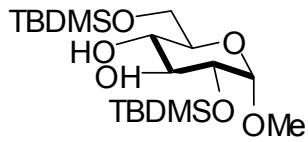


1,2-*O*-isopropylidene-6-*O-tert*-butyldiphenylsilyl-α-D-gluco-furanose (16).[77] ^{1}H NMR (400 MHz, $CDCl_3$):δ = 7.80-7.30 (aromatic H), 5.96 (d, *J* = 3.2 Hz, 1 H, 1-H), 4.54 (d,*J* = 3.2 Hz, 1H, 2-H),4.40 (d, *J* = 1.6Hz, 1 H, 3-H), 4.21 (dd,

J = 1.6 and 6.4 Hz, 1 H, 4-H), 4.12 (m, 1 H, 5-H), 3.91 (dd, *J* = 4.0 and 10.4 Hz, 1H, 6-Ha), 3.85 (dd, *J* = 5.2 and 10.0 Hz, 1 H, 6-Hb), 1.44 and 1.28 (2 x s, 6 H), 0.89 (s, 9 H), 0.06 (s, 6H, -Si(CH_3)$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 111.4, 104.8, 84.5, 79.4, 75.3, 69.9, 64.0, 26.6, 26.0, 25.7, 18.1, -5.6 ppm. Anal. Calcd. for $C_{25}H_{34}O_6Si$: C, 65.47; H, 7.47. Found: C, 65.67; H, 7.35. MALDI-MS [M + Na]$^+$ calcd. for ($C_{25}H_{34}O_6Si$) 481.20, found 481.30.

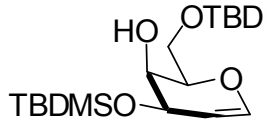


Methyl 3,6-di-*O-tert*-butyldimethylsilyl-α-D-manno-pyranoside (17).[22] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.71 (s, 1 H, 1-H), 3.86 (d, *J* = 5.6 Hz, 2 H, 6-H_2), 3.83 (dd, *J* = 3.6 and 9.2 Hz, 1 H, 3-H), 3.74 (bd, *J* = 2.0 Hz, 1 H, 2-H), 3.70 (t, *J* = 9.2 Hz, 1 H, 4-H), 3.55 (m, 1H, 5-H), 3.36 (s, 3 H, 1-OCH_3), 2.70 (bs, exchangeable, 1 H), 2.57 (bs,exchangeable, 1 H), 0.91 and 0.90 (2 x s, 18 H, *t*-butyl protons); 0.15, 0.13, 0.09 (x2) (3 x s, 18H, 2 x -Si(CH_3)$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 100.0, 72.9, 71.0, 70.4, 64.9, 54.8, 25.8, 25.7, -4.5, -4.9, -5.5 (x2) ppm. Anal. Calcd. for $C_{19}H_{42}O_6Si_2$: C, 53.99; H, 10.01. Found: C, 53.80; H, 9.95. MALDI-MS [M + Na]$^+$ calcd. for ($C_{19}H_{42}O_6Si_2$) 445.24, found 445.45.

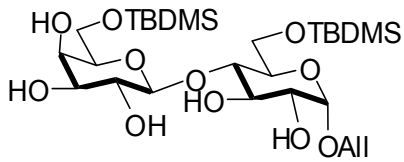


Methyl 2,6-di-*O-tert*-butyldimethylsilyl-α-D-gluco-pyranoside (18).[78] ^{1}H NMR (400 MHz, $CDCl_3$):δ = 4.60 (d, *J* = 3.2 Hz, 1 H, 1-H), 3.85-3.82 (overlapped signals, 2 H), 3.80 (t, *J* = 9.2 Hz, 1 H, 3-H), 3.60 (m, 1 H, 5-H), 3.54 (dd, *J* = 3.2 and 9.2 Hz, 1 H, H-2), 3.51 (t, *J* = 9.2 Hz, 1 H, H-4), 3.38 (s, 3 H), 0.90 (s, 18 H), 0.14, 0.11, 0.10 (x2) (3

x s, 12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$):δ = 99.8, 73.9, 73.7, 71.8, 71.0, 70.6, 64.0, 55.2, 25.6, 25.4, 18.3, 18.1, -4.6, -5.4 ppm. Anal. Calcd. for $C_{19}H_{42}O_6Si_2$: C, 53.99; H, 10.01. Found: C, 53.95; H, 10.05. MALDI-MS $[M + Na]^+$ calc. for ($C_{19}H_{42}O_6Si_2$) 445.24, found 445.10.

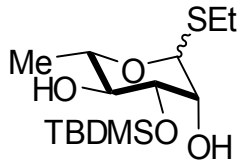


3,6-di-*O-tert*-butyldimethylsilyl-D-galactal (19).[21] ^{1}H NMR (400 MHz, $CDCl_3$):δ = 6.45 (d, *J* = 6.0 Hz, 1 H, 1-H), 4.63 (d, *J* = 6.0 Hz, 1 H, 2-H), 4.57 (d, *J* = 2.4 Hz, 1 H), 4.20-3.95 (overlapped signals, 4H), 2.82 (s, exchangeable 1 H), 1.03 and 1.02 (2 x s, 18H, *t*-butyl protons), 0.24 and 0.21 (2 x s, 12H, 2 x -Si(CH_3)$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$):δ = 144.2, 102.2, 76.8, 65.0, 64.8, 61.9, 25.9, 25.8, 18.3, 18.0, -4.6, -4.9, -5.3, and – 5.4 ppm.Anal. Calcd. for $C_{18}H_{38}O_4Si_2$: C, 57.70; H, 10.22. Found: C, 57.75; H, 10.35. MALDI-MS $[M + Na]^+$ calc. for ($C_{18}H_{38}O_4Si_2$) 397.22, found 397.45.

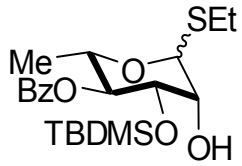


Allyl 6′-*O-tert*-butyldimethylsilyl-β-D-galacatopyranosyl-(1→4)-6-*O-tert*-butyldimethylsilyl-β-D-glucopyranose (21). $[\alpha]_D^{25}$+41 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 6.00-5.90 (m, 1 H, -C*H*=CH_2), 5.41 (bd, *J* = 17.6 Hz, 1 H, -CH=CH_aH$_b$), 5.41 (bd, *J* = 10.4 Hz, 1 H,-CH=CH$_a$$H_b$),4.98 (d, *J* = 3.2 Hz, 1 H, 1-H), 4.47 (d, *J* = 7.6 Hz, 1 H, 1′-H), 4.26 (dd, *J* = 6.0 and 12.8 Hz, 1 H, –C*Ha*HbCH=CH_2), 4.13 (dd, *J* = 6.0 and 12.8 Hz, 1 H, –CHa*Hb*CH=CH_2), 4.09 (bs, 1 H, 4′-H), 4.00-3.70 (overlapped signals), 1.00 (s, 18 H, *t*-butyl protons), 0.18 (s, 9 H, -Si(CH_3)$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.7, 117.8, 98.9, 79.0, 75.1, 73.8, 72.2, 72.3, 71.3, 70.7, 68.4, 68.3, 62.4, 61.7, 25.8, 18.3, -5.28 ppm. Anal. Calcd.

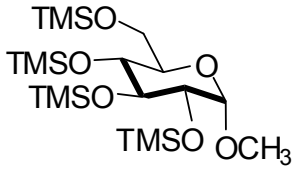
for $C_{27}H_{54}O_{11}Si_2$: C, 53.09; H, 8.91. Found: C, 53.15; H, 8.80. MALDI-MS $[M + Na]^+$ calcd. for ($C_{27}H_{54}O_{11}Si_2$) 633.31, found 633.15.



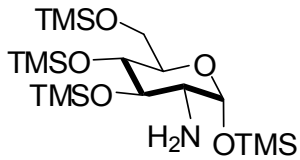
Ethyl 3-*O*-*tert*-butyldimethylsilyl-α/β-L-1-thio-rhamno-pyranoside (23). (α/β ca 4:1).^{1}H NMR (400 MHz, $CDCl_3$): signals of prevalent α-anomer at δ = 5.26 (s, 1 H, 1-H), 3.98 (m, 1 H, 5-H), 3.85 (bs, 1 H, 2-H), 3.75 (dd, *J* = 3.2 and 8.8 Hz, 1 H, 3-H), 3.49 (t, *J* = 8.8 Hz, 1 H, 4-H), 2.70-2.50 (m, 2 H, -C*H*$_2$CH$_3$), 1.27 (t, *J* = 5.6 Hz, 3 H, -CH$_2$C*H*$_3$), 0.88-0.85 (overlapped signals), 0.11 and 0.09 (2 x s, 6 H, -Si(CH$_3$)$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 83.0, 74.0, 73.6, 73.2, 68.0, 25.7, 24.9, 17.5, 14.8, -4.6, -4.7 ppm.Anal. Calcd. for $C_{14}H_{28}O_4SSi$: C, 52.13; H, 9.38. Found: C, 52.30; H, 9.30. MALDI-MS $[M + Na]^+$ calcd. for ($C_{14}H_{28}O_4SSi$) 345.15, found 345.35.



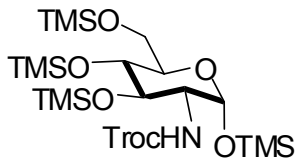
Ethyl 4-*O*-benzoyl-3-*O*-*tert*-butyldimethylsilyl-α/β-L-1-thio-rhamno-pyranoside (25). (α:β 4:1).^{1}H NMR (400 MHz, $CDCl_3$): signals of prevalent α-anomer at *δ* = 8.00-7.30 (aromatic Hs, H), 5.38 (s, 1 H, 1-H), 5.28 (t, *J* = 8.8 Hz, 1 H, 4-H), 4.25 (m, 1 H, 5-H), 4.08 (dd, *J* = 2.4 and 9.2 Hz, 1 H, 3-H), 3.97 (bs, 1 H, 2-H), 2.75-2.50 (m, 2 H, -C*H*$_2$CH$_3$), 1.31 (t, *J* = 7.2 Hz, 3 H, -CH$_2$C*H*$_3$), 1.21 (d, *J* = 6.0 Hz, 3 H, 6-H$_3$), 0.77 (s, 9 H, t-butyl protons), 0.04, -0.1 (2 x s, 6 H, -Si(CH$_3$)$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.5, 133.1, 129.7, 128.4, 82.9, 74.5, 73.1, 71.2, 66.6, 25.4. 24.9, 17.3, 14.8, -4.8, -4.9 ppm. Anal. Calcd. for $C_{21}H_{34}O_5SSi$: C, 59.12; H, 8.05. Found: C, 59.00; H, 8.15. MALDI-MS $[M + Na]^+$ cald. for ($C_{21}H_{34}O_5SSi$) 449.18, found 449.05.



Methyl 2,3,4,6-tetra-*O*-trimethylsilyl-α-D-gluco-pyranoside (26).[62] ^{1}H NMR (400 MHz, $CDCl_3$):δ = 4.68 (d, *J* = 3.6 Hz, 1 H, 1-H), 3.85-3.80 (overlapped signals, 2 H), 3.76 (dd, *J* = 4.8 and 11.6 Hz, 1 H, 6-H_a), 3.60-3.50 (overlapped signals, 3 H), 3.41 (s, 3H, -OCH_3); 0.24, 0.23 (x2), 0.20 (3 x s, 12H, 4 x -$Si(CH_3)_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 99.6, 75.2, 73.9, 72.1, 71.9, 62.1, 54.4, 1.2, 0.8, 0.4 -0.3.Anal. Calcd. for $C_{19}H_{46}O_6Si_4$: C, 47.26; H, 9.60. Found: C, 47.05; H, 9.70.

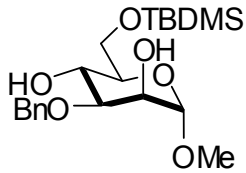


2-amino-2-deoxy-1,3,4,6-tetra-*O*-trimethylsilyl-α-D-gluco-pyranose (27).[66] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.05 (d, *J* = 3.2 Hz, 1 H, 1-H), 3.70-3.55 (overlapped signals, 3 H), 3.47 (t, *J* = 8.8 Hz, 1 H, 3-H), 3.43 (t, *J* = 8.8 Hz, 1 H, 4-H), 2.47 (dd, *J* = 3.2 and 8.8 Hz, 1 H, 2-H), 0.14, 0.11, 0.09, 0.03 (4 x s, 12 H, 4 x -$Si(CH_3)_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 94.5, 77.5, 72.7, 71.9, 61.9, 57.3, 1.2, 0.7, -0.2, -0.4 ppm. Anal. Calcd. for $C_{18}H_{45}NO_5Si_4$: C, 46.22; H, 9.69. Found: C, 46.10; H, 9.80.

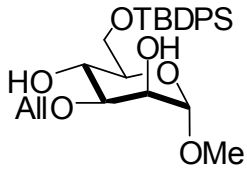


2-deoxy-2-trichloroathoxycarbonylamino-1,3,4,6-tetra-*O*-trimethylsilyl-α-D-gluco-pyranose (28).[67] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.08 (d, *J* = 2.4 Hz, 1 H, 1-H), 4.87 (d, *J* = 9.2 Hz, 1 H, -NHTroc), 4.81 and 4.59 (2 x d, AB, *J* = 12.0 Hz, 2 H, -C*H*$_2$$CCl_3$), 3.75-3.50 (overlapped signals, 6H),0.16, 0.14, 0.13, 0.08 (4 x s, 12 H, 4 x -$Si(CH_3)_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.1, 92.5, 74.7, 73.8, 72.4, 71.9, 61.6, 56.8,0.9, 0.7, -0.2,

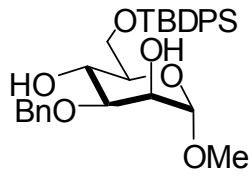
-0.3 ppm. Anal. Calcd. for $C_{21}H_{46}Cl_3NO_7Si_4$: C, 39.21; H, 7.21. Found: C, 39.20; H, 7.10.



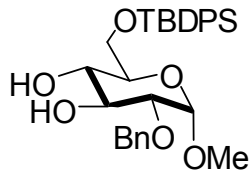
Methyl 3-O-benzyl-6-*O*-*tert*-butyldimethylsilyl-α-D-manno-pyranoside (29).[79] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40-7.20 (aromatic H), 4.71 (s, 1 H, 1-H), 4.67 (s, 2 H, -C*H*$_2$Ph), 3.94 (bs, 1 H, 2-H), 3.90-3.84 (overlapped signals, 3 H), 3.66 (dd, *J* = 2.8 and 8.8 Hz, 3-H), 3.58 (m, 1 H, 5-H), 3.34 (s, 3 H, -OCH_3), 0.90 (s, 9 H, *t*-butyl protons), 0.08 (s, 6 H, -$Si(CH_3)_2$). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 137.9, 128.5, 127.9, 127.8, 100.3, 79.4, 72.0, 71.0, 68.6, 67.7, 64.4, 54.7, 25.8, 18.2, -5.5. Anal. Calcd. for $C_{20}H_{34}O_6Si$: C, 60.27; H, 8.60. Found: C, 60.45; H, 8.50. MALDI-MS $[M + Na]^+$ calcd. for ($C_{20}H_{34}O_6Si$) 421.20, found 421.55.



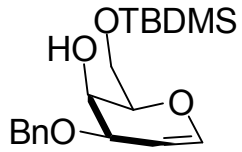
Methyl 3-*O*-allyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-manno-pyranoside (30).[80] ^{1}H NMR (400 MHz, $CDCl_3$):δ = 7.85-7.30 (aromatic H), 6.00-5.90 (m, 1 H, -C*H*=CH_2), 5.33 (bd, *J* = 17.2 Hz, 1 H, -CH=C$H_a$$H_b$), 5.22 (bd, *J* = 10.4 Hz, 1 H, -CH=$CH_a$$H_b$), 4.75 (s, 1 H, 1-H), 4.20-4.10 (m, 2 H, -C*H*$_2$CH=CH_2), 4.00 (bs, 1 H, 2-H), 3.99-3.85 (overlapped signals, 3 H), 3.67 (m, 1 H, 5-H), 3.62 (dd, *J* = 2.8 and 8.8 Hz, 1 H, 3-H), 3.34 (s, 3 H, -OCH_3), 1.07 (s, 9 H, *t*-butyl protons) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.5, 134.4, 132.0, 129.6, 127.6 117.6, 100.3, 79.0, 71.2, 70.7, 68.3, 67.6, 64.9, 54.6, 26.7, 19.1 ppm. Anal. Calcd. for $C_{26}H_{36}O_6Si$: C, 66.07; H, 7.68. Found: C, 66.25; H, 7.55. MALDI-MS $[M + Na]^+$ calcd. for ($C_{26}H_{36}O_6Si$) 495.22, found 495.30.



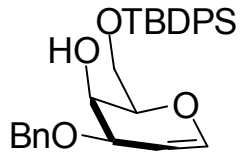
Methyl 3-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-manno-pyranoside (31).[81] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90-7.25 (aromatic H), 4.88 (s, 1 H, 1-H), 4.84 (s, 2 H, -CH_2Ph), 4.13 (bs, 1 H, 2-H), 4.10-4.03 (overlapped signals, 3 H), 3.90-3.75 (overlapped signals, 2 H), 3.48 (s, 3 H, -OCH_3), 2.93 (bs, exchangeable, 1 H), 2.61 (bs, exchangeable, 1 H), 1.22 (s, 9 H, *t*-butyl protons) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9, 135.6, 133.0, 128.7, 128.5, 127.9, 127.7, 100.2, 79.5, 72.0, 71.1, 68.5, 67.7, 64.9, 54.7, 26.7, 19.1 ppm.Anal. Calcd. for $C_{30}H_{38}O_6Si$: C, 68.93; H, 7.33. Found: C, 68.75; H, 7.40. MALDI-MS $[M + Na]^+$ calcd. for ($C_{30}H_{38}O_6Si$) 545.23, found 545.40.



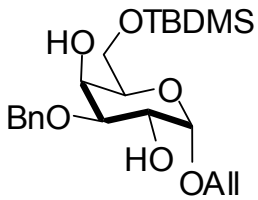
Methyl 2-*O*-benzyl-6-*O*-*tert*-butyldiphenylsilyl-α-D-gluco-pyranoside (32).[82] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85-7.25 (aromatic H), 4.85 and 4.82 (2 x d, AB, *J* = 12.0 Hz, 2 H), 4.76 (d, *J* = 3.2 Hz, 1 H, 1-H), 4.07 (t, *J* = 9.2 Hz, 1 H, 3-H), 4.04 (dd, *J* = 3.2and 10.4 Hz, 1 H, 6a H), 3.97 (dd, *J* = 5.2 and 10.4 Hz, 1 H, 6b-H), 3.78 (m, 1 H, 5-H), 3.66 (t, *J* = 9.2 Hz, 1 H, 4-H), 3.48 (dd, *J* = 3.2 and 9.2 Hz, 1 H, 2-H), 3.48 (s, 3H, OCH_3), 3.20 (bs, exchangeable, 1 H), 1.20 (s, 9 H, *t*-butyl protons) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 137.9, 135.5, 133.1, 129.6, 128.4,128.0, 127.9, 127.6, 97.4, 79.2, 73.0, 72.9, 71.6, 70.6, 64.3, 54.9, 26.7, 19.1 ppm. Anal. Calcd. for $C_{30}H_{38}O_6Si$: C, 68.93; H, 7.33. Found: C, 68.80; H, 7.35. MALDI-MS $[M + Na]^+$ calcd. for ($C_{30}H_{38}O_6Si$) 545.23, found 545.55.



3-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-D-galactal (33).[83] ^{1}H NMR (400 MHz, $CDCl_3$):δ = 7.40-7.30 (aromatic H), 6.40 (d, *J* = 6.0 Hz, 1 H, H-1), 4.70 (d, *J* = 6.0 Hz, 1 H, H-2), 4.69-4.60 (AB, *J* = 12.0 Hz, 2 H, -C*H*$_2$Ph), 4.21 (bs, 1 H), 4.14 (bs, 1 H), 3.97 (m, 1 H), 3.90-3.80 (m, 2 H), 2.63 (bs, 1 H), 0.92 (s, 9 H, *t*-butyl protons), 0.11 (s, 6 H, -Si(CH_3)$_2$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.9, 137.7, 128.5, 127.9, 127.7, 99.5, 76.6, 70.9, 70.4, 62.4, 62.1, 26.0, 19.2, -5.4 ppm. Anal. Calcd. for $C_{19}H_{30}O_4Si$: C, 65.10; H, 8.63. Found: C, 65.25; H, 8.55. MALDI-MS $[M + Na]^+$ calcd. for ($C_{19}H_{30}O_4Si$) 350.42, found 350.55



3-O-benzyl-6-*O*-*tert*-butyldiphenylsilyl-D-galactal (34).$[\alpha]_D^{25}$ - 3 (*c* 1.9, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.90-7.30 (aromatic H), 6.50 (d, *J* = 6.0 Hz, 1 H, 1-H), 4.84 (d, *J* = 6.0 Hz, 1 H, 2-H), 4.82-4.75 (AB, *J* = 12.0 Hz, 2 H, -C*H*$_2$Ph), 4.35 (s, 2 H), 4.23 (m, 1 H), 4.15-4.00 (overlapped signals, 2 H), 2.73 (s, 1 H), 1.22 (s, 9 H, *t*-butyl protons) ppm. ^{13}C NMR (100 MHz, $CDCl_3$):δ = 144.9, 137.7, 135.5, 133.1, 129.7-127.7, 99.5, 76.5, 70.9, 70.4, 62.6, 62.5, 26.7, 19.2 ppm.Anal. Calcd. for $C_{29}H_{34}O_4Si$: C, 73.38; H, 7.22. Found: C, 73.20; H, 7.40. MALDI-MS $[M + Na]^+$ calc. for ($C_{29}H_{34}O_4Si$) 497.21, found 497.45.



Allyl 3-*O*-benzyl-6-*O*-*tert*-butyldimethylsilyl-α-D-galacto-pyranoside (35).$[\alpha]_D^{25}$ +81 (*c* 1.6, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40-7.20 (aromatic H), 6.00-5.90 (m, 1 H, -C*H*=CH_2), 5.28 (bd, *J* = 1.6 and 17.2 Hz, 1 H, -CH=CH_aH$_b$), 5.20 (bd,

J = 1.6 and 10.4 Hz, 1 H, -CH=CH$_a$*H$_b$*), 4.95 (d, *J* = 4.0 Hz, 1 H, 1-H), 4.76 and 4.71 (2 x d, AB, *J* = 11.6 Hz, 2 H, -C*H*$_2$Ph), 4.19 (bdd, *J* = 5.2 and 12.8 Hz, 1 H, -C*Ha*HbCH=CH$_2$), 4.05 (d, *J* = 3.2 Hz, 1 H, 4-H), 4.02 (dd, *J* = 6.6 and 12.8 Hz, 1 H, -CHa*Hb*CH=CH$_2$), 3.84 (dd, *J* = 5.6 and 9.6 Hz, 1 H, 6a-H), 3.80-3.70 (overlapped signals, 2 H), 3.63 (dd, *J* = 2.8 and 9.6 Hz, 1 H, 3-H), 2.63 (bs, exchangeable, 1 H), 2.23 (bs, exchangeable, 1 H), 0.89 (s, 9 H, *t*-butyl protons), 0.07 (s, 6 H, -Si(CH$_3$)$_2$). ^{13}C NMR (100 MHz, CDCl$_3$): δ = 137.9, 133.6, 128.5, 127.9, 127.8, 117.8, 97.6, 78.7, 72.0, 70.2, 68.6, 68.4, 66.9, 62.5, 25.8, 18.2, -5.4. Anal. Calcd. for $C_{22}H_{36}O_6Si$: C, 62.23; H, 8.55. Found: C, 62.10; H, 8.60. MALDI-MS $[M + Na]^+$ calcd. for ($C_{22}H_{36}O_6Si$) 447.22, found 447.40.

References

1) For a very recent review: Agoston, K.; Streicher, H.; Fügedi, P. *Tetrahedron Asimmetry* **2016**, 707-728.
2) Wuts, P. G. M. in *Greene's Protective Groups in Organic Synthesis*, Wiley, **2014**.
3) Corey, E.J.; Venkateswarlu, A. *J. Am. Chem. Soc.***1972**, *94*, 6190-6191.
4) For use of iodine as the catalyst (also ref 5): Bartoszewicz, A.; Kalek, M.; Stawinski, J. *Tetrahedron* **2008**, *64*, 8843-8850.
5) Bartoszewicz, A.; Kalek, M.; Nilsson, J.; Hiresova, R.; J. Stawinski, *Synlett* **2008**, 37-40.
6) For use of an N-oxide catalyst: Yoshida, K.; Fujino, Y.; Itatsu, Y.; Inoue, H.; Kanoko, Y.; Takao, K. I. *Tetrahedron Lett.* **2016**, *57*, 627-631.
7) For use of DIPEA as a catalyst: Lombardo, L. *Tetrahedron Lett.* **1984**, *25*, 227-228.
8) For use of DBU as the base: Aizpurua, J. M.; Palomo, C. *Tetrahedron Lett.* **1985**, *26*, 475-476.
9) For use of tetramethylguanidine as the catalyst: Kim, S.; Chang, H. *Synth. Comm.***1984**,*14*, 899-904.
10) Corey, E. J.; Cho, H.; Rücker, C.; Hua, D. H. *Tetrahedron Lett.* **1981**, *22*, 3455-3458.
11) Mander, L. N.; Sehti, S. P. *Tetrahedron Lett.* **1984**, *25*, 5953-5956.
12) Boschelli, D.; Takemasa, T.; Nishitani, Y.; Masamune, S. *Tetrahedron Lett.* **1985**, *26*, 5239-5242.
13) Gassman, P. G.; Haberman, L. M. *J. Org. Chem.* **1986**, *51*, 5010-5013.
14) Lee, D.; Taylor, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 3724-3727.

15) El-Badri, M. H. Willenbring, D. Tantillo, D. J. Gervay-Hague, J. *J. Org. Chem.* **2007**, *72*, 4663-4672.

16) Chambers, D. J.; Evans, G. R.; Fairbanks, A. J. *Tetrahedron* **2005**, *61*, 7184-7192.

17) Mikkelsen, L. M.; Krintel, S. L.; Jimenez-Barbero, J. ; Skrydstrup, T. *J. Org. Chem.* **2002**, *67*, 6297-6308.

18) Belaissaoui, A.; Saez, I. M.; Cowling, S. J.; Zeng, X.; Goodby, J. W. *Chem. Eur. J.* **2012**, *18*, 2366-2373.

19) Lam, S. N.; Gervay-Hague, J. *Carbohydr. Res.* **2002**, *337*, 1953–1965.

20) Suriano, F.; Coulembier, O.; Dubois, P. *J. Polym. Sci. Pol.Chem* . **2010**, *48*, 3271-3280.

21) Nakagawa, Y.; Doi, T.; Taketani, T.; Takegoshi, K.; Igarashi, Y.; Ito, Y. *Chem. Eur. J.* **2013**, *19*, 10516-10525.

22) Chung, M.-K.; Orlova, G.; Goddard, J. D.; Schlaf, M.; Harris, R.; Beveridge, T. J.; White, G.; Hallett, F. R. *J. Am. Chem. Soc.* **2002**, *124*, 10508-10518.

23) Markovic, D.; Tchawou, W. A.; Novosjolova, I.; Laclef, S.; Stepanovs, D.; Turksm, M.; Vogel, P. *Chem. Eur. J.* **2016**, *22*, 4196-4205.

24) Halmos, T.; Montserret, R.; Filippi, J.; Antonakis, K. *Carbohydr. Res.* **1987**, *170*, 57-69.

25) Arias-Perez, M. S.; Santos, M. J. *Tetrahedron* **1996**, *52*, 10785-10798

26) Ikeda, Y.; Furukawa, K.; Yamada, H. *Carbohydr. Res.* **2002**, *337*, 1499-1501.

27) Chung, M.-K.; Schlaf, M. *J. Am. Chem. Soc.* **2005**, *127*, 18085-18092.

28) Teumelsan, N.; Huang, X. *J. Org. Chem.* **2007**, *72*, 8976-8979.

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

30) Heuckendorff, M.; Pedersen, C. M.; Bols, M. *J. Org. Chem.* **2013**, *78*, 7234-7248.

31) Zhang, Y.; Chen, C.; Jin, L.; Tan, H.; Wang, F.; Cao, H. *Carbohydr. Res.* **2015**, *401*, 109-114.

32) Garro, H. A.; Garcia, C.; Martin, V. S.; Tonn, C. E.; Pungitore, C. R. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 914-918.

33) Lee, D.; Taylor, M. S. *Org. Biomol. Chem*. **2013**, *11*, 5409–5412.

34) a) Ref. 137 in *Chapter 1*; b) Ref. 138 in *Chapter 1*. For an example of these procedures see also Scheme 30 in *Chapter 1*.

35) Bredenkamp, M. W. *South African J. Chem.***1995**, *48*,154-156.

36) TBAB was reported to catalyze the trimethylsilylation of alcohols in the presence of trimethylsilyl azide: Amantini, D.; Fringuelli, F.; Pizzo, F.; Vaccaro, L. *J. Org. Chem.* **2001**, *66*, 6734-6737.

37) Saidhareddy, P.; Ajay, S.; Shaw, A- K. *RSC Adv.* **2014**, *4*, 4253-4259.

38) Fei, X.; Holmes, T.; Diddle, J.; Hintz, L.; Delaney, D.; Stock, A.; Renner, D.; McDevitt, M. B.; Berkowitz, D.; Soukup, J K. *ACS Chem. Biol.* **2014**, *9*, 2875-2882.

39) Hirofumi, D.; Yoshihiro, N.: Tae, T.; Kazukiyo, K. *Carbohydr. Res.* **2002**, *337*, 983-989.

40) Despras, G.; Robert, R.; Sendid, B.; Machez, E.; Poulain, D.; Mallet, J.-M. *Bioorg. Med. Chem*. **2012**, *20*, 1817-1831.

41) Peng, P.; Xiong, D.-C.; Ye, X.-S. *Carbohydr. Res.* **2014**, *384*, 1-8.

42) Tam, P. H.; Lowary, T. L. *Org. Biomol. Chem*. **2010**, *8*, 181-192.

43) Cai, C.; Dickinson, D. M.; Li, L.; Masuko, S.; Suflita, M.; Schultz, V.; Nelson, S. D.; Bhaskar, U.; Liu, J.; Linhardt, R. J. *Org. Lett.* **2014**, *16*, 2240-2243.

44) Huang, X.; Huang, L.; Wang, H.; Ye, X.-S. *Angew. Chem. Int. Ed.* **2004**, *43*, 5221-5224.

45) Guillemineau, M.; Auzanneau, F.-I. *J. Org. Chem.***2012**, *77*, 8864-8878.

46) Lemanski, G.; Ziegler, T. *Helv. Chim. Acta* **2000**, *83*, 2655-2675.

47) Keliris, A.; Ziegler, T.; Mishra, R.; Pohmann, R.; Sauer, M. G.; Ugurbil, K.; Engelmann, J. *Bioorg. Med. Chem.* **2011**, *19*, 2529-2540.

48) McGavin, R. S.; Gagne, R. A.; Chervenak, M. C.; Bundle, D. R. *Org. Biomol. Chem.* **2005**, *3*, 2723-2732;

49) Srivastava, J.; Khare, A.; Khare, N. K. *ARKIVOC* **2009**, *7*, 180-188.

50) Xiong, J.; Lu, Z.; Ding, N.; Ren, S.; Li, Y.*Eur. J. Org. Chem.* **2013**, *27*, 6158-6166.

51) Pozsgay, V. *J. Org. Chem*. **1999**, *64*, 7277-7280.

52) McGavin, R.; Bundle, D. R. *Org. Biomol. Chem.* **2005**, *3*, 2733-2740

53) Tanaka, Y. Nakahara, Y. Hojo, H. Nakahara, Y.*Tetrahedron* **2003**, *59*, 4059-4067.

54) Chang, S.-M.; Tu, Z.; Jan, H.-M.; Pan, J.-F.; Lin, C.-H. *Chem. Comm.* **2013**, *49*, 4265-4267.

55) Roy, S.; Roy, N. *J. Carbohydr. Chem.* **2003**, *22*, 521-535.

56) Boto, A.; Hernandez, D.; Hernandez, R.; Suarez, E. *J. Org. Chem.* **2006**, *72*, 1938-1948.

57) Krylov, V. B.; Argunov, D. A.; Vinnitskiy, D. Z.; Verkhnyatskaya, S. A.; Gerbst, A. G.; Ustyuzhanina, N. E.; Dmitrenok, A. S.; Huebner, J.; Holst, O.; Siebert, H.-C.; Nifantiev, N. E. *Chem. Eur. J.***2014**, *20*, 16516-16522.

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

59) Bedini, E.; Carabellese, A.; Comegna, D.; De Castro, C.; Parrilli, M. *Tetrahedron* **2006**, *62*, 8474-8483.

60) 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.

61) Francais, A.; Urban, D; Beau, J.-M. *Angew. Chem. Int. Ed.* **2007**, *46*, 8662-8665.

62) Wang, C.-C.; Kulkarni, S. S.; Lee, J.-C.; Luo, S.-Y.; Hung, S.-C. *Nature Protoc.* **2008**, *3*, 97-113

63) Bourdreux, Y.; Lemètais, A.; Urban, D.; Beau, J.-M. *Chem. Commun.* **2011**, *47*, 2146-2148.

64) Patil, P. S.; Lee, C.-C.; Huang, Y.-W.; Zulueta, M. M.; Hung, S.-C. *Org. Biomol. Chem.* **2013**, *11*, 2605-2612.

65) Joseph, A. A.; Verma, V. P.; Liu, X.-Y.; Wu, C.-H.; Dhurandhareand, V. M.; Wang, C.-C. *Eur. J. Org. Chem.* **2012**, 744-753.

66) Irmak, M.; Groschner, A.; Boysen, M. M. K. *Chem. Commun.* **2007**, 177-179.

67) Joseph, A.; Dhurandhare, V. M.; Chang, C. W.: Verma, V. P.: Mishra, G. P.; Ku, C. C.; Lin, C.-C.; Wang, C.-C. *Chem. Commun*. **2015**, *51*, 104-106.

68) Lim, J.; Grove, B. C.; Roth, A.; Breaker, R. R. *Angew. Chem. Int. Ed.* **2006**, *45*, 6689-6693.

69) George, J.; Reddy, B. V. S. *Org. Biomol. Chem.* **2012**, *10*, 4731-4738.

70) Minuth, T.; Irmak, M.; Groschner, A.; Lehnert, T.; Boysen, M. M. K. *Eur. J. Org. Chem.* **2009**, 997-1008.

71) Tran, A. T.; Jones, R. A.; Pastor, J.; Boisson, J.; Smith N.; Galan, M. C. *Adv. Synth. Catal.* **2011**, *353*, 2593-2598.

72) Tatina, M.; Yousuf , S. K.; Mukherjee, D. *Org. Biomol. Chem.* **2012**, *10*, 5357-5360.

73) Xu, H.; Ren, B.; Zhao, W.; Xin, X.; Lu, Y.; Pei, Y.; Dong, H.; Pei, Z. *Tetrahedron* **2016**, *72*, 3490-3499.

74) For a recent review: Zulueta, M. M. L.; Janreddy, D.; Hung, S.-C. *Isr. J. Chem*. **2015**, *55*, 347-359.

75) Ref. 137 in *Chapter 1*. See also Scheme 30 – reaction a) in *Chapter 1* for an example of this method)

76) Levecque, P.; Gammon, D. W.; Kinfe, H. H.; Jacobs, P.; De Vos, D.; Sels, B. *Adv. Syn. Catal.* **2008**, *350*, 1557-1568.

77) Kumar, P. S.; Kumar, G. D. K.; Baskaran, S. *Eur. J Org. Chem.* **2008**, 6063-6067.

78) Chen,N.; Xie, J. *Org. Biomol. Chem*. **2016**, *14*, 1102-1110.

79) Saikam, V.;Dara, S.; Yadav, M.; Singh, P.;Vishwakarma, R. A. *J. Org. Chem.* **2015**, *80*, 11916-11925.

80) Novikov, Y. Y.;Sampson, P. *J. Org. Chem*. **2005**, *70*, 10247-10259.

81) Herradon, B.;Morcuende, A.;Valverde, S. *Synlett* **1995**, *5*, 455-458.

82) Ren, B.;Ramstroem, O.;Zhang, Q.; Ge, J.; Dong, H *Chem. Eur. J.* **2016**, *22*, 2481-2486.

83) Bieg, T.; Kral, K.;Paszkowska, J.;Szeja, W.;Wandzik, I. *J. Carbohyd. Chem*. **2012**, *31*, 593-601.

Chapter 4

Solvent-Free One-Pot Diversified Protection of Saccharide Polyols via Regioselective Tritylations

Introduction

As introduced in the previous chapters, installation of an orthogonal set of protecting groups is an essential, but often very laborious, step in the synthetic manipulation of highly functionalized molecules.[1] This represents a key topic in carbohydrate chemistry, since carbohydrates are often privileged precursors in the synthesis of both oligosaccharides and chiral molecules.[1-3] Importance of this topic has been widely demonstrated by the increasing interest addressed over the years towards development of straightforward strategies for accessing saccharide building blocks with a diversified profile of protection. As evidenced by the numerous contributions from several research groups, this effort culminated with implementation of one-pot sequences yielding saccharide building blocks partially and orthogonally protected.[4-6] Most of these strategies are experimentally demanding due to the application of moisture sensitive conditions of activation, and most of them are also requiring a preliminary per-*O*-trimethylsilylation step.

In previous chapters were described some practical methodologies recently developed in our laboratory, aimed at regioselective protection

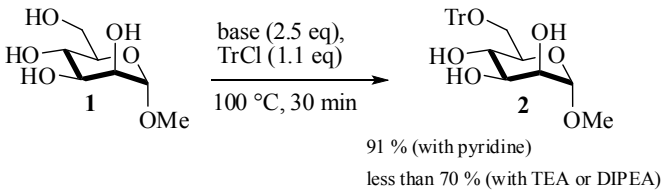
of carbohydrates under solvent-free conditions;[7] among the several advantages associated with these developed methods, the avoided use of solvents supports the very simple experimental procedures, both for setting the reactions (simply mixing the requisite reagents under air), and in the work-up, avoiding the tedious removal of high boiling and toxic solvents. In particular, in *Chapter 3* it was introduced a solvent-free silylation protocol that proved compatible with the one-pot installation of further protecting groups in the same saccharide residue. Keeping in line with this approach, this chapter deals with the extension of the solvent-free methodology to the tritylation reaction and the possible incorporation of this step into one-pot orthogonal protection sequences. Indeed, similarly to silylations, Trityl *O*-protection is widely applied in organic synthesis with alcohols present in highly functionalized substrates, and it is appreciated because of its stability to a broad range of conditions and the feasible removal under mild acidic conditions compatible with many other protecting groups.[1] Generally, *O*-tritylation is performed by exposing an alcohol to cheap trityl chloride (TrCl) in the presence of a stoichiometric amount of a base. Pyridine is frequently used for this purpose,[8] and is also serving as the solvent with polar substrates (see below); use of alternative bases such as 2,6-di-substituted pyridines,[9] DMAP,[10] DABCO,[11] and DBU[12] was described too. Some tritylation protocols are relying on TrCl activation with silver salts,[13] and are also known strategies based either on tritylating agents equipped with oxygenated leaving groups (activatable under mild acid conditions)[14] or suitably preformed tritylium salts.[15] Bulkiness of trityl group allows its easy regioselective installation on primary alcohols, and the steric hindrance can also be exploited for regio- and stereoselective control of reactions committing *O*-tritylated compounds. For example, reactivity of functional groups

adjacent to a tritylated site is generally reduced because of the limited accessibility; in addition, trityl groups can exert a long range effect in glycosidation chemistry favoring the selective construction of the synthetically demanding α-glycoside linkages.[16] Regioselective tritylation of saccharide primary alcohols is routinely performed exposing the sugar to TrCl in the presence of high boiling polar solvents such as pyridine (also acting as the base)[17] or DMF. With this latter solvent, tertiary amines are mainly used as the base[18] and the additional use of catalytic amounts of DMAP (along with the stoichiometric base) can also be found in numerous described protocols.[19] Regardless of the specific conditions adopted, tritylation of saccharide polyols is generally taking long reaction times (from several hours to days)[17-19] in dependence on the temperature, and there is some indication that the application of too high temperatures for a rate acceleration can be detrimental to the final yield due to partial product decomposition.[20]

In the first part of this chapter is reported a new practical and very simple strategy to carry out regioselective tritylation of saccharide polyol substrates, with reactions conducted with a limited stoichiometric excess of pyridine at high temperature within short times (generally less than one hour). In the second part, the scope of the tritylation process is significantly extended with its incorporation into one-pot, fully solvent-free protocols allowing a streamlined regioselective access to saccharide building-blocks bearing both a trityl group at the primary position and an alkyl (or silyl) protecting group at a defined secondary site.

