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Glycosylation Strategies in Oligosaccharide Synthesis

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Abstract

The four major classes of compounds essential to life are nucleic acids, proteins, lipids and carbohydrates. Over the past 30 years the first three classes have received much attention from chemists and biologists, whereas during most of that time the carbohydrates were largely neglected, partly in the belief that their chemistry and biology had been fully worked out. In the past decade, however, research on carbohydrates has been revived and is now expanding rapidly. As a result of many new developments carbohydrate research is today broad and diverse. The study of carbohydrates within biological systems has illustrated that they in the form of glycoconjugates are involved in various fundamental biological functions such as cell-cell recognition and cell-external agent interactions. These interactions can initiate many beneficial biological events, such as fertilization, cell growth and differentiation as well as immune responses. However they can also led to detrimental processes such as inflammation, viral and bacterial infections, cancer metastatis, providing a multitude of opportunities for therapeutic invention. Therefore, the view that carbohydrates are of limited importance within biological systems has been challenged and renewed interest in the science of 'Glycobiology' has emerged.

Owing to the remarkable biological relevance of carbohydrate, the synthesis of oligosaccharides or carbohydrate derivatives has long been the goal pursued by researchers from various areas. The complexity and diversity of carbohydrates found in nature, however, makes the synthesis of carbohydrates a challenging task despite numerous efforts documented in the literature. One of the reasons is that different carbohydrate scaffolds often manifest moderate to drastic different reactivity in various reactions thus resulting in the requirement of optimizing conditions for each individual carbohydrate scaffold. The vast number of developed and employed protecting groups further fuel the complexity in carrying out carbohydrate synthesis, one such example being glycosylation. The difference in the reactivity of glycosyl donors as a result of the employed protecting groups and the intrinsic structure-associated reactivity, numerous methods designed for activating various glycosyl donors have been reported. Sophisticated methods, like chemoenzymatic synthesis, one-pot glycosylation, solid-phase oligosaccharide synthesis, and iterative glycosylation, have been developed for the goal of alleviating the challenges in oligosaccharide synthesis.

Keywords: Oligosaccharide synthesis, glycosylation, stereo selectivity, regeo selectivity, glycosyl donor, glycosyl acceptor, protecting group.

Introduction

The field of synthetic carbohydrate chemistry grew up exceptionally in the last twenty years mainly in the area of biological processes. From a chemical point of view, the synthesis of oligosaccharides with high regio- and stereoselectivity similar to the natural occurring ones still presents an important challenge to synthetic chemists in spite of major advances in the area. In this chapter we will briefly review the important and newer synthetic methods available for glycoside bond formation. Although some methods for glycoside synthesis are more popular than others, since there is no universal protocol that can be applied to any combinations of active glycosyl donors (an electrophile) and acceptors (a nucleophile) without consideration of their substitution patterns, Configurations, or position of the hydroxyl groups. It is, therefore, necessary to discuss briefly about the different aspect of the glycosidic bond formation using different types of donors.

General aspects of oligosaccharide synthesis

1. Formation of a glycosidic bond.
2. General mechanistic pathway for glycosidic bond formation.
3. Choices, challenges and problems of the glycosidic bond.
4. Structure and reactivity of glycosyl donors and of glycosyl acceptors used in oligosa--ccharide synthesis. 5. Promoters, solvents and experimental conditions.
6. Anomeric control in chemical glycosylations. Methods for stereoselective formation of glycosidic linkages.

6.1. Preparation of 1,2-*trans*-glycosides by neighbouring group participation.

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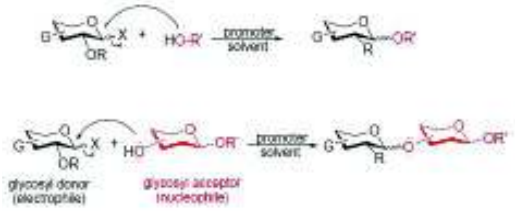
6.2. *In situ* anomerization for the synthesis of α-glycosides (Lemieux approach.)
6.3. Heterogeneous catalysis (Paulsen approach).
6.4. Stereoselective preparation of α- and β-glycosides by participation of the solvent.
6.5. Intramolecular aglycon delivery approach.
7. Common protecting groups used in oligosaccharide synthesis.