Results and Discussion

In a preliminary set of experiments, aimed at optimizing the *O*-tritylation step, methyl mannopyranoside **1** was selected as the model substrate and exposed to trityl chloride under air in the presence of a slight or moderate excess of a liquid base such as pyridine, diisopropylethylamine (DIPEA) or triethylamine (TEA) (**Scheme 1**).



Scheme 1 Optimization of regioselective *O*-tritylation under solvent free conditions.

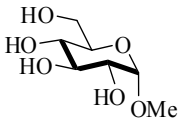
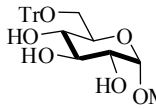
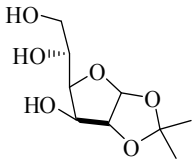
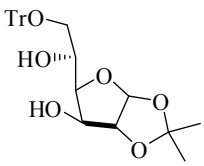
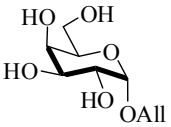
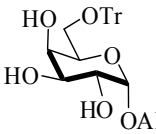
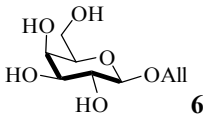
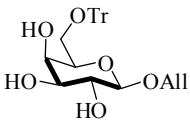
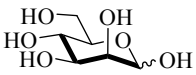
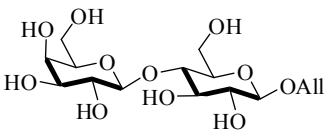
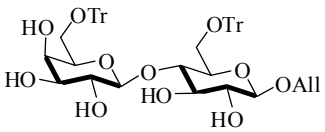
These preliminary experiments evidenced that the nature of the base is critical for the reaction outcome, and as high the temperature as 100 °C was found necessary to carry out the tritylation at an appreciable rate. Indeed, with a moderate excess of pyridine (2.5 eq) and a slight excess of trityl chloride (1.1 eq), the reaction yield was very high (91 %) in 30 minutes, whereas with the tertiary amines a partial conversion (less than 70% yield) was observed even after a prolonged reaction time (**Scheme 1**). As expected, in all cases the process displayed excellent regioselectivity in the functionalization of the primary position. In view of the applied high temperature, it is interesting to note the stability of the trityl ether in a reaction medium containing, at the end of the reaction, an almost equimolar amount of pyridine and pyridinium chloride; also relevant is the absence of significant amounts of di-*O*-tritylated products, reported in the literature as possible products upon a

prolonged exposure of sugar polyols to 1.5 eq of trityl chloride in pyridine at high temperatures.[21] Additionally, the avoided use of an inert atmosphere evidenced the favourable opportunity to achieve high yields through a very simple experimental procedure.

Although pyridine is a frequently employed solvent for tritylation of polar polyols,[17] the conditions herein described can be referred to as "solvent-free" because of the very limited amount used, that is by far not sufficient for the dissolution of polar polyol substrates. As a matter of fact, in all so far reported literature examples of sugar polyol *O*-tritylations is observed the use of stoichiometric amounts of pyridine always exceeding at least ten equivalents with respect to the substrate.[17,19]

With optimized conditions in hand, the protocol for regioselective *O*-tritylation was tested on a range of saccharide precursors and in most cases good yields were achieved in short times (**Table 1**). Especially good results were observed with *gluco*- and *manno*- glycosides (entries 1-3), whereas *galacto*-configured substrates gave relatively lower but still satisfying yields (almost 70 %), once again in reduced times (ca 90 minutes) (entries 4-6). Interestingly, an attempt of improving the outcome in the *O*-tritylation of allyl galactoside **5**, with a higher excess of pyridine and trityl chloride, resulted in an almost identical yield with just a slight acceleration in the conversion (compare entries 4 and 5 in **Table 1**).

Table 1. Regioselective tritylation of saccharide primary alcohols under solvent-free conditions

Entry	Substrate	Time (min)	Product, yield
1	**1**	30	**2**, 91 %
2	 **3**	30	 **8**, 84 %
3	 **4**	30	 **9**, 93 %
4	 **5**	90	 **10**, 69 %
5[a)]	**5**	50	**10**, 67 %
6	 **6**	90	 **11**, 67 %
7[b)]	 D-Man	60	 **12**, 66%
8[c)]	 **7**	150	 **13**, 67 %

General conditions: substrate (1 eq), pyridine (2.5 eq), TrCl (1.1 equiv), 100 °C. [a)] For entry 5: pyridine (4 eq), TrCl (2 eq), 100 °C. [b)] For entry 7: 70 °C instead of 100 °C. Then addition of pyridine and acetic anhydride, rt, 4 h. [c)] For entry 8: pyridine (5 eq), TrCl (2.2 eq), 80 °C, 1h; then further pyridine (5 eq), 1.5 h.

In almost all cases it was observed that reactions progressed despite the generation of a difficultly stirred paste-like medium. Only in the case of the di-*O*-tritylation of allyl lactoside **7** (entry 8), an additional amount of pyridine was added in the course of the reaction, with a beneficial effect on both mobility of the mixture and reaction yield. Collectively, results in **Table 1** indicate that with a range of substrates, solvent-free tritylations performed at 70-100 °C are much faster than under standard solution conditions; indeed from a survey of the literature,[17,19] a very few number of examples were found of saccharide *O*-tritylations lasting less than 4 hours,[17b,c,19a,f] also including procedures relying, unlike the protocols herein described, on DMAP catalysis.

Having established the scope of regioselective tritylations conducted with a minimal excess of pyridine, the investigation was next focused on incorporating this protocol into one-pot sequences for regioselective tritylation/alkylation of saccharide polyols. Aiming at developing one-pot solvent-free procedures for multi-protection of saccharides working under air and simplified experimental conditions, we tried to combine the present tritylation protocol with the previously reported tin-catalyzed procedures for regioselective benzylation/allylation of saccharide secondary alcohols (**Table 2**).[7a, 7d]

Initial experiments were carried out on methyl mannoside **1** in order to optimize conditions for the benzylation step to be applied directly to the mixture resulting from the preliminary tritylation step. As shown in entries 1-3 of **Table 2**, benzylation of the *in situ* generated 6-*O*-tritylated intermediate **2** (**Scheme 1**) occurred at 80 °C, whereas the corresponding process on the untritylated precursor (namely methyl mannoside **1**) occurs at 70 °C.[7a]

Table 2. One-pot protection of saccharides with a trityl and other alkyl (silyl) groups

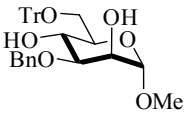
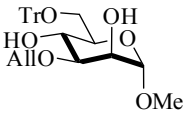
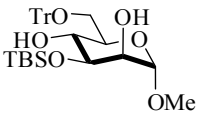
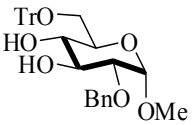
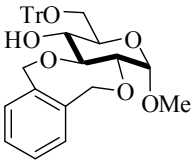
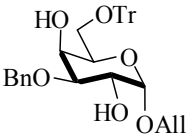
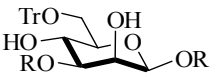
Entry	Substrate	First step conditions(eq.)	Second step conditions (eq.)	Product, yield
1	**1**	TrCl (1.1), pyridine (2.5); 100 °C, 30 min	Bu_2SnO (0.1), TBAB (0.2), DIPEA (5), BnBr (6); 80 °C, 2.5 h	 **14**, 79 %
2	**1**	TrCl (1.1), pyridine (2.5); 100 °C, 30 min	Bu_2SnO (0.1), TBAB (0.1), DIPEA (4), BnBr (4.5); 80 °C, 2.5 h	**14**, 68 %
3	**1**	TrCl (1.1), pyridine (2.5); 100 °C, 30 min	Bu_2SnO (0.1), TBAB (0.2), DIPEA (5), BnBr (4.5); 80 °C, 2.5 h	**14**, 68 %
4	**1**	TrCl (1.1), pyridine (2.5); 100 °C, 30 min	Bu_2SnO (0.1), TBAB (0.2), DIPEA (5), AllBr (8); 90 °C, 3.5 h	 **15**, 68 %
5	**1**	TrCl (1.1), pyridine (2.5); 100 °C, 30 min	pyridine (2.5), TBAB (0.3), TBSCl (1.5); 50 °C, 4 h	 **16**, 58 %

Table 2. (Continued)

Entry	Substrate	First step conditions(eq.)	Second step conditions (eq.)	Product, yield
6	**3**	TrCl (1.1), pyridine (2.5); 100 °C, 30 min	Bu_2SnO (0.2), TBAB (0.3), DIPEA (5), BnBr (6); 80 °C, 6 h	 **17**, 52 %
7	**3**	TrCl (1.1), pyridine (2.5); 100 °C, 30 min	Bu_2SnO (0.2), TBAB (0.2), DIPEA (10), α,α′–dibromo xylene (6);[a] 100 °C, 5.5 h	 **18**, 68 %
8	**5**	TrCl (1.1), pyridine (2.5); 100 °C, 90 min	Bu_2SnO (0.1), TBAB (0.2), DIPEA (5), BnBr (6); 80 °C, 2.5 h	 **19**, 67 %
9	**D-Man**	Bu_2SnO (0.1), TBAB (0.3), DIPEA (2.5), BnBr (4);70 °C, 2.5 h	TrCl (1.1), pyridine (6); 70 °C, 1.5 h	 **20** R: Bn, 63 %
10	**D-Man**	Bu_2SnO (0.1), TBAB (0.3), DIPEA (4), AllBr (8); 90 °C, 3 h	TrCl (1.1), pyridine (5); 80 °C, 2 h	**21** R: All, 38 %

General conditions: upon completion of the first step (see times in pertinent entries), temperature was modified as indicated and reagents for the second step added.

[a] Added in three portions (2 eq each) at 2 hour intervals.

In addition, in this case a higher excess of benzyl bromide (six rather than four equivalents)[7a] was necessary for achieving improved yields (compare conditions of entry 1 with those of entries 2 and 3). This is reasonably due to the partial consumption of the benzylating reagent with the residual pyridine amount of the first step. On the other hand, the TBAB amount was reduced (0.2 rather 0.3 equiv) due to generation of ammonium chloride salts in the preceding tritylation step, potentially useful for activation of the stannylene acetal intermediate. At this stage, it is worthy of note that the tritylation/3-*O*-benzylation sequence proceeds with a higher overall yield (79 %, entry 1) than the 3-*O*-benzylation step alone (64 %).[7a] This comparison indicates that the tin-mediated solvent-free benzylation of polyols can afford improved yields as the polarity of the substrate is reduced; this might be rationalized by taking into account that tritylation blocks a primary site, that is a potentially competitive site for the benzylation step,[7b] and reduces reactivity of adjacent alcohol sites.

Alternative sequences of 6-*O*-tritylation/3-*O*-allylation or 6-*O*-tritylation/3-*O*-silylation also proved viable on mannoside **1** and good yields were achieved in relatively short times (less than five hours overall) (**Table 2**, entries 4-5). The sequence terminating with the allylation protection gave satisfying yields when this latter step was conducted at 90 °C (as previously reported in the direct 3-*O*-allylation of **1**).[7a] The one-pot sequence concluding with the silylation step could be conducted under tin-free conditions with high regioselectivity[7d] (entry 5) in ca 5 hours. Interestingly, an analogous one-pot sequence of 6-*O*-tritylation and 3-*O*-TBS protection was reported under standard conditions (with pyridine and DMF as the solvents) to take about 30 hours overall.[22]

Application of the solvent free tin-catalyzed benzylation of methyl glucoside **3** (structure in entry 2 of **Table 1**), lacking *cis*-diol motifs in its structure, was previously found to proceed with a very poor regio-selectivity.[7a] When the same approach was instead applied (**Table 2**, entry 6) to the corresponding 6-*O*-tritylated intermediate **8** (structure in **Table 1**, entry 2), suitably generated *in situ*, 2-*O*-benzylated glucoside **17** was accessed in a synthetically useful yield (52 %). Because of the lower propensity of *gluco*-substrates to generate reactive stannylene intermediates, the benzylation step yielding **17** (entry 6) required both a longer time and a higher loading of Bu_2SnO and TBAB than the analogous step yielding mannoside **14** (**Table 2**, entry 1). Interestingly, glucoside building-block **18** (entry 7), bearing a single unprotected hydroxyl, was also directly accessible adapting the tin-catalyzed procedure for the installation of a *o*-xylylene protecting group, selective for 1,2-*trans*-diequatorial diols.[23] It is worthy of note that the obtained overall yield for **18** (68 %, entry 7) was about 20 % higher than the corresponding *o*-xylylenation step alone, previously performed[22] with NaH in DMF on isolated 6-*O*-tritylated glucoside **8** (structure in **Table 1**, entry 2). On the other hand, in the procedure herein reported a higher excess of the di-brominated *o*-xylylenation reagent was necessary (6 eq *vs* 1.5 eq).

Application of the tritylation/benzylation sequence on α-allyl galactoside **5** gave desired **19** in a good 67 % overall yield (**Table 2**, entry 8), very close to that of the tritylation step alone (**Table 1**, entry 4). This result provides a further evidence that the tin-catalyzed step works especially well with less polar tritylated intermediates with a blocked primary alcohol.

The one-pot solvent free strategy was also investigated on a reducing sugar such as D-mannose which was previously found to provide 1,3-

di-*O*-benzylated or 1,3-di-*O*-allylated β-mannosides in good yields *via* tin-catalyzed procedures.[7a] In this case, the double-alkylation/tritylation sequence (entries 9 and 10) was found to provide synthetically useful results, especially with the sequence starting with the double *O*-benzylation (entry 9). Taking into account the results previously obtained from the step 1 alone of entries 9 and 10 (with the corresponding 1,3-di-*O*-alkylated β-mannosides obtained in ca 60 % yield),[7a] the different yield of **20** and **21** seems to indicate that the tritylation step is much less effective when performed in the mixture derived from the allylation step, whereas it is nearly quantitative in the benzylation medium. A synthetic route to **20** through the reverse one-pot solvent-free tritylation/di-*O*-benzylation sequence was also attempted, but the overall yield (45 %) was sensibly lower (data not shown).

Conclusions

In the first part of this chapter it was introduced a very simple approach to carry out the quick and selective tritylation of carbohydrate primary alcohols with cheap trityl chloride in the presence of a very limited amount of pyridine at 70 - 100 °C. The method can indeed be regarded as a solvent-free approach because of the limited stoichiometric amount of the base that is not sufficient to dissolve the highly polar substrates. Besides the reduced use of pyridine, the proposed method is endowed with further practical advantages such as the experimental ease (all reactions herein reported were conducted in air), and high reaction rates, nearly always comparing favourably with literature examples, in spite of the poor solubility of the starting substrates in the reaction medium.

The scope of the tritylation protocol was significantly extended when it was coupled with a recently reported[7a] approach allowing the tin-catalyzed regioselective benzylation and allylation of sugar polyols under solvent-free conditions. It is indeed demonstrated (in the second part of this chapter) that merging these strategies allows the quick generation of orthogonally and selectively protected sugar building-blocks carrying a trityl group at primary positions and a set of other different groups (such as benzyl, allyl, silyl, and *o*-xylilene groups) at defined secondary positions, through one-pot and fully solvent-free sequences.

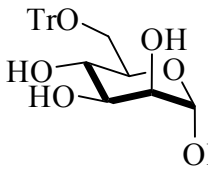
Experimental Section

General procedure for regioselective tritylation of saccharide polyols. To a mixture of a monosaccharide polyol substrate (0.5 – 1 mmol) and trityl chloride (1.1 eq), anhydrous pyridine (2.5 eq) was added under air. The mixture was kept under stirring at 100 °C for 30-90 min in dependence on the substrate (see Table 1). The mixture was then concentrated under vacuum and submitted to silica-gel flash cromatography (eluents: ethyl acetate or ethyl acetate/hexane mixtures) to afford the mono-*O*-tritylated products in the yields indicated in Table 1. In the case of the lactoside substrate **7** (Table 1, entry 8), trityl chloride (2.5 eq) and anhydrous pyridine (5 eq) were added, the mixture was kept under stirring at 80 °C for 1 hour, and then a further amount of anhydrous pyridine (5 eq) was added. The reaction was worked-up as described above after 2.5 hours from start.

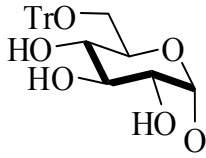
General procedure for the one-pot solvent-free regioselective tritylation/alkylation or tritylation/silylation of saccharide polyols Upon completion of the tritylation step (see paragraph above), the reaction flask was kept at rt during the addition (under air) of Bu_2SnO, TBAB, the requisite alkylating agent (allyl or benzyl bromide, or α,α′-dibromo-*o*-xylene) (see Table 2 for the adopted stoichiometric amounts). The reaction mixture was then placed in an oil bath at the required temperature for the second step and kept under stirring until TLC analysis indicated optimal conversion (see Table 2 for temperature and times). The reaction flask was then cooled to rt and the mixture diluted with DCM. The organic phase was washed with aqueous NaOH and the water phase re-extracted with DCM. Combined organic phases were dried with anhydrous sodium sulfate and concentrated under vacuum. The residue was submitted to silica-gel flash cromatography (eluents: ethyl acetate/hexane mixtures) to afford the orthogonally protected products in the yields indicated in Table 2. In the synthesis of **16** (Table 2, entry 5), the second step was performed in absence of Bu_2SnO by adding to the tritylation mixture *tert*-butyldimethylsilyl chloride (TBSCl) (1.5 eq), TBAB (0.3 eq), and a further aliquot of pyridine (2.5 eq), and stirring the resulting mixture at 50 °C for 4 hours. The reaction was worked-up as described above for the tritylation/alkylation sequence.

General procedure for the one-pot solvent-free regioselective alkylation/tritylation of D-mannose: synthesis of 20 and 21. To a mixture of D-mannose (1 – 1.5 mmol), Bu_2SnO (0.1 eq), and TBAB (0.3 eq), were sequentially added DIPEA (2.5 or 4 eq, see last two entries in Table 2), and benzyl bromide (4 eq) or allyl bromide (8 eq). The mixtures were kept for 2.5 - 3 hours at 70 ° C (for the 1,3-di-O-

benzylation) or 90 °C (for the 1,3-di-O-allylation), afterthen anhydrous pyridine (5 - 6 eq) and trityl chloride (1.1 eq) were added at rt, and the resulting mixtures placed in an oil bath at 70 or 80 °C or for 1.5-2 h. The reaction flask was then cooled to rt and the mixture diluted with DCM. The organic phase was washed with diluted aqueous NaOH and the aqueous phase re-extracted with DCM. Combined organic phases were dried with anhydrous sodium sulfate and concentrated under vacuum. The residue was submitted to silica-gel flash cromatography (eluents: ethyl acetate/hexane mixtures) to afford the orthogonally protected products **20** and **21** in the yields indicated in Table 2, entries 9 and 10, respectively.

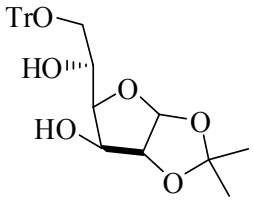


Methyl 6-*O*-trityl-α-D-manno-pyranoside (2):[19a] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.55-7.15 (aromatic, m, 15H), 4.65 (H-1, bs, 1 H), 3.75 (H-2, bs, 1 H), 3.68-3.60 (m, 2 H), 3.56 (H-4, t, J = 9.2 Hz, 1 H), 3.44 (H-6a, m, 1 H), 3.36 (-OCH_3, s, 3 H,), 3.35 (H-6b, m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.7 (aromatic C), 128.8-126.9 (aromatic CH), 100.5 (C-1), 86.9, 71.6, 70.6, 70.2, 69.0, 64.4, 54.6. HRMS (ESI-TOF): calcd for $C_{26}H_{28}O_6Na$ $[M + Na]^+$ 459.1778; found, 459.1767.

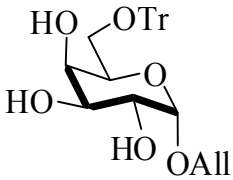


Methyl 6-*O*-trityl-α-D-gluco-pyranoside (8): [17b,17g,18b] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50-7.10 (aromatic, m, 15 H), 4.75 (H-1, d, J = 3.2 Hz, 1 H), 3.71-3.65 (m, 2 H), 3.51 (H-2, dd, J = 3.6 and 9.2 Hz,1 H), 3.49 (H-4, t, J = 9.2 Hz, 1 H), 3.44 (-OCH_3, s, 3 H), 3.45-3.33 (H_2-6, m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.8 (aromatic C); 128.6, 127.8 and 127.0 (aromatic CH); 99.1 (C-1), 86.7, 74.4, 71.9, 71.3, 70.3, 63.8,

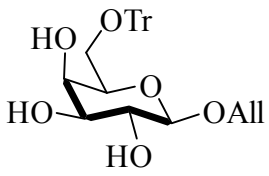
55.0. HRMS (ESI-TOF): calcd for $C_{26}H_{28}O_6Na$ $[M + Na]^+$ 459.1778; found, 459.1768.



1,2-*O*-isopropylidene-6-*O*-trityl-α-D-gluco-furanoside (9). [11] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60-7.10 (aromatic, m, 15 H), 5.95 (H-1, J = 3.6 Hz, d, 1 H), 4.52 (H-2, d, J = 3.6 Hz, 1 H), 4.34 (bs, 2 H), 4.30-4.15 (m, 2 H), 3.50-3.30 (m, 2 H, H_2-6), 1.50 and 1.32 (2 x s, 6H, 2 x $-CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.5 (aromatic C); 128.5, 127.8, and 127.0 (aromatic CH), 111.4 (q), 104.7 (C-1), 86.8, 85.0, 79.3, 75.4, 69.5, 64.8, 26.6, 26.1. HRMS (ESI-TOF): calcd for $C_{28}H_{30}O_6Na$ $[M + Na]^+$ 485.1940; found, 485.1951.

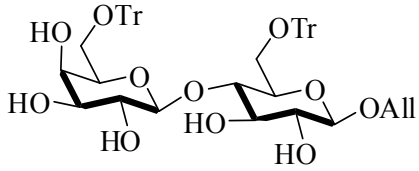


Allyl 6-*O*-trityl-α-D-galacto-pyranoside (10). $[\alpha]_D^{25}$ +48.6 (*c* 1.67, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50-7.20 (aromatic, m, 15 H), 6.00-5.85 (-C*H*=CH_2, m, 1 H), 5.30 (-CH=$CH_{cis}H_{trans}$, bd, J = 17.2 Hz, 1 H), 5.21 (-CH=C$H_{cis}H_{trans}$, bd, J = 10.4 Hz, 1 H), 4.98 (H-1, d, J = 4.0 Hz, 1 H), 4.25 (-CH_aH_bCH=CH_2 bdd, J =5.2 and 12.8 Hz, 1 H), 4.05 (-CH_aH_bCH=CH_2 , bdd, J=6.0 and 12.8 Hz, 1 H), 4.01 (H-4, bd, J = 2.8 Hz, 1 H), 3.89 (H-5, t, J = 5.6 Hz, 1 H), 3.81 (H-2, dd, J = 3.6 and 9.6 Hz, 1 H), 3.75 (H-4, dd, , J = 2.8 and 9.6 Hz, 1H), 3.42 (H-6a, dd, J = 5.6 and 10.0 Hz, 1 H), 3.35 (H-6b, dd, J = 5.6 and 10.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.8 (aromatic C), 133.7 (-*C*H=CH_2); 128.7, 127.9, and 127.0 (aromatic CH); 117.8 (-CH=*C*H_2), 97.5 (C-1), 71.1, 69.8, 69.5, 69.4, 68.4, 63.3. HRMS (ESI-TOF): calcd for $C_{28}H_{30}O_6Na$ $[M + Na]^+$ 485.1940; found, 485.1928.

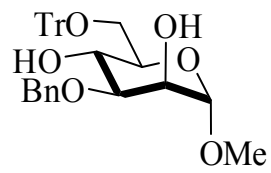


Allyl 6-O-trityl-β-D-galacto-pyranoside (11):[24] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50-7.15 (aromatic H, m, 15 H), 6.00-5.85 (-C*H*=CH_2, m, 1 H), 5.29 (bd, 1H, J = 17.2 Hz,), 5.15 (-CH=$CH_{cis}H_{trans}$, bd, J = 10.0 Hz, -CH=C$H_{cis}H_{trans}$, 1 H), 4.34 (-C$H_a$$H_b$CH=$CH_2$, bdd, J = 5.2 and 12.8 Hz, 1 H), 4.23 (H-1, d, J = 7.6 Hz, 1 H), 4.12 (-$CH_a$$H_b$CH=$CH_2$, bdd, J = 6.0 and 12.8 Hz, 1 H), 3.87 (H-4, bs, 1 H), 3.66 (H-2, t, J = 8.4 Hz, 1 H), 3.60-3.30 (m, 3 H), 3.29 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.8 (aromatic C), 133.9 (-*C*H=CH_2); 128.6, 127.8, and 127.0 (aromatic CH), 118.0(-CH=*C*H_2), 101.8 (C-1), 86.7, 73.8, 73.6, 71.4, 69.9, 69.2, 62.8. HRMS (ESI-TOF): calcd for $C_{28}H_{30}O_6Na$ $[M + Na]^+$ 485.1940; found, 485.1928.

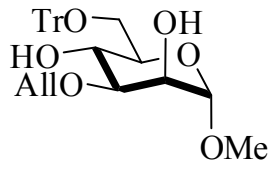
1,2,3,4-tetra-O-acetyl-6-O-trityl-α/β-D-manno-pyranose (12). Anomeric ratio α/β ca 1. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60-7.10 (m, aromatic H, 30H), 6.19 (H-1 α, s, 1 H), 5.88 (H-1 β, s, 1 H), 5.53 and 5.34 (H-4 α and β, 2 x t, J =10.0 Hz, 2 H), 5.48 and 5.28 (H-2 α and β, 2 x bs, 2 H), 5.29 (H-3 α, bd, J = 10.0 Hz, 1 H), 5.09 (H-3 β, bd, J = 10.0 Hz, 1 H), 3.93 (H-5 α, m, 1 H), 3.68 (H-5 β, m, 1 H), 3.36-3.05 (H_2-6 α and β, m, 4 H), 2.22, 2.21, 2.13, 2.10, 1.98, 1.96, 1.75, 1.74 (8 x –$COCH_3$, 8 x s, 24 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.9, 169.7, 169.6, 168.9, 168.8, 168.3, and 168.0 (8 x –*C*OCH3); 143.5 (aromatic C); 128.6, 127.6, and 126.8 (aromatic CH), 90.6 and 90.4 (C-1 α and β), 86.5, 74.5, 72.0, 70.8, 69.1, 68.5, 68.3, 65.8, 65.7, 62.0, 61.5, 20.8-20.4 (8 x –CO*C*H_3); HRMS (ESI-TOF): calcd for $C_{33}H_{34}O_{10}Na$ $[M + Na]^+$ 613.2050; found, 613.2027.



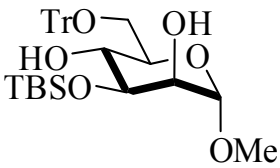
Allyl 6′-*O*-trityl-β-D-galacatopyranosyl-(1→4)-6-*O*-trityl-β-D-glucopyranoside (13). $[\alpha]_D$ ^{25} -13.0 (*c* 0.56, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$ + one drop of D_2O): δ = 7.50-7.10 (m, aromatic H, 30H), 6.10-5.95 (-C*H*=CH_2 , m, 1 H), 5.33 (-CH=$CH_{cis}H_{trans}$, bd, *J* = 17.2 Hz, 1 H), 5.20 (-CH=C$H_{cis}H_{trans}$, bd, *J* = 10.4 Hz, 1 H), 4.39 (-CH_aH_bCH=CH_2, bdd, *J* = 7.8 and 12.5 Hz, 1 H), 4.33 (H-1′, d, *J* = 7.6 Hz, 1 H), 4.13 (-CH_aH_bCH=CH_2, bdd, *J* = 6.4 and 12.4 Hz, 1 H), 4.07 (H-1, d, *J* = 7.6 Hz, 1 H), 3.88 (H-3, t, *J* = 9.2 Hz, 1 H), 3.79 (H-4′, d, *J* = 2.4 Hz, 1 H), 3.60-3.20 (m, 7 H), 3.25-3.15 (m, 2 H), 3.10 (dd, 1 H, *J* = 2.8 and 9.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.7 and 143.5 (aromatic C); 134.0 (-*C*H=CH_2), 128.6, 127.8, and 127.1 (aromatic CH); 117.8 (-CH=*C*H_2); 101.9 and 101.2 (C-1 and C-1′); 87.0, 86.4, 77.0, 74.4, 73.9, 73.6, 73.1, 70.9, 69.8, 69.4, 62.2, 61.8. HRMS (ESI-TOF): calcd for $C_{53}H_{54}O_{11}Na$ $[M + Na]^+$ 889.3564; found, 889.3550.



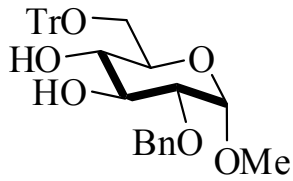
Methyl 3-*O*-benzyl-6-*O*-trityl-α-D-manno-pyranoside (14). $[\alpha]_D$ ^{25} +16.8 (*c* 1.64, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60-7.20 (m, aromatic, 20H), 4.82 (H-1, s, 1 H), 4.75-4.65 (-CH_2Ph, AB, d, *J*=12.4 Hz, 2 H), 4.03 (bs, 1 H), 3.88 (t, 1H, *J*=9.2 Hz, H-4), 3.79 (m, 1H, H-5), 3.71 (dd, 1H, *J*=3.2 and 8.8 Hz, H-3), 3.55-3.45 (m, 2H, H_2-6), 3.47 (-OCH_3, s, 3 H), 2.79 (2x OH, bs, exchangeable with D_2O, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.7 and 137.8 (aromatic C); 128.5-126.9 (aromatic CH), 100.2 (C-1), 86.9, 79.4, 71.9, 70.3, 68.3, 67.7, 64.5, 54.6. HRMS (ESI-TOF): calcd for $C_{33}H_{34}O_6Na$ $[M + Na]^+$ 549.2253; found, 549.2264.



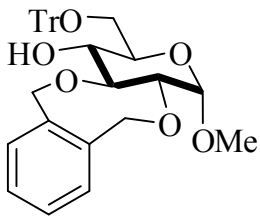
Methyl 3-*O*-allyl 6-*O*-trityl-α-D-manno-pyranoside (15). $[\alpha]_D^{25}$ +20.9° (c 0.73, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.60-7.20 (aromatic, m, 15 H), 6.00-5.90 (-C*H*=CH_2, m, 1 H), 5.32 (-CH=$CH_{cis}H_{trans}$, bd, J = 17.2 Hz, 1 H), 5.20 (-CH=C$H_{cis}H_{trans}$, bd, J = 10.4 Hz, 1 H), 4.79 (H-1, s, 1 H), 4.25-4.10 (-OCH_2CH=CH_2, m, 2 H), 4.05 (H-2, bs, 1 H), 3.81 (H-4, t, J = 9.2 Hz, 1 H), 3.75 (H-5, m, 1 H), 3.59 (H-3, dd, J = 3.2 and 8.8 Hz, 1 H), 3.50-3.35 (H_2-6, m, 2 H), 3.42 (-OCH_3, s, 3 H), 2.79 (bs, exchangeable with D_2O, 1H, OH), 2.63 (OH, bs, exchangeable with D_2O, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.6 (aromatic C), 134.0 (-*C*H=CH_2), 128.6-126.9 (aromatic CH), 117.6 (-CH=*C*H_2), 100.2 (C-1), 86.9, 78.9, 70.7, 70.2, 68.7, 68.3, 64.6, 54.7. HRMS (ESI-TOF): calcd for $C_{29}H_{32}O_6Na$ $[M + Na]^+$ 499.2097; found, 499.2084.



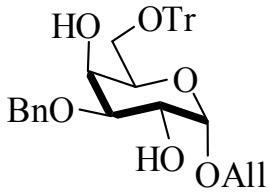
Methyl 3-*O*-tertbutyldimethylsilyl-6-*O*-trityl-α-D-manno-pyranoside (16). $[\alpha]_D^{25}$ +20.8 (*c* 1.51, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.55-7.20 (aromatic H, 15 H), 4.82 (H-1, s, 1 H), 3.87 (H-3, t, J = 3.2 and 8.4 Hz, 1 H), 3.82 (H-2, d, J = 3.2 Hz, 1 H), 3.75 (H-5, m, 1 H), 3.68 (H-4, t, J = 9.2 Hz, 1 H), 3.50-3.40 (H_2-6, m, 2 H), 3.45 (-OCH_3, s, 3 H), 2.66 (OH, bs, exchangeable with D_2O, 1 H), 2.30 (OH, bs, exchangeable with D_2O, 1 H), 0.95 (-$C(CH_3)_3$, s, 9 H), 0.17 (-$Si(CH_3)_2$, 6 H, s). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.7 (aromatic C); 128.5, 127.7, 126.9 (aromatic CH); 99.9 (C-1), 86.9, 73.0, 71.0, 70.1, 69.4, 64.6, 54.6, 25.6, 17.5 (q), - 4.6, -4.9. HRMS (ESI-TOF): calcd for $C_{32}H_{42}O_6SiNa$ $[M + Na]^+$ 573.2648; found, 573.2640.



Methyl 2-*O*-benzyl-6-*O*-trityl-α-D-gluco-pyranoside (17). $[\alpha]_D^{25}$ +32.2 (*c* 1.58, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50-7.20 (aromatic H, m, 20 H), 4.74-4.63 (-C*H*$_2$Ph, AB d, *J* = 12.0 Hz, 2 H), 4.67 (H-1, d, *J* = 3.2 Hz, 1 H), 3.90 (3-H, t, *J* = 9.2 Hz, 1 H), 3.71 (H-5, m, 1 H), 3.48 (H-4, t, *J* = 9.2 Hz, 1 H), 3.39 (-OCH_3, s, 3 H), 3.40-3.20 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.7 and 137.9 (aromatic C); 128.6-126.9 (aromatic CH), 97.4 (C-1), 86.7, 79.1, 73.0, 72.9, 71.4, 69.7, 63.7, 54.9. HRMS (ESI-TOF): calcd for $C_{33}H_{34}O_6Na$ $[M + Na]^+$ 549.2253; found, 549.2244.

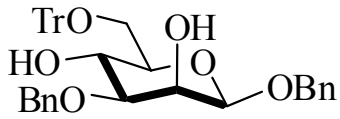


Methyl 6-*O*-trityl-2,3-*O*-(o-xylylene)-α-D-gluco-pyranoside (18).[23] ^1H NMR (400 MHz, $CDCl_3$): δ = 7.60-7.10 (m, aromatic, 19H), 5.25-4.90 (-C*H*$_2$Ar, 2 x AB, *J* = 13.2 Hz, 4 H),4.86 (H-1, d, *J* = 3.6 Hz, 1 H), 3.79 (3-H, t, *J* = 9.2 Hz, 1 H), 3.72 (H-5, m, 1 H), 3.60-3.50 (m, 2 H), 3.42 (-OCH_3, s, 3 H), 3.40-3.30 (H_2-6, m, 2 H), 2.67 (OH-4, bs, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.7, 136.8 and 136.5 (aromatic C); 130.6-127.0, (aromatic CH), 98.3 (C-1), 86.7, 81.1, 79.9, 73.7, 73.0, 71.2, 69.4, 64.0, 55.0. HRMS (ESI-TOF): calcd for $C_{34}H_{34}O_6Na$ $[M + Na]^+$ 561.2253; found, 561.2265.

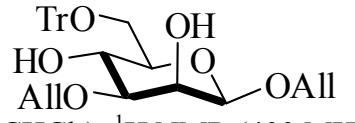


Allyl 3-*O*-benzyl 6-O-trityl-α-D-galacto-pyranoside (19). $[\alpha]_D^{25}$ +61.3 (*c* 1.40, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.50-7.10 (20 H, m, aromatic H), 6.10-5.95 (-C*H*=CH_2, m, 1

H), 5.35 (-CH=CH$_{cis}$*H*$_{trans}$, bd, *J* = 16.8 Hz, 1 H), 5.26 (-CH=C*H*$_{cis}$H$_{trans}$, bd, *J* = 10.8 Hz, 1 H), 5.02 (H-1, d, *J* = 4.0 Hz, 1 H), 4.78-4.70 (-C*H*$_2$Ph, AB, d, , *J* =12.4 Hz, 2 H), 4.29 (-C*H*$_a$H$_b$CH=CH$_2$, bdd, *J* = 5.2 and 12.8 Hz, 1 H), 4.29 (-CH$_a$*H*$_b$CH=CH$_2$, bdd, *J* = 6.0 and 12.8 Hz, 1 H), 4.10-3.90 (m, 2 H), 3.89 (H-5, t, *J* =5.6 Hz, 1 H), 3.65 (H-3, dd, *J* = 2.8 and 9.6 Hz, 1 H), 3.47 (H-6a, dd, *J* = 6.8 and 9.6 Hz, 1 H), 3.34 (H-6b, dd, *J* = 5.2 and 9.6 Hz, 1 H), 2.47 (OH, bs, 1 H), 2.26 (OH, bs, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.8 and 137.8 (aromatic C), 133.7 (-*C*H=CH$_2$); 128.5, 127.9, 126.9 (aromatic CH), 117.9 (-CH=*C*H$_2$), 97.4 (C-1), 86.7, 78.5, 72.0, 69.2, 68.4, 67.3, 63.2. HRMS (ESI-TOF): calcd for $C_{35}H_{36}O_6Na$ $[M + Na]^+$ 575.2410; found, 575.2426.



Benzyl 3-*O*-benzyl-6-*O*-trityl-β-D-manno-pyranoside (20). $[\alpha]_D^{25}$ -61.5 (*c* 1.35, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.70-7.20 (aromatic H, m, 20 H), 5.00-4.60 (2 x -C*H*$_2$Ph, 2 x AB d, *J* = 12.0 Hz, 4 H), 4.49 (H-1, s, 1 H), 4.12 (H-2, bs, 1 H), 3.97 (H-4, t, *J* = 9.6 Hz, 1 H), 3.60-3.40 (m, 2 H), 3.40-3.25 (m, 2 H), 2.68 (OH, bs, 1 H), 2.52 (OH, bs, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.7, 137.6 and 136.6 (aromatic C); 128.6- 126.9 (aromatic CH), 97.6 (C-1), 86.8, 81.0, 74.6, 71.2, 70.0, 67.8, 67.7, 64.1. HRMS (ESI-TOF): calcd for $C_{39}H_{38}O_6Na$ $[M + Na]^+$ 625.2566; found, 625.2571.



Allyl 3-*O*-allyl 6-*O*-trityl-β-D-manno-pyranoside (21). $[\alpha]_D^{25}$ -46.7° (c 1.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.50-7.15 (aromatic H, m, 10 H), 6.10-5.85 (2 x -C*H*=CH$_2$, m, 2 H), 5.35-5.15 (m, 4H, 2 x -CH=C*H*$_2$), 4.53 (s, 1H, H-1), 4.50-4.10 (2 x - OC*H*$_2$CH=CH$_2$, m, 4 H),

4.11 (H-2, bs, 1 H), 3.90 (H-4, t, J = 9.2 Hz, 1 H), 3.50-3.35 (m, 3 H), 3.32 (bd, J = 8.8 Hz, 1 H), 2.69 (2 x OH, bs, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.6 (aromatic C), 134.4 and 133.6 (2 x -*C*H=CH_2); 128.5, 127.7, 126.9 (aromatic CH); 118.0 and 117.8 (2 x -CH=*C*H_2), 98.4 (C-1), 86.8, 80.9, 74.4, 70.3, 69.6, 67.9, 67.7, 64.2. HRMS (ESI-TOF): calcd for $C_{31}H_{34}O_6Na$ $[M + Na]^+$ 525.2253; found, 525.2245.

References

1) P. G. M. Wuts in *Greene's Protective Groups in Organic Synthesis*, *5th ed.*, John Wiley & Sons, **2014**.

2) For recent reviews on orthogonal and regioselective strategies in synthetic carbohydrate chemistry: a) Agoston, K.; Streicher, H.; Fügedi, P. *Tetrahedron Asimmetry* **2016**, 707-728; b) Lawandi, J.; Rochelau, S.; Moitessier, N. *Tetrahedron* **2016**, *72*, 6283-6319.

3) Hsu, C.-H.; Hung, S.-C.; Wu, C.-Y.; Wong, C.-H. *Angew. Chem. Int. Ed.* **2011**, *50*, 11872-11923.

4) For rapid preparation of saccharide building-blocks via one-pot procedures: 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 Protoc.* **2008**, *3*, 97-113; d) Tran, A. T.; Jones, R. A.; Pastor, J.; Boisson, J.; Smith, N.; Galan, M. C. *Adv. Synth. Catal.* **2011**, *353*, 2593-2598; (e) Bourdreux, Y.; Lemètais, A.; Urban, D.; Beau, J.-M. *Chem. Commun.* **2011**, *47*, 2146-2148; f) Joseph, A. A.; Verma, V. P.; Liu, X.-Y.; Wu, C.-H.; Dhurandhareand, V. M.; Wang, C.-C. *Eur. J. Org. Chem.* **2012**, 744-753; g) Tatina, M.; Yousuf, S. K.; Mukherjee, D. *Org. Biomol. Chem.* **2012**, *10*, 5357-5360; h) Patil, P. S.; Lee, C.-C.; Huang, Y.-W.; Zulueta, M. M.; Hung, S.-C. *Org. Biomol. Chem.* **2013**, *11*, 2605-2612.

5) a) Xu, H.; Ren, B.; Zhao, W.; Xin, X.; Lu, Y.; Pei, Y.; Dong, H.; Pei, Z. *Tetrahedron* **2016**, *72*, 3490-3499; b) Mancini, R. S.; Lee, J.; Taylor, M. S. *Org. Biomol. Chem.* **2017**, *15*, 132-143; c) Rocheleau, S.; Pottel, J.; Huskic, I.; Moitessier, N. *Eur. J. Org. Chem.* **2017**, 646-656.

6) For a very recent review on one-pot elaboration of carbohydrates: Zulueta, M. M. L.; Janreddy, D.; Hung, S.-C. *Isr. J. Chem.* **2015**, *55*, 347-359.

7) For solvent-free alkylation protocols: a) Ref. 137 in *Chapter 1* (see also Scheme 30-reaction a) in *Chapter 1* for an example); b) Ref. 138 in *Chapter 1*; for solvent-free acetalation: c) Traboni, S.; Bedini, E.; Giordano, M.; Iadonisi, A. *Adv. Synt. Catal.* **2015**, *357*, 3562-3572 (work discussed in *Chapter 2*); for solvent-free silylations and one-pot silylation/alkylation: d) Traboni, S.; Bedini, E.; Iadonisi, A. *Beilstein J. Org. Chem.* **2016**, *12*, 2748-2756 (work discussed in *Chapter 3*).

8) Frechet, J. M. J.; Haque, K. E. *Tetrahedron Lett.* **1975**, *16*, 3055-3056.

9) a) Reddy, M. P.; Rampal, J. B.; Beaucage, S. L. *Tetrahedron Lett.* **1987**, *28*, 23-26; b) Hirama, M.; Noda, T.; Yasuda, S.; Ito, S. *J. Am. Chem. Soc.* **1991**, *113*, 1830-1832.

10) Chaudary, S. K.; Hernandez, O. *Tetrahedron Lett.* **1979**, *20*, 95-98.

11) Gadakh, B. K.; Patil, P. R.; Malik, S.; Kartha, K. P. R. *Synth. Commun.* **2009**, *39*, 2430-2438.

12) Colin-Messager, S.; Girard, J.-P.; Rossi, J.-C. *Tetrahedron Lett.* **1992**, *33*, 2689-2692.

13) Lundquist IV, J. T.; Satterfield, A. D.; Pelletier, J. C. *Org. Lett.* **2006**, *8*, 3915-3918.

14) a) Murata, S.; Noyori, R. *Tetrahedron Lett.* **1981**, *22*, 2107-2108; b) Adinolfi, M.; Barone, G.; Iadonisi, A.; Schiattarella, M. *Tetrahedron Lett.* **2003**, *44*, 3733-3735; c) Maltese, M.; Vergari, M. C.; Donzello, M. P. *Tetrahedron Lett.* **2011**, *52*, 483-487.

15) a) Hanessian, S.; Staub, A. P. A. *Tetrahedron Lett.* **1973**, *14*, 3555; b) Hernandez, O.; Chaudhary, S. K.; Cox, R. H.; Porter, J.

Tetrahedron Lett. **1981**, *22*, 1491-1494. For a very recent example based on the *in situ* generation of a tritylium intermediate: Shahsavari, S.; Chen, J.; Wigstrom, T.; Gooding, J.; Gauronskas, A.; Fang, S. *Tetrahedron Lett.* **2016**, *57*, 3877-3880.

16) a) Adinolfi, M.; Iadonisi, A.; Schiattarella, M. *Tetrahedron Lett.* **2003**, *44*, 6479-6482; b) Valerio, S.; Iadonisi, A.; Adinolfi, M.; Ravidà, A. *J. Org. Chem.* **2007**, *72*, 6097-6106; c) Matsumura, F.; Tatsumi, S.; Oka, N.; Wada, T. *Carbohydr. Res.* **2010**, *345*, 1211-1215.

17) For some recent examples: a) Encinas, L.; Chiara, J. L. *Eur. J. Org. Chem.* **2009**, 2163-2173; b) Monrad, R. N.; Pipper, C. B.; Madsen, R. *Eur. J. Org. Chem.* **2009**, 3387-3395; c) Yamamoto, K.; Noguchi, S.; Takada, N.; Miyairi, K.; Hashimoto, M. *Carbohydr. Res.* **2010**, *345*, 572-585; d) Kanemaru, M.; Kuwahara, S.; Yamamoto, K.; Kaneko, Y.; Kadokawa, J. *Carbohydr. Res*. **2010**, *345*, 2718-2722; e) Herczeg, M.; Lazar, L.; Mandi, A.; Borbas, A.; Komaromi, I.; Liptak, A.; Antus, S. *Carbohydr. Res.* **2011**, *346*, 1827-1836; f) Zhu, S.-Y.; Yang J.-S. *Tetrahedron* **2012**, *68,* 3795-3802; g) Singh, M. K.; Xu, R.; Moebs, S.; Kumar, A.; Queneau, Y.; Cowling, S. J.; Goodby, J. W. *Chem. Eur. J.* **2013**, *19*, 5041-5049; h) Lattova, E.; Svetlıkova, Z.; Mikusova, K.; Perreaulta, H.; Polakova, M. *RSC Adv.* **2013**, *3*, 17784-17792; i) Kurimoto, K.; Yamamura, H.; Miyagawa, A. *Carbohydr. Res*. **2015**, *401*, 39-50; l) Hofmann, A.; Sommer, R.; Hauck, D.; Stifel, J.; Gottker-Schnetmann, I.; Titz, A. *Carbohydr. Res.* **2015**, *412*, 34-42; m) Jiao, Y.; Ma, Z.; Ewing, C. P.; Guerry, P.; Monteiro, M. A. *Carbohydr. Res*. **2015**, *418*, 9-12.

18) For some recent examples: a) Berndt, F.; Sajadi, M.; Ernsting, N. P.; Mahrwald, R. *Carbohydr. Res.* **2011**, *346*, 2960-2964; b)

Dorgeret, B.; Khemtemourian, L.; Correia, I.; Soulier, J.-L.; Lequin, O.; Ongeri, S. *Eur. J. Med. Chem.* **2011**, *46*, 5959-5969.

19) For some recent examples: a) Tennant-Eyles, R.; Davis, B. G.; Fairbanks, A. J. *Tetrahedron: Asymmetry* **2000**, *11*, 231-243; b) Breitinger, H.-G. *Biopolymers* **2003**, *69*, 301-310; c) Dalpozzo, R.; De Nino, A.; Maiuolo, L.; Procopio, A.; Sindona, G.; Tagarelli, A. *Synth. Commun.* **2004**, *34*, 4207-4217; d) Kim, S.; Tsuruyama, A.; Ohmori, A.; Chiba, K. *Chem. Comm.* **2008**, 1816-1818; e) Fekete, A.; Borbas, A.; Antus, S.; Liptak, A. *Carbohydr. Res.* **2009**, *344*, 1434-1441; f) Goellner, C.; Philipp, C.; Dobner, B.; Sippl, W.; Schmidt, M. *Carbohydr. Res.* **2009**, *344*, 1628-1631; g) Kaji, E.; Komori, T.; Yokoyama, M.; Kato, T.; Nishino, T.; Shirahata, T. *Tetrahedron* **2010**, *66*, 4089-4100; h) Xiao, D.; Kang, S.-T.; Li, G.-Y.; Li, X.; Wang, J.-H. *Molecules* **2011**, *16*, 3580-3596; i) Li, Y.; Sun, J.; Gong, Y.; Yu, B. *J. Org. Chem.* **2011**, *76*, 3654-3663.

20) Casanova, E.; Perez-Perz, M. J.; Kappe, C. O. *Synlett* **2007**, 1733-1735.

21) Koto, S.; Morishima, N.; Yoshida, T. *Bull. Chem. Soc. Jap.* **1983**, *56*, 1171-1175.

22) Du, Y.; Zhang, M.; Kong, F. *Org. Lett.* **2000**, *2*, 3797-3400.

23) Balbuena, P.; Goncalves-Pereira, R.; Jimenez Blanco, J. L.; García-Moreno, M. I.; Lesur, D.; Ortiz Mellet, C.; Garcia Fernandez, J. M. *J. Org. Chem.* **2013**, *78*, 1390-1403.

24) Gigg, R.; Warren, C. D. *J. Chem. Soc.* **1965**, 2205-2210.

Chapter 5

One-Pot Preparation of Orthogonally Protected Saccharide Building-Blocks Through Sequential Base-Promoted Alkylation and Acid-Catalyzed Diol Protection Under Solvent-Free Conditions

Introduction

As extensively discussed in the previous chapters, the broad synthetic potential of carbohydrates has spurred over the years development of highly efficient protocols for both discrimination of the numerous saccharide reactive sites and for stereoselective assembly of glycosidic bonds. Indeed, owing to the multifunctional nature of sugars, lengthy procedures are often required for setting a suitable profile of protecting groups on saccharide residues. In this frame, effective sequential procedures have recently been designed to streamline the access to partially and differentially protected sugars, either in a few rapid steps or via one-pot protocols;[1] however, the need for experimentally demanding conditions is a common issue for the most straightforward one-pot protocols, as reactions are largely performed under inert and strictly anhydrous atmosphere and in the presence of highly sensitive acidic reagents. In addition, most of these strategies are claiming to follow a one-pot approach but are instead requiring a preactivation of substrates through a separate per-*O*-silylation preliminary step.[1] On this

basis, the development of simplified experimental one-pot procedures, entailing cheap and easy to handle reagents, is still an important area of investigation.

Benzylation and acetylation represent the most popular approaches to the protection of alcohols in organic synthesis; consequently, the selective partial benzylation of polyols and carbohydrates is a key step for accessing valuable saccharide building blocks.[2]

Regioselective *O*-benzylation approaches are mainly based on transient metal chelates, where the nucleophilic reactivity of the committed carbinol sites is largely discriminated. For example, glycosides of D-manno and D-galacto compounds are known to be preferentially benzylated at *O*-3 when stannylene intermediates from vicinal *cis*-diols are exploited, because of the higher rate of the following alkylation step at the equatorial position with respect to the axial.[2,3] Dibutyltin oxide is the most used reagent for the generation of stannylene acetals owing to its cheapness and ease of handling. Despite this large popularity, the stannylene-mediated regioselective alkylations of carbohydrates suffer from several practical issues such as: 1) the employment of toxic tin reagents in stoichiometric or excess amounts; 2) a laborious multistep sequence entailing the preliminary generation of the tin acetal, the removal of the initial solvent (in most cases MeOH) and the execution of the final alkylation step in high-boiling solvents (mainly toluene or DMF), at high temperatures, and in prolonged reaction times; 4) a laborious work-up for the removal of the high-boiling solvents and reagents.

Recently new approaches to regioselective alkyl protections of carbohydrates have been developed in our laboratory; one of these protocols allows the regioselective benzylation of polyols at the primary position in the presence of a moderate excess of

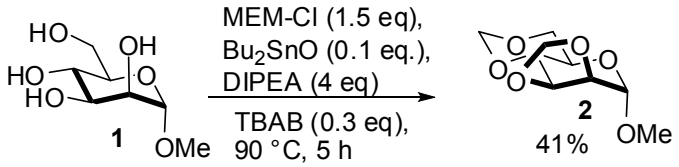
diisopropylethyl amine (DIPEA) and benzyl bromide, and a substoichiometric amount (0.3 equiv) of tetrabutylammonium iodide (TBAI) at 90 °C;[4] a following investigation led to development of an even more attractive strategy based on the unprecedented use of catalytic amounts of dibutyltin oxide for the regioselective alkylation of secondary hydroxyls in a single reaction step.[5] Both methodologies involve minimally demanding experimental procedures with reactions performed under air, reduced reaction times, the absence of any solvent and a wide target scope. Since the development of these methods, many other convenient solvent-free approaches were developed in our laboratory for the practical synthetic manipulation of carbohydrates; the whole set of developed methods provided a remarkably simplified access to a variety of differentiated saccharide building-blocks in comparison to current protocols reported for analogous processes.[6-8] In chapters 3 and 4 in particular, it was highlighted the compatibility of the solvent-free tin-mediated alkylation in one-pot orthogonal protection sequences of saccharide polyols entailing the selective silylation or tritylation at the primary position. On the other hand, it will be shown in the following chapter 7, that such solvent-free alkylation approaches can also be successfully adapted to intramolecular processes for the easy preparation of anhydrosugars.

Given the numerous experimental advantages associated with the developed procedures, further effort was also addressed to the extension of the solvent-free one-pot methodologies to different combinations of orthogonal protecting groups. Herein is presented an original solvent-free strategy for the one-pot sequential regioselective alkylation and protection of a defined saccharide diol with a cyclic protecting group (acetal or othoester), this latter process being promoted under the in situ generated buffered conditions without the

purported addition of further caralysts.

Results and Discussion

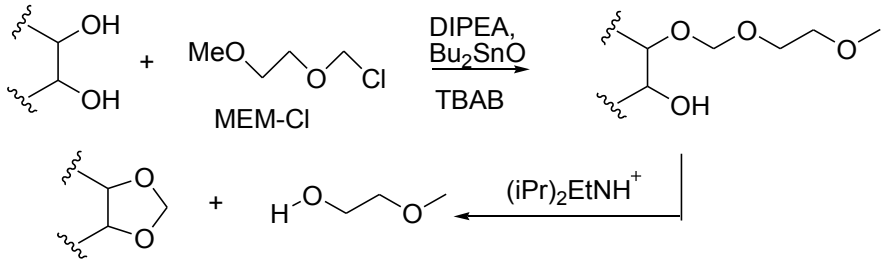
The herein presented one-pot strategy was developed in the course of some experiments,[9] initially aimed at extending the above mentioned solvent-free alkylation procedures to the regioselective installation of synthetically useful MEM (2-methoxyethoxymethyl) protecting group adopting the corresponding chloride. Surprisingly, cyclic acetals were obtained instead of the expected partially alkylated products (which are composed of an acyclic acetal). For example, as shown in **Scheme 1**, application of a solvent-free alkylation approach to methyl α-mannopyranoside **1**, resulted in predominant formation in a moderate yield (41%) of the completely protected derivative **4** bearing two methylidene acetals at O-2/O-3 and O-4/O-6, respectively.



Scheme 1. Attempted solvent-free installation of MEM protecting group on a saccharide polyol.

This outcome can be accounted for by a sequential mechanism passing through an initial base promoted O-alkylation, followed by an acid catalysed *trans*-acetalization step, namely an entropically favoured cyclization of the initially generated MEM acetal (**Scheme 2**). This latter process is very likely catalysed by the diisopropylethylammonium ion $(i\mathrm{Pr})_2\mathrm{EtNH}^+$, gradually generated in the reaction medium; indeed, the progress of the alkylation step entails a gradual consumption of DIPEA and the concomitant generation of the

corresponding conjugate acid (**Scheme 2**).



Scheme 2. Generation of cyclic acetals from the attempted regioselective installation of MEM groups

This result appeared mechanistically intriguing, highlighting that despite the presence of an excess of base (4 eq. of DIPEA were initially used), the ammonium salts gradually generated in the reaction medium might be usefully exploited to trigger acid-catalyzed events, also taking advantage of the highly-concentrated conditions associated with a solvent-free process. In other words, this outcome suggested the very attractive possibility to carry out sequentially and in the same reaction vessel, both a base promoted reaction, such as an alkylation, and an acid-catalyzed one.

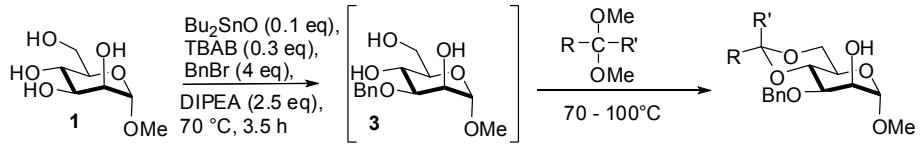
Probability of success of the hypothesized mechanism was expected to be even higher in the case of alkylation procedures involving a lower amount of base, as for the solvent-free tin-mediated 3-O-benzylation;[5] since only 2.5 eq. of DIPEA are usually employed for this process, an approximate DIPEA/ammonium ratio of ca. 1 is present in the reaction medium as the mono-O-alkylation is close to completion, thus resulting in the generation of a "buffered" system, that would reasonably facilitate the occurrence of an acid-catalyzed process.

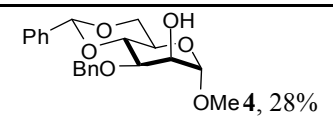
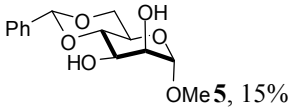
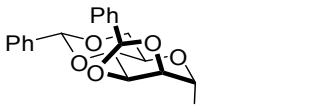
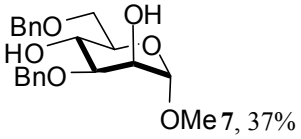
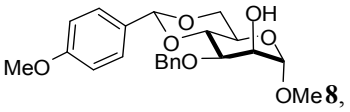
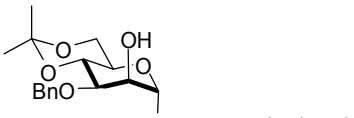
Thus, in order to assess the synthetic potential of this sequential scheme, commercially available and cheap methyl α-mannopyranoside

1 was selected as a model compound and submitted to several one-pot synthetic sequences where the initial step was the regioselective tin-mediated benzylation at *O*-3 under the established optimized conditions,[5] followed by attempted acid catalyzed 4,6-O acetalization by addition of a suitable acetalating agent to the same reaction flask. In the first trials, commercially available dimethyl acetals were selected as acetalating agents to be added in situ after the tin-directed 3-*O*-benzylation and the feasibility of the desired one-pot protection was investigated at different temperatures (**Table 1**). Expected success of this sequence was further supported by our recent finding that solvent-free conditions can be also successfully exploited for the acetalization of saccharide diols catalyzed by very reduced amounts of acidic promoters.[6]

As shown in **Table 1**, attempted 4,6-*O*-benzylidenation of in situ generated mono-*O*-benzylated intermediate **3** at 100°C led to generation of desired product **4** in a moderate yield (28%), together with other alternative products **5** and **6 (**see entry1). Though unoptimized, result achieved in this preliminary experiment was quite encouraging and supported the hypothesized mechanism, being observed the generation of several benzylidenated products. Thus, a subsequent experiment was performed where the temperature was gradually raised from 70 °C to 100 °C just after the addition of benzaldehyde dimethyl acetal, in an attempt to minimize undesired collateral events. Unfortunately, under these conditions a 6-*O*-benzylation reaction (providing diol **7**, entry2), turned out to be competitive, determining once again a moderate yield (32%) for the desired product **4**.

Table 1. One-pot regioselective benzylation/acetalization with dimethyl acetals under solvent- free conditions.



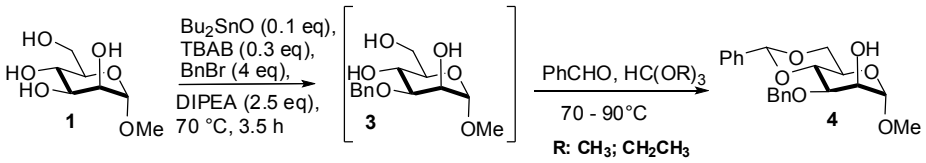
Entry	Second step conditions(eq.)	Product, isolated yield
1	$PhCH(OMe)_2$ (2), 100°C, 2h	 **4**, 28%  **5**, 15%  **6**, 10%
2	$PhCH(OMe)_2$ (2), 70°C to 100°C, 2h	**4**, 32%  **7**, 37%
3	*p*-MeO-$ArCH(OMe)_2$(2.5), 80°C to 90°C, 2h	 **8**, 41%
4	$(CH_3)_2C(OMe)_2$ (4) 90°C to 100°C, 2h	 **9**, not isolated **7**, 55%

In order to optimize the reaction yields, the use of alternative acetal/ketal protecting groups was next considered; indeed, anisaldehyde dimethyl acetalor dimethoxypropane were employed in the second step of the sequence. While *para*-methoxybenzylidene group was installed in satisfying yields (41%) under the described solvent-free one-pot conditions (entry 3) a disappointing result was instead observed in the attempted 4,6-O-isopropylidenation (entry4).

The best performance of the *p*-methoxybenzylidene group in comparison with the unsubstituted counterpart (entry1) is reasonably due to the higher reactivity of the anisaldehyde dimethyl acetal, that allows the acetalation process to occur at lower temperatures (in the range of 80-90 °C) than with benzaldehyde dimethylacetal, thus minimizing the occurrence of competitive side-processes.

Taking advantage of the existence of alternative approaches for carrying out the acetalation, a different strategy was also evaluated in an attempt to improve the outcome of the second step. In this regard, a useful opportunity was provided by a solvent-free methodology[6] allowing the acetalation of diols by the exclusive use of a aldehyde, methylorthoformate and a very low amount of camphorsulphonic acid (CSA). Reasoning that, as with the former dimethylacetal approach, a stoichiometric amount of ammonium salts might be effective in triggering the acetalation process in place of a very low catalytic loading of CSA, the aldehyde/orthoester combined system was examined under several conditions in an effort to achieve improved yields for the desired one-pot sequence (**Table2**).

Table 2. One-pot regioselective benzylation/acetalization with the aldehyde/orthoester combined system under solvent-free conditions.



Entry	Second step conditions (eq.)	Product, isolated yield
1	PhCHO (3), $HC(OMe)_3$ (2), 90°C, 2h	+ **4**, 42% **7**, 25%
2	PhCHO (3), $HC(OEt)_3$ (2), 70°C, 3h	**4**, 45%
3	PhCHO (3), $HC(OEt)_3$ (3), 70°C, 3h	**10:**R=H, R'=OEt, 26% **11**: R= OEt, R'=H, 31%
4	PhCHO (4), $HC(OEt)_3$ (3), 70°C, 2.5h	**4**, 65%

Attempted installation of a benzylidene acetal in the second step in the presence of benzaldehyde and trimethylorthoformate at 90°C (conditions optimized for the original acetalation protocol)[6] evidenced a higher rate of the acetlization process over the competitive 6-O-benzylation in comparison with the experiments with benzaldehyde dimethyl acetal, allowing a higher yield to be achieved for the desired product **4**, though 3,6-di-O-benzylated product **7** was still obtained in non negligible amount (**Table2**, entry1).

Having observed as a general trend that higher yields were obtained as much as the competitive 6-O-benzylation was minimized, in the following experiments an alternative orthoester, triethylorthoformate, was examined in view of the expected higher reactivity, reasonably arising from the higher degree of substitution of the alkyl groups (primary instead of methyl groups). As a matter of fact, bezylidenation in the presence of triethylorthoformate occurred at a temperature as low as 70°C(entry 2), that was instead not sufficient to neither trigger the 6-O-benzylation side-process.[4,5] nor the acetlization mediated by trimethylorthoformate.[6,10] Different aldehyde/triethylorthoformate stoichiometric ratios were then explored,evidencing that a slight excess of the carbonyl compound over the orthoesterwas necessary to provide the 4,6 –O-acetalation; indeed, when equimolar amounts of aldehyde and orthoester(3 eq. of both) were employed (entry 3), the exclusive generation of the 4,6- sugar orthoesters**10** and **11** was observed. The desired benzylation/benzylidenation one-pot sequence was instead achieved with a very satisfying result by a slight increase of both reagents with respect to the original conditions (compare entry 2 with entry 4); the yield obtained in this last experiment is indeed essentially comparable with the optimized yield of the only benzylation step,[5] thus indicating the second step to occur in nearly quantitative yield under

these conditions.

Once established the optimized procedure, the scope of the one-pot base promoted alkylation/acid catalyzed diol protection sequence was explored in the following experiments by varying either the nature of the alkylating agent or the protecting group installed in the second step and testing its compatibility with different substrates; best results so far achieved are summarized in **Table 3**.The first set of experiments with the optimized conditions was addressed to a screening of further orthogonal protections on α-methyl-mannoside**1**, which evidenced the feasible one-pot 3-O-benzylation and acetalation with more functionalized aldehydes, such as p-methoxybenzaldehyde and 2-Naphtaldehyde (entries 1 and 2).

Table 3. Screening of one-pot base promoted alkylation/acid catalyzed diol protection sequences on saccharide polyols under solvent-free conditions

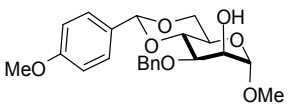
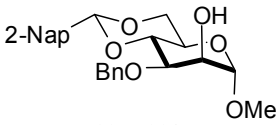
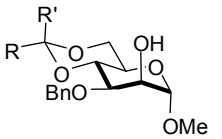
Entry	Substrate	1st step conditions (eq.)	2nd step conditions (eq.)	Product, Isolated yield
1	**1**	Bu_2SnO (0.1), DIPEA (2.5), BnBr (4), TBAB (0.3) 70°C, 3.5 h	p-MeO-ArCHO (4), $HC(OEt)_3$ (3), 80°C, 3h	 **8**, 60%
2	**1**	See entry 1	2-NapCHO (4), $HC(OEt)_3$ (3), 100°C, 3 h	 **12,** 53%
3	**1**	See entry 1	$HC(OEt)_3$ (3), 80°C, 2 h	 **10:**R=H, R'=OEt, 28% **11**: R= OEt, R'=H, 30%

Table 3. (Continued)

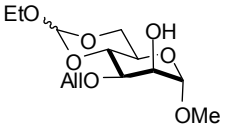
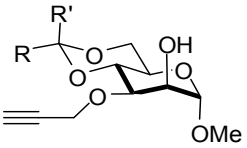
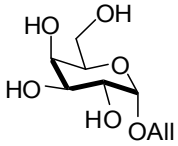
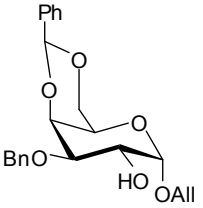
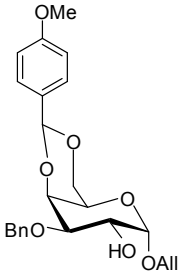
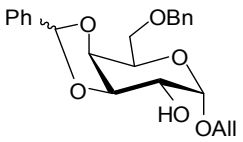
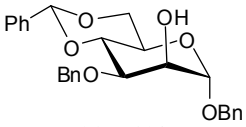
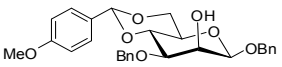
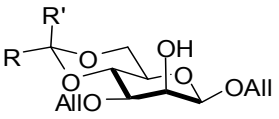
Entry	Substrate	1st step conditions (eq.)	2nd step conditions (eq.)	Product, Isolated yield
4	**1**	Bu_2SnO (0.1), DIPEA (4), AllBr (8), TBAB (0.3) 90°C, 4 h	$HC(OEt)_3$ (3), 100°C, 2.5 h	 **13,**36%
5	**1**	Bu_2SnO (0.1), DIPEA (4), $CHCCH_2Br$ (8), TBAB (0.3) 90°C, 2.5 h	$HC(OEt)_3$ (3), 90°C, 2.5 h	 **14:** R=H, R'=OEt, 27% **15**: R= OEt, R'=H, 42%
6	 **16**	Bu_2SnO (0.1), DIPEA (2.5), BnBr (4), TBAB (0.3) 70°C, 2 h	PhCHO (4), $HC(OEt)_3$ (3), 70°C, 2.5h	 **17**, 60%
7	**16**	See entry 6	p-MeO-ArCHO (4), $HC(OEt)_3$ (3), 80°C, 2.5 h	 **18**, 62%

Table 3. (continued)

Entry	Substrate	1st step conditions (eq.)	2nd step conditions (eq.)	Product, isolated yield
8	**16**	DIPEA (4), BnBr (4), TBAI (0.3), 90°C, 5h	PhCHO (4), $HC(OEt)_3$ (3), 90°C, 6h	 **19**, 32%
9	**D-mannose**	See entry 1	PhCHO (4), $HC(OEt)_3$ (3), 70°C, 2 h	 **20**, 58%
10	**D-mannose**	See entry 1	p-MeO-ArCHO (4), $HC(OEt)_3$ (3), 80°C, 2.5h	 **21**, 46%
11	**D-mannose**	See entry 4	$HC(OEt)_3$ (3), 100°C, 3 h	 **22:**R=H, R'=OEt, 21% **23:**R=OEt, R'=H, 19%

Surprisingly, contrary to the trend observed with the dimethylacetal approach, in these latter cases a higher temperature was needed for the second step in comparison to benzylidenation (**Table 2**, entry 4), (**Table 1**) probably due to the different mechanistic pathway; indeed, according to a orthoester-mediated activation of the carbonyl compound,[6] a more sterically hindered reactive intermediate should be involved in the acetalation process, in place of the benzyloxonium

cation deriving from simple acidic activation of dimethyl acetals; this effect may be further enhanced under the mild activation conditions of the buffered reaction medium.

An analogous sequence was performed on substrate **1** for the one-pot 3-*O*-benzylation/4,6-*O*-protection with the ethyl orthoester by omitting the aldehyde in the second step, thus obtaining a nearly equimolar diastereoisomeric mixture of **10** and **11**, with a overall yield comparable to the alkylation/acetalation sequences. 4,6-Orthoester protection was also found efficient when different alkyl functionalities such as allyl or propargyl groups were regioselectively installed in the first step via tin-mediated alkylation[5] (entries 4-5).

Subsequent experiments showed the applicability of these solvent-free one-pot sequences on different saccharide substrates. As evidenced in **Table 3**, successful results were obtained for the alkylation/acetalation of galacto-configured glycoside **16**, even through a complementary sequence of 6-*O*-benzylation and acetal protection of the 3,4 *cis*-diol, (entry 8) though in this case, with lower yield and rate. Preparation of orthogonally protected building-blocks was efficiently performed by application of the analogous sequences even from reducing sugars, as shown by the streamlined preparation of compounds **20**-**23** from fully unprotected mannose (entries 9-11).

Conclusions

In the present chapter the synthetic potential of a novel solvent-free strategy for the orthogonal protection of saccharide polyols was explored. The described strategy allows the regioselective base-promoted alkylation and the acid-catalyzed protection of a saccharide diol with acetals or orthoesters to be performed in a sequential one-pot fashion. Besides the established advantages associated with the solvent-

free conditions, especially in synthetic applications involving polar substrates as carbohydrates, the strategy is endowed with the advantage of a remarkable experimental simplicity, in contrast to other known one-pot protocols to functionally differentiated sugars that are relying on moisture sensitive reactions and require a preliminary functionalization (per-*O*-silylation). In addition, the presented method displays remarkable originality, since it relies on the non-trivial occurrence of a base promoted process and an acid catalyzed one in the same reaction vessel without any intermediate work-up, with the ammonium salt generated as a side product of the former alkylation acting as the promoter of the following acid catalyzed protection.

Results so far reported highlight a good versatility of the presented strategy with different saccharide substrates and protecting groups (alkyl, acetal or orthoester groups). On this basis, and in light of the compatibility of other developed solvent-free methods with one-pot protection schemes,[7,8] it is expected that further experiments will enlarge the scope of this innovative methodology to a wider set of orthogonal protecting groups.

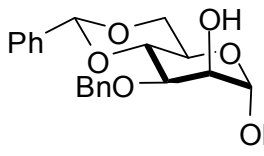
Experimental Section

General Methods

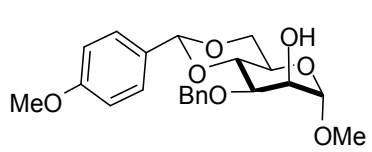
The reactions were all monitored by TLC analysis by treating the plates with a 95/5 ethanol/sulfuric acid (conc.) solution and subsequently heating up to 230° C. All products were purified through by flash-chromatography (mixtures eluents: hexane/ethyl acetate, hexane/acetone, ethyl acetate or acetone alone), and characterized by NMR spectroscopy, running H^1 and C^{13} NMR spectra on a Brucker spectrometer (400 MHz).

General one-pot procedure for the selective functionalization of carbohydrates via sequential installation of alkyl- and acetal- (or orthoester) groups

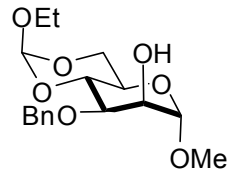
To a solid mixture of the substrate (0.5−1 mmol), Bu_2SnO (0.1 eq), and TBAB (0.3 eq), weighed in a round-bottomed flask, were sequentially added under air DIPEA and the requisite alkylating agent (benzyl-, allyl- or propargyl bromide; see pertinent entries in Table 3 for amounts). The flask, under magnetic stirring, was sealed with a glass stopper and then placed to an oil bath set at the desired temperature (see pertinent entries for specific conditions).For the 6-O-benzylation reaction (Table3, entry 8), Bu_2SnO was not employed, TBAI was used in place of TBAB, and the overall amount of DIPEA and BnBr was added in two portions with an interval of 4 hours. Upon heating, the initial slurry gradually turned to a mixture composed of a syrupy phase and an immiscible transparent phase. The reaction was monitored through TLC analysis using an appropriate eluent. When an optimal advance of the alkylation step is monitored by TLC (see pertinent entries for the corresponding times), to the reaction flask were added the appropriate reagents for the second step and the flask was placed to the suitable temperature for the reaction to occur (see pertinent entries for specific conditions). When TLC analysis indicated optimal conversion, the flask was cooled, and volatiles compounds were removed in vacuum. The residue was dissolved in an appropriate solvent (MeOH or DCM) and adsorbed by evaporation of this solvent to a pad of silica gel that was loaded onto the top of a silica-gel column. Flash chromatography (eluent: hexane/ethyl acetate mixtures) provided pure products in the yields indicated in the pertinent entries.



Compound 4. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.30 (aromatic H), 5.65 (1H, s, benzylidene CHPh), 4.90-4.74 (2H, AB, J = 11.6 Hz, -CH_2Ph), 4.77 (1H, s, H-1), 4.31 (1H, dd, J = 3.6 and 10.2 Hz, H-6eq), 4.15 (1H, t, J = 10.2 Hz, H-4), 4.05 (1H, bd, J = 3.5 Hz, H-2), 3.95-3.80 (3H, overlapped signals; H-3, H-6ax and H-5), 3.40 (3H, s, -OCH_3), 2.92 (1H, s, 2-OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9 and 137.5 (aromatic C), 128.8-125.9 (aromatic CH), 101.5 and 101.0 (-CHPh and C-1), 78.7, 75.6, 73.0, 69.7, 68.8, 63.1, 54.8.

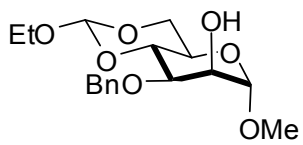


Compound 8. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-6.95 (m, aromatic H), 5.64 (1H, s, ArCHO-), 4.91 (1H, d, J = 1.2 Hz, H-1), 4.92-4.74 (2H, AB, $PhCH_2O$-), 4.33 (1H, dd, J = 4.0 and 9.2 Hz, H-6eq), 4.15 (1H, t, J = 9.2 Hz, H-4), 4.09 (1H, dd, J = 1.2 and 3.2 Hz, H-2), 3.96 (1H, dd, J = 3.2 and 9.2 Hz, H-3), 3.94 (1H, t, J = 9.2 Hz, H-6 ax), 3.89 (3H, s, aryl –OCH_3), 3.80-3.75 (1H, m, H-5), 3.43 (3H, s, 1–OCH_3), 3.04 (1H, bs, OH-2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 137.9, 130.0 (quaternary ipso C), 128.4-127.3 (aromatic CH), 113.5 (aromatic CH), 101.5, 100.0 (ArCHO- and C-1), 78.6, 75.5, 72.9, 69.7, 68.7, 63.1, 55.2, 54.9.

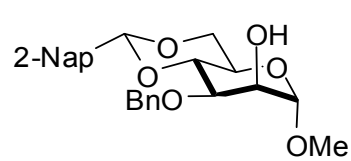


Compound 10. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48-7.39 (Ar), 5.63 (1H, s, EtOCH), 4.96 – 4.77 (3H, AB $PhCH_2O$ and H-1), 4.51 (1H, bt, J = 9.6 Hz, H-6eq), 4.19 (1H, t, J = 10.2 Hz, H-4), 4.12 (1H, bd, J = 3.2 Hz, H-2), 3.91 (4H, m, overlapped signals, $CH_3C\mathit{H}_2O$-,

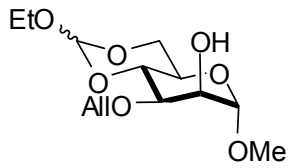
H-5 and H-3), 3.75-3.68 (1H, m, H-6ax), 3.47 (3H, s, OCH_3), 1.38 (3H, t, J = 7.0 Hz, C*H*$_3$CH$_2$O-).



Compound 11. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49-7.38 (Ar), 5.46 (1H, s, EtOCH), 4.98-4.78 (3H, overlapped signals, AB PhC*H*$_2$O and H-1), 4.26 (1H, dd, J = 3.2 and 9.2 Hz, H-6eq), 4.11 (1H, bd, J = 3.2 Hz, H-2), 4.07 (1H, t, J = 9.5 Hz, H-4), 3.97 (1H, dd, J = 3,2 and 9.5 Hz, H-3), 3.94-3.82 (4H, m, overlapped signals, CH$_3$C*H*$_2$O-, H-5 and H-6ax), 3.47 (3H, s, OCH_3), 1.40 (3H, t, J = 7.0 Hz, C*H*$_3$CH$_2$O-).

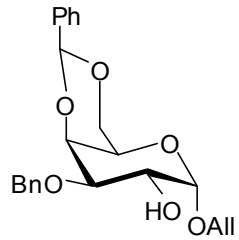


Compound 12. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.33 (Ar), 5.79 (1H, s, Naphthyl-CHO), 4.89-4.74 (3H, overlapped signals, AB C*H*$_2$Ph and H-1), 4.36 (1H, dd, J = 4.0 and 9.2 Hz, H-6eq), 4.20 (1H, t, J = 9.0 Hz, H-4), 4.07 (1H, bd, J = 3.2 Hz, H-2), 3.98-3.89 (3H, m, overlapped signals, H-3, H-5 and H-6ax), 3.39 (3H, s, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 135.0, 133.6, 132.9, 128.5-123.9 (aromatic CH), 101.8, 101.2 (-CHNaphthyl and C-1), 78.9, 75.7, 72.9, 69.9, 69,0, 63.3, 54.9.

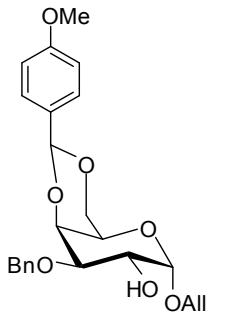


Compound 13. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.09 (1H, s, EtOCH), 5.88-5.84 (1H, m, -C*H*=CH$_2$), 5.31-5.19 (2H, m, CH=C*H*$_2$), 4.74 (1H, bs, H-1), 4.27-4.18 (1H, bd, J = 12.0 Hz, -C*Ha*HbCH=CH$_2$), 4.15-4.12 (2H, overlapped signals, -CHa*Hb*CH=CH$_2$ and H-6$_{eq}$), 4.03 (1H, bs, H-2), 3.87 (1H, t, J = 9.0 Hz, H-4), 3.81-3.66 (5H, overlapped

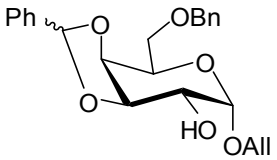
signals, H-6_{ax}, H-5, H-3 and CH_3CH_2O-), 3.37 (3H, s, -OCH_3), 1.27 (3H, t, J = 7.0 Hz, CH_3CH_2O-).



Compound 17. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.20 (aromatic H), 6.88 (2H, J = 8.4 Hz, aromatic H), 6.00-5.85 (1H, m, -C*H*=CH_2), 5.45 (1H, s, benzylideneCHPh), 5.32-5.19 (2H, m, -CH=C*H*$_2$), 5.12 (1H, J = 3.6 Hz, H-1), 4.87 (2H, s, -CH_2Ph), 4.30-4.20 (3H, overlappedsignals; -C*Ha*HbCH=CH_2, H-6a, H-4), 4.21 (1H, dd, J = 5.6 and 12.0 Hz, -CHa*Hb*CH=CH_2), 4.14 (1H, d, J = 10.0 Hz, H-6b), 3.79 (1H, s, H-5). ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.6, 137.9, 128.9-126.2 (aromatic CH), 100.9 and 98.2 (-CHPh and C-1), 82.9, 73.6, 71.5, 69.4, 68.7, 67.8, 62.9.

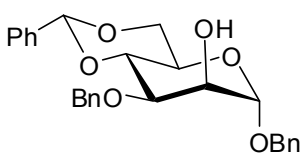


Compound 18. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-6.90 (aromatic H), 6.10-6.00 (1H, m, -C*H*=CH_2), 5.58 (1H, s, benzylideneCHPh), 5.45-5.35 (2H, m, -CH=C*H*$_2$), 5.24 (1H, d, J = 4.0 Hz, H-1), 4.86 (2H, s, -CH_2Ph), 4.35-4.15 (3H, overlappedsignals; -C*Ha*HbCH=CH_2, H-6a, H-4), 4.21 (1H, dd, J = 4.4 and 12.0 Hz, -CHa*Hb*CH=CH_2), 4.10 (1H, d, J = 10.0 Hz, H-6b), 3.89 (3H, s, -OCH_3), 3.74 (1H, s, H-5).

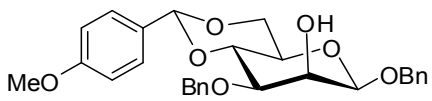


Compound 19 (1:1 A:B diastereoisomeric ratio). ^{1}H NMR (400 MHz, $CDCl_3$) significant signals at δ 8.12-7.26 (aromatic H), 6.19 (1H, s, benzylidene CHPh-A), 5.98-5.92 (2H, m, overlapped signals, -

C*H*=CH_2-A and -C*H*=CH_2-B), 5.89 (1H, s, benzylidene CHPh-B), 5.35-5.21 (4H, m, overlapped signals, CH=C*H*$_2$-A and CH=C*H*$_2$-B), 5.03 (1H, d, J = 3.9 Hz, H-1-A), 4.99 ((1H, d, J = 3.9 Hz, H-1-B), 4.69-4.55 (6H, m, overlapped signals, C*Ha*HbCH=CH_2-A, C*Ha*HbCH=CH_2-B and 2x CH_2Ph).



Compound 20. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67-7.44 (aromatic H), 5.77 (1H, s, benzylidene CHPh), 5.11 (1H, bs, H-1), 5.03 – 4.65 (4H, 2 x AB, 2 x PhCH_2O-), 4.42 (1H, bd, J = 9.0 Hz, H-6eq), 4.29 (1H, t, J = 9.2 Hz, H-4), 4.23 (1H, bd, J =3.2 Hz, H-2), 4.13 (1H, dd, J = 3.2 and 9.2 Hz, H-3), 4.07-4.02 (2H, m, overlapped signals, H-5 and H-6ax). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 137.5, 136.8 (quaternary C), 128.8-125.9 (aromatic CH), 101.5, 99.3 (CHPh and C-1), 78.8, 75.7, 72.9, 69.9, 69.2, 68.7, 63.5.



Compound 21. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-6.90 (m, aromatic H), 5.59 (1H, s, ArCHO-), 4.96-4.65 (4H, 2 x AB, 2 x PhCH_2O-), 4.53 (1H, s, H-1), 4.36 (1H, dd, J = 4.5 and 10.0 Hz, H-6eq), 4.17 (1H, t, J = 9.5 Hz, H-4), 4.13 (1H, bd, J = 1.5 Hz, H-2), 3.93 (1H, t, J = 9.5 Hz, H-6 ax), 3.82 (3H, s, aryl –OCH_3), 3.62 (1H, dd, J = 3.0 and 9.0 Hz, H-3), 3.33 (1H, m, H-5), 2.70 (1H, bs, 2-OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.9, 137.8, 136.5, 129.8 (quaternary ipso C), 128.4-127.3 (aromatic CH), 113.5 (aromatic CH), 101.4 and 98.6 (ArCHO- and C-1), 78.2, 76.6, 72.3, 70.6, 69.8, 68.4, 66.8, 55.2.

References

1) See Ref. 4 in *Chapter 4.*
2) See *Chapter 1*– "Regioselectivity of Glycosylation Reactions" .
3) a) Ref. 136 in *Chapter 1*; b) Grindley, T. B. *Adv. Carbohydr. Chem. Biochem.***1998**, *53*, 17. For a mechanistic overview of the tin-mediated alkylations see also: c) **Scheme 29** in *Chapter 1*.
4) Ref. 138 in *Chapter 1;* For an example of this method see also **Scheme 30**, reaction b) in *Chapter 1.*
5) Ref. 137 in *Chapter 1;* For an example of this method see also **Scheme 30**, reaction a) in *Chapter 1.*
6) For solvent-free acetalation: Traboni, S.; Bedini, E.; Giordano, M.; Iadonisi, A. *Adv. Synt. Catal*. **2015**, *357*, 3562-3572. (Work discussed in *Chapter 2*)
7) For solvent-free silylations or tritylations and one-pot orthogonal protections: a) Traboni, S.; Bedini, E.; Iadonisi, A. *Beilstein J. Org. Chem*. **2016**, *12*, 2748-2756. (Work discussed in *Chapter 3*); b) Traboni, S.; Bedini, E.; Iadonisi, A. *ChemistrySelect* **2017**, *2*, 4906-4911. (Work discussed in *Chapter 4*)
8) For solvent-free synthesis and one-pot elaborationsof alkyl iodides: see work discussed in *Chapter 7*.
9) Experiments inherent to a previous study carried out in our laboratory.
10) In a previous experiment attempting the second step of acetalation at 70°C with benzaldehyde and trimethylorthoformate, no reactivity was observed.

Chapter 6

Solvent-Free Synthesis of Glycosyl Chlorides Based on the Triphenylphosphine /Hexachloroacetone System

Introduction

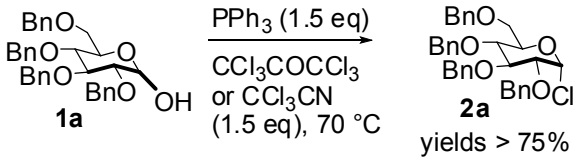
Glycosyl chlorides are useful glycosyl donors in the synthesis of *O*- and *C*- glycosides.[1-4] As anticipated in the introduction in *Chapter 1*, these compounds can be referred to as the first class of glycosyl donors originally employed in glycosylations. In comparison to brominated and iodinated counterparts, they can be appreciated because of the higher stability, a feature that is especially evident in the feasible chromatographical purification of some per-*O*-benzylated glycosyl chlorides; in contrast, the corresponding bromo and iodo donors are commonly too reactive and have to be directly used *in situ* just after their preparation. Nevertheless, their use as glycosyl donors has drastically decreased over the years, even due to the many drawbacks associated with their preparation. Known methods for the synthesis of glycosyl chlorides entail stoichiometric amounts of sensitive reagents such as $CHCl_2OMe$,[5] $SOCl_2$,[6] $TiCl_4$,[7] oxalyl chloride,[8] chloroenamine derivatives,[9] BuLi,[10] chlorodiphenylphosphate,[10] PCl_5,[11] triphosgene,[12] DMF/trichlorotriazine combination[13] and strictly controlled experimental conditions are thereby required. In addition, in most of

these approaches is lacking a compatibility with both acid- and base-labile groups.

Works discussed in the previous chapters highlight our recent interest in developing practically simple approaches for the synthetic manipulation of carbohydrates; this effort was addressed in part to the implementation of very convenient methodologies for the regioselective and orthogonal protection of carbohydrates under solvent-free conditions.[14-17] Our attention was next addressed to extending the scope of the solvent-free derivatization of carbohydrates to different types of elaborations; as a result of this attempt, in this chapter is reported a convenient method for the quick and high yielding preparation of glycosyl chlorides in the absence of solvent based on the use of cheap and easy to handle reagents.

Results and Discussion

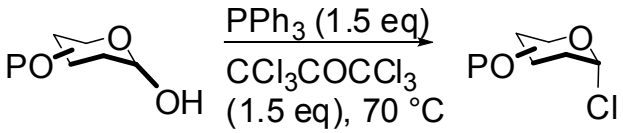
In order to develop a practical method of anomeric chlorination in the absence of solvent, attention was especially addressed towards procedures of carbinol chlorinations based on liquid reagents, expected to be more suitable for providing a minimal mobility to the reaction medium. As a matter of fact, a preliminary screening demonstrated that the combination of triphenylphosphine with liquid hexachloroacetone[18,19] or trichloroacetonitrile[19] proved compatible with a solvent-free application. As shown in **Scheme 1**, exposure at 70 °C of tetra-O-benzyl glucose **1a** to just a moderate excess of PPh_3 and a liquid chlorinating agent such as trichloroacetonitrile or hexachloroacetone provided the corresponding glycosyl chloride **2a** in good yields within short times.



Scheme 1 Solvent-free anomeric chlorination of sugar hemiacetals

Both agents gave good yields (in the 75-85 % range), and so perchloroacetone was preferentially adopted to investigate the scope of the method in subsequent experiments, because of its much lower cost and its best performance in the chlorination of simple model alcohols reported in previous studies.[19] A slight yield improvement up to 89 % (**Table 1**, entry 1) was achieved through a procedure based on a very short preliminary interaction of PPh_3 and hexachloroacetone (for one minute) and subsequent addition of the sugar hemiacetal. On this basis, this latter procedure was applied in all cases where the physical state of the hemiacetal allowed its addition in a neat form. The scope of the methodology was assessed on a wide range of sugar hemiacetals and results are summarized in **Table 1**. The protocol was initially examined on per-*O*-benzylated and per-*O*-acetylated hexoses and good yields were invariably obtained in short times with different sugar precursors (entries 1, 2, 4 and 5). The methodology was then assessed on more elaborated hexose hemiacetals carrying other functional groups such as **1c**[20] (allylated at *O*-3) (entry 3), **1f** (with an azido group) (entry 6), and **1g** (with a benzylidene, a Fmoc carbonate and a Troc carbamate in the same structure)[21] (entry 7) with satisfying isolated yields being obtained.

Table 1. Synthesis of glycosyl chlorides under solvent-free conditions[a]



P: protecting group

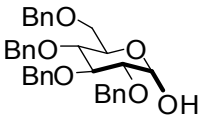
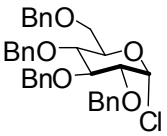
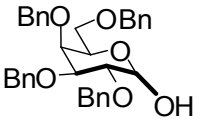
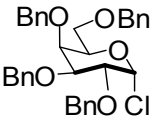
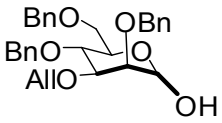
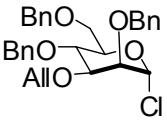
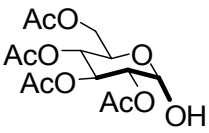
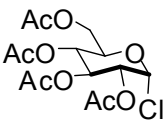
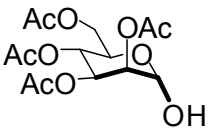
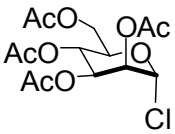
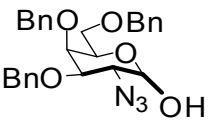
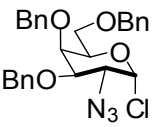
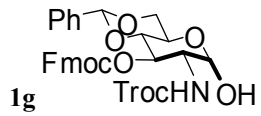
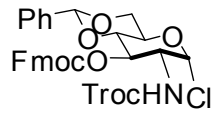
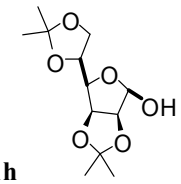
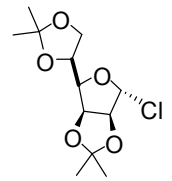
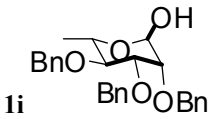
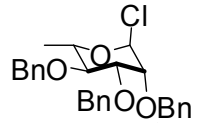
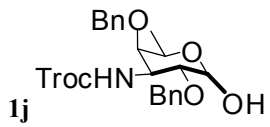
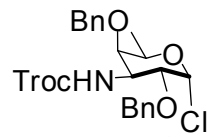
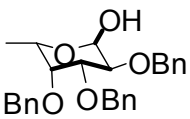
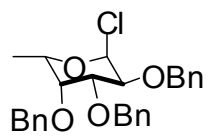
Entry	Substrate	Time (min)	Product, yield[b)]
1	 **1a**	45	 **2a**, 89%
2	 **1b**	45	 **2b**, 92 %
3	 **1c**	60	 **2c**, 81 %
4	 **1d**	60	 **2d**, 85 %
5	 **1e**	45	 **2e**, 92 %
6	 **1f**	60	 **2f**, 76 %

Table 1. (Continued)

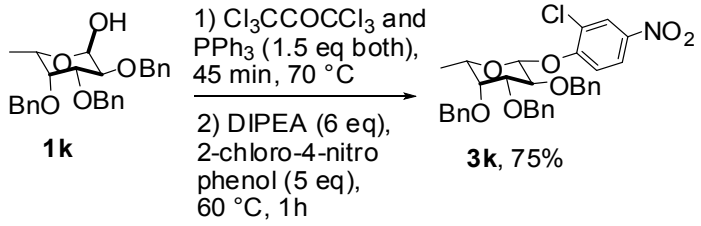
Entry	Substrate	Time (min)	Product, yield[b)]
7	 **1g**	45	 **2g,** 44 %
8	 **1h**	45	 **2h,** 95 % (α:β > 10)
9	 **1i**	45	 **2i**, > 90 %[c)]
10	 **1j**	45	 **2j**, > 90 %[c)]
11	 **1k**	45	 **2k**, > 90 %[c)]

[a)]General conditions: hexachloroacetone (1.5 eq) added to a mixture of hemiacetal (1 eq) and PPh_3 (1.5 eq) at rt (caution: hexothermic reaction) , then heating to 70 °C. For entries 1, 2, 7, 8, 11: hexachloroacetone (1.5 eq) and PPh_3 (1.5 eq) premixed at rt for 1 minute (caution: hexothermic reaction), then addition of hemiacetal (1 eq) and heating to 70 °C. [b)] Isolated yield, except for entries 9-11. [c)] Yield evaluated by NMR analysis of the crude mixture.

An excellent result was also recorded with the di-isopropylidene mannofuranose **1h** (entry 8). Interestingly, glycosyl chlorides were generally obtained with an excellent α-selectivity, and detectable lower amounts of β-anomers were observed only when starting from manno-precursors, both in the pyranose (entries 3, 5) and furanose (entry 8) form.

All the glycosyl chlorides thus far described generally displayed a satisfying stability to silica gel chromatography, as evidenced by the good to excellent yields recorded after isolation (except for **2g** which exhibited some instability). When the methodology was applied to L-rhamno **1i**,[22] D-fucosamine **1j**,[23] and commercially available L-fuco **1k** 6-deoxysugar hemiacetals (entries 9-11), an effective chlorination process was still observed, as evidenced by NMR analysis of the reaction mixture; unfortunately in these cases chromatograpical purification caused extensive degradation of the generated chlorides to the detriment of the isolated yield.

In order to ascertain the feasible applicability of these labile glycosyl chlorides in a crude form, an attempt was made to exploit them in the synthesis of *O*-glycosides. In a test reaction, commercial L-fucose hemiacetal **1k** was converted into the corresponding chloride **2k**, and then 2-chloro-4-nitro phenol and DIPEA were added to the mixture. The reaction occurred smoothly at 60°C, affording aryl-*O*-fucoside **3k** with high β-selectivity (**Scheme 2**).



Scheme 2 One-pot solvent-free chlorination/*O*-glycosylation of 2,3,4-tri-*O*-benzylated L-fucose hemiacetal

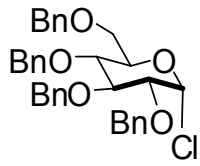
Conclusions

In conclusion, in this chapter is presented a very simple approach for the solvent-free chlorination of sugar hemiacetals. Unlike most reported approaches, the proposed method is based on cheap and easy to handle reagents, does not require application of an inert atmosphere, and is experimentally very simple. In addition, the conditions are compatible with a large set of protecting groups of common application in organic synthesis.

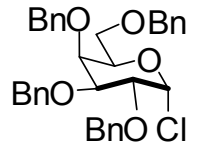
Experimental Section

General procedure for the synthesis of glycosyl chlorides: hexachloroacetone (1.5 eq) and PPh_3 (1.5 eq) were premixed at rt for 1 minute (CAUTION: hexothermic reaction). To the resulting mixture, hemiacetal (1 eq) was added and the reaction flask was placed in an oil bath at 70 °C (see **Table 1** for details) with continuous stirring. On completion of the reaction, the mixture was cooled to rt, adsorbed on a plug of silica gel, and loaded on the top of the silica gel column. Elution with hexane/ethyl acetate mixtures afforded glycosyl chlorides in the yields indicated in **Table 1**. When the hemiacetal was difficult to

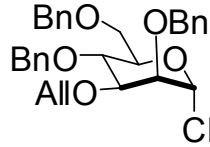
be added in a neat form, the hemiacetal, hexachloroacetone (1.5 eq) and PPh_3 (1.5 eq) were mixed altogether at the start of the reaction and then an analogous procedure was followed.



Compound 2a. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.25 (aromatic H), 6.22 (1H, d, J = 3.2 Hz, H-1), 5.15-4.55 (4 x AB, 4 x CH_2Ph), 4.24 (1H, m, H-5), 4.19 (1H, t, J = 9.6 Hz, H-3), 3.95-3.85 (2H, overlapped signals, H-6a and H-4), 3.79 (1H, bd, J = 10.0 Hz, H-6b).^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 137.8, 137.4 and 137.3 (aromatic C), 128.6-127.7 (aromatic CH), 93.4 (C-1), 81.3, 79.7,76.3, 75.8, 75.1, 73.4, 73.2, 72.9, 67.6.

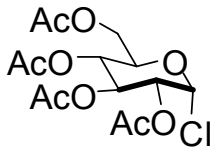


Compound 2b. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.25 (aromatic H), 6.22 (1H, d, J = 3.2 Hz, H-1), 5.15-4.55 (4 x AB, 4 x CH_2Ph), 4.24 (1H, m, H-5), 4.19 (1H, t, J = 9.6 Hz, H-3), 3.95-3.85 (2H, overlapped signals, H-6a and H-4), 3.79 (1H, bd, J = 10.0 Hz, H-6b). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.3, 137.8, 137.4 and 137.3 (aromatic C), 128.6-127.7 (aromatic CH), 93.4 (C-1), 81.3, 79.7,76.3, 75.8, 75.1, 73.4, 73.2, 72.9, 67.6.

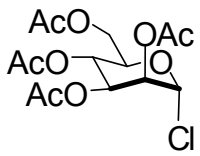


Compound 2c. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.15 (aromatic H), 6.12 (1H, d, J = 1.6 Hz, H-1), 6.00-5.90 (1H, m, -CH=CH_2), 5.29 (1H, bd, J = 17.4 Hz, -CH_2CH=CHcisH*trans*), 5.19 (1H, bd, J = 10.4 Hz, -CH_2CH=CH*cis*Htrans), 4.90-4.50 (3 x AB, 3 x CH_2Ph), 4.25-3.95 (overlapped signals, 5 H), 3.92 (1H, dd, J = 1.6 and 2.4 Hz, H-3), 3.80-3.65 (2H, m, H_2-6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 139.3, 138.9,

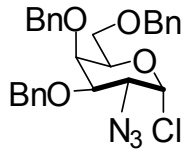
135.9, 129.7-128.8 (aromatic CH), 118.5, 92.9 (C-1), 79.3, 78.9, 76.6, 75.8, 75.3, 74.7, 74.2, 72.7, 69.6.



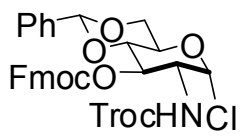
Compound 2d. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (1H, d, J = 4.0 Hz, H-1), 5.68 (1H, t, J = 10.4 Hz, H-3), 5.25 (1H, t, J = 10.4 Hz, H-4), 5.13 (1H, dd, J = 4.0 and 10.4 Hz, H-2), 4.46-4.40 (2H, overlapped signals, H-6a and H-5), 4.24 (1H, dd, J = 3.2 e 12.0 Hz, H-6b), 2.22 (x2), 2.17 and 2.15 (12H, 3 x s, 4 x -$COCH_3$). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 170.0, 169.9 and 169.7 (-*C*OCH_3), 90.0 (C-1), 70.7, 70.3, 69.4, 67.4, 61.1, 20.5.



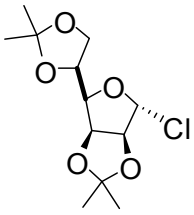
Compound 2e. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.96 (1H, d, J = 1.4 Hz, H-1), 5.57 (1H, dd, J = 3.4 and 10.1 Hz, H-3), 5.36-5.29 (2H, overlapped signals, H-2 and H-4), 4.31-4.22 (2H, overlapped signals, H-5 and H-6a), 4.11 (1H, dd, J = 1.7 and 12.1 Hz, H-6b), 2.15 (3H, s, -$COCH_3$), 2.04 (3H, s, -$COCH_3$), 2.02 (3H, s, -$COCH_3$), 1.98 (3H, s, -$COCH_3$).^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 169.5(x3), 88.7 (C-1), 71.4, 71.2, 67.6, 65.2, 61.5, 20.5(x4).



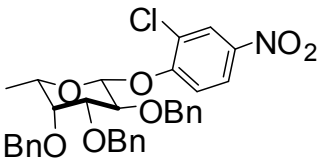
Compound 2f. ^{1}H NMR (400 MHz, $CDCl_3$)δ 7.50-7.25 (aromatic H), 6.16 (1H, bs, J = 3.2 Hz, H-1), 4.92-4.25 (3 x AB, 3 x CH_2Ph), 4.25 (1H, m), 4.20-4.10 (2H, overlapped signals), 4.02 (1H, bd, J = 9.2 Hz), 3.70-3.50 (2H, m, H_2-6). ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.6-127.8 (aromatic CH), 94.5 (C-1), 77.6, 75.0,73.5, 72.7, 72.6, 72.4, 67.7, 60.7.



Compound 2g. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76-7.15 (aromatic H), 6.21 (1H, d, J = 3.6 Hz, H-1), 5.59 (1H, s, -CHPh), 5.54 (1H, d, J = 9.3 Hz, -NH), 5.28 (1H, t, J = 10.0 Hz, H-3), 4.61 (2H, AB, CH_2CCl_3), 4.39-4.36 (4H, overlapped signals, Fmoc-$CHCH_2$ and H-2), 4.28-4.24 (2H, overlapped signals, H-5 and H-6_{eq}), 3.95-3.83 (2H, overlapped signals, H-4 and H-6_{ax}). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 154.1, 143.0, 141.2, 129.3,128.2, 127.9, 127.2, 126.2, 125.0, 120.0, 101.8, 93.6 (C-1), 78.0, 74.7, 72.8, 70.7, 68.0, 65.7, 56.3, 46.4, 45.9.



Compound 2h. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.06 (1H, bs, H-1), 4.94 (1H, bs, H-2), 4.87 (1H, dd, J = 5.8 and 3.6 Hz, H-3), 4.43 (1H, m, H-4), 4.13 (1H, m, H-5), 4.09 (1H, dd, J = 8.8 and 6.2 Hz, H-6a), 4.00 (1H, dd, J = 8.8 and 4.4 Hz, H-6b), 1.45 (6H, s, 2x –CH_3), 1.37 (3H, s, -CH_3), 1.32 (3H, s, -CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 113.2, 109.5, 97.6 (C-1), 89.1, 82.3, 78.5, 72.2, 66.7, 26.8, 25.7, 25.1, 24.6.



Compound 3k. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31-7.18 (Ar), 5.13-4.74 (7H, overlapped signals, 3x CH_2Ph and H-1), 4.25 (1H, dd, J = 9.4 and 7.6 Hz, H-2), 3.73-3.66 (3H, overlapped signals, H-3, H-4 and H-5), 1.28 (3H, d, J = 6.3 Hz, -CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 142.0, 138.1, 128.2-126.7, 126.0, 123.6, 114.8, 101.3, 81.9, 78.1, 75.7, 75.6, 74.8, 73.2, 71.3, 16.8.

References

1) (a) Matwiejuk, M.; Thiem, J. *Eur. J. Org. Chem*. **2011**, 5860–5878; (b) Boettcher, S.; Matwiejuk, M.; Thiem, J. Beilstein *J. Org. Chem*. **2012**, *8*, 413–420.
2) Richardson, M. B.; Torigo, S.; Yamasaki, S.; Williams, S. J. *Chem. Commun*. **2015**, *51*, 15027-15030.
3) Matsuo, I.; Wada, M.; Manabe, S.; Yamaguchi, Y.; Otake, K.; Kato, K.; Ito, Y. *J. Am. Chem. Soc*., **2003**, *125* , 3402–3403.
4) Ohrui, H.; Fox, J. J. *Tetrahedron Lett*. **1973**, *14*, 1951–1954.
5) (a) Bednarczyk, D.; Walczewska, A.; Grzywacz, D.; Sikorski, A.; Liberek, B.; Myszka, H. *Carbohydr. Res*. **2013**, *367*, 10–17; (b) Ziegler, T.; Seidl, U. *J. Carbohydr. Chem*. **1991**, *10*, 813-831.
6) a) Singhamahapatra, A.; Sahoo, L.; Paul, K. J. V.; Varghese, B.; Loganathan, D. *Tetrahedron Lett*. **2013**, *54*, 6121–6124; b) Watt, G. M.; Boons, G. J. *Carbohydr. Res*. **2004**, *338*, 181-193.
7) Bonomi, P.; Attieh, M. D.; Gonzato, C.; Haupt, K. *Chem. Eur. J*. **2016**, *22*,10150 –10154.
8) (a) Iversen, T.; Bundle, D. R. *Carbohydr. Res.* **1982**, *103*, 29–40; (b) Sugiyama, S.; Diakur, J. M. *Org. Lett.* **2000**, *2*, 2713-2715; c) Encinas, L.; Chiara, J.L. *J. Comb. Chem*. **2008**, *10*, 361-363.
9) Ernst, B.; Winkler, T. *Tetrahedron Lett*. **1989**, *30*, 3081-3084.
10) Hung, S. C.; Wong, C.-H. *Tetrahedron Lett*. **1997**, *37*, 4903-4906.
11) Ibatullin, F. M.; Selivanov, S.I. *Tetrahedron Lett.* **2002**, *43*, 9577, 9580.
12) Cicchillo, R. M.; Norris, P. *Carbohydr. Res.* **2000**, *328*, 431-434.
13) Chang, C.-W.; Chang, S.-S.; Chao, C.-S.; Mong, K. K.-T. *Tetrahedron Lett*. **2009**, *50*, 4536-4540.

14) For solvent-free alkylation methods: a) Ref. 137 in *Chapter 1* (see also Scheme 30-reaction a) in *Chapter 1* for an example); b) Ref. 138 in *Chapter 1*.

15) For solvent-free acetalation: Traboni, S.; Bedini, E.; Giordano, M.; Iadonisi, A. *Adv. Synt. Catal* .**2015**, *357*, 3562-3572. (Work discussed in *Chapter 2*)

16) For solvent-free silylations or tritylations and one-pot orthogonal protections: a) Traboni, S.; Bedini, E.; Iadonisi, A. *Beilstein J. Org. Chem*. **2016**, *12*, 2748-2756. (Work discussed in *Chapter 3*); b) Traboni, S.; Bedini, E.; Iadonisi, A. *ChemistrySelect* **2017**, *2*, 4906-4911. (Work discussed in *Chapter 4*)

17) For solvent-free one-pot orthogonal protection with alkyl and acetal/cyclic protecting groups: see work discussed in *Chapter 5*.

18) Magid, R. M.; Fruchey, S.; Johnson, W. L.; Allen, T. G. *J. Org. Chem.* **1979**, *44*, 359-361.

19) Pluempanupat, W.; Chantarasriwong, O.; Taboonpong, P.; Jangb, D. O.; Chavasiria, W. *Tetrahedron Lett*. **2007**, *48*, 223-226.

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

21) Obtained from the corresponding allyl glycoside: Lewicky, J.D.; Vlanova, M.; Jiang, Z.-H. *Carbohydr. Res*. **2011**, *346*, 1705-1713.

22) Obtained from the corresponding 1-O-acetylated precursor: (a) Cirillo, L.; Bedini, E.; Parrilli, M. Eur. *J. Org. Chem*. **2008**, *34*, 5704-5714; (b) Cirillo, L.; Di Nola, A.; Bedini, E.; Parrilli, M. *Carbohydr. Res*. **2009**, *344*, 2406-2411.

23) Obtained from the corresponding thioethyl glycoside: Comegna, D.; Bedini, E.; Parrilli, M. *Tetrahedron* **2008**, *64*, 3381-3391.

Chapter 7

Solvent-Free Conversion of Alcohols to Alkyl Iodides and One-Pot Elaborations Thereof

Introduction

Alkyl halides are versatile intermediates in organic synthesis, frequently involved in a great variety of synthetic transformations such as substitution by different nucleophiles, elimination reactions and rearrangements. For this reason, the transformation of alcohols into their corresponding alkyl halides, especially the most reactive iodides, is broadly applied in the synthetic elaboration of hydroxylated precursors. Several methods have been reported for iodination of alcohols. A possible strategy relies on a sulphonylation/iodination two-step sequence with an external iodide source. This approach suffers from some drawbacks such as prolonged reaction times, need for high boiling solvents and, very often, large amounts of metal halides.

A more direct approach is based on the combination of inorganic iodides with acidic promoters, such as KI/BF_3Et_2O,[1] NaI/BF_3Et_2O,[2] NaI/Amberlyst,[3] CsI/BF_3Et_2O,[4] KI/P_2O_5.[5] $ZrO_2/SO_4^{2-}/NaI$,[6] XtalFluorE/TEAI/NaI,[7] KSFclay supported/NaI.[8] Iodination of hydroxyl groups via O-alkyl isoureas[9] represents another example of alternative strategies. Typical drawbacks of all the mentioned approaches can be attributed to the low atom economy, use of

expensive, toxic or non commercially available reagents and limited target scope, being often restricted to highly reactive substrates.

Substitution reactions through oxyphosphonium intermediates[10] represent the most common approach currently used for alcohol iodination. Among several phosphine based systems reported to date such as PPh_3/CI_4,[11] PPh_3/NIS,[12] PPh_3/DEAD/MeI,[13] PPh_3/DEAD/LiI,[14] PPh_3/DDQ/TBAI,[15] polymer supported PPh_3/I_2/ImH,[16] PPh_3/I_2/polymer supported DMAP,[17] PPh_3/N-iodosaccharine,[18] the most common method relies on the combination of triphenylphosphine with I_2 in the presence of a base, usually imidazole, under homogeneous conditions. Popularity of this latter approach is likely due to the use of inexpensive and easy to handle reagents; reaction conditions usually depend on the nature of the substrates; as a general trend, longer times and higher boiling solvents (toluene, benzene or pyridine) are required for iodination of polar and more complex substrates such as, for example, carbohydrates.[19]

In the previous chapters have been introduced several practical methods entailing experimentally simple procedures for the synthetic manipulation of carbohydrates. Development of these methods highlighted that application of solvent-free conditions turns out to be especially advantageous to achieve a variety of derivatizations in a very short time and through simplified experimental procedures; solvent-free approaches have indeed proved effective both in the synthesis of glycosyl donors and in the regioselective and orthogonal protection of carbohydrates and polyols, easily accessible by fast one-pot sequences.[20-24]

Among the existing iodination methods, some greener procedures, eventually relying on solvent-free conditions, can be also found in literature, though in most cases, mainly applied to simple and reactive

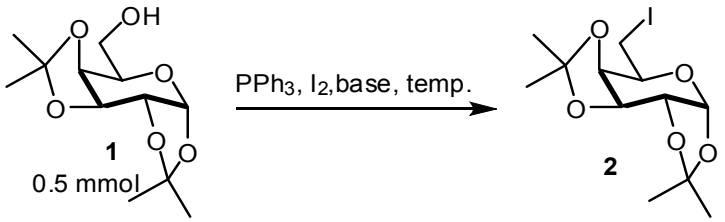
substrates such as benzylic or allylic alcohols.[25] Furthermore, most of these methods require additional equipment, often relying on microwave irradiation, ultrasonication or the use of ionic liquids which are environmentally safe but often expensive or non - commercially available.

In this chapter is shown the feasible application of a convenient solvent-free approach both to the quick conversion of hydroxyl groups to alkyl iodides, based on an unprecedented revisiting of the cheap PPh_3/I_2/base system, and in the streamlined one-pot transformation of thus obtained iodides to a wide number of targets, traditionally accessed through lengthy and unpractical procedures. As already discussed, application of a solvent-free and one-pot methodology to complex substrates as carbohydrates is especially appropriate to appreciate its advantages, due to the demanding experimental conditions often required for their derivatizations (high boiling solvents, inert atmosphere, lengthy multi-step synthetic sequences); on the other hand, the high degree of functionalization makes these substrates suitable to test the regioselectivity and compatibility of the method with different functional groups. Nevertheless, synthetic relevance of the herein discussed transformations, most of which being fundamental reactions in organic synthesis, spurred us to investigate this method in a more general fashion, testing its applicability both on simple alcohols and extending its scope to more complex saccharide substrates.

Results and Discussion

A preliminary set of experiments was aimed at the optimization of reaction conditions. We investigated iodination of model compound **1** in the presence of a slight stoichiometric excess of triphenylphosphine, iodine and a liquid amine, both serving as a base and allowing the mixing of reagents to obtain a mobile suspension. As shown in **Table 1**, iodination occurred slowly and with modest yields in the presence of DIPEA at 70°C (entry 1).

Table 1. Optimization of solvent-free iodination reaction



Entry	Base (equiv.)	PPh_3/I_2 (equiv.)	Temp., Time	Isolated yield (%)
1	DIPEA (3)	1.2 : 1.2	70°C, 2h	52
2	DIPEA (4)	1.2 : 1.2	80°C, 2h	60
3	DIPEA (3)	1.5 : 1.5	80°C, 1.5h	81
4	Pyridine (3)	1.5 : 1.5	80°C, 1.5h	54
5	2,6-Lutidine (3)	1.5 : 1.5	80°C, 0.5 h	91
6[a)]	2,6-Lutidine (3)	1.5 : 1.5	80°C, 0.5 h	90

[a)]The reaction was performed at a gram-scale.

The reaction was nearly unaffected by an increased amount of base as well as a higher temperature (entry 2), while better results were observed at 80°C with a slight increase of the stoichiometric excess of

phosphine and iodine (entry 3). It is worth noting that stoichiometric ratios are comparable to those adopted in the standard protocols both concerning the iodinating system and the base, therefore not sufficient to act as a solvent. In further experiments, alternative aromatic bases were analyzed. Interestingly, much lower yield was obtained in the presence of pyridine (entry 4), while its more hindered analogue, namely 2,6-lutidine, provided the best results (entry 5) in terms of both yield and rate. A plausible explanation of such behavior may be accounted for by the higher nucleophilicity of unsubstituted pyridine, resulting in the easier generation of alkyl-pyridinium adducts unable to evolve into desired iodinated products. In a subsequent experiment, reproducibility of Ph_3P/I_2/2,6-lutidine iodination method on a larger scale was also demonstrated (compare entry 5 with entry 6).

With optimized conditions in hand, solvent – free iodination was performed on different substrates, and in most cases occurred in very short times and excellent yields (see **Table 2**). At first, iodination of simple substrates (small and long chain alcohols, including the polar tetraethyleneglycol) was investigated, obtaining the desired products within a few minutes (entries 1-4).

Not unexpectedly, application of iodination conditions to diol **7**[26] directly provided five membered cyclic product **25** in quantitative yield (entry 5); it is worth noting in this regard that construction of cyclic ethers from diols usually entails very prolonged times and the use of much stronger bases.[27]

Satisfying results, though with low stereocontrol, were also observed with some secondary hydroxyls (entries 6 - 8) at a higher temperature. Especially good yields were observed with steroidal substrates (entries 6 – 7), while *tert*-butyl cyclohexanol afforded a lower iodination yield, in accordance with a trend evidenced by previous literature reports.[28]

Table 2. Iodination of alcohols and primary saccharide carbinols under solvent-free conditions.[a]

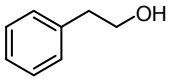
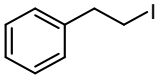
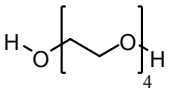
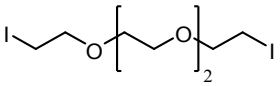
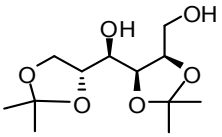
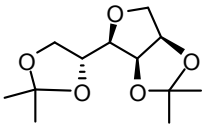
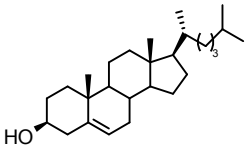
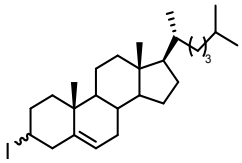
Entry	Substrate	Time (min)[b]	Product, isolated yield
1	$CH_3(CH_2)_7CH_2OH$ **3**	15	$CH_3(CH_2)_7CH_2I$ **21**, 88%
2	 **4**	20	 **22**, 76%
3[c]	 **5**	30	 **23**, 85%
4	$BrCH_2(CH_2)_9CH_2OH$ **6**	15	$BrCH_2(CH_2)_9CH_2I$ **24a** + $ICH_2(CH_2)_9CH_2I$ **24b** 89%[d] (1:1 ratio)
5	 **7**	30	 **25**, 99%
6[e]	 **8**	90	 α/β 1:5 **26**, 86%

Table 2. (Continued)

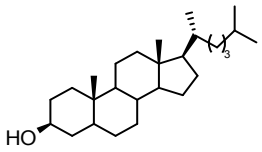
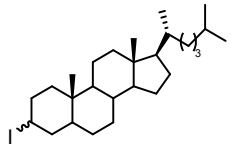
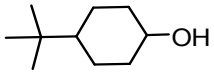
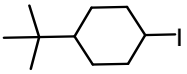
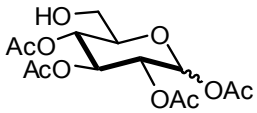
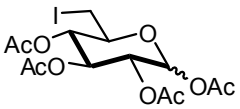
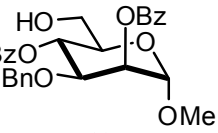
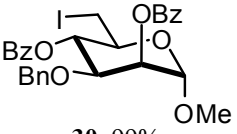
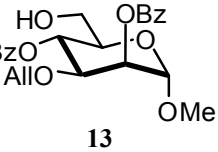
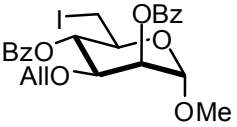
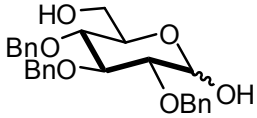
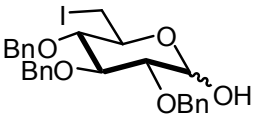
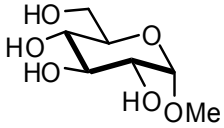
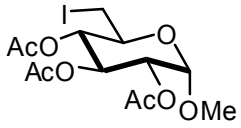
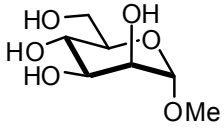
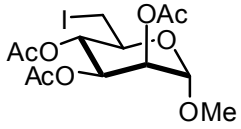
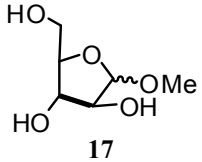
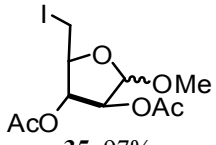
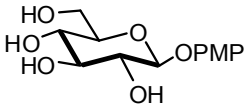
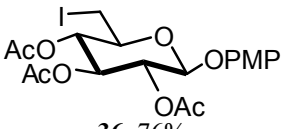
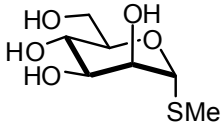
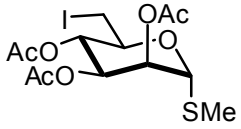
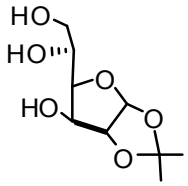
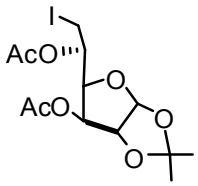
Entry	Substrate	Time (min)[b)]	Product, isolated yield
7[e)]	 **9**	60	 α/β 1:0.4 **27**, 90%
8[e)]	 **10** 1:2 *cis/trans*	60	 **28**, 30% 1:2 *cis/trans*
9	 **11**	30	 **29**, 95%
10	 **12**	30	 **30**, 99%
11	 **13**	30	 **31**, 99%
12	 **14**	30	 **32**, 98%

Table 2. (Continued)

Entry	Substrate	Time (min)[b)]	Product, isolated yield
13[f)]	 **15**	30	 **33**, 88%
14[f)]	 **16**	30	 **34**, 85%
15[f)]	 **17**	30	 **35**, 97%
16[f)]	 **18**	30	 **36**, 76%
17[f)]	 **19**	30	 **37**, 82 %
18[f)]	 **20**	15	 **38**, 82 %

[a)]General conditions: PPh_3 (1.5 equiv.), I_2 (1.5 equiv.), 2,6–lutidine (3 equiv.), 80°C.
[b)] Reaction time not including *in situ* per–*O*–acetylation step, when required.
[c)] Double amount of PPh_3, I_2 and 2,6 - lutidine was employed. [d)] Overall yield referred to hydroxyl group iodination. [e)] The reaction was performed at 100°C. [f)] Per-*O*–acetylation was performed after iodination by *in situ* addition of Ac_2O and pyridine at room temperature.

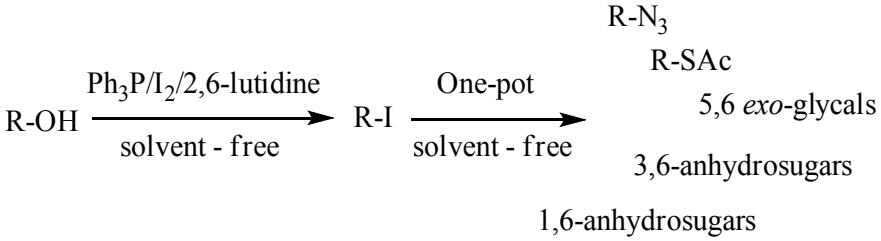
Subsequent iodination experiments were addressed to highly functionalized molecules such as saccharide substrates. As evidenced in **Table 2**, solvent - free iodination of primary hydroxyls on differently protected carbohydrates was achieved in nearly quantitative yields within a short time (entries 9 - 12). Interestingly, a selective iodination was also observed with 1,6-diol **14**,[29] leaving the anomeric hemiacetal unreacted. Regioselective iodination proved also effective on a variety of unprotected furanosides and pyranosides bearing different aglycones, (including the versatile thioglycoside moiety),[30] whose corresponding iodides were more conveniently isolated in a per–*O*–acetylated form (see entries 13 - 18). Interestingly, iodination of **20** under these conditions was found remarkably efficient, leading to only minimal amounts of 5,6 - unsaturated byproduct in comparison to the standard protocols.[31]

In order to extend the scope of this method, a further effort was aimed at developing fast one – pot elaborations of the obtained alkyl iodides. As a general principle, installation of a good leaving group in place of a hydroxyl functionality paves the way towards many useful transformations. In this regard, one–pot strategies addressed to derivatization of hydroxylated substrates are receiving ever more attention.[32] Also in carbohydrate chemistry, the transformation of a saccharide alcohol into a leaving group represents a key preliminary step to a variety of important elaborations, often involving the anomeric position, but many useful targets and building blocks can also be prepared through displacement of a leaving group at the primary position. Some important examples that were selected in the course of this investigation, are the installation of azides and sulfur-containing functionalities, useful precursors in several synthetic applications, including the broadly applied click conjugations (as also anticipated in

Chapter 1);[33] further effort was also addressed towards the generation of *exo*-glycals[34] and anhydrosugars[35]representing relevant structures in organic and oligosaccharide synthesis.[36]

The most common strategies adopted for these transformations involve halides or sulphonate intermediates, though alternative approaches relying on either Appel or Mitsunobu conditions have been also widely employed.[11,37] As a general observation, many practical drawbacks are associated with the reported procedures, requiring high boiling solvents such as DMF or DMSO, very long reaction times, the need for harsh reaction conditions and the frequent use of toxic, unsafe, labile or expensive reagents. As with iodination of alcohols, more advanced methods have also been developed for some of these transformations[38] either entailing solvent–free conditions or the use of expensive or non commercially available ionic liquids. In these approaches, microwave irradiation is often required and the scope is usually restricted to simple substrates. Thus, some model compounds were selected to demonstrate the general feasibility of the mentioned elaborations in a convenient solvent–free one–pot sequence (**Table 3**). Iodination was performed in the first step as previously described, followed by simple addition of the requisite reagents and adjustment, if required, of the reaction temperature.; the desired targets were obtained in high yields both from alcohols and saccharide substrates within very short reaction times if compared to current protocols. At first, one–pot generation of azides was investigated. As shown in **Table 3**, displacement of iodide by azide ion occurred quickly in high yields by in situ addition of a moderate excess of tetrabutylammonium azide (entries 1-3). Interestingly, attempted solvent–free substitution in the presence of sodium azide, mostly employed in the standard azidation procedures, resulted in an almost quantitative recovery of the iodinated intermediate (entry 4).

Table 3. One – pot elaborations of iodinated intermediates through solvent – free sequences.



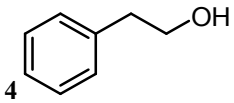
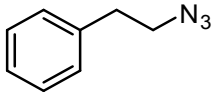
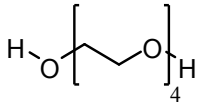
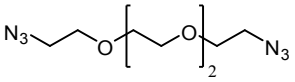
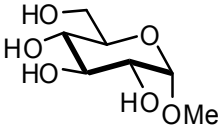
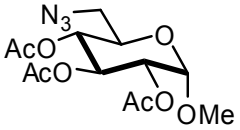
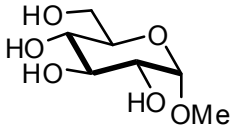
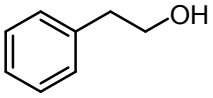
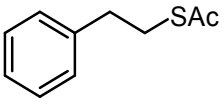
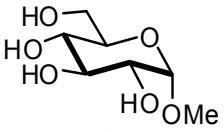
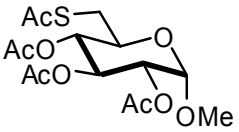
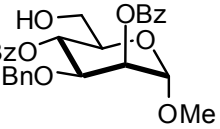
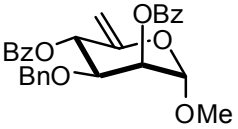
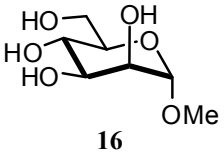
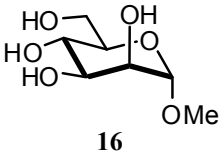
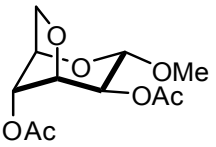
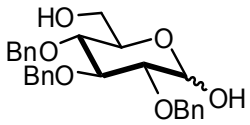
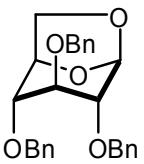
Entry	Substrate	2nd step conditions (eq.)[a)]	Product, yield[b)]
1	 **4**	$TBAN_3$ (3), 80°C, 1h	 **39**, 95%
2	 **5**	$TBAN_3$ (6), 80°C, 80 min	 **40**, 98%
3[c)]	 **15**	$TBAN_3$ (3), 80°C, 75 min	 **41**, 80%
4[c)]	 **15**	NaN_3 (3), 80°C, 75 min	No reaction (iodide recovered)
5	 **4**	KSAc (3), 80°C, 20 min	 **42**, 82 %

Table 3. (Continued).

Entry	Substrate	2nd step conditions (eq.)[a]	Product, yield[b]
6[c]	 **15**	KSAc (3), 80°C, 20 min	 **43**, 91%
7	 **12**	DBU (5), 80°C, 45 min	 **44**, 72%
8[c]	 **16**	DIPEA (4), 80°C to 110°C, 5 h	No reaction (iodide recovered)
9[c]	 **16**	DIPEA (4), Bu_2SnO (0.1) 100°C, 45 min	 **45**, 92%
10	 **14**	DIPEA (4),[d] 110°C, 80 min	 **46**, 76 %

[a] Upon completion of iodination step (as described in Table 2), the requisite reagents were added and the reaction temperature adjusted if necessary. Reaction times do not include *in situ* per – *O* – acetylation, when required. [b] Isolated yield over 2 steps.
[c] Per –*O*– acetylation was performed after completion of second step by *in situ* addition of Ac_2O and pyridine at room temperature.[d] DIPEA was added portionwise: 3 equiv. after completion of iodination, then further addition (1 equiv.) after 1 h.

This result may suggest a significant role of tetrabutylammonium counterpart in improving nucleophilicity and miscibility of azide ions

in a solvent–free environment, thus allowing the reaction to occur in the absence of polar solvents used in the standard protocols. Even more efficient was the substitution reaction of saccharide and alkyl iodides with a sulfur nucleophile. Addition of potassium thioacetate to the iodination mixture, resulted in the very fast generation of thioacetate esters **42** and **43** in high yields (entries 5 and 6). Rapid access to useful 5,6 exo – glycals was also demonstrated by the efficient one – pot generation of **44** (entry 7), achieved by a DBU-promoted elimination of the corresponding 6-iodo derivative.

In further experiments, a one-pot iodination/cyclization was attempted on saccharide substrates, resulting in the fast and easy generation of either 3,6- or 1,6-anhydrosugars, usually requiring harsh reaction conditions such as the use of strong acids or bases and prolonged reaction times. To achieve 3,6–anhydromannoside **45** (entry 9), we took advantage of a recent protocol developed in our laboratory allowing solvent–free selective alkylation of polyols catalyzed by Bu_2SnO.[20a] Application of similar reaction conditions proved effective in the intramolecular substitution affording **45** in a short time and very high yield. Success of the reaction is critically dependent on the generation of a 2,3-*O*-stannylene-acetal[39] as evidenced by the lack of cyclization observed in the absence of Bu_2SnO (entry 8). This one-pot strategy provided a convenient alternative both to strong alkali-promoted cyclization and to previous examples of Bu_2SnO mediated intramolecular etherification of tosylates,[35,40] requiring a stoichiometric amount of the toxic tin reagent, longer reaction times and high boiling solvents. Unlike tin–mediated intermolecular alkylations, no ammonium halide additive was needed for the cyclization. This indicates that iodide ions produced in the first step are sufficient for opening the stannylene intermediate, which is a critical step in the

alkylation mechanism.[39] A 1,6-cyclization was achieved on **14** by addition of only a slight excess of DIPEA at a higher temperature after the first iodination step, to provide 1,6 anhydrosugar **46** in high yield (entry 10), reasonably due to the higher acidity of the hemiacetal hydroxyl.

It is worth noting that undesired generation of anhydrosugars was never detected in the herein described preparation and elaborations of saccharide iodides, though representing a frequent side-process in standard synthetic elaborations of 6-O-sulphonyl or 6-halo–6-deoxy sugars.[37 l,41]

Conclusions

In conclusion, in this chapter is described a cheap reagent system based on the combination of triphenylphosphine, iodine and 2,6-lutidine allowing fast iodination of alcohols under mild solvent–free conditions. This method is convenient and experimentally practical also in comparison to previously described solvent–free strategies, owing to the avoided use of microwaves, ultrasound or expensive reagents. In addition, the proposed method is compatible with the one–pot generation of several useful compounds (azides, thio-derivatives, *exo*-glycals and anhydrosugars) through fully solvent–free sequences involving an iodinated intermediate.

Experimental Section

General remarks

Both triphenylphosphine and iodine were slightly grinded prior to their use in solvent – free iodination reactions. Reactions were always monitored by TLC analysis. After elution, detection of compounds on the plates was performed by treatment with 5% concentrated H_2SO_4 in ethanol followed by heating at 230°C. Eventual detection of UV-visible compounds under UV lamp preceded the acidic treatment. NMR spectra were recorded in a 400 MHz device.

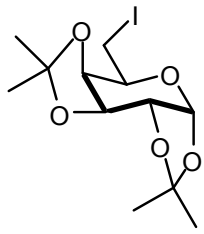
General procedure for solvent - free iodination of alcohols

A mixture of hydroxylated substrate (0.5 mmol), triphenylphosphine (0.75 mmol, 197 mg) and 2,6 – lutidine (1.5 mmol, 174 μL) was vigorously stirred at room temperature for few seconds until obtainment of a mobile suspension. The mixture was then heated in a oil bath at the requisite temperature and iodine (0.75 mmol, 191 mg) was added. Immobilization of the magnetic bar due to generation of solid byproducts may occur after addition of iodine. If necessary, a homogeneous stirring was restored by a brief solicitation with an external magnet. After completion of the reaction (see **Table 2** for experimental conditions and times), the system was allowed to cool to room temperature. The mixture was diluted with dichloromethane and washed with water containing a little amount of $Na_2S_2O_3$ (sufficient to reduce residual iodine in organic phase). The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude residue was submitted to silica – gel flash chromatography (eluent: hexane / ethyl acetate mixtures) affording the purified iodinated product. Where necessary (according to **Table2**), Ac_2O and pyridine

were added in situ at room temperature after iodination. Upon completion of per – O – acetylation, excess of acetic anhydride was quenched with MeOH followed by extractive work – up as described.

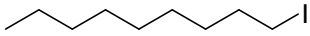
General procedure for solvent – free iodination and one – pot elaboration sequences

Iodination was performed in the first step as above described. As TLC displayed completion of the reaction, the reagents involved in the second step were added *in situ*, without any intermediate work–up and the mixture was stirred at the requisite temperature (see **Table3** for reagents and reaction conditions). After completion of the second step (as observed by TLC), standard extractive work – up was performed, as described for simple iodination, followed by chromatographic purification of the final product. When necessary, (according to **Table3**) per–*O*–acetylation was directly performed after the second step, prior to the extractive work – up.

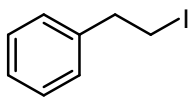


1,2:3,4-Di-*O*-isopropylidene-6-iodo-α-D-galactopyranose (2):[42] Foam; R_f= 0.33 (9:1 v/v hexane / ethyl acetate);^{1}H NMR (400 MHz, $CDCl_3$): δ 5.52 (1H, d, J = 5.0 Hz, H-1), 4.59 (1H, dd, J = 7.8, 2.4 Hz, H-3), 4.38 (1H, dd, J = 7.8, 1.7 Hz, H-4), 4.28 (1H, dd, J = 5.0, 2.4 Hz, H-2), 3.94 – 3.90 (1H, m, H-5), 3.29 (1H, dd, J = 9.9, 6.8 Hz, H-6a), 3.18 (1H, dd, J = 9.9, 7.2 Hz, H-6b), 1.52, 1.42, 1.33, 1.31 (each 3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 109.4, 108.7, 96.6 (C-1), 71.5, 71.0, 70.5, 68.8, 25.8 (x2), 24.8, 24.3, 2.2 (C-6). MALDI-MS $[M+Na]^+$ Calcd for ($[C_{12}H_{19}O_5I$ +

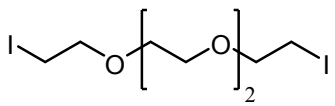
Na]$^+$): 393.02; found 393.10; Anal. Calcd for $C_{12}H_{19}O_5I$: C, 38.93; H, 5.17. Found C, 39.00; H, 5.15.



1-Iodononane (21):[43] Colorless oil; R_f = 0.82 (hexane); oil;^{1}H NMR (400 MHz, $CDCl_3$): δ 3.19 (2H, t, J = 7.0 Hz, CH_2-I), 1.83 (2H, m, C*H*$_2$CH$_2$I), 1.39 – 1.28 (12H, m, alkyl chain CH_2 protons), 0.89 (3H, t, J = 6.8 Hz, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.6, 31.8, 30.5, 29.3, 29.2, 28.5, 22.6, 14.1, 7.2 (CH_2I). MALDI-MS [M+Na]$^+$ Calcd for ([$C_9H_{19}I$ + Na]$^+$): 277.04; Found 277.00; Anal. Calcd for $C_9H_{19}I$: C, 42.53; H, 7.54. Found C, 42.35; H, 7.60.

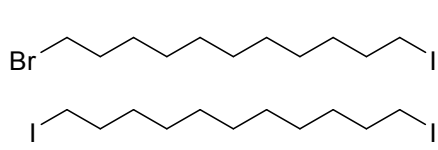


(2-Iodoethyl) benzene (22):[5] Colorless oil; R_f= 0.79 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.35 – 7.21 (5H, m, Ar), 3.37 (2H, t, J = 7.8 Hz, CH_2Ph), 3.21 (2H, t, J = 7.8 Hz, CH_2I); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.5 (quaternary carbon), 128.6 – 126.8 (Ar), 40.3 (CH_2Ph), 5.6 (CH_2I). MALDI-MS [M+Na]$^+$ Calcd for ([C_8H_9I + Na]$^+$): 254.96; found 255.00; Anal. Calcd for C_8H_9I: C, 41.41; H, 3.91. Found C, 41.35; H, 3.90.

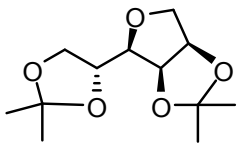


1-Iodo-2-(2-(2-(2-iodoethoxy)ethoxy)ethoxy)ethane (23):[44] Yellowish oil; R_f = 0.44 (7:3 v/v hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.77 (4H, t, J = 6.9 Hz, O-C*H*$_2$CH$_2$I), 3.65 – 3.69 (12H, m, OCH_2CH_2O units), 3.28 (4H, t, J = 6.9 Hz, CH_2I); ^{13}C NMR (100 MHz, $CDCl_3$): δ 71.9, 70.6, 70.2, 2.9 (CH_2I). MALDI-MS [M+Na]$^+$ Calcd for ([$C_8H_{16}I_2O_3$ + Na]$^+$):

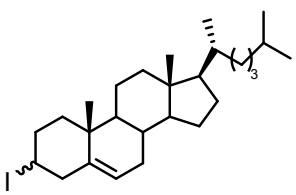
435.91; found 435.80; Anal. Calcd for $C_8H_{16}I_2O_3$: C, 23.21; H, 3.90. Found C, 23.25; H, 3.85.



Compounds 24 a and 24 b (1:1 ratio):[9] Colorless oil; R_f = 0.64 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.39 (2H, t, J = 6.8 Hz, CH_2Br), 3.17 (6H, t, J = 7.0 Hz, CH_2I), 1.82 – 1.79 (8H, m, overlapped signals, C*H*$_2$CH$_2$Br and C*H*$_2$CH$_2$I), 1.39 – 1.27 (20H, m, alkyl chain protons); ^{13}C NMR (100 MHz, $CDCl_3$): δ 33.9 – 28.1, 7.3 (CH_2I).

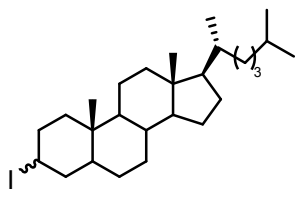


Compound 25: Colorless oil; $[\alpha]_D^{23}$: -46.2 (*c* 1.0, $CHCl_3$); R_f = 0.67 (1:1 hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.77 and 4.71 (1H each, dd, J = 6.0, 3.6 Hz, H-2 and H-3), 4.39 (1H, m, H-5), 4.10 – 4.04 (2H, m, overlapped signals, H-6a and H-6b), 4.01 (1H, bd, J = 10.8 Hz, H-1a), 3.50 – 3.45 (2H, m, overlapped signals, H-1b and H-4), 1.47 (3H, s, CH_3), 1.43 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.32 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 112.2, 108.9 (quaternary carbons), 82.6, 80.9, 80.2, 73.1, 73.0, 66.7, 26.8, 25.8, 25.1, 24.4. MALDI-MS $[M+Na]^+$ Calcd for ($[C_{12}H_{20}O_5 + Na]^+$): 267.12: Found 267.05; Anal. Calcd for $C_{12}H_{20}O_5$: C, 59.00; H, 8.25. Found C, 59.13; H, 8.15.

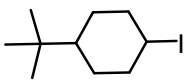


Compound 26 (α/β ratio 1:5):[45] Yellowish oil; R_f = 0.94 (hexane); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.33 (1H, bs, C=CH), 4.88 (1H, bs, $CH_{eq}I$), 4.03 (1H, m, $CH_{ax}I$), 2.93 (1H, m, allyl H), 2.67 (1H, m, allyl H), 2.15 – 0.67 (m, aliphatic protons); ^{13}C

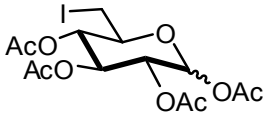
NMR (100 MHz, $CDCl_3$): δ 142.8, 121.7 (C=C), 56.7 – 11.8. MALDI-MS $[M+Na]^+$ Calcd for ($[C_{25}H_{41}I + Na]^+$): 491.22; found 491.27; Anal. Calcd for $C_{25}H_{41}I$: C, 64.09; H, 8.82. Found C, 64.15; H, 8.73.



Compound 27 (α/β ratio 1:0.4):[45] Foam; R_f = 0.83 (hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 4.95 (1H, bs, $CH_{eq}I$), 4.16 (1H, m, $CH_{ax}I$), 2.01 – 0.60 (m, aliphatic protons); ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.4, 56.3, 54.4, 49.6, 42.9, 42.6, 41.2, 39.9, 39.5, 36.5, 36.1, 35.7, 35.4, 31.8, 30.6, 28.2, 27.9, 24.1, 23.8, 22.8, 22.5, 20.9, 18.6, 12.0. MALDI-MS $[M+Na]^+$ Calcd for ($[C_{25}H_{43}I + Na]^+$) 493.23; found 493.15; Anal. Calcd for $C_{25}H_{43}I$: C, 63.82; H, 9.21. Found C, 63.87; H, 9.11.

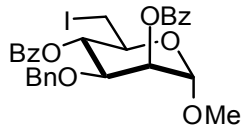


4-*tert*-Butyl-cyclohexyl iodide (*cis*/*trans* ratio 1:2) (28):[28] Colorless oil; R_f = 0.79 (hexane); ^1H NMR (400 MHz, $CDCl_3$): δ 4.89 (1H, bs, CHI *cis* isomer), 4.09 (1H, m, CHI *trans* isomer), 2.48 – 1.09 (18H, m, ring backbone protons), 0.87 (9H, s, *tert*-butyl CH_3 *cis* isomer), 0.85 (9H, s, *tert*-butyl CH_3 *trans* isomer); ^{13}C NMR (400 MHz, $CDCl_3$): δ 46.7, 41.1, 36.8, 32.6, 30.8, 30.3, 27.4, 23.3. MALDI-MS $[M+Na]^+$ Calcd for ($[C_{10}H_{19}I + Na]^+$) 289.04: found 289.00; Anal. Calcd for $C_{10}H_{19}I$: C, 45.13; H, 7.20. Found C, 45.07; H, 7.12.

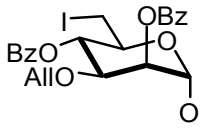


1,2,3,4-Tetra-*O*-acetyl-6-deoxy-6-iodo-α/β-D-glucopyranoside (29) (α/β ratio 1:2):[19b] Foam; R_f = 0.53 (3:2 v/v hexane/ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$): δ 6.31 (1H, d, J = 3.8 Hz, H-1α), 5.72 (1H, d, J = 8.2, H-1β),

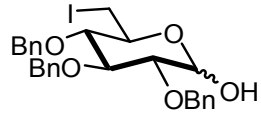
5.44 (1H, t, J = 9.6 Hz, H-3 α), 5.23 (1H, t, J = 9.4, H-3β), 5.10 (1H, t, J = 8.2 Hz, H-2 β), 5.06 (1H, dd, J = 9.6, 3.8 Hz, H-2α), 4.96 (2H, overlapped signals, t, J = 9.4 Hz, H-4α and H-4β), 3.80 (1H, m, H-5α), 3.55 (1H, m, H-5β), 3.29 (2H, m, H-6α), 3.14 (2H, m, H-6β), 2.16 – 1.98 (24H, overlapped signals, CH_3C=O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0 – 168.8 (C=O), 91.3 (C-1β), 88.8 (C-1α), 73.3, 72.3, 72.1, 71.9, 70.4, 70.2, 69.4, 69.1, 20.7 –20.5 (acetyl CH_3), 3.3 (C-6 α), 2.4 (C-6 β). MALDI-MS $[M+Na]^+$ Calcd for ($[C_{14}H_{19}O_9I + Na]^+$): 481.00; found 481.05; Anal. Calcd for $C_{14}H_{19}O_9I$: C, 36.70; H, 4.18. Found C, 36.73; H, 4.14.



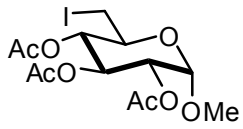
Methyl 2,4-di-*O*-benzoyl-3-O-benzyl-6-deoxy-6-iodo-α-D-mannopyranoside (30): Colorless oil; $[\alpha]_D^{23}$: -52.8 (*c* 1.0, $CHCl_3$); R_f = 0.61 (7:3 v/v hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.14 – 7.09 (15H, m, Ar), 5.63 (1H, dd, J = 3.3, 1.8 Hz, H-2), 5.49 (1H, t, J = 9.7 Hz, H-4), 4.93 (1H, d, J = 1.8 Hz, H-1), 4.64 and 4.47 (2H, 2 AB d, J = 12.5 Hz, CH_2Ph), 4.09 (1H, dd, J = 9.7, 3.3 Hz, H-3), 3.88 (1H, m, H-5), 3.51 (3H, s, OCH_3), 3.40 (1H, dd, J = 10.8, 2.5 Hz, H-6a), 3.31 (1H, dd, J = 10.8, 8.6 Hz, H-6b); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 166.2, 137.4, 133.4 – 127.8 (Ar), 99.0 (C-1), 73.8, 71.8, 70.9, 70.5, 68.5, 55.6, 4.9 (C-6). MALDI-MS $[M+Na]^+$ Calcd for ($[C_{28}H_{27}O_7I + Na]^+$): 625.07; found 625.13; Anal. Calcd for $C_{28}H_{27}O_7I$: C, 55.83; H, 4.52. Found C, 55.74; H, 4.60.



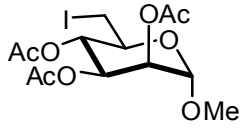
Methyl 3-*O*-allyl-2,4-di-*O*-benzoyl-6-deoxy-6-iodo-α-D-mannopyranoside (31): Colorless oil; R_f= 0.64 (7:3 v/v hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 – 7.45 (10H, m, Ar), 5.73 – 5.62 (1H, m), 5.55 (1H, dd, J = 3.3, 1.8 Hz, H-2), 5.45 (1H, t, J = 9.7 Hz, H-4), 5.14 (1H, dd, J = 17.2, 1.6 Hz), 5.03 (1H, dd, J = 10.4, 1.6 Hz), 4.92 (1H, d, J = 1.8 Hz, H-1), 4.09 – 3.93 (4H, m, overlapped signals, H-3, H-5, OCH_2), 3.54 (3H, s, OCH3), 3.42 (1H, dd, J = 10.8, 2.4 Hz, H-6a), 3.31 (1H, dd, J = 10.8, 8.7 Hz, H-6b); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 166.1, 134.1 – 117.6 (Ar and sp^2 C), 98.9 (C-1), 74.1, 72.1, 70.8, 70.5, 69.1, 55.6, 4.9 (C-6). MALDI-MS $[M+Na]^+$ Calcd for ($[C_{24}H_{25}O_7I + Na]^+$) 575.05; found 575.02; Anal. Calcd for $C_{24}H_{25}O_7I$: C, 52.19; H, 4.56. Found C, 52.12; H, 4.59.



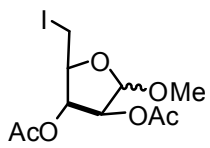
2,3,4-Tri-*O*-benzyl-6-deoxy-6-iodo-α/β-D-glucopyranose (32) (α/β ratio 2:1): Colorless oil; R_f= 0.61 (3:2 v/v hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 - 7.29 (30H, m, Ar), 5.24 (1H, d, J = 3.6 Hz, H-1α), 4.99 - 4.69 (5H, m, overlapped signals, CH_2Phα, CH_2Phβ and H-1β), 4.04 (1H, t, J = 9.2 Hz, H-3α), 3.71 (1H, t, J = 9.1 Hz, H-3β), 3.65 - 3.62 (1H, m, H-5α), 3.59 (1H, dd, J = 9.2, 3.6 Hz, H-2α), 3.49 - 3.33 (7H, m, overlapped signals, H-6aα, H-6aβ, H-6bα, H-6bβ, H-4α, H-4β and H-2β), 3.16 (1H, m, H-5β) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9, 137.7, 137.6, 128.5 – 127.9 (Ar), 97.2 (C-1β), 91.1(C-1α), 83.9, 83.2, 81.3, 81.2, 80.2, 75.7, 75.4, 74.7, 73.3, 68.9, 8.6(C-6α), 6.8(C-6β). MALDI-MS $[M+Na]^+$ Calcd for ($[C_{27}H_{29}O_5I + Na]^+$) 583.10; found 583.14; Anal. Calcd for $C_{27}H_{29}O_5I$: C, 57.87; H, 5.22. Found C, 57.96; H, 5.12.



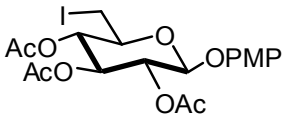
Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside (33):[46] Foam; R_f = 0.39 (7:3 v/v hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.42 (1H, t, J = 9.7, H-3), 4.92 (1H, d, J = 3.7, H-1), 4.86 – 4.81 (2H, m, overlapped signals, H-2 and H-4), 3.75 (1H, m, H-5), 3.44 (3H, s, OCH_3), 3.26 (1H, dd, J = 10.9, 2.4 Hz, H-6a), 3.10 (1H, dd, J = 10.9, 8.3 Hz, H-6b), 2.03 (3H, s, CH_3C=O), 2.01 (3H, s, CH_3C=O), 1.96 (3H, s, CH_3C=O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9 (x2), 169.5, 96.6 (C-1), 72.3, 70.7, 69.5, 68.5, 55.6, 21.0 (x3), 3.6 (C-6). MALDI-MS $[M+Na]^+$ Calcd for ($[C_{13}H_{19}O_8I + Na]^+$) 453.00; found 452.94; Anal. Calcd for $C_{13}H_{19}O_8I$: C, 36.30; H, 4.45. Found C, 36.37; H, 4.40.



Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-mannopyranoside (34):[37m] Foam; R_f = 0.34 (7:3 v/v hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.36 (1H, dd, J = 9.8, 3.4 Hz, H-3), 5.27 (1H, dd, J = 3.4, 1.7 Hz, H-2), 5.17 (1H, t, J = 9.8 Hz, H-4), 4.79 (1H, d, J = 1.7 Hz, H-1), 3.86 (1H, m, H-5), 3.54 (3H, s, OCH_3), 3.37 (1H, dd, J = 10.8, 2.4 Hz, H-6a), 3.24 (1H, dd, J = 10.8, 8.9 Hz, H-6b), 2.21 (3H, s, CH_3C=O), 2.13 (3H, s, CH_3C=O), 2.05 (3H, s, CH_3C=O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 169.6 (x2), 98.3 (C-1), 69.9, 69.8, 69.4, 68.5, 55.4, 20.6 – 20.4 (acetyl CH_3), 3.7 (C-6). MALDI-MS $[M+Na]^+$ Calcd for ($[C_{13}H_{19}O_8I + Na]^+$) 453.00: Found 452.94; Anal. Calcd for $C_{13}H_{19}O_8I$: C, 36.30; H, 4.45. Found C, 36.37; H, 4.40.

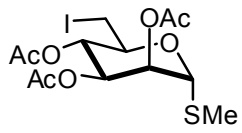


Methyl 2,3-di-*O*-acetyl-5-deoxy-5-iodo-α/β-D-arabinofuranoside (35) (α/β ratio 2.5:1): Yellowish oil; R_f = 0.33 (7:3 v/v hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.26 (1H, dd, J = 6.5, 4.5 Hz, H-3β), 5.11 (1H, d, J = 4.5 Hz, H-1β), 5.06 (1H, bd, J = 1.5 Hz, H-2α), 5.04 (1H, dd, J = 6.5, 4.5 Hz, H-2β), 4.93 (1H, bs, H-1α), 4.86 (1H, dd, J = 5.2, 1.5 Hz, H-3α), 4.11 – 4.07 (1H, m, H-4β), 4.06 – 4.02 (1H, m, H-4α), 3.55 – 3.48 (2H, m, overlapped signals, H-5aα and β), 3.42 (3H, s, OCH_3 β), 3.40 – 3.38 (4H, m, overlapped signals, H-5bα and OCH_3α), 3.33 (1H, m, H-5bβ), 2.09 (12H, s, CH_3C=O);^{13}C NMR (400 MHz, $CDCl_3$): δ 170.1 (x2), 169.7 (x2), 106.4 (C-1α), 101.2 (C-1β), 81.8 (x2), 81.2 (x2), 80.2, 78.3, 55.8, 54.9, 20.7 (x4), 7.5 (C-5β), 5.1 (C-5α). MALDI-MS $[M+Na]^+$ Calcd for ($[C_{10}H_{15}O_6I + Na]^+$) 380.98; found 381.07; Anal. Calcd for $C_{10}H_{15}O_6I$: C, 33.54; H, 4.22. Found C, 33.57; H, 4.15.

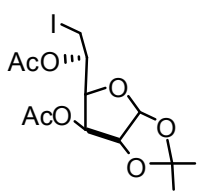


***p*-Methoxy -phenyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-α-D-glucopyranoside (36):** Glassy solid; $[\alpha]_D^{23}$: -22.1 (*c* 1.2, $CHCl_3$); R_f= 0.28 (7:3 v/v hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.05 (2H, d, J = 9.1 Hz, Ar), 6.82 (2H, d, J = 9.1 Hz, Ar), 5.27 – 5.19 (2H, m, overlapped signals, H-2 and H-3), 4.97 – 4.93 (2H, m, overlapped signals, H-1 and H-4), 3.76 (3H, s, OCH_3), 3.69 – 3.63 (1H, m, H-5), 3.31 (1H, dd, J = 11.0, 2.5 Hz, H-6a), 3.16 (1H, dd, J = 11.0, 8.8 Hz, H-6b), 2.06 (6H, s, CH_3C=O x2), 2.01 (3H, s, CH_3C=O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.1, 169.4, 169.2, 155.7, 150.8, 118.8, 114.5, 100.2 (C-1), 74.1, 72.2, 71.9, 71.3, 55.6, 20.6 (x3), 2.4 (C-6). MALDI-MS [M+Na]+ Calcd for ($[C_{19}H_{23}O_9I + Na]^+$) 545.03: Found

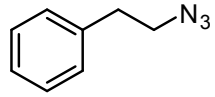
544.95; Anal. Calcd for $C_{19}H_{23}O_9I$: C, 43.69; H, 4.44. Found C, 43.78; H, 4.38.



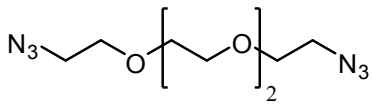
Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-iodo-1-thio-α-D-mannopyranoside (37):[47] Yellowish oil; R_f = 0.36 (7:3 v/v hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.32 (1H, dd, J = 3.4, 1.5 Hz, H-2), 5.24 (1H, dd, J = 9.8, 3.4 Hz, H-3), 5.17 (1H, d, J = 1.5 Hz, H-1), 5.14 (1H, t, J = 9.8 Hz, H-4), 4.19 (1H, m, H-5), 3.30 (1H, dd, J = 10.8, 2.5 Hz, H-6a), 3.20 (1H, dd, J = 10.8, 8.8 Hz, H-6b), 2.24 (3H, s, SCH_3), 2.14 (3H, s, CH_3C=O), 2.07 (3H, s, CH_3C=O), 1.98 (3H, s, CH_3C=O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.7 (x2), 169.6, 83.5 (C-1), 70.8, 70.4, 70.1, 69.0, 20.8 – 20.5 (acetyl CH_3), 13.9, 3.5 (C-6). MALDI-MS $[M+Na]^+$ Calcd for ($[C_{13}H_{19}O_7SI + Na]^+$) 468.98: Found 469.03; Anal. Calcd for $C_{13}H_{19}O_7SI$: C, 34.99; H, 4.29. Found C, 35.03; H, 4.31.



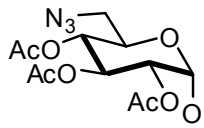
1,2-*O*-Isopropylidene 3,5-di-*O*-acetyl-6-deoxy-6-iodo-α-D-glucofuranose (38):[48] Colorless oil; R_f = 0.53 (7:3 v/v hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90 (1H, d, J = 3.5 Hz, H-1), 5.35 (1H, d, J = 2.8 Hz, H-3), 4.72 (1H, m, H-5), 4.48 (1H, d, J = 3.5 Hz, H-2), 4.36 (1H, dd, J = 9.8, 2.8 Hz, H-4), 3.58 (1H, dd, J = 10.8, 2.8 Hz, H-6a), 3.45 (1H, dd, J = 10.8, 4.9 Hz, H-6b), 2.06 (6H, s, CH_3C=O), 1.55 (3H, s, CH_3), 1.32 (3H, s, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.6 (x2), 112.7 (quaternary carbon), 105.0 (C-1), 83.4, 79.7, 74.5, 67.2, 26.9, 26.4, 20.7 (x2), 7.5 (C-6). MALDI-MS $[M+Na]^+$ Calcd for ($[C_{13}H_{19}O_7I + Na]^+$) 437.01; found 436.96; Anal. Calcd for $C_{13}H_{19}O_7I$: C, 37.70; H, 4.62. Found C, 37.62; H, 4.68.



(2-Azido-ethyl)benzene (39):[49] Colorless oil; R_f = 0.81 (4:1 v/v hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.36 – 7.23 (5H, m, Ar), 3.52 (2H, t, J = 7.3 Hz, -CH_2N_3), 2.92 (2H, t, J = 7.3 Hz, -CH_2Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9 (quaternary carbon), 128.7 – 126.7 (Ar), 52.4 (CH_2N_3), 35.3 (CH_2Ph). MALDI-MS $[M+Na]^+$ Calcd for ($[C_8H_9N_3 + Na]^+$) 170.07; found 170.15; Anal. Calcd for $C_8H_9N_3$: C, 65.29; H, 6.16. Found C, 65.33; H, 6.14.

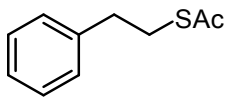


Compound 40:[50] Colorless oil; R_f = 0.38 (3:2 v/v hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.69 – 3.67 (12H, bs, CH_2O), 3.39 (4H, t, J = 4.9 Hz, CH_2N_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 70.7, 69.9, 50.6 (CH_2N_3). MALDI-MS $[M+Na]^+$ Calcd for ($[C_8H_{16}O_3N_3 + Na]^+$) 267.12; found 267.05; Anal. Calcd for $C_8H_{16}O_3N_3$: C, 39.34; H, 6.60. Found C, 39.37; H, 6.54.

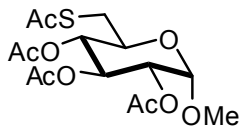


Methyl 2,3,4-tri-*O*-acetyl-6-azido-6-deoxy-α-D-glucopyranoside (41):[37i] Colorless oil; R_f = 0.45 (3:2 v/v hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.40 (1H, t, J = 10.1 Hz, H-3), 4.95 – 4.90 (2H, m, overlapped signals, H-1 and H-4), 4.81 (1H, dd, J = 10.1, 3.7 Hz, H-2), 3.90 (1H, m, H-5), 3.39 (3H, s, OCH_3), 3.29 – 3.22 (2H, m, overlapped signals, H-6a and H-6b), 2.01 (3H, s, CH_3C=O), 1.97 (3H, s, CH_3C=O), 1.94 (3H, s, CH_3C=O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9 (x2), 169.4, 96.5 (C-1), 70.6, 69.7, 69.6, 68.4, 55.4, 50.8 (C-6), 20.4 (x3). MALDI-MS $[M+Na]^+$ Calcd for ($[C_{13}H_{19}O_8N_3 + Na]^+$) 368.11: Found

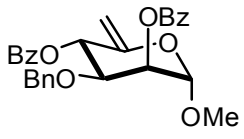
368.05; Anal. Calcd for $C_{13}H_{19}O_8N_3$: C, 45.22; H, 5.55. Found C, 45.18; H, 5.61.



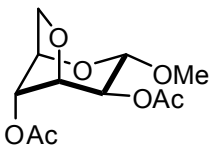
(2-Thioacetyl-ethyl)benzene (42):[51] Colorless oil; R_f = 0.64 (4:1 v/v hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.22 (5H, m, Ar), 3.13 (2H, t, J = 7.3 Hz, -CH_2SAc), 2.88 (2H, t, J = 7.3 Hz, -CH_2Ph), 2.34 (3H, s, CH_3C=O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 195.6 (C=O), 139.9 (quaternary carbon), 128.5 – 126.4 (Ar), 35.7 (CH_2Ph), 30.6, 30.4 (CH_2S and acetyl CH_3). MALDI-MS $[M+Na]^+$ Calcd for ($[C_{10}H_{12}OS + Na]^+$) 203.05: Found 203.01; Anal. Calcd for $C_{10}H_{12}OS$: C, 66.63; H, 6.71. Found C, 66.68; H, 6.62.



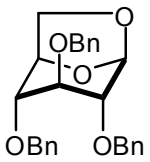
Methyl 2,3,4-tri-*O*-acetyl-6-deoxy-6-thioacetyl-α-D-glucopyranoside (43):[52] Yellow oil; R_f = 0.27 (7:3 v/v hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.39 (1H, t, J = 9.9 Hz, H-3), 4.90 (1H, t, J = 9.9 Hz, H-4), 4.85 (1H, d, J = 3.6 Hz, H-1), 4.81 (1H, dd, J = 9.9, 3.6 Hz, H-2), 3.90 – 3.86 (1H, m, H-5), 3.36 (3H, s, OCH_3), 3.16 (1H, dd, J = 14.2, 3.0 Hz, H-6a), 3.03 (1H, dd, J = 14.2, 7.0 Hz, H-6b), 2.31 (3H, $SCOCH_3$), 2.04 (3H, s, CH_3C=O), 2.03 (3H, s, CH_3C=O), 1.96 (3H, s, CH_3C=O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 194.5, 170.0 (x3), 96.5 (C-1), 70.8 (x2), 69.9, 68.1, 55.2, 30.3 (C-6), 29.9 (thioacetyl CH_3), 20.6 (x3). MALDI-MS $[M+Na]^+$ Calcd for ($[C_{15}H_{22}O_9S + Na]^+$) 401.09: Found 401.16; Anal. Calcd for $C_{15}H_{22}O_9S$: C, 47.61; H, 5.86. Found C, 47.58; H, 5.92.



Methyl 2,4-di-*O*-benzoyl-3-*O*-benzyl-α-D-lyxo-hex-5-enopyranoside (44): Colorless oil; $[\alpha]_D^{23}$: -89.3 (*c* 1.3, $CHCl_3$); R_f = 0.44 (4:1 v/v hexane/ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$): δ 8.07 – 7.13 (15H, m, Ar), 6.08 (1H, dt, J = 9.8, 1.9 Hz, H-4), 5.69 (1H, dd, J = 3.3, 2.1 Hz, H-2), 4.98 (1H, d, J = 2.1 Hz, H-1), 4.78 (1H, t, J = 1.9 Hz, H-6a), 4.68 and 4.53 (2H, 2 AB d, J =12.5 Hz, CH_2Ph), 4.62 (1H, t, J = 1.6 Hz, H-6b), 4.16 (1H, dd, J = 9.8, 3.3 Hz, H-3), 3.49 (3H, s, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.7, 165.3, 152.0 (C-5), 137.5, 133.4 – 127.8 (Ar), 99.8 (C-1), 96.6 (C-6), 74.0, 71.3, 69.3, 68.9, 55.6. MALDI-MS [M+Na]+ Calcd for $C_{28}H_{26}O_7$ 497.16: Found 497.14; Anal. Calcd for $C_{28}H_{26}O_7$: C, 70.87; H, 5.52. Found C, 70.78; H, 5.58.



Methyl 2,4-di-*O*-acetyl-3,6-anhydro -α-D-mannopyranoside (45): Yellowish oil; $[\alpha]_D^{23}$: +42.2 (*c* 1.1, $CHCl_3$); R_f = 0.36 (1:1 v/v hexane/ethyl acetate); ^1H NMR (400 MHz, $CDCl_3$): δ 4.94 (1H, dd, J = 6.4, 2.8 Hz, H-4), 4.91(1H, dd, J = 7.2, 1.1 Hz, H-2), 4.81 (1H, d, J = 7.2 Hz, H-1), 4.54 (1H, bt, J = 2.7 Hz, H-5), 4.35 (1H, dd, J = 6.2, 1.1 Hz, H-3), 4.11 (1H, bd, J = 10.7 Hz, H-6a), 4.00 (1H, dd, J = 10.7, 2.8 Hz, H-6b), 3.47 (3H, s, OCH_3), 2.14 (3H, s, $CH_3C=O$), 2.07 (3H, s, $CH_3C=O$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 169.8, 99.8 (C-1), 73.9, 73.0, 71.9, 70.7, 69.5, 56.7, 20.9, 20.8. MALDI-MS [M+Na]+ Calcd for C11H16O7 283.08: Found 283.13; Anal. Calcd for C11H16O7: C, 50.77; H, 6.20. Found C, 50.75; H, 6.26.



1,6-Anhydro-2,3,4-tri-*O*-benzyl-β−D-glucopyranose (46):[53] Colorless oil; R_f = 0.29 (4:1 v/v hexane/ethyl acetate); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.11 (15H, m, Ar), 5.47 (1H, bs, H-1), 4.64 – 4.53 (5H, 2xAB, overlappedsignals, CH_2Ph and H-5), 4.48 – 4.40 (2H, AB, J = 12.4 Hz, CH_2Ph), 3.91 (1H, bd, J = 7.0 Hz, H-6a), 3.68 (1H, bt, J = 7.0 Hz, H-6b), 3.60 (1H, bs), 3.36 (2H, bs); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.9 (x3, quaternarycarbon), 129.2 – 128.1(Ar), 100.6 (C-1), 76.1 (x3), 74.4, 72.0, 71.8, 71.2, 65.4. MALDI-MS [M+Na]+ Calcd for C27H28O5 455.18: Found 455.11; Anal. Calcd for C27H28O5: C, 74.98; H, 6.53. Found C, 74.90; H, 6.62.

References

1) Bandgar, B. P.; Sadavarte, V. S.; Uppalla, L. S. *Tetrahedron Lett.* **2001**, *42*, 951-953.

2) Vankar, Y. D.; Trinadha Rao, C. *Tetrahedron Lett.* **1985**, *26*, 2717-2720.

3) Tajbakhsh, M.; Hosseinzadeh, R.; Lasemi, Z. *Synlett* **2004**, *4*, 635-638.

4) Hayat, S.; Rahman, A.; Khan, K. M.; Choudhary, M. I.; Maharvi, G. M.; Ullah, Z.; Bayer, E. *Synth Commun* **2003**, *33,* 2531-2540.

5) Khazdooz, L.; Zarei, A.; Aghaei, H.; Azizi, G.; Gheisari, M. M. *Tetrahedron Lett.* **2016**, *57*, 168-171.

6) Satam, J. R. ; Jayaram, R. V. *Catal Commun* **2008**, *9*, 1033-1039.

7) Pouliot, M.; Mahé, O.; Hamel, J.; Desroches, J.; Paquin, J. *Org. Lett.* **2012**, *14*, 5428-5431.

8) Tajbakhsh, M.; Hosseinzadeh, R.; Lasemi, Z.; Rostami, A. *Synth Commun* **2005**, *35*, 2905-2911.

9) Li, Z.; Crosignani, S.; Linclau, B. *Tetrahedron Lett.* **2003**, *44*, 8143-8147.

10) Castro, B. *Organic Reactions*,*Vol. 29*, John Wiley & Sons, **1983**, Chapter 1.

11) de Andrade, Vitor, S. C.; de Mattos, Marcio, C. S. *Current Organic Synthesis* **2015**, *12*, 309-327.

12) Hanessian, S.; Ponpipom, M. M.; Lavallee, P. *Carbohydr. Res.* **1972**, *24*, 45-56.

13) Loibner, H.; Zbiral, E. *Helv. Chim. Acta* **1976**, *59*, 2100-2113.

14) Manna, S.; Falck, J. R.; Mioskowski, C. *Synth Commun* **1985**, *15*, 663-668.

15) Iranpoor, N.; Firouzabadi, H.; Aghapour, G.; Vaezzadeh, A. R. *Tetrahedron* **2002**, *58*, 8689-8693.

16) Anilkumar, G.; Nambu, H.; Kita, Y. *Org Process Res Dev* **2002**, *6*, 190-191.

17) Das, D.; Anal, J. M. H.; Rokhum, L. *J. Chem. Sci.* **2016**, *128*, 1695-1701.

18) Firouzabadi, H.; Iranpoor, N.; Ebrahimzadeh, F. *Tetrahedron Lett.* **2006**, *47*, 1771-1775.

19) a) Garegg, P. J.; Samuelsson, B. *J. Chem. Soc., Chem. Commun.* **1979**, 978-980; b) Classon, B.; Liu, Z. *J. Org. Chem.* **1988**, *53*, 6126-6130; c) Skaanderup, P. R.; Poulsen, C. S.; Hyldtoft, L.; Jørgensen, M. R.; Madsen, R. *Synthesis* **2002**, *12*, 1721-1727; d) Villalobos, A.; Danishefsky, S. J. *J. Org. Chem.* **1990**, *55*, 2776-2786; e) Aspinall, G. O.; Carpenter, R. C.; Khondo, L. *Carbohydr. Res.* **1987**, *165,* 281-298; f) Selvaraj, P. R.; Paquette, L. A. *Heterocycles* **2007**, *73*, 165-168; g) Kashem, A.; Anisuzzaman, M.; Whistler, R. L. *Carbohydr. Res.* **1978**, *61*, 511-518; h) Junior, C. O. R.; Castro, S. B. R.; Pereira, A. A.; Alves, C. C. S.; Oliveira, E. E.; Rêgo, R. T.; Ferreira, A. P.; de Almeida, M. V. *Eur J Med Chem* **2014**, *85*, 615-620.

20) For solvent-free alkylation methods: a) Ref.. *137 in Chapter 1*; b) Ref. *138 in Chapter 1*.

21) For solvent-free acetalation: Traboni, S.; Bedini, E.; Giordano, M.; Iadonisi, A. *Adv. Synth. Catal.* **2015**, *357*, 3562-3572. (Work discussed in *Chapter 2)*

22) For solvent-free silylations or tritylations and one-pot orthogonal protections: a) Traboni, S.; Bedini, E.; Iadonisi, A. *Beilstein J. Org. Chem.* **2016**, *12*, 2748-2756 (work discussed in *Chapter 3*); b)

Traboni, S.; Bedini, E.; Iadonisi, A. *ChemistrySelect* **2017**, *2*, 4906-4911 (work discussed in *Chapter 4*).

23) For solvent-free one-pot orthogonal protections with alkyl and acetal/cyclic protecting groups: see work discussed in *Chapter 5*.

24) For solvent-free synthesis of glycosyl chlorides: Traboni, S.; Liccardo, F.; Bedini, E.; Giordano, M.; Iadonisi, A. *Tetrahedron Lett.* **2017**, *58*, 1762-1764 (work discussed in *Chapter 6*).

25) a) Hajipour, A. R.; Falahati, A. R.; Ruoho, A. E. *Tetrahedron Lett.* **2006**, *47*, 4191-4196; b) Hajipour, A. R.; Azizi, G.; Ruoho, A. E. *Synth Commun* **2008**, *39*, 242-250; c) Hajipour, A. R.; Mostafavi, M.; Ruoho, A. E. *Org Prep Proced Int* **2009**, *41*, 87-91; d) Hajipour, A. R.; Rafiee, F.; Ruoho, A. *Synth Commun* **2011**, *41*, 603-611; e) Gupta, N.; Kad, G. L.; Singh, J. *J Mol Catal A Chem* **2009**, *302*, 11-14; f) Ranu, B. C.; Jana, R. *Eur. J. Org. Chem.* **2005**, 755-758; g) Liu, Y.; Xu, Y.; Jung, S. H.; Chae, J. *Synlett* **2012**, *23*, 2692-2698

26)Synthesis of compound **7** was performed according to literature: Shen, X.; Wu, Y. L.; Wu, Y. *Helv. Chim. Acta* **2000**, *83*, 943-953.

27) Asai, S.; Kato, M.; Monguchi, Y.; Sajiki, H.; Sawama, Y. *Chem. Commun.* **2017**, *53*, 4787-4790.

28) a) Cheung, C. W.; Ren, P.; Hu, X. *Org. Lett.* **2014**, *16*, 2566-2569; b) Seel, S.; Dagousset, G.; Thaler, T.; Frischmuth, A.; Karaghiosoff, K.; Zipse, H.; Knochel, P. *Chem. Eur. J.* **2013**, *19*, 4614-4622;

29) Synthesis of compound **14** was performed according to literature: Giordano, M.; Iadonisi, A.; Pastore, A. *Eur. J. Org. Chem.* **2013**, 3137 – 3147.

30)Synthesis of thioglycoside **19** was performed according to literature: Valerio, S.; Iadonisi, A.; Adinolfi, M.; Ravidà, A. *J. Org. Chem.* **2007**, *72*, 6097-6106.

31) a) Mereyala, H. B.; Goud, P. M.; Gadikota, R. R.; Reddy, K. R. *J Carbohydr Chem* **2000**, *19*, 1211-1222; b) Liu, Z.; Classon, B. *J. Org. Chem.* **1990**, *55*, 4273-4275; c) a previous experiment aimed at iodination of 1,2–*O*–isopropylidene-α-D– glucofuranose in THF by PPh_3/I_2/imidazole system provided **19** in 46% yield and a substantial amount of 5,6-unsaturated byproduct.

32) a) Alvarez-Manzaneda, E. J.; Chahboun, R.; Cabrera Torres, E.; Alvarez, E.; Alvarez-Manzaneda, R.; Haidour, A.; Ramos López, J. M. *Tetrahedron Lett.* **2005**, *46*, 3755-3759; b) Rad, M. N. S.; Behrouz, S.; Khalafi-Nezhad, A. *Tetrahedron Lett.* **2007**, *48*, 3445-3449; c) Rokhum, L.; Bez, G. *J. Chem. Sci.* **2012**, *124*, 687-691.

33)a) Bräse, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem. Int. Ed.* **2005**, *44*, 5188-5240; b) Daniellou, R.; Le Narvor, C. *Adv. Synth. Catal.* **2005**, *347*, 1863-1868; c) Hoyle, C. E.; Bowman, C. N. *Angew. Chem. Int. Ed.* **2010**, *49*, 1540-1573; d) Buhl, M.; Vonhören, B.; Ravoo, B. J. *Bioconjugate Chem.* **2015**, *26*, 1017-1020; e) Wendeln, C.; Singh, I.; Rinnen, S.; Schulz, C.; Arlinghaus, H. F.; Burley, G. A.; Ravoo, B. J. *Chem. Sci.* **2012**, *3*, 2479-2484; f) Wendeln, C.; Rinnen, S.; Schulz, C.; Arlinghaus, H. F.; Ravoo, B. J. *Langmuir* **2010**, *26*, 15966-15971; g) see also Ref. 169 in *Chapter 1*.

34) Taillefumier, C. ; Chapleur, Y. *Chem. Rev.* **2004**, *104*, 263-292.

35) Xie, W.; Lin, A.; Xu, J.; Wu, X. *Asian J. Org. Chem.* **2017**, *6*, 6-26.

36) For more details on the applications of anhydrosugars and *exo*-glycals see *Chapter 1*.

37) a) But, T. Y. S.; Toy, P. H. *Chem. Asian J.* **2007**, *2*, 1340-1355; for some examples of azidation: b) Gouin, S. G.; Kovensky, J. *Tetrahedron Lett.* **2007**, *48*, 2875-2879; c) Rao, M.; Yousuf, L. S. K.; Mukherjee, D.; Taneja, S. C. *Org. Biomol. Chem.* **2012**, *10*, 9090-9098; d) Hanessian, S.; Ducharme, D.; Massé, R.; Capmau, M. L. *Carbohydr. Res.* **1978**, *63*, 265-269; e) Besset, C.; Chambert, S.; Fenet, B.; Queneau, Y. *Tetrahedron Lett.* **2009**, *50*, 7043-7047; for some examples of installation of sulfur functionalities: f) Volante, R. P. *Tetrahedron Lett.* **1981**, *22*, 3119-3122; g) Snow, A. W.; Foos, E. E. *Synthesis* **2003**, *4*, 509-512; h) Combemale, S.; Assam-Evoung, J.; Houaidji, S.; Bibi, R.; Barragan-Montero, V. *Molecules* **2014**, *19*, 1120-1149; i) Cagnoni, A. J.; Kovensky, J.; Uhrig, M. L. *J. Org. Chem.* **2014**, *79*, 6456-6467; for some examples of cyclization: j) Liu, L.; Wang, C.; Liu, D.; He, W.; Xu, J.; Lin, A.; Yao, H.; Tanabe, G.; Muraoka, O.; Xie, W.; Wu, X. *Org. Lett.* **2014**, *16*, 5004-5007; k) McDonnell, C.; López, O.; Murphy, P.; FernándezBolaños, J. G.; Hazell, R.; Bols, M. *J. Am. Chem. Soc.* **2004**, *126*, 12374-12385; for some examples of 5,6 *exo*–glycals preparation l) Chrétien, F. *Synth Commun* **1989**, *19*, 1015-1024; m) O'Brien, J. L.; Tosin, M.; Murphy, P. V. *Org. Lett.* **2001**, *3*, 3353-3356; n) Ref. 176 in *Chapter 1*.

38) a) Chiappe, C.; Pieraccini, D.; Saullo, P. *J. Org. Chem.* **2003**, *68*, 6710-6715; b) Hajipour, A. R.; Rajaei, A.; Ruoho, A. E. *Tetrahedron Lett.* **2009**, *50*, 708-711; c) Javaherian, M.; Kazemi, F.; Ghaemi, M. *Chin Chem Lett* **2014**, *25*, 1643-1647; d) Liu, Y.; Xu, Y.; Jung, S. H.; Chae, J. *Synlett* **2012**, *23*, 2692-2698.

39) a) Ref. 136 in *Chapter 1* and see also mechanism in Scheme 29 in *Chapter 1*; b) Grindley, T. B. *Adv. Carbohydr. Chem. Biochem.* **1998**, *53*, 17.

40) a) Tusda, Y.; Noguchi, S.; Niino, H. *Chem. Pharm. Bull.* **2001**, *49*, 1210-1213.

41) Tikad, A.; Delbrouck, J. A.; Vincent, S. P. *Chem. Eur. J.* **2016**, *22*, 9456-9476.

42) Sennari, G.; Hirose, T.; Iwatsuki, M.; Omura, S.; Sunazuka, T. *Chem. Commun.* **2014**, *50*, 8715-8718.

43) Khan, K. M.; Ullah, Z.; Perveen, S.; Hayat, S.; Ali, M.; Voelter, W. *Nat. Prod. Res.* **2008**, *22*, 1270-1275.

44) Bonifazi, A.; Yano, H.; Ellenberger, M. P.; Muller, L.; Kumar, V.; Zou, M.; Cai, N. S.; Guerrero, A. M.; Woods, A. S.; Shi, L.; Newman, A. H. *J. Med. Chem.* **2017**, *60*, 2890-2907.

45) Moerdyk, J. P.; Bielawski, C. W. *Chem. Eur. J.* **2014**, *20*, 13487-13490.

46) Ueda, T.; Hayashi, M.; Ikeuchi, Y.; Nakajima, T.; Numagami, E.; Kobayashi, S. *Org. Process Res. Dev.* **2014**, *18*, 1728-1739.

47) Belz, T.; Williams, S. J. *Carbohydr. Res.* **2016**, *429*, 38-47.

48) Hersant, G.; Ferjani, M. B. S.; Bennett, S. M. *Tetrahedron Lett.* **2004**, *45*, 8123-8126.

49) Dìaz, L.; Bujons, J.; Casas, J.; Llebaria, A.; Delgado, A. *J. Med. Chem.* **2010**, *53*, 5248-5255.

50) Goswami, L. N.; Houston, Z. H.; Sarma, S. J.; Jalisatgi, S. S.; Hawthorne, M. F. *Org. Biomol. Chem.* **2013**, *11*, 1116-1126.

51) Martínez, C.; Bosnidou, A. E.; Allmendinger, S.; Muñiz, K. *Chem. Eur. J.* **2016**, *22*, 9929-9932.

52) Ellis, D.; Norman, S. E.; Osborn, H. M. I. *Tetrahedron* **2008**, *64*, 2832-2854.

53) Hori, H.; Nishida, Y.; Ohrui, H.; Meguro, H. *J. Org. Chem.* **1989**, *54*, 1346-1353.

Chapter 8

On Surface *O*-Glycosylation by Catalytic Microcontact Printing

Introduction

As introduced in *Chapter 1*,[1] immobilization and patterning of carbohydrates on surfaces represents a key topic connecting several research fields, since it enables a wide range of analytical and diagnostic applications. Owing to the enormous importance of carbohydrates in all living cells, carbohydrates biochips and arrays have been extensively used for biochemical studies concerning recognition with proteins and antibodies, the role of multivalent interactions in the binding affinity, development of biosensors;[2] surface bound carbohydrates have been also used for medical applications, for example in the development of anti-inflammatory biomaterials.[3]

Most of these attractive applications need the carbohydrate to be covalently and site specifically attached to the underlying surface; thus, development of efficient methods for immobilization is an important area of research. As previously discussed in *Chapter 1*,[1] the most adopted approach to this purpose relies on a preliminary modification of the carbohydrate with a suitable linker displaying selective reactivity towards the surface of choice; click reactions are typically exploited to

this aim, though many others have been also reported, such as Diels Alder reaction or Michael addition.[4]

Due to the intrinsic complexity of *O*-glycosylation, direct immobilization of carbohydrates as glycosides represents an ambitious alternative and this kind of approach has been only occasionally explored. In some cases, enzymatic catalysis was exploited to achieve the on-surface glycosylation of acceptors previously immobilized on glass or gold substrates through amide bond formation,[5] while only few examples have been reported to date for direct coupling of glycosyl donors onto surfaces through a cheaper chemical glycosylation.

In this regard, the on-surface generation of glycosyl hydrazides and *N*–glycosyl oxyamines has been exploited[6] as an easier alternative to the challenging *O*–glycosylation;[7] though representing the most described method for direct immobilization[8] this strategy also displays significant drawbacks, such as the non-trivial preparation of highly functionalized surfaces, prolonged reaction times, generation of product mixtures and impossibility to modulate the anomeric configuration of the obtained *N*-glycoside. Direct chemical *O*-glycosylation using trichloroacetimidate donors has been reported as an advanced strategy for on-chip synthesis of oligosaccharides,[9] though not free of drawbacks, due to the multistep preparation of functionalized and expensive gold surfaces.

Widely used techniques for the generation of carbohydrate surface patterns take advantage of robotic microarray printers, which drop-cast carbohydrate probes on chemo-active surfaces[4e,10] providing attachment of the carbohydrate through either non-covalent interactions[11] or chemical conjugations such as epoxide opening with amines.[12] The resulting arrays contain a high number of spots that can be automatically analyzed by an array scanner based on fluorescence microscopy. Nevertheless this method for

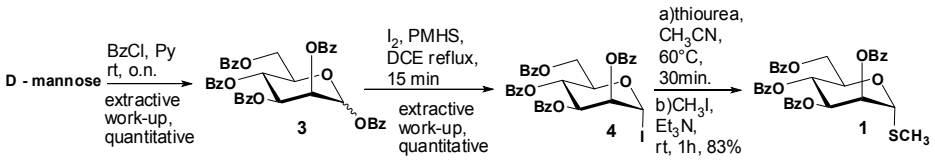
the generation of surface patterns has some disadvantages; indeed the resolution of the patterns is limited, the probe density is not easily reproducible, and a large excess of carbohydrate is required for each spot. In certain cases, pattering by microcontact printing (μCP) can be a good alternative.[13] In this method, the carbohydrate "ink" is delivered on to substrate using a microstructured elastomer stamp, typically made from polydimethylsiloxane (PDMS).[14] μCP is a low cost, easy and fast method to form high resolution patterns on a large area with a very low substance consumption. Furthermore μCP is compatible with a broad spectrum of reactions such as thiol-ene, Cu(I) azide alkyne cycloaddition (CuAAC), Strain promoted alkyne azide cycloaddition (SPAAC) and Diels-Alder.[15] A limited number of examples of catalytic μCP, in which a catalyst was immobilized on a stamp to induce a reaction on the target substrate, has also been reported.[16]

Consistently with the aim of this thesis, highlighted in the previous chapters with the description of new practical synthetic methods for carbohydrates derivatization (regioselective and orthogonal protections, synthesis of glycosyl donors and other several transformations of functional groups from alcohols and saccharide polyols),[17-22] an analogously simplified and convenient approach is herein extended to an applicative context, for the efficient immobilization of carbohydrates onto surfaces. In this chapter is indeed presented the first example of covalent immobilization and patterning of carbohydrates through direct *O*-glycosylation by catalytic microcontact printing; it is herein demonstrated that direct printing of easily prepared glycosyl donors on cheap and readily available hydroxyl terminated

substrates under air provides the easy generation of sugar-modified surfaces which are also suitable for ligand-protein recognition.

Results and Discussion

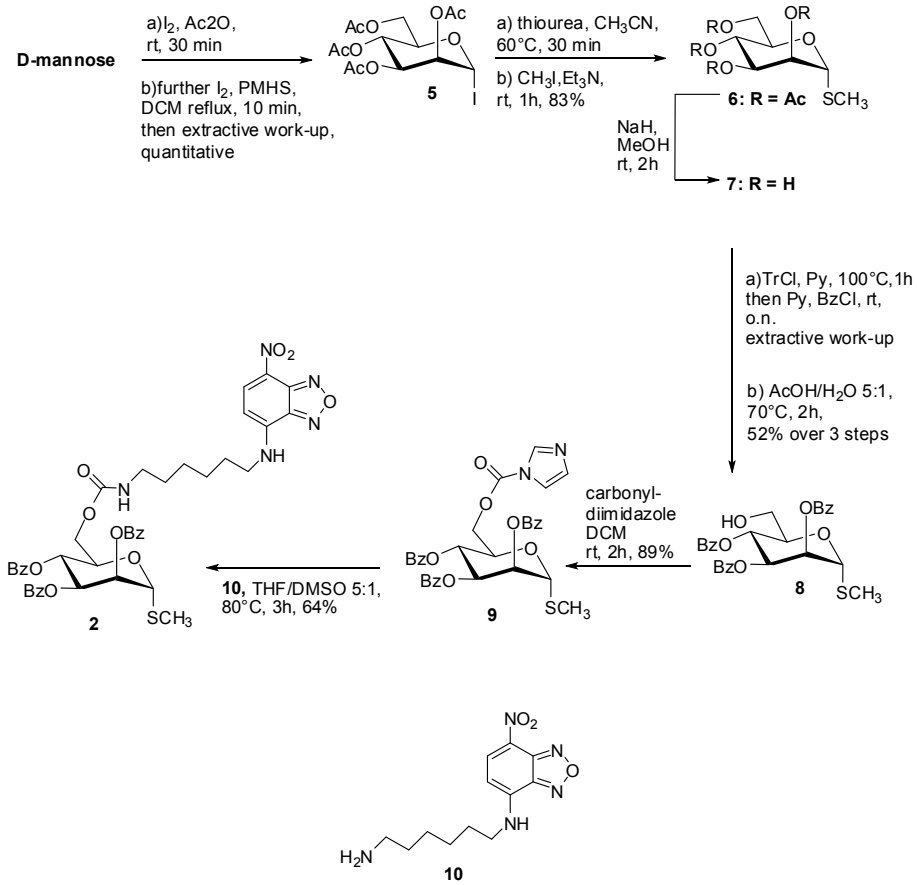
Initially, suitable glycosyl donors were prepared to be tested in the printing experiments. Among the most adopted glycosyl donors, thioglycosides were selected given their high stability to a wide range of conditions and ease of preparation, while the choice of the activation method was inspired by the most common adopted combination of stoichiometric N-iodosuccinimide (NIS) and catalytic trimethylsilyl triflate (TMSOTf).[23] Two different thiomannosides **1** and **2** were prepared. Benzoyl protecting groups were selected because of their easy installation and removal as well as their neighboring group effect that would ensure a 1,2-*trans* stereocontrolled glycosylation.[24] Both thioglycosides were easily synthesized in few steps (synthesis in **Scheme1** and **Scheme 2** respectively). Donor **1** was prepared in few hours via a convenient strategy, passing through a glycosyl iodide intermediate **4**.[25]



Scheme 1. Synthesis of Thioglycoside Donor **1**

An analogous procedure afforded thioglycoside **6** that was readily converted to intermediate **8** bearing a free primary hydroxyl group,

through a fast reaction sequence of de–*O*–acetylation, 6-*O*-tritylation,[19b] followed by one–pot per– *O*–benzoylation and cleavage of trityl group by acid hydrolysis, with just one purification step.



Scheme 2. Synthesis of Thioglycoside Donor **2**

Final conjugation with fluorescent nitrobenzoxadiazole (NBD) group was then performed through an unprecedented strategy, relying on the generation of a carbamate at C-6. NBD tagged donor **2** served as a probe in a range of experiments, for both

fluorescence microscopy and XPS analysis given the high content of nitrogen atoms (see below).

On the other hand, preparation of hydroxyl functionalized surfaces was performed according to literature through generation of self – assembled monolayers (SAMs) of 11-acetoxy undecenyl trichlorosilane on glass and silica substrates and subsequent de-*O*-acetylation in 2 M HCl, revealing the terminal hydroxyl groups (**Figure 1**).[26]

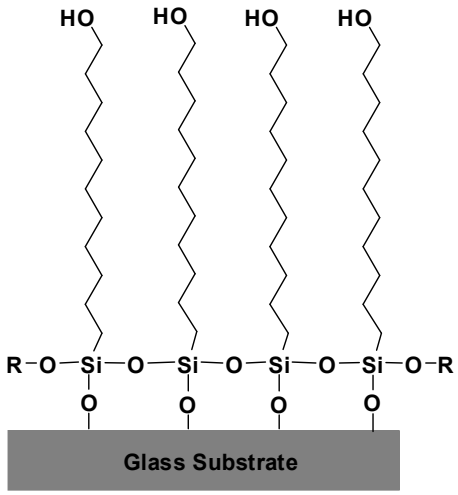
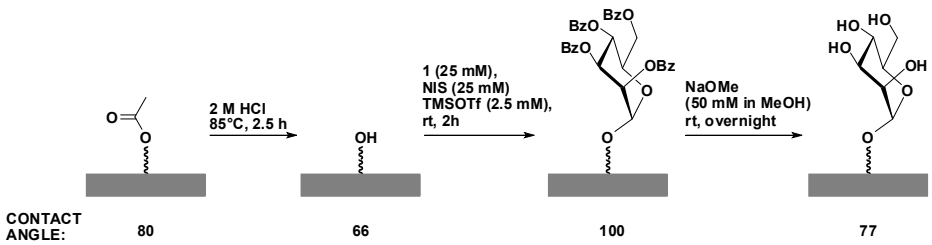


Figure 1. Hydroxyl-Terminated Self-Assembled Monolayer

Microcontact Printing experiments for the immobilization of the mannosides were next performed. In order to verify the feasibile attachment of carbohydrates through a direct glycosylation, simple flat stamps were used in the first experiments. To this end, the surfaces were incubated with a solution of mannoside **1** (25 mM) and NIS (25 mM) in dry DMF for 5 min. Simultaneously a flat PDMS stamp was incubated with a solution of TMSOTf (2.5 mM) in dry DMF for 1 min. The excess of solution was removed in a stream of argon and it was taken care that the TMSOTf

incubated stamp was placed on the dried surface for 2 h directly after the removal of the ink solution. Afterwards the substrates were washed carefully with acetone and ethanol abs. It is worth mentioning that the choice of DMF as the solvent of the ink solutions (not frequently employed as solvent in glycosylations) was driven by two main reasons. Primarily it was found suitable to avoid the stamp swelling that might occur with non-polar solvents decreasing the pattern resolution; in addition, it would support the stereoselectivity of glycosylation, according to its reported α-directing effect.[27] For the deprotection of the anchored carbohydrate, the surfaces were stirred in a sodium methanolate solution (50 mM) in methanol overnight.

The freshly prepared acetoxy-terminated SAMs showed a contact angle of 80.7±0.2. Upon removal of the acetyl groups from the SAMs, the contact angle decreased to a value of 66±0.5 reflecting the higher hydrophilicity of the hydroxyl groups. After immobilization of the protected carbohydrate the hydrophobicity of the surface increased resulting in a contact angle of 100.9±0.8 (**Scheme 3**). These findings match the expectations based on the polarity of the immobilized protected carbohydrate and are a first indication for the successful modification of the surface with an *O*-mannoside.



Scheme 3. Schematic Representation of the Surface Functionalization Process With Corresponding Contact Angles

Finally, after the deprotection of the carbohydrate the contact angle decreased again to 77.1±0.4 due to the increasing polarity of the free hydroxyl groups.

For further proof of the immobilization of the carbohydrates, NBD tagged thio-mannoside **2** was immobilized analogously on a silicon surface. The nitrogen containing fluorophore could be easily detected by XPS (**Figure 2**); the experiment was performed with (black) and without (red) the promotors TMSOTf and NIS. The appearance of the N1s signal in the positive experiment and the lack of any signal in the negative experiment indicate the successful immobilization of mannoside according to our suggested mechanism.

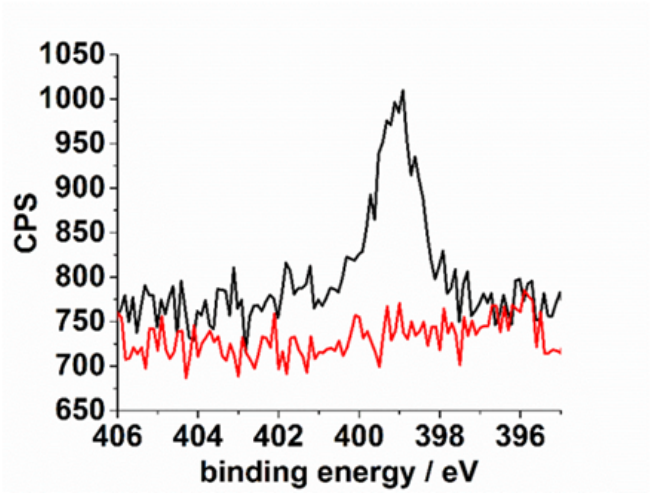


Figure 2. XPS of a NBD tagged mannoside **2** printed on a hydroxyl-terminated SAM with (black) and without (red) promoter

In the following experiments, microstructured PDMS stamps were used to form carbohydrate patterns on the hydroxyl terminated

SAM. In all other aspects, the immobilization procedure was identical.

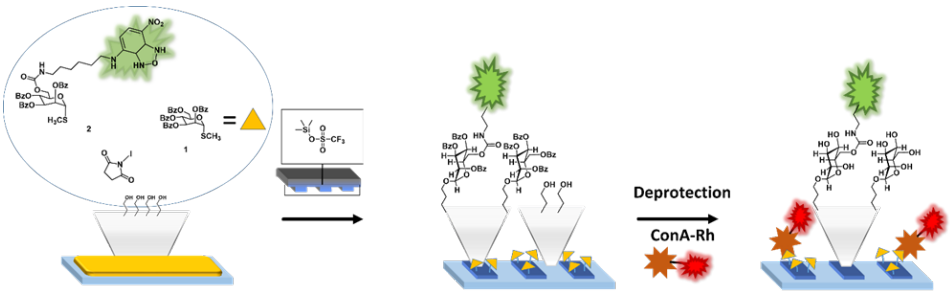


Figure 3. Schematic overview of µCP for the immobilization and patterning of α-mannosides and selective protein recognition

Mannoside **1** was printed in a line pattern (5 µm stripes spaced by 10 µm) and deprotected. Selective water condensation on the functionalized substrate clearly revealed stripes identical to the patterns of the stamp (**Figure 4A**). In the negative experiments (µCP without TMSOTf and NIS), no patterns were observed **(Figure 4B**). To visualize the suitability of the deprotected carbohydrate for protein recognition, the patterned surfaces were incubated with the corresponding fluorescein tagged concanavalin A (ConA-FITC), which binds exclusively to α–D–mannoside.

To exclude unspecific binding, surfaces were first incubated with a solution of bovine serum albumin (BSA). BSA adsorbs to the surface and is only displaced by proteins that undergo specific interactions with surface bound ligands. After the incubation, the solution was removed in an argon stream and the substrates were bathed twice in HEPES buffer for 5 min to remove the excess of BSA. Subsequently the surfaces were incubated with a solution of ConA-FITC (100 µg ml^{-1}) in HEPES buffer for 30 min and again carefully washed with HEPES buffer.

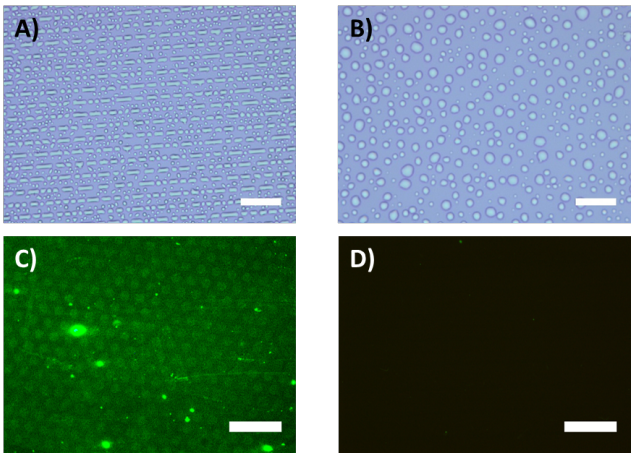


Figure 4. Light microscopy of selective water condensation on A) mannoside patterns (5 µm stripes spaced by 10 µm) B) in comparison with the corresponding negative experiment. Fluorescence microscopy of ConA FITC bound to C) immobilized mannoside (10 µm dots spaced by 5 µm) in comparison with D) the corresponding negative experiment. Scale bar: 50 µm.

Fluorescence microscopy analysis showed patterns (10 µm dots spaced by 5 µm) indicating the selective binding of ConA-FITC to immobilized mannoside (**Figure 4C**) while the negative experiment showed no pattern, thus further supporting success of the immobilization (**Figure 4D**).

For further proof of concept, NBD tagged mannoside **2** was employed. A patterned stamp (10 µm stripes spaced by 5 µm) was incubated with a solution of TMSOTf (2.5 mM) in dry DMF for 5 min. Simultaneously the hydroxyl terminated SAM modified surfaces were incubated with a solution of **2** (25 mM) and NIS (25 mM) in dry DMF. After the removal of the excess solution from the surfaces, the stamps were dried as well and directly carefully placed on the substrates. As negative control experiment µCP was performed without TMSOTf and NIS. After 2 h the stamps were removed and the surfaces were rinsed with

acetone and dry ethanol and directly analyzed using fluorescence microscopy and ToF-SIMS (**Figure 5**).

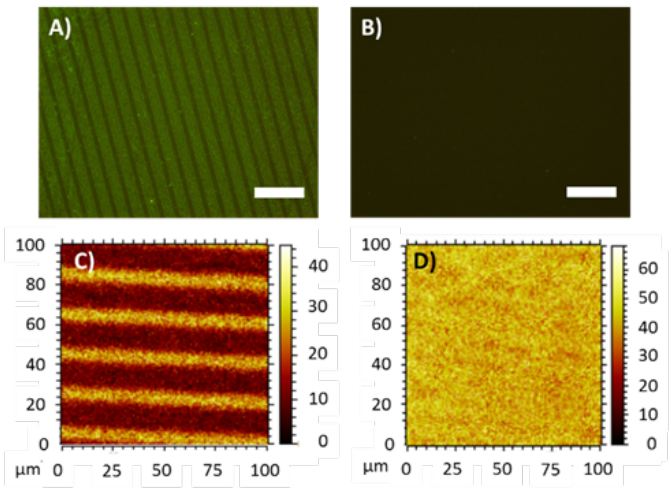


Figure 5. Fluorescence microscopy and ToF-SIMS (sum of several CxHy+ ions) of NBD-tagged mannoside **2** patterned on hydroxyl-terminated SAMs. A) Fluorescence microscopy, B) negative control without NIS and TMSOTf. C) ToF-SIMS, D) negative control without NIS and TMSOTf.

Fluorescence microscopy indicates the immobilization of NBD tagged mannoside in line patterns. ToF-SIMS shows the distribution of the sum of several $C_xH_y^+$ ions (including benzyl ions resulting from the benzoyl protecting groups). In the positive experiments (**Figure 5A and 5C**) high resolution line patterns are clearly visible, whereas no structures are observed by microscopy or ToF-SIMS in the negative experiments (**Figure 5B and 5D**).

The selective binding of lectin to the mannoside was confirmed in an experiment in which a 4 to 1 mixture of **1** and **2** (20 mM **1**, 5 mM **2**) with NIS (25 mM) in dry DMF was incubated to freshly prepared surfaces for 5 min. A TMSOTf incubated structured stamp (5 µm dots spaced by 3 µm) was placed carefully on the dried substrates for 2 h. After deprotection the surfaces were

rinsed with acetone and dry ethanol, dried and incubated with a BSA solution (3 wt% in HEPES buffer, pH = 7.5) for 30 min.The surfaces were bathed in HEPES buffer twice for 5 min each to remove excess of BSA. Next, the patterned substrates were incubated with rhodamine tagged ConA (ConA-Rh, 100 μM in HEPES buffer, pH = 7.5) for 30 min, washed carefully with HEPES buffer and analyzed with fluorescence microscopy (**Figure 6**). Upon excitation of NBD at 540-550 nm green dots are visible.

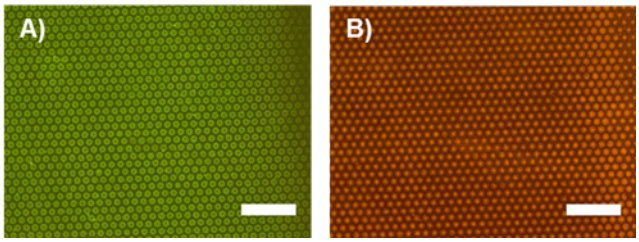
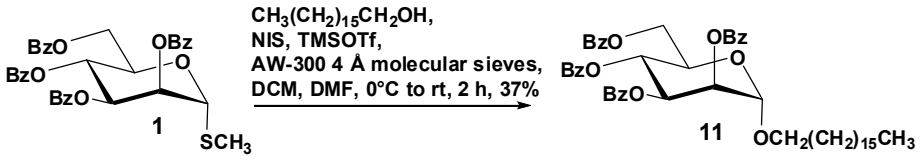


Figure 6. Fluorescence microscopy of printed mannoside **1** and **2** (5 μm dots, spaced by 3 μm) incubated with ConA-Rh. A) NBD excitation. B) Rhodamine excitation

We note that each dot shows reduced fluorescence intensity in the center. This observation can be explained from differences in the solubility of **1** and **2** in DMF resulting in the accumulation of fluorescent **2** in the edges of the patterns. Upon excitation of rhodamine at 460-495 nm, red dots with homogeneous fluorescence intensity are observed. The co-localization of mannoside and ConA-Rh is another very strong indication that the carbohydrate is immobilized as an α-mannoside during μCP.

Finally, glycosylation of donor **1** with a long chain primary alcohol in the presence of DMF was also performed through the standard procedure in solution. (**Scheme 4**). NMR analysis of the reaction

product after purification confirmed the generation of glycoside **11** with exclusive α - stereoselectivity.



Scheme 4. Glycosylation of a Long-Chain Primary Alcohol with Thioglycoside **1** in Solution

This result supports the reaction outcome obtained by μCP and confirms the immobilization of mannose through α-*O*-glycosylation. It is worth noting that more demanding conditions were necessary in solution, namely a larger amount of both NIS and TMSOTf, in comparison to μCP. This may be accounted for by multiple effects, such as the low intrinsic reactivity of disarmed mannosyl donors[28] and the mild DMF basicity, resulting in the need for at least a stoichiometric amount of TMSOTf to activate the thioglycoside donor.[27, 29] All these effects were found to be minimized in the μCP conditions, highlighting the great potential of this technique for even complex reactions on surfaces.

Conclusions

This chapter describes an innovative method for the efficient covalent immobilization and micropatterning of carbohydrates on surfaces; the presented method is based on a direct chemical *O*-glycosylation between thioglycoside donors and simple hydroxyl functionalized glass substrates by catalytic microcontact printing; combination of the advantages of microcontact printing with a very direct conjugation approach allows both the carbohydrate inks and the surface to be

quickly prepared by few and simple chemical derivatizations. Other relevant advantages of the proposed method compared to the current approaches for carbohydrate immobilization, are the use of cheap materials and chemicals and the reduced amounts of ink required, short experimental times, high pattern resolution. Even remarkable is the successful outcome of a challenging reaction, such as a chemical *O*-glycosylation, under air on a solid support. Success of surface immobilization of the carbohydrates is verified through different techniques (condensation assays, contact angle, XPS, fluorescence microscopy, ToF-SIMS); in addition, it is herein demonstrated that modified surfaces thus prepared are suitable for selective glycan-protein recognition. The developed strategy provides a very simplified access to carbohydrate modified surfaces and is thus expected to be a promising approach for future development of chips and nano-devices of broad applicative potential.

Experimental Section

Instrumentation

Contact angle analysis was performed using a *DSA 100* (KRÜSS) in combination with *Drop Shape Analysis v1.90.0.14*. Static contact angles were measured with 7 µl drops of ultrapure water. **X-Ray photoelectron spectroscopy** was performed with a *Kratos Axis Ultra* (KRATOS) using monochromated Al Kα irradiation with an excitation energy of 1486.6 eV. For region scans a pass energy of 0.02 eV was employed. The obtained data was analyzed with *CasaXPS Software Suite* v2315. All spectra were calibrated to the binding energy of the C-1s-orbital in aliphatic carbon-carbon chains (285 eV). **Fluorescence microscopy** was performed with a BX 53 microscope (OLYMPUS) operated with an XC 10 camera (OLYMPUS) and a X-Cite® Series

120Q (LUMEN DYNAMICS) as the irradiation source. For **light microscopy**, a CKX 41 (OLYMPUS) microscope with an XC 30 (OLYMPUS) camera and a X-Cite® Series120Q (LUMEN DYNAMICS) as the irradiation source were used. Data processing was carried out with the software *Olympus Stream Start 1.8*, *Photoshop CS* and *ImageJ v1.50*. **ToF-SIMS** measurements were carried out using a TOF V (IONTOF GmbH, Münster) compatible instrument equipped with a 30 keV liquid metal ion gun (IONTOF GmbH, Münster). As primary ions Bi_3^+ clusters with a pulsed current of 0.05 pA were used. ^1H and ^{13}C **NMR spectra** were recorded on a Bruker Avance-DRX 400 (^1H: 400 MHz, ^{13}C: 100 MHz) instrument or on a Bruker DRX-600 (^1H: 600 MHz, ^{13}C: 150 MHz) instrument. **High resolution MALDI spectra** were measured with a AB Sciex TOF/TOF 5800 System instrument.

Preparation of hydroxyl-terminated SAMs

Hydroxyl-terminated SAMs was prepared according to a literature procedure.[26] Silicon and glass slides were cut in suitable sizes and cleaned by treatment in an ultra-sonic bath first in acetone then in ethanol and afterwards in distilled water for 10 min each time. To activate the surface the substrates were exposed to a mixture of conc. sulfuric acid and 30% hydrogen peroxide (3:1 vol.) for 30 min. After cleaning the activated substrates and removal of the activation reagent by extensively rinsing the substrates with distilled water, they were carefully dried in an argon stream. The activated cleaned and dried glass or silicon slides were put in a solution of 11-acetoxyundecenyltricholosilane (0.10 vol%) in toluene for about 1 h. Afterwards the substrates were rinsed with acetone and ethanol and the success of the SAM generation was verified by contact angle measurements. For the removal of the acetyl protecting group the

substrates were stirred for 2.5 h and 85 °C in 2 M HCl. Afterwards the substrates were rinsed with water and acetone and dried properly.

Microcontact printing of methylthiomannosides

Hydroxyl-terminated substrates were incubated with a solution of **1** or **2** (25 mM) and NIS (25 mM) in dry N,N-dimethylformamide (DMF) for 5 min. For the combined printing of both methylthiomannosides, a solution of **1** (20 mM), **2** (5 mM) and NIS (25 mM) in dry DMF was drop casted to the substrates. Structured or homogenous stamps were incubated with a solution of TMSOTf (2.5 mM) for 1 min. The excess of the solution was removed and the stamps were brought into contact with the surfaces. The TMSOTf incubated stamps were used in the printing process directly after drying. After 2 h, the substrates were rinsed with acetone and ethanol. For the removal of the benzoyl group the substrates were stirred in 50 mM sodium methoxide overnight at room temperature. The success of the procedure was monitored via contact angle measurements.

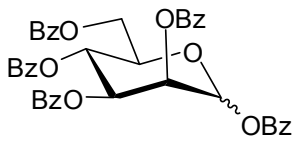
Incubation of Proteins at Surface Bound Ligands

To verify the successful immobilisation of mannose to the surfaces, the substrates were stained with fluorescein modified concanavalin A (ConA-FITC) or rhodamine modified concanavalin A (ConA-Rh). To reduce unspecific binding of the proteins to the surface the dried substrates were incubated with a 3 wt% solution of BSA in HEPES buffer (20 mM HEPES, 150 mM NaCl, 1 mM CaCl2, 1 mM MnCl2, pH 7.5) for 30 min. and washed with HEPES buffer (2 x 5 min.) afterwards. The substrates were then incubated with a solution of ConA-FITC (100 µg/mL in HEPES buffer) or ConA-Rh (100 µg/mL

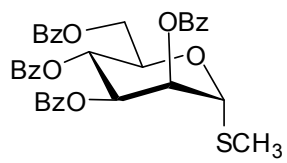
in HEPES buffer) for 30 min. Prior to fluorescence microscopy, the substrates were washed with HEPES buffer and dried carefully.

Preparation of PDMS Stamps

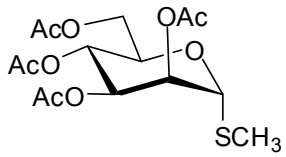
PDMS stamps were prepared using *Sylgard® 184 Silicone Elastomer Kit* (DOW CORNING). PDMS was mixed with the curing agent in a 10:1 ratio and agitated with a glass bar for 5 min. The mixture was put on a silicon master and residual gas in the mixture was removed in vacuum using a desiccator. The PDMS mixture was cured at 80°C overnight. If not mentioned otherwise, the stamps were cut into suitable pieces (ca 1 x 1 cm) and treated in a UV ozonizer (*PSD-UV*, *Novascan Technologies Inc*.) for 55 min. The freshly oxidized stamps were immediately stored in distilled water. Prior to use, the stamps were carefully dried in an argon stream.



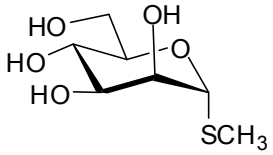
1,2,3,4,6, per-O-benzoyl-D-mannopyranoside (3): To a suspension of D-mannose (314 mg, 1.74 mmol) in pyridine (4 mL) was added benzoyl chloride (1.2 mL, 10.4 mmol) at 0°C. After 10 min the reaction was allowed to warm to rt and stirred overnight. The mixture was diluted with ethyl acetate and sequentially washed with aq. NaOH and a saturated solution of aq. $CuSO_4$. The organic phase was then dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield crude compound **3** which was submitted to the subsequent thioglycoside synthesis as illustrated below.



Methyl 2,3,4,6-tetra-O-benzoyl-1-thio-α-D-mannopyranoside (1): Polymethylhydrosiloxane (114 µL, 1.91 mmol) was added to a solution of the crude per-O-benzoylated compound **3** and iodine (486 mg, 1.91 mmol) in anhydrous 1,2-dichloroethane (8 mL) and refluxed under stirring until complete consumption of the starting material was observed by TLC (15 min). The mixture was then diluted with dichloromethane (DCM) and washed with aq. Na_2CO_3 containing a slight amount of sodium thiosulfate (sufficient to reduce residual iodine in the organic phase). The organic phase was then dried over anhydrous Na_2SO_4 and concentrated under vacuum. Subsequently, thiourea (199 mg, 2.61 mmol) was added to the obtained crude iodide **4** and the mixture was suspended in dry CH_3CN (8 mL) and stirred at 60°C until the quantitative generation of a polar product (30 min). After cooling to rt, CH_3I (217 µL, 3.48 mmol) and Et_3N (970 µL, 7.0 mmol) were sequentially added. After stirring for 1 h, the mixture was diluted with DCM and washed with water. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude residue was purified by chromatography to yield compound **1** (900 mg, 83% overall yield) as a white foam. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.13 – 7.28 (Ar), 6.17 (1H, t, J = 10.0 Hz, H-4), 5.87 (1H, dd, J = 3.0 and 10.0 Hz, H-3), 5.85 (1H, bd, J = 3.0 Hz, H-2), 5.49 (1H, bs, H-1), 4.84 – 4.81 (1H, m, H-5), 4.71 (1H, dd, J = 2.6 Hz and 12.0 Hz, H-6a), 4.56 (1H, dd, J = 4.5 Hz and 12.0 Hz, H-6b), 2.28 (3H, s, -SCH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.7, 166.2, 165.6, 165.5, 134.8 (x2), 134.5, 134.4, 131.1 – 129.6, 84.9, 73.1, 71.8, 70.5, 68.4, 64.2, 15.1.

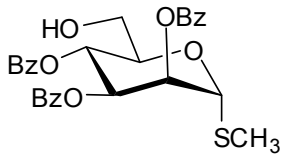


Methyl 2,3,4,6-tetra-O-acetyl-1-thio-α-D-mannopyranoside (6) To a suspension of D-mannose (994 mg, 5.52 mmol) in acetic anhydride (2.66 mL, 28.1 mmol) was added iodine (98.1 mg, 0.39 mmol) and the mixture was stirred at room temperature until completion of the acetylation (30 min). After dilution with DCM (4 mL), further iodine (1.44 g, 5.68 mmol) and polymethylhydrosiloxane (363 µL, 6.07 mmol) were sequentially added and the mixture was refluxed until TLC displayed quantitative iodination of the per-acetylated compound (10 min). The mixture was then diluted with DCM and washed with aq. Na_2CO_3 containing a slight amount of sodium thiosulfate (sufficient to reduce residual iodine in the organic phase). The organic phase was then dried over anhydrous Na_2SO_4 and concentrated under vacuum. Subsequently, thiourea (630 mg, 8.28 mmol) was added to the obtained crude iodide **5** and the mixture was suspended in dry CH_3CN (8 mL) and stirred at 60°C until the quantitative generation of a polar product (30 min). After cooling to rt, CH_3I (687 µL, 11.04 mmol) and Et_3N (3.07 mL, 22.08 mmol) were sequentially added. After stirring for 1 h, the mixture was diluted with DCM and washed with water. The organic phase was dried and concentrated under vacuum. The crude residue was purified by chromatography to yield compound **6** (1.753 g, 84% overall yield) as a white foam.

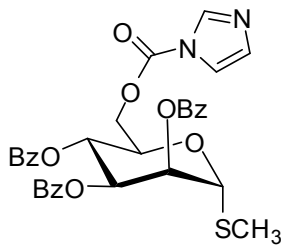


Methyl 1-thio-α-D-mannopyranoside (7): A 0.5 M solution of NaH in methanol (400 µL) was added to a solution of compound **6** (1.753 g, 4.64 mmol) in methanol/DCM 9:1 (15 mL). The mixture was stirred at room temperature until TLC displayed complete

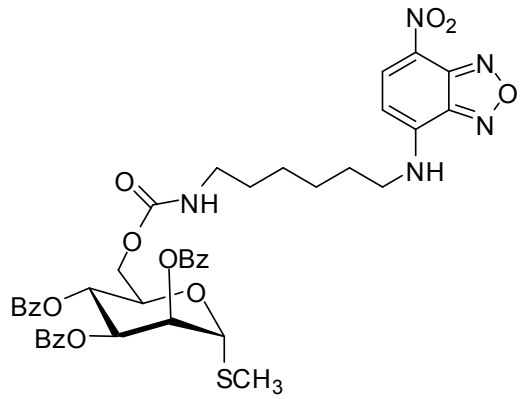
de-O-acetylation and then neutralized with Amberlyst resin. After filtration, the product was concentrated under vacuum to yield deprotected thioglycoside **7** (974 mg, 100% yield) as a white solid, which was directly submitted to the subsequent step.



Methyl 2,3,4-tri-O-benzoyl-1-thio-α-D-mannopyranoside (8): A mixture of compound **7** (974 mg, 4.64 mmol) and trityl chloride (1.42 g, 5.1 mmol) was suspended in pyridine (2 mL) and stirred at 100°C for 1.5 h. After cooling to room temperature, further pyridine (3.75 mL, 46.4 mmol) and benzoyl chloride (2.96 mL, 25.5 mmol) were sequentially added and the mixture was stirred until complete per-O-benzoylation of the tritylated compound (TLC). The reaction was quenched with methanol (2 mL), then the mixture was diluted with DCM and washed with water. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude residue was suspended in acetic acid/H_2O 5:1 (40 mL) and stirred for 3h at 70 °C. The mixture was then diluted with DCM and sequentially washed with water and aq. Na_2CO_3. The organic phase was dried and concentrated under vacuum and the crude residue was purified by chromatography to afford compound **8** (1.26 g, 52% yield) as a white foam. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.10 – 7.26 (Ar), 5.94 (1H, dd, J = 3.0 and 10.0 Hz, H-3), 5.90 (1H, t, J = 10.0 Hz, H-4), 5.82 (1H, bd, J = 3.0 Hz, H-2), 5.49 (1H, bs, H-1), 4.45 – 4.43 (1H, m, H-5), 3.86 (1H, dd, J = 2.1 Hz and 12.8 Hz, H-6a), 3.84 (1H, dd, 3.8 Hz and 12.8 Hz, H-6b), 2.26 (3H, s, -SCH_3).

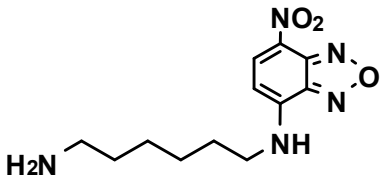


Methyl 2,3,4-tri-O-benzoyl-6-O-imidazoyl-1-thio-α-D-mannopyranoside (9): Carbonyldiimidazole (781 mg, 4.82 mmol) was added to a solution of compound **8** (1.26 g, 2.41 mmol) in dry DCM (10 mL) and the mixture was stirred at room temperature until completion of the reaction (2 h). The mixture was diluted with DCM and washed with water. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum and the product was purified by chromatography, yielding compound **9** (1.33 g, 89% yield) as a white foam. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.32 – 7.14 (Ar), 6.09 (1H, t, J = 10.0 Hz, H-4), 5.86 (1H, dd, J = 3.0 and 10.0 Hz, H-3), 5.84 (1H, dd, J = 1.2 and 3.0 Hz, H-2), 5.46 (1H, bs, H-1), 4.82 – 4.80 (2H, overlapped signals, H-5, H-6a), 4.61 (1H, dd, J = 4.2 and 12.0 Hz, H-6b), 2.26 (3H, s, -SCH_3).

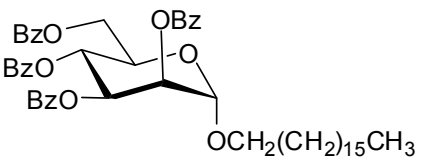


Compound (2): A mixture of compound **9** (1.33 g, 2.15 mmol) and amine **10** was suspended in tetrahedrofurane/dimethylsulfoxide 5:1 (18 mL) and heated at 80°C. After 3 h, the mixture was cooled to room temperature, diluted with ethyl acetate and washed with water. The organic phase was dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude residue was purified by chromatography to yield compound **2** (1.14 g, 64% yield) as a deep orange foam. ^{1}H NMR ($CDCl_3$, 600 MHz)δ 8.47 (1H, d, J = 8.6 Hz, NBD aromatic proton),

8.11 – 7.26 (Ar), 6.51 (1H, s, -NH-NBD), 6.14 (1H, d, J = 8.6 Hz, NBD aromatic proton), 5.95 (1H, t, J = 10.0 Hz, H-4), 5.82 (1H, dd, J = 3.2 and 10.0 Hz, H-3), 5.77 (1H, bs, H-2), 5.48 (1H, bs, H-1), 4.76 (1H, t, J = 6.0 Hz, -NH), 4.69 – 4.66 (1H, m, H-5), 4.39 (2H, m, H-6a, H-6b), 3.44-3.48 (2H, m, -CH_2-NH-), 3.20 – 3.17 (2H, m, - m, -CH_2-NH-), 2.26 (3H, s, -SCH_3), 2.06 – 1.27 (alkyl chain protons). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.1, 165.5, 165.3, 156.0, 144.2, 143.8, 136.4, 133.6, 133.5, 133.2 – 128.3, 83.6, 71.9, 70.3, 69.3, 67.3, 63.3, 43.5, 40.4, 29.8, 28.2, 26.0, 25.7, 13.8.



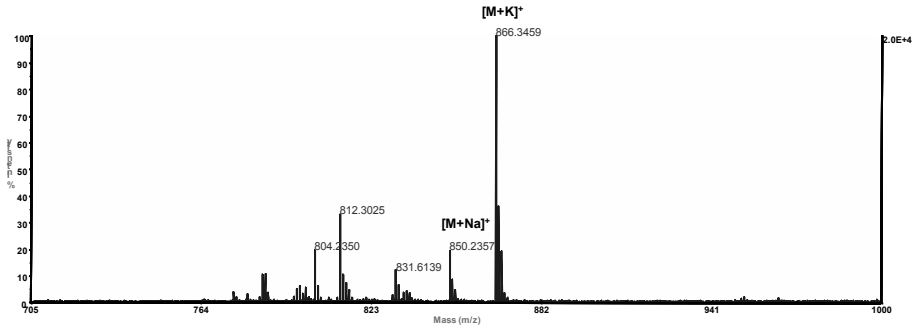
Compound (10): The synthesis of NBD-conjugated hexamethylenediamine **10** was performed according to literature.[30]



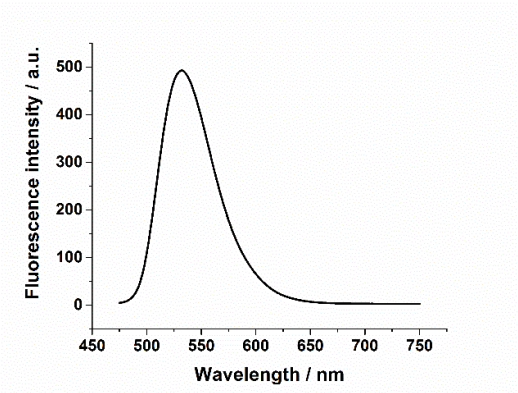
1–Heptadecyl 2,3,4,6–tetra–O–benzoyl-α-D-mannopyranoside (11): 1-Heptadecanol (6 mg, 0.0223 mmol) and mannosyl thioglycoside **1** (21 mg, 0.0335 mmol) were coevaporated three times with dry toluene. Freshly activated AW-300 4 Å molecular sieves and then NIS (16 mg, 0.0711 mmol) were sequentially added to the mixture under argon. DCM (0.4 mL) and then DMF (26 µL, 0.335 mmol), freshly dried over 4 Å molecular sieves, were added and the mixture was stirred at 0°C for 5 min before the addition of TMSOTf in DCM (0.67 M, 100 µL, 0.067 mmol). After 10 min the mixture was allowed to warm to rt and stirred for 2 h. The reaction was quenched with triethylamine and then the mixture was diluted with DCM and washed with water. The organic phase was dried

over anhydrous Na_2SO_4 and concentrated under vacuum and the crude product was purified by chromatography to yield compound **11** (7 mg, 37% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 8.12 – 7.27 (Ar), 6.12 (1H, t, J = 10.1 Hz, H-4), 5.94 (1H, dd, J = 3.4 Hz and 10 Hz, H-3), 5.71 (1H, dd, J = 1.7 Hz and 3.4 Hz, H-2), 5.10 (1H, d, J = 1.7 Hz, H-1), 4.71 (1H, dd, J = 2.5 Hz and 12.1 Hz, H-6a), 4.51 (1H, dd, J = 4.6 Hz and 12.1 Hz, H-6b), 4.46 – 4.43 (1H, m, H-5), 3.86 – 3.82 (1H, bd, J = 9.5 Hz -O-CH_aH$_b$- aglycone), 3.61 – 3.57 (1H, bd, J = 9.5 Hz -O-CH$_a$$H_b$- aglycone), 1.73 – 1.27 (alkyl chain CH_2 protons), 0.92 (3H, t, J = 6.2 Hz, -CH_3).

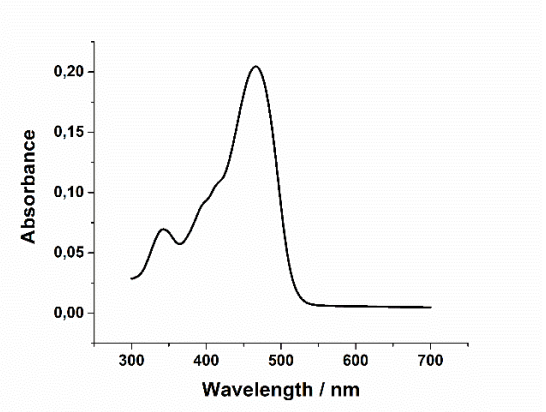
MALDI-TOF Mass Spectrum (Positive Ion Mode) of 2



Fluorescence Emission Spectrum of 2 (10 µM in DMF)



UV/vis Spectrum of 2 (10 µM in DMF)



References

1) See *Chapter 1* – "Glycosylation on Solid Surfaces"
2) a) Zeng, X; Andrade, C. A. S.; Oliveira, M. D. L.; Sun, X. L. *Anal. Bioanal. Chem.* **2012**, *402*, 3161; b) Liang, C.-H.; Wang, S.-K.; Lin, C.-W.; Wang, C.-C.; Wong, C.-H.; Wu, C.-Y. *Angew. Chem. Int. Ed.* **2011**, *50*, 1608.
3) Tsai, I. Y.; Kuo, C.-C.; Tomczyk, N.; Stachelek, S. J.; Composto, R. J. and D. M. Eckmann, *Soft Matter*, **2011**, *7*, 3599.
4) a) Yang, J.; Moraillon, A.; Siriwardena, A.; Boukherroub, R.; Ozanam, F.; Gouget-Laemmel, A. C.; Szunerits, S. *Anal. Chem.* **2015**, *87*, 3721; b) Wijdeven, M. A.; Nicosia, C.; Borrmann, A.; Huskens, J.; van Delft, F.L. *RSC Adv*. **2014**, *4*, 10549; c) Kuzmin, A.; Poloukhtine, A.; Wolfertand, M. A.; Popik, V. V. *Bioconjug. Chem*. **2010**, *21*, 2076; d) Beckmann, H. S. G.; Niederwieser, A.; Wiessler, M.; Wittmann, V. Chem. Eur. J. 2012, 18, 6548; e) Wang, D. N.; Liu, S. Y.; Trummer, B. J.; Dengand, C.; Wang, A. L. *Nat. Biotechnol*. **2002**, *20*, 275; f) Park, S.; Shin, I. *Angew. Chem. Int. Ed*. **2002**, *41*, 3180; g) Ratner, D. M.; Adams, E. W.; Su, J.; O'Kleefe, B. R.; Mrksich, M.; Seeberger, P. H. *ChemBioChem* **2004**, *5*, 379; h) Ref. 161 in *Chapter 1*.
5) a) Serna, S.; Etxebarria, J.; Ruiz, N.; Martin-Lomas, M.; Reichardt, N. C. *Chem. Eur. J.* **2010**, *16*, 13163; b) Laurent, N.; Haddoub, R.; Voglmeir, J.; Wong, S. C. C.; Gaskell, S. J.; Flitsch, S. L. *ChemBioChem* **2008**, *9*, 2592; c) Sardzik, R.; Sharma, R.; Kaloo, S.; Voglmeir, J.; Crocker, P. R.; Flitsch, S. L. *Chem. Commun*. **2011**, *47*, 5425.
6) a) Lee, M. R.; Shin, I. *Org. Lett.* **2005**, *7*, 4269; b) Park, S.; Lee, M. R.; Shin, I. *Bioconjug. Chem.* **2009**, *20*, 155.

7) Kwase, Y. A.; Cochran, M.; Nitz, M. in *Modern Synthetic Methods in Carbohydrate Chemistry* Wiley-VCH Verlag GmbH & Co. KGaA, **2013**, pp. 67-96.

8) a) Park, S.; Lee, M.-R.; Shin, I. *Chem. Commun*. **2008**, 4389; b) Ref. 161 in *Chapter 1*.

9) Ref. 157 in *Chapter 1* (see also Scheme 38 in *Chapter 1*).

10) Ref. 162 in *Chapter 1.*

11) Puvirajesinghe, T.; Turnbull, J. *Microarrays* **2016**, *5*, 3.

12) Zhang, Y.; Campbell, C.; Li, Q.; Gildersleeve, J. C. *Mol. Biosyst.* **2010**, *6*, 1583.

13) Voskuhl, J.; Brinkmann, J.; Jonkheijm, P. *Curr. Opin. Chem. Biol.* **2014**, *18*,1.

14) Ref. 163 in *Chapter 1* (see also Figure 17 in *Chapter 1*).

15) a) Wendeln, C.; Rinnen, S.; Schulz, C.; Arlinghaus, H. F.; Ravoo, B. J. *Langmuir* **2010**, *26*, 15966; b) Wendeln, C.; Rinnen, S.; Schulz, C.; Kaufmann, T.; Arlinghaus, H. F.; Ravoo, B. J. *Chem. Eur. J.* **2012**, *18*, 5880; c) Wendeln, C.; Singh, I.; Rinnen, S.; Schulz, C.; Arlinghaus, H. F.; Burley, G. A.; Ravoo, B. J. *Chem. Sci.* **2012**, *3*, 2479; d) Ref. 164 in *Chapter 1*; e) see Figure 18 in *Chapter 1* for some previous examples of attachment of carbohydrates via μCP).

16) a) Li, X.; Peter, M.; Huskens, J.; Reinhoudt, D. N. *Nano Letters* **2003**, *3*, 1449; b) Mizuno, H.; Buriak, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 17656; c) Spruell, J. M.; Sheriff, B. A.; Rozkiewicz,D. I.; Dichtel, W. R.; Rohde, R. D.; Reinhoudt, D. N.; Stoddart, J. F.;Heath, J. R. *Angew*. *Chem*. *Int*. *Ed*. **2008**, *47*, 9927.

17) For solvent-free alkylation methods: a) Ref.. *137 in Chapter 1*; b) Ref. *138 in Chapter 1*.

18) For solvent-free acetalation: S. Traboni, E. Bedini, M. Giordano, A. Iadonisi, *Adv. Synth. Catal.* **2015**, *357*, 3562-3572. (Work discussed in *Chapter 2)*

19) For solvent-free silylations or tritylations and one-pot orthogonal protections: a) S. Traboni, E. Bedini, A. Iadonisi, *Beilstein J. Org. Chem.* **2016**, *12*, 2748-2756 (work discussed in *Chapter 3*); b) S. Traboni, E. Bedini, A. Iadonisi, *ChemistrySelect* **2017**, *2*, 4906-4911 (work discussed in *Chapter 4*).

20) For solvent-free one-pot orthogonal protections with alkyl and acetal/cyclic protecting groups: see work discussed in *Chapter 5.*

21) For solvent-free synthesis of glycosyl chlorides: S. Traboni, F. Liccardo, E. Bedini, M. Giordano, A. Iadonisi, *Tetrahedron Lett.* **2017**, *58*, 1762-1764 (work discussed in *Chapter 6*).

22) For solvent-free synthesis and one-pot elaborations of alkyl iodides: see work discussed in *Chapter 7*.

23) See *Chapter 1* – "Glycosylation Methods"

24) See *Chapter 1* – "Stereoselectivity of Glycosylation"

25) Ref. 46b in *Chapter 1*.

26) Kettling, F.; Vonhören, B.; Krings, J. A.; Saito, S.; Ravoo, B. J. *Chem. Commun*. **2015**, *51*, 1027.

27) Lu, S.; Lai, Y.; Chen, J.; Liu, C.; Mong, K. T. *Angew. Chem. Int. Ed.* **2011**, *50*, 7315.

28) Zhang, Z.; Ollmann, I. R.; Ye, X.; Wischnat, R.; Baasov, T.; Wong, C. *J. Am. Chem. Soc.* **1999**, *121*, 734.

29) Laezza, A.; Iadonisi, A.; De Castro, C.; De Rosa, M.; Schiraldi, C.; Parrilli, M.; Bedini, E. *Biomacromolecules* **2015**, *16*, 2237.

30) Yamaguchi, T.; Asanuma, M.; Nakanishi, S.; Saito, Y.; Okazaki, M.; Dodo, K.; Sodeoka, M. *Chem. Sci.* **2014**, *5*, 1021.

Chapter 9

Novel Approaches for the Stereoselective Synthesis of Glycosides Based on Solvent-Free Reactions

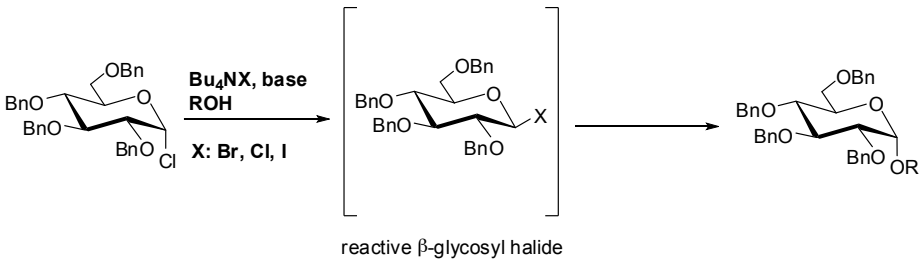
Introduction

Glycosylation reaction represents a pivotal process in most synthetic applications of carbohydrates. Several issues are notoriously associated with glycosylation schemes, both in the preliminary synthesis of suitably differentiated building-blocks, being often highly laborious, and in the effective construction of glycosidic linkages. Successful achievement of the glycosylation step is not conceptually trivial, being strongly dependent on the efficiency of the planned synthetic strategy, including the accurate choice of building-blocks and reaction conditions suitable to provide a highly stereoselective glycosylation.[1] In addition, the high moisture-sensitivity inherent to this kind of reactions entails a wide number of experimental complications burdening the overall process. Since highly reactive species are involved in the reaction, amenable to rapid hydrolysis under air, even low traces of moisture can strongly affect the final yield; this results in the need for rigorously anhydrous conditions, and reactions have to be performed under inert atmosphere and in the presence of previously activated molecular sieves (also serving to dry each solvent or solution to be added in the reaction flask). Reiterated co-distillation under vacuum of glycosyl donor and acceptor in dry toluene is also usually conducted prior to the reaction, in order to further dry the system. Each

step of the procedure needs to be rapidly performed taking care to minimize the moisture contamination.

In the frame of glycosylation chemistry, stereoselective synthesis of α-glycosides is an especially central topic. As also introduced in *Chapter 1*,[2] exclusive α-selectivity in glycosylation reactions is not an easy achievement and very often-sophisticated strategies are pursued for this purpose. The most effective ones are typically requiring a suitable preliminary functionalization of the donor with suitable groups capable of directing the approach of the incoming nucleophilicacceptor.[3] Installation of these groups entails extra synthetic steps and the use of expensive functionalizing agents.

In this context, a well established methodology to carry out selective α-glycosylations under very mild conditions is represented by Lemieux's strategy, relying on the in situ generation of a reactive beta glycosyl halide from a glycosyl halide donor (usually bromides or chlorides) in the presence of an external promoter (**Scheme1**).[4]



Scheme 1. Lemieux's Methodology for α-Glycosylation

This approach is still applied, but reactions are generally very slow so that the method is commonly restricted to especially reactive donors (such as fucosyl donors).

In light of these considerations as well as the recent development of a solvent-free protocol for the quick preparation of glycosyl chlorides,[5] a

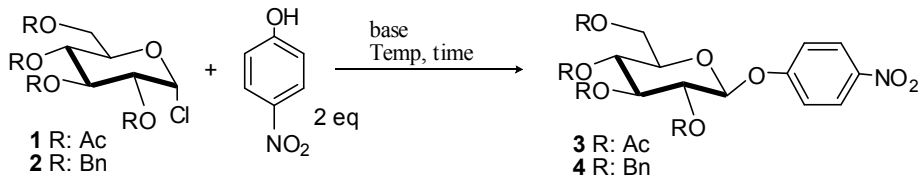
follow-up investigation was aimed at clarifying whether the solvent-free conditions might find applicability in the development of practical glycosylation protocols. In this chapter is described the feasible use of easily prepared[5] glycosyl chlorides as donors in glycosylation reactions performed under air and in the absence of solvent. In particular it is demonstrated that selective α-glycosylations can be conveniently achieved with variously protected glycosyl chlorides with excellent stereoselectivity through an original solvent-free application of Lemieux's methodology.

Results and Discussion

Aiming at first verifying the applicability of solvent-free conditions in glycosylation reactions with glycosyl chlorides, initial experiments were addressed to glycosylation of a simple model acceptor, such as p-nitrophenol, in the presence of a slight excess of a liquid base. Results of these experiments, where either a per-*O*-acetylated or benzylated glucosyl chloride was employed, are summarized in **Table 1**. Favorable expectations about such scheme were supported by a previous experiment where a per-O benzylated fucosyl O-glycoside was successfully obtained from the *in situ* generated highly reactive chloride under solvent-free conditions.[6] Not surprisingly, the reaction of disarmed[7] donor **1** with the model phenol was slow at 60°C, according to its relatively low reactivity; at 80 °C the reaction occurred at a satisfying rate, but the yield was strongly plagued by competitive elimination processes when either DIPEA or triethylamine was used as the base (entries 1 and 2). As expected, exclusive β-selectivity was observed in these cases due to the possible occurrence of either a direct S_N2 pathway or a multistep mechanism involving the participation

effect of the *O*-2 acetyl group (addressing the nucleophilic attack once again from the β-face)[2] (see **Scheme 2** below).

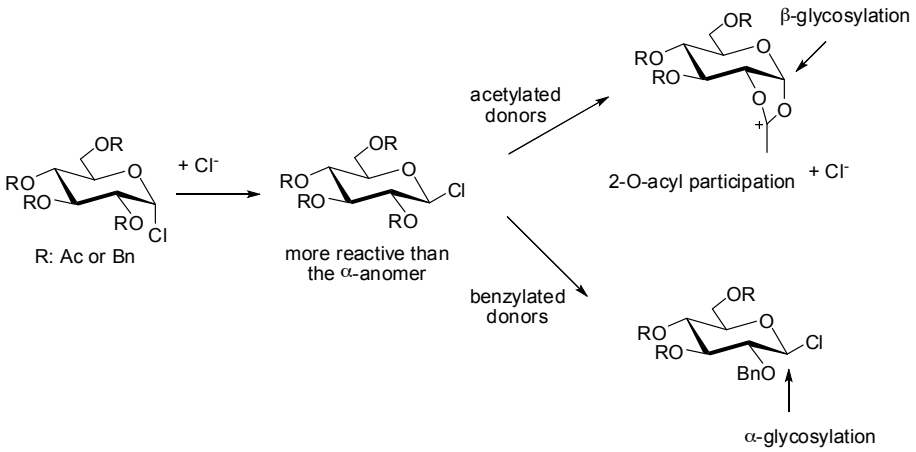
Table 1. Solvent-Free Glycosylation of p-Nitrophenol With Glycosyl Chlorides



Entry	Donor	Temperature, Time	Base (eq.)	Product, isolated yield(α/β)
1	**1**	80 °C, 3 h	TEA (2)	**3**, 28% (only β)
2	**1**	80 °C, 3 h	DIPEA (2)	**3**, 26% (onlyβ)
3	**2**	60 °C,1 h	TEA (3)	**4**, 51 % (1:4)
4	**2**	60 °C, 2 h	DIPEA (3)	**4**, 48 % (1:3)

Better yields, but a lower diastereoselectivity, were instead observed when the armed benzylated donor **2** was coupled with *p*-nitro-phenol (**Table 1**, entries 3 and 4). The lower stereocontrol is a consequence of the non-participating attitude of benzyl groups and might be explained by the initial occurrence of an S_N2 process (β-glycosidation), with release and gradual accumulation of chloride anion (the leaving group) that can act as a competitor nucleophile as the donor consumption advances. Thus, the nucleophilic attack of the chloride anion to unreacted α-glucosyl chloride might generate a reactive β-glucosyl chloride (much more reactive than the more stable α-anomer) which in

turn can undergo an S_N2 process to give α-linked glycosides (**Scheme 2)**.

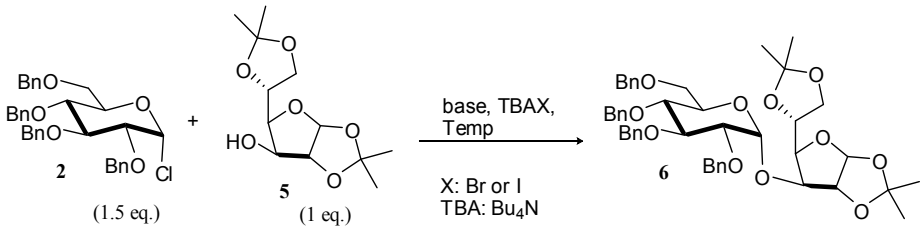


Scheme 2. Different Diastereoselectivity in the Glycosylation of Phenols with Benzylated or Acetylated Glycosyl Chlorides

Having ascertained the feasible solvent-free glycosylation with not necessarily highly reactive donors, some experiments were next addressed to extend the scope of a solvent-free approach to the synthesis of disaccharides by the coupling of glycosyl chlorides with non-trivial saccharide acceptors. The effort was especially targeted to the challenging stereocontrolled synthesis of α-glycosides; for this purpose, it was attempted a solvent-free version of Lemieux's methodology, assuming that the solvent-free conditions would enhance reactivity of this system, favouring nucleophilic attack of an encumbered saccharide acceptor. The first trials were conducted by mixing under air glucosyl chloride **2** and the di-isopropylidenated acceptor **5** (commercially available) in the presence of a liquid base (in a slight stoichiometric excess) and an halide salt activator. Results of

these initial experiments (summarized in **Table 2**) indicated that a high temperature was needed for the reaction to occur (higher than in the case of a phenol acceptor, see **Table 1**). Comparable results were achieved with both DIPEA and lutidine as the base, and TBAI (tetrabutylammoniun iodide) as the halide source.

Table 2. Glycosylation of Glucosyl Donor **2** and Acceptor **5** Under Solvent-Free Conditions



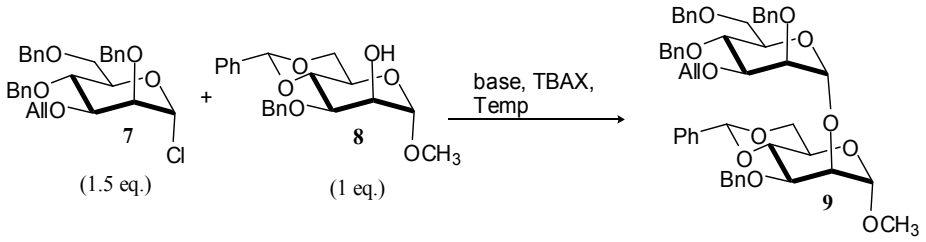
Entry	Temperature, Time	Base (eq.)	TBAX (eq.)	Isolated yield of **6**
1	80-100 °C, 7 h	DIPEA (2.5)	TBAB (0.4)	40%
2	70-90 °C, 6 h	DIPEA (2.5)	TBAI (0.4)	44%
3	70-110 °C, 7 h	Lutidine(3.5)	TBAB (0.4)	22%
4	110 °C, 6 h	Lutidine (2.5)	TBAI (0.4)	41%

Although yields were not especially good, it should be highlighted that in all cases reactions proceeded with excellent α-selectivity, consistent with the expected mechanistic pathway passing through in situ generation of a β-glycosyl intermediate, more reactive than the α-counterpart (**Scheme 1)**.

In order to assess the generality of the solvent-free glycosylations, a further set of experiments was then performed adopting the mannosyl chloride **7** and mannosyl acceptor **8** (**Table 3**). The 2-OH acceptor was selected because linked 2-O-α-linked di-mannosides are frequently

found in oligo-mannan structures of biological interest (for example the gP 120 glycoprotein exposed by HIV, or PI-88, a highly sulfated pentasaccharide currently under clinical trials).[8] Additionally, axially oriented hydroxyls are commonly regarded as poorly nucleophilic, and so these trials might provide indications on the scope of the solvent-free glycosylation.

Table 3. Glycosylation of Mannosyl Donor **7** and Acceptor **8** Under Solvent-Free Conditions



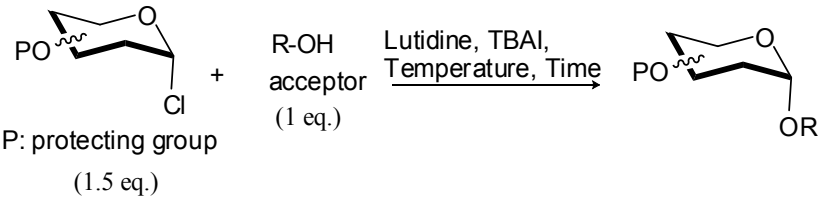
Entry	Temperature, Time	Base (eq.)	TBAX (eq.)	Isolated yield of **9**
1	90 °C, 3 h	Lutidine (3.5)	TBAI (0.3)	32 %
2	70 °C, 6 h	DIPEA (3.5)	TBAI (1.0)	27 %
3	90 °C, overnight	collidine (3.5)	TBAI (0.5)	34 %
4	100 °C, overnight	collidine (3.5)	TBAB (0.5)	39 %

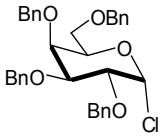
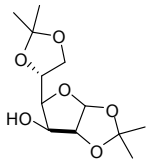
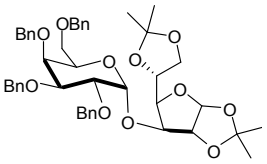
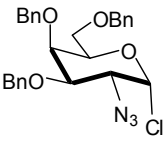
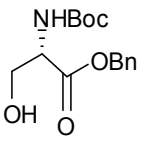
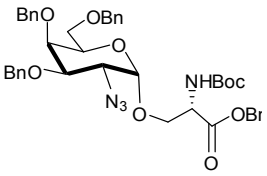
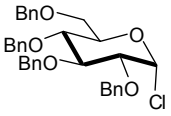
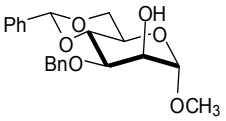
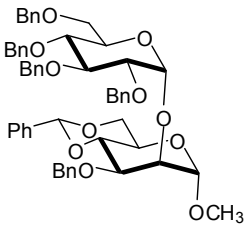
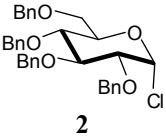
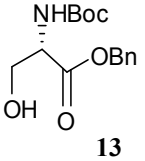
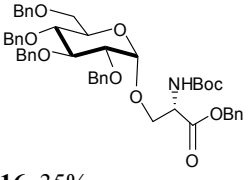
Once again these experiments, summarized in **Table 3**, resulted in glycosylations proceeding with moderate yields but exclusive α-selectivity. As with experiments in **Table 2**, lutidine and DIPEA provided similar yields, the former giving a slightly improved result at a higher temperature (**Table 3**, compare entries 1 and 2). Another substituted pyridine, such as collidine, was also tried at this stage, and provided the best results in terms of yield (**Table 3**, entries 3 and 4) albeit at a higher temperature and after prolonged reaction times.

Having generally observed as the main side-product a 1,2-glycal (together with the hemiacetal derived from the glycosyl chloride), these results might be accounted for the lower basicity of substituted pyridines with respect to DIPEA (resulting in a lower tendency to promote elimination side-processes), despite these effect may be partially counterbalanced by the higher temperature required in the experiments with the weaker bases. In light of these considerations, it was decided to use lutidine as the standard base in the following experiments that were aimed at testing the applicability of the solvent-free glycosylation procedure witha wider set of substrates (**Table 4**). To this aim, *galacto*-configured donors were examined at this stage; as shown in **Table 4**, result obtained in the coupling of donor **10** with acceptor **5** confirmed the trend of previous experiments, providing satisfying yield and complete α-selectivity. The same procedure was also applied to a different galactosyl donor and addressed to the synthesis of a biologically interesting glycoside by coupling galactosazido-chloride **12** with the serine acceptor **13** (easily obtained from the corresponding commercial chlorohydrate). The reaction proceeded in a moderate 33% yield but with an excellent α-selectivity; this is an interesting result, as the achievement of high α-selectivity is especially difficult with primary alcohols. The obtained product corresponds to a protected form of Tn antigen, a fragment highly expressed in cancer cells but not found in healthy cell surfaces.[9] In order to get more data for a comparison of reactivity among the several donors prepared, serine acceptor **13** and mannoside 2-OH acceptor **8** were coupled with the glucosyl donor **2** (**Table 4,** entries 3 and 4). In both cases, modest yields were achieved with excellent α–selectivity. Comparison of the experimental conditions applied to the serine

acceptor (compare entries 2 and 4) evidence a higher reactivity for the galactosazido donor **12** (activated at 70 °C) than the glucosyl donor **2**.

Table 4. Glycosylation of Several Donors and AcceptorsUnder Solvent-Free Conditions[a]



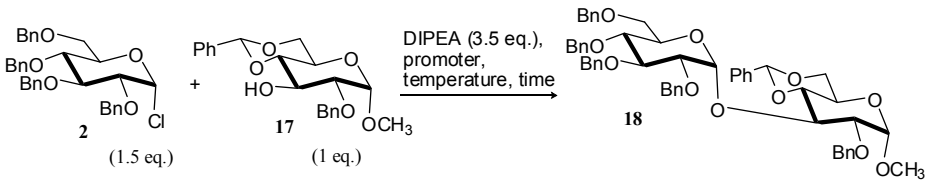
Entry	Donor	Acceptor	Time	Product, isolated yield
1	 **10**	 **5**	3h	 **11**, 42%
2[b]	 **12**	 **13**	4h	 **14**, 33%
3	 **2**	 **8**	4h	 **15**, 30%
4	 **2**	 **13**	6h	 **16**, 35%

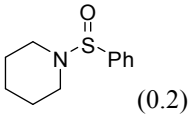
[a]General conditions: Lutidine (3.5 eq.), TBAI (0.3 eq.),90°C.
[b]The reaction was performed ad 70°C.

The reported experiments highlighted the applicability of a solvent-free procedure for the synthesis of α-glycosides from several couples of donors and acceptors with excellent stereocontrol, though in moderate yields. On this basis, it was decided to investigate a wider number of variables to attempt a further optimization of glycosylation yields. To this purpose, coupling of donor **2** with acceptor **17** was examined and DIPEA was reconsidered as the base, having observed in most of the reported experiments substantial generation of the hemiacetal side-product deriving from hydrolysis of the glycosyl donor. It was supposed that the lower temperatures needed to achieve glycosylation with DIPEA than with other bases (see **Tables 2** and **3)** would support minimization of side-processes. Thus, a screening of alternative promoters was initially conducted in this new set of experiments (**Table 5**). Slow reaction and low yields were observed in the presence of sulfonamide **19** or ethyldisulfide at 80-90°C (entries 1 and 2); much improved results were instead obtained with DMF, phenyldisulfide or phenyldiselenide as promoters with yields around 80% though a satisfying but lower α-selectivity was observed (see entries 3,4,5 and 6). In these experiments, the gradual increasing of reaction temperature from 80 to 100°C proved useful in minimizing the generation of side-products, as evidenced by TLC analysis. The following experiments were performed in the presence of different ammonium salts that provided the highest α-selectivity; especially TBAB proved the best compromise providing at only 80°C exclusive generation of the α disaccharide and a yield of 60% being, however, remarkably improved in respect to the average previous results. It is worth noting that unlike the experiments with lutidine, hydrolysis side-products were not detected though reactions were always performed under air. Finally, as shown in last experiment in entry 10, a double amount of TBAB was

found to enable the fully stereoselective glycosylation at even lower temperature (70°C), with a slight increasing of the yield.

Table 5. Optimization of the Solvent-Free Glycosylation Procedure with DIPEA by Screening Several Promoters



Entry	Promoter (eq.)	Temperature, time	Isolated yield of **18** (α/β)
1	 (0.2) **19**	80-90°C, 5h	21% (5:1)
2	$(EtS)_2$(1.5)	80-90°C, 6h	20% (5:1)
3	DMF (1.5)	80°C, 4h	73% (6:1)
4	DMF (1.5)	80-100°C, 3h	82% (6:1)
5	$(PhS)_2$(1.5)	90°C, 4.5 h	80% (3:1)
6	$(PhSe)_2$(0.1)	80-100°C, 4h	81% (6:1)
7	TBAI (0.3)	80°C, 3h	65% (8:1)
8	TBAB (0.3)	80°C, 3h	60% (only α)
9	TBAC (0.3)	80-90°C, 4h	60% (5.5 : 1)
10	TBAB (0.6)	70°C, 5h	65%(only α)

Conclusions

This chapter describes the optimization of remarkably practical glycosylation procedures relying on reactions performed under air, in the absence of solvent and involving easily prepared[5]glycosyl chlorides as donors. A special focus is addressed to the challenging α-glycosylations with introduction of an unprecedented version of Lemieux's methodology in which glycosyl donor, acceptor and promoter are simply mixed under air in the presence of a reduced stoichiometric excess of a liquid base, being the only liquid medium in the reaction. Experiments herein reported highlight the solvent-free conditions to be essential for extending the scope of Lemieux's strategy, traditionally restricted to highly reactive donors and acceptors. Indeed, according to results so far reported, glycosylations with excellent α-stereoselectivitycan be achieved from several couples of gluco-, manno- and galacto-configured donors and acceptors variously protected, though with moderate yields. Most recent experiments aimed at further optimization showed the feasible improvement of reaction yields by the use of a more reactive combination of base and promoter allowing the reaction to occur at a lower temperature with reduced generation of byproducts. In light of the promising results herein shown and of the many experimental advantages associated with the solvent-free approaches,[10] it is expected that the presented strategy may provide a valuable method in oligosaccharide synthesis for the streamlined access to more complex targets.

Experimental Section

General Methods

Reaction progress was monitored by TLC analysis, by soaking the eluted plates in ethanol/sulfuric acid 95:5 (v:v) and heating them at ca 230 °C. Reaction products were purified by silica gel chromatography (eluents: hexane/ethyl acetate mixtures or ethyl acetate) and purified products characterized by NMR spectroscopy. H^1 e C^{13} NMR spectra were recorded on a Brucker 400 MHz device.

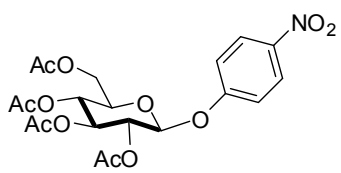
General procedure for solvent-free p-nitrophenol glycosylation

Glycosyl chloride (0.5 mmol), *p*-nitro phenol (139 mg, 1 mmol) and a tertiary amine (DIPEA or TEA) were mixed in a round-bottomed vessel. The mixture was exposed to the suitable temperature until completion of the reaction (see Table 1 for specific conditions). At the end of reaction, the mixture was dissolved in DCM and adsorbed on a small amount of silica by solvent evaporation. Silica thus obtained was loaded on a chromatographic column and the product purified by flash chromatography (see Table 1 for yields).

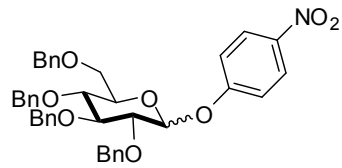
General procedure for solvent-free glycosidation of saccharide or serine acceptors

The alcohol acceptor (0.5 mmol, 1 eq), the glycosyl chloride (0.75 mmol, 1.5 eq), the promoter and the liquid basewere mixed in a round-bottomed vessel (see **Table 2**, **Table 3**, **Table 4** and **Table 5** for relative amounts of employed reagents). The mixture was exposed to the suitable temperature until completion of the reaction (see **Table 2**, **Table 3**, **Table 4** and **Table 5**for reaction times and temperature). At the end of reaction, the mixture was dissolved in DCM and adsorbed on a small amount of silica by solvent evaporation. Silica thus obtained

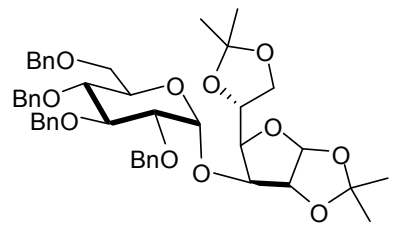
was loaded on a chromatographic column and the product purified by flash chromatography (see corresponding tables for yields).



Compound 3. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (2H, d, J = 8.8 Hz), 7.05 (2H, d, J = 8.8 Hz), 5.30-5.00 (overlapped signals, H-1, H-2, H-3, H-4), 4.26-4.00(2H, m, H_2-6), 3.93 (1H, m, H-5), 2.05, 2.04, 2.03, 2.03. ^{13}C NMR (100 MHz, $CDCl_3$) δ170.5, 170.2, 169.4, 169.2 (-$COCH_3$), 161.2, 143.3, 125.8, 116.7, 98.1 (C-1), 72.5, 71.0, 68.1, 61.9, 20.7-20.6.

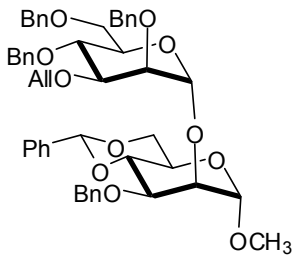


Compound 4. Anomeric mixture α:β ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (2H, d, J = 9.2 Hz), 7.80-7.15 (aromatic H), 5.56 (1H, d, J = 3.6 Hz, H-1 α), 5.21 (1H, d, J = 7.2 Hz, H-1 β), 5.20-4.50 (8 x AB, 8 x CH_2Ph), 4.31 (1H, t, J = 9.6 Hz, H-3 α), 4.00-3.60 (overlapped signals, H-2 α andβ, H-3 β, H-4 α andβ, H-5 α andβ, H_2-6 α andβ). ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.4-125.6 and 116.4 (aromatic CH), 106.6 (C-1 β), 97.5 (C-1 α), 84.4, 81.6, 77.3, 75.7, 75.2, 75.1, 75.0, 73.4, 68.5.

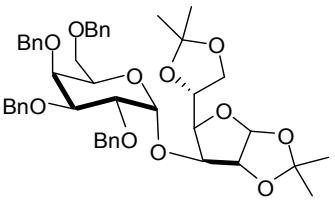


Compound 6. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.00 (aromatic protons), 5.87 (1H, d, J = 3.6 Hz, H-1), 5.23 (1H, d, J = 3.6 Hz, H-1´), 4.97-4.45 (4 x AB, 4 x –CH_2Ph, 8H), 4.50-4.45 (2H, m, overlapped signals, H-5 and H-2), 4.23 (1H, d, J = 2.4 Hz, H-3), 4.13 (1H, dd, J = 2.8 and 9.6 Hz, H-4), 4.10-4.00 (2H, m, H_2-6), 3.93 (1H, t, J = 9.2 Hz, H-3´), 3.78 (1H,

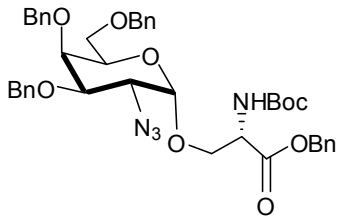
dt, J = 2.8 and 9.6 Hz, H-5′), 3.77-3.70 (2H, d, J = 2.8 Hz, H_2-6′), 3.62 (1H, t, J = 9.2 Hz, H-4′), 3.55 (1H, dd, J = 3.6 and 9.2 Hz, H-2′), 1.48, 1.41, 1.28, 1.25 (12H, 4 x s, isopropylidene CH_3).



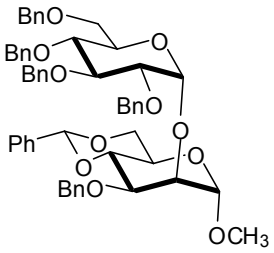
Compound 9. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.10 (aromatic protons), 6.00-5.85 (1H, m, -CH=CH_2), 5.62 (1H, s, benzylidene –CHPh), 5.34 (1H, bd, J = 17.4 Hz, -CH_2CH=CHcisH*trans*), 5.21(1H, bs, H-1′),5.20 (1H, bd, J = 10.0 Hz, -CH_2CH=CH*cis*Htrans), 4.90-4.45 (4 x AB, 4 x –CH_2Ph, 8H), 4.24 (1H, dd, J = 4.0 and 9.6 Hz, H-6eq), 4.10-3.70 (overlapped signals), 3.22 (3H, s, -OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4-138.3, 137.6 (aromatic C), 135.1 (CH_2=*C*H-), 128.9-127.4 (aromatic CH), 116.6 (*C*H_2=CH-), 101.5, 100.9 (C-1 and C′-1), 79.4, 79.2, 77.5, 75.8, 75.3, 74.9, 74.8, 73.2, 73.2, 72.2, 71.0, 69.5, 68.9, 63.6, 54.8.



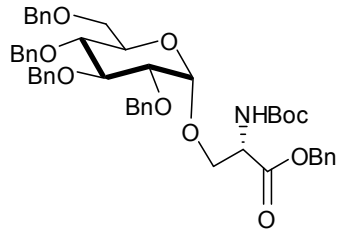
Compound 11. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.00 (aromatic protons), 5.91 (1H, d, J = 3.6 Hz, H-1), 5.33 (1H, d, J = 3.2 Hz, H-1′), 5.10-4.50 (4 x AB, 4 x –CH_2Ph, 8H), 4.50-4.40 (2H, m, overlapped signals, H-5 and H-2), 4.18 (1H, d, J = 2.4 Hz, H-3), 4.10 (1H, dd, J = 2.8 and 9.6 Hz, H-4), 4.00-3.90 (3H, overlapped signals, H_2-6 and H-4′), 3.85 (1H, dd, J = 2.8 and 9.2 Hz, H-3′), 3.81 (1H, m, H-5′), 3.75-3.65 (2H, m, H_2-6′), 3.65 (1H, dd, J = 3.2 and 9.2 Hz, H-2′), 1.51, 1.43, 1.29, 1.25 (12H, 4 x s, isopropylidene CH_3).



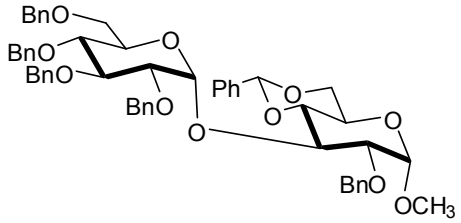
Compound 14. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.20 (aromatic H), 5.94 (1H, d, J = 8.0 Hz, -NHBoc), 5.33 (1H, d, J = 4.0 Hz, H-1), d 5.23 (s, -CO_2CH_2Ph), 5.05-4.50 (3 x AB, 3 x CH_2Ph), 4.30 (1H, dd, J = 3.2 and 10.2 Hz, 1H), 4.14 (1H, dd, J = 3.6 and 10.2 Hz, 1H), 4.05 - 3.98 (2H, overlapped signals), 3.95 - 3.90 (2H, overlapped signals), 3.70-3.55 (2H. m, H_2-6), 1.55 (9H, s).^{13}C NMR (100 MHz, $CDCl_3$) δ155.5, 138.6, 138.5, 137.9, 128.6-127.3 (aromatic CH), 99.2 (C-1), 79.8, 78.6, 76.3, 74.7, 73.4, 73.1, 72.9, 70.3, 69.7, 68.5, 67.9, 67.0, 28.2.



Compound 15. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.15 (aromatic protons), 5.21 (1H, J = 2.8 Hz, H-1′), 5.62 (1H, s), 5.17-4.50 (8H, 4 x AB, 4 x -CH_2Ph), 4.42 (1H, t, J = 9.2 Hz, H-3′), 4.42-4.30 (2H, overlapped signals, H-6eq and H-2), 4.15 (2H, overlapped signals), 4.00-3.80 (5H, overlapped signals), 3.74 (1H, t, J = 9.2 Hz, H-4′),3.71 (1H, dd, J = 2.8 and 9.2 Hz, H-2′), 3.42 (3H, s, -OCH_3).



Compound 16. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50-7.20 (aromatic H), 5.87 (1H, d, J = 8.0 Hz, -NHBoc), 5.36 (1H, d, J = 4.0 Hz, H-1), 5.13 (2H, s, -CO_2CH_2Ph), 5.05-4.50 (3 x AB, 3 x CH_2Ph), 4.38 (1H, dd, J = 3.2 and 10.2 Hz, 1H), 4.15 (1H, dd, J = 3.6 and 10.2 Hz, 1H), 4.05 (1H, t, J = 9.2 Hz, H-3), 3.90 – 3.85 (3H, overlapped signals), 3.85 -3.75 (2H, overlapped signals), 3.69 (1H,dd, J = 4.0 and 9.2 Hz, H-2), 1.57 (9H, s).



Compound 18. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58-7.07 (aromatic H), 5.73 (1H, d, J = 3.6 Hz, H-1´), 5.60 (1H, s, benzylidene –CHPh), 5.15-4.51 (9H, 4xAB, 4x –CH_2Ph and H-1), 4.46 (1H, dd, J = 4.0 and 12.2 Hz, H-6eq), 4.37 (1H, m, H-5´), 4.11 (1H, t, J = 9.3 Hz, H-3), 4.00 (1H, m, H-5), 3.92 (1H, bt, J = 9.3 Hz, H-6ax), 3.85 (1H, t, J = 10.0 Hz, H-3´), 3.82-3.77 (2H, overlapped signals, H-2 and H-4´), 3.63-3.60 (4H, overlapped signals, H_2-6´, H-4 and H-2´), 3.55 (3H, s, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.9(x2), 138.0, 137.8, 137.4 and 137.0 (aromatic C), 129.3-126.3 (aromatic CH), 102.0, 98.4 and 96.1 (acetal CH), 82.9, 81.6, 78.7, 77.9 (x2), 75.4, 74.7, 73.3(x2), 72.7, 71.0, 69.7, 69.1, 68.0, 61.7, 55.3.

References

1) See *Chapter 1* for a detailed discussion of these issues.
2) *Chapter 1* – "Stereoselectivity of Glycosylation Reactions" .
3) a) Kim, J. H.; Yang, H; Boons, G. J. *Angew. Chem. Int. Ed.***2005**, *44*, 947; b) Yasomanee, J. P.; Demchenko, A. V. *Angew. Chem. Int. Ed.***2014**, *53*, 10453; c) Nigudkar, S. S.; Demchenko, A. V. *Chem. Sci.* **2015**, *6*, 2687.
4) See Ref. 25 in *Chapter 1*.
5) S. Traboni, F. Liccardo, E. Bedini, M. Giordano, A. Iadonisi, *TetrahedronLett.* **2017**, *58*, 1762-1764 (work discussed in *Chapter 6*).
6) See Scheme 2 in *Chapter 6*.
7) Concepts of armed and disarmed in glycosylations is discussed in *Chapter 1*.
8) For a very recent contribution specifically addressed to this disaccharide: Reina, J. J.; Di Maio, A.; Ramos-Soriano, J.; Figueiredo, R. C.; Rojo, J. *Org. Biomol. Chem.*, **2016**, *14*, 2873.
9) Pinho, S. S.; Ceis, R. A. *Nature Rev. Canc.***2015**, *15*, 540.
10) See previous chapters for other solvent-free protocols developed in the context of this PhD thesis or previously in our laboratory.

Appendix

PhD Course Activity Summary

1) Attended Courses:

- Spettrometria di Massa; Pucci P.; from 11/07/2015 to 15/07/2015; 4 CFU.
- Glicoscienza; Parrilli M., Bedini E.; 5-12/07/2015; 3 CFU.
- Tecniche estrattive Solido-Liquido impiegate nella preparazione del campione per l'analisi chimica e nella produzione di estratti per usi industriali; Naviglio D.; 09-17/12/2014; 3 CFU.
- Sintesi, struttura ed applicazioni di oligonucleotidi naturali e modificati; Montesarchio D.; 04-13/02/2015; 3 CFU.
- Neutron scattering techniques; C. Zorn; 27-30/10/2015; 3 CFU.
- Applications of neutron scattering techniques in soft matter and bio-relevant systems. How to study their structure and dynamics; Y. Gerelli; 9-13/11/2015; 3 CFU.
- Reazioni organiche nei sistemi biologici; Iadonisi A.; 21-25/07/2017; 3 CFU.

2) Attended Seminars:

Title	Speaker	Place	Date
Multifunctional bioinspired cathechol - based coatings and nanoparticles	Daniel Ruiz-Molina	Dept Chemical Sciences, University of Naples Federico II	05/11/2014
Le fitotossine: un'avventura lunga 40 anni	Antonio Evidente	Dept Chemical Sciences, University of Naples Federico II	10/12/2014
New chiral catalysts derived from Iron(II) and Bismut (III) for asymmetric synthesis	Thierre Ollevier	Dept Chemical Sciences, University of Naples Federico II	15/12/2014

DNA-based strategies for the inihibitor of HMGB1 cytochine activity	Domenica Musumeci	Dept Chemical Sciences, University of Naples Federico II	22/01/ 2015
Gli accertamenti sulle impronte del Ra.C.I.S	Luca Niola	Dept Chemical Sciences, University of Naples Federico II	17/03/ 2015
Dall'analisi dei reflui alla depurazione degli impianti	Antonio Riccio	Dept Chemical Sciences, University of Naples Federico II	30/04/ 2015
Matrix metalloproteinase: inter-domain flexibility and recognition of substrates	Marco Fragai	Dept Chemical Sciences, University of Naples Federico II	08/05/ 2015
European large scale facilities: neutron and synchroton source	Serge Perez	Dept Chemical Sciences, University of Naples Federico II	06/05/ 2015
Lectins from bacteria and fungi: therapeutical targets and research tools	Anne Imberty	Dept Chemical Sciences, University of Naples Federico II	15/05/ 2015
Characterizing biomolecular interactions: Biacore experience	Silvia Pileri	Dept Chemical Sciences, University of Naples Federico II	19/05/ 2015
Pharmaceutical companies: external manufacturing and quality assurance	D. Demasi	Dept Chemical Sciences, University of Naples Federico II	25/05/ 2015
Biosensing and bioelectronics based on organic electrochemical devices: from monitoring drug dynamics to hybrid bio-organic devices	Salvatore Iannotta	Dept Chemical Sciences, University of Naples Federico II	11/06/ 2015
The bacterial cell wall by liquid state, standard and DNP solid state NMR	Jean-Pierre Simorre	Dept Chemical Sciences, University of Naples Federico II	29/06/ 2015
Synthetic and biofunctional studies of microbial and animal glycan toward immunoregulation	Koichi Fukase	Dept Chemical Sciences, University of Naples Federico II	29/09/ 2015
Innovative approaches for polysaccharide-based vaccines	Francesco Berti	Dept Chemical Sciences, University of Naples Federico II	20/11/ 2015
Industria e ricerca nel settore biofarmaceutico: bisogni attuali e sviluppi futuri	Sara Carillo	Dept Chemical Sciences, University of Naples Federico II	25/02/ 2016

Basics of detergents formulations and challenges	Giulia Bianchetti	Dept Chemical Sciences, University of Naples Federico II	16/03/ 2016
La Chimica: un diamante	Mario Marzullo	Dept Chemical Sciences, University of Naples Federico II	21/04/ 2016
Chemical biology and medicinal chemistry of glycosphingolipid metabolism	Herman Overkleeft	Dept Chemical Sciences, University of Naples Federico II	19/12/ 2016
Modified nucleosides and oligonucleotides for biomedical applications	Daniela Montesarchio	Dept Chemical Sciences, University of Naples Federico II	18/01/ 2017
Antigens on the move – Structure and mechanism of translocation machineries in adaptive immunity	Robert Tampé	Dept Chemical Sciences, University of Naples Federico II	20/09/ 2017

3) Visiting periods in Institutions different from University of Naples "Federico II":

Host Institution	Country	Start Date	End Date
Westfälische Wilhelms-Universität Münster	**Germany**	**01/04/2016**	**31/07/2016**

4) Publications (include accepted and in preparation):

- Traboni, S. et al. *"Novel Approaches for the Stereoselective Synthesis of Glycosides Based on Solvent-Free Reactions"*, in preparation

- Traboni, S. et al. *"One-Pot Preparation of Orthogonally Protected Saccharide Building-Blocks Through Sequential Base-Promoted Alkylation and Acid-Catalyzed Diol Protection Under Solvent-Free Conditions"*, in preparation

- Traboni, S.; Bedini, E.; Iadonisi, A. *"Solvent-Free Conversion of Alcohols to Alkyl Iodides and One-Pot Elaborations Thereof"*, *ChemistrySelect* **2018**, accepted

- Traboni, S.; Bedini, E.; Iadonisi, A. *"Solvent-Free One-Pot Diversified Protection of Saccharide Polyols via Regioselective Tritylations"*, *ChemistrySelect* **2017**, *2*, 4906-4911

- Buhl, M.;‡ Traboni, S.;‡ Körsgen, M.; Lamping, S.; Arlinghaus, H. F.; Ravoo, B. J. *"On Surface O-Glycosylation by Catalytic Microcontact Printing"*, *Chem. Commun*. **2017**, *53*, 6203-6206
  ‡These authors contributed equally

- Traboni, S.; Liccardo, F.; Bedini, E.; Giordano, M.; Iadonisi, A. *"Solvent-Free Synthesis of Glycosyl Chlorides Based on the Triphenylphosphine/Hexachloroacetone System"*, *Tetrahedron Lett*. **2017**, *58*, 1762-1764

- Traboni, S.; Bedini, E.; Iadonisi, A. *"Orthogonal Protection of Saccharide Polyols Through Solvent-Free One-Pot Sequences Based on Regioselective Silylations"*, *Beilstein J. Org. Chem*. **2016**, *12*, 2748-2756

- Traboni, S.; Bedini, E.; Giordano, M.; Iadonisi, A. *"Three Solvent-Free Catalytic Approaches to the Acetal Functionalization of Carbohydrates and Their Applicability to One-Pot Generation of Orthogonally Protected Building-Blocks"*, *Adv. Synth. Catal*. **2015**, *357*, 3562-3572

5) Attended congresses/workshops/summer schools/contribution:

- **1st Napoli-Osaka Meeting**; 10/07/2017, Napoli (Italy); **Oral Communication:** Novel strategies for the synthetic manipulation of saccharide functional groups and use thereof towards targets of application interest (Traboni, S., Bedini, E.; Giordano, M.; Iadonisi, A.)

- **19th European Carbohydrate Symposium EUROCARB**; 02-06/07/2017, Barcelona (Spain); **Poster Presentation**: Solvent-Free Approaches to Regioselective Protection of Carbohydrates. Applicability to One-Pot Sequences (Traboni, S., Bedini, E.; Giordano, M.; Iadonisi, A.)

- **TOLLerant 4th Meeting "Molecular Aspects of Host/Microbe Dialogue"**; 05-07/06/2017, Naples (Italy).

- **XV Meeting School on Carbohydrate Chemistry**; 19-22/06/2016, Pontignano, Siena (Italy); **Oral Communication**: Solvent-Free Approaches to Regioselective Protection of Carbohydrates. Applicability to One-Pot Sequences (Traboni, S., Bedini, E.; Giordano, M.; Iadonisi, A.)

- **XV Edizione Delle Giornate Scientifiche C.I.N.M.P.I.S.**; 11-12/12/2015, Napoli, (Italy).

- **COST Action BM 1003 "Glycoscience: a complex discipline with a central role in modern biology, biotechnology and medicine"**; June 2014, Napoli (Italy).