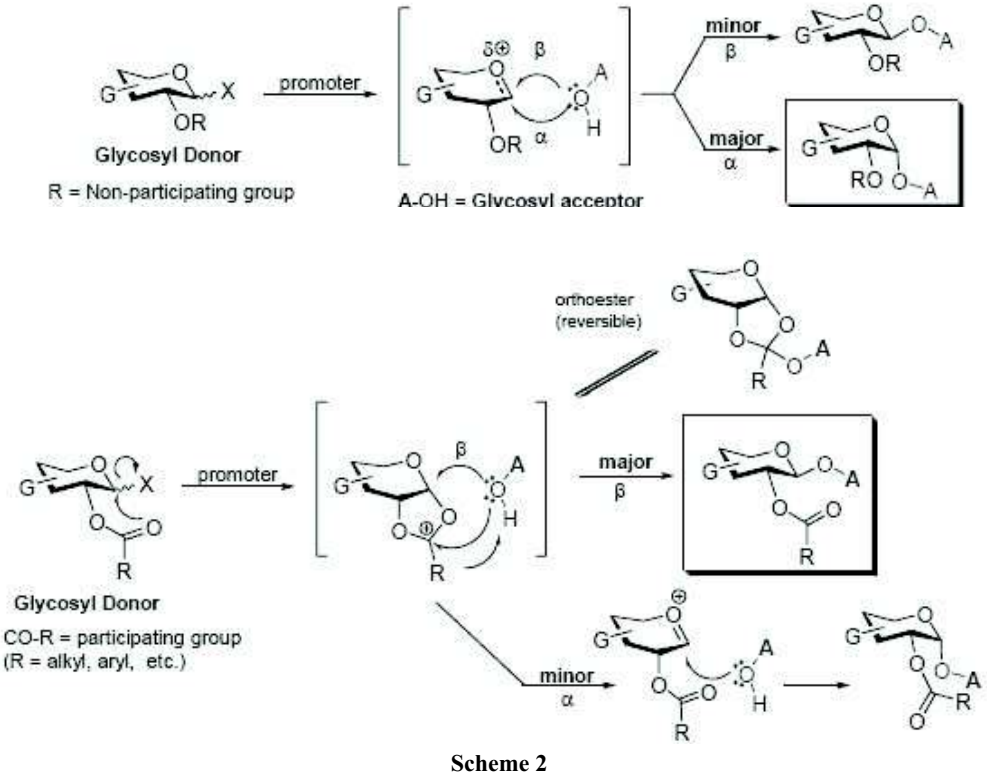
1. Formation of a glycosidic bond

This bond is formed by a nucleophilic displacement of a leaving group (X) attached to the anomeric carbon of a sugar moiety by an alcohol ROH, or by the OH group of a partially protected sugar moiety. The compound that gives the glycosyl moiety, is called the *glycosyl donor*, and the alcohol that receives it, is known as *glycosyl acceptor*. The reaction generally is performed in the presence of an activator called "promoter". The role of the promoter is to assist the departure of the leaving group. Promoters are often used in catalytic amounts, although in some instances they are used stoichiometrically. In some cases, other additives such as molecular sieves or any base that may act as acid scavenger are used.

It is much more complicated than the synthesis of other biopolymers such as peptides or nucleic acids because of the greater number of possibilities for the combination of monomeric units and because the glycosidic linkages have to be introduced in a stereospecific way.



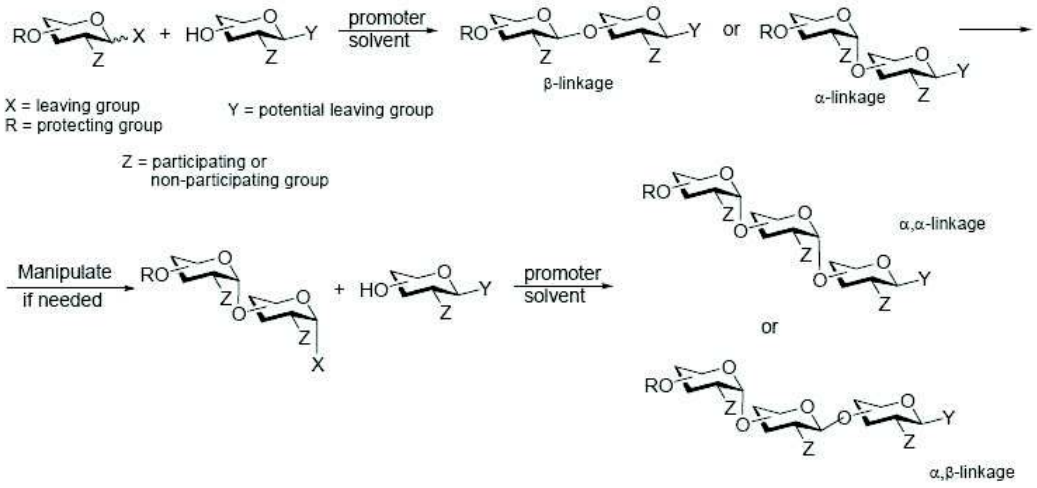
Scheme 1



Scheme 2

2. General mechanistic pathway for glycosidic bond formation [1]

The General Mechanistic Pathways for Glycosidic Bond Formation is represented in (Scheme 2). There are some exceptions such as *in situ* anomerization, intramolecular aglycon delivery and the use of additives such as acetonitrile, which appears to react at the anomeric center itself. The timing of events heavily depends on the structures of the glycosyl donors, acceptors and promoters. If the productive glycoside forming reactions proceed too slowly, numerous side reactions imply the degradation of the labile glycosyl donor. However, under more vigorous conditions, the acceptors can be also destroyed.



Scheme 3

3. Choices, challenges and problems of the glycosidic bond

The success of a coupling reaction between two sugars depends on the reactivity of the donor and acceptor, on the promoter, on the kind of substituents on both saccharide units and, of course, on the preferred selectivity of the reaction towards the α- or the β-anomeric form. The experience of the person conducting the experiment also plays a role. If we take the synthesis of a simple trisaccharide molecule as a target we can enumerate the choices, challenges and potential problems listed in the following.

Choices

1. Choice of X and Z in the donor
2. Choice of Y and Z in the acceptor
3. Choice of the promoter or catalyst
4. Choice of solvent and temperature
5. Choice of protecting groups

Challenges and problems

1. Anomeric selectivity for 1,2-*cis* or 1,2-*trans* linkages.
2. Site selectivity and reactivity of acceptor OH groups (e.g. axial, equatorial, primary.
3. Configuration, substituent, steric and electronic effect in the donor and acceptor (e. g D-glucopyranosyl and D-galactopyranosyl donors with identical substituents sometimesgive different α/β ratios with the same alcohol acceptor).
4. Stoichiometry relative to the ratio donor: acceptor equivalents.
5. Selective activation of anomeric groups (if X, Y are orthogonal groups i.e having different reactivities), Y can be activated in the presence of X.
6. Iterative glycosylation in a stepwise manner or by block synthesis.
7. Minimum manipulation of protecting groups.
8. Prospects for solid-phase oligosaccharide and automated synthesis.

4. Structures and reactivity of glycosyl donors and of glycosyl acceptors used in oligosaccharide synthesis.

Structures of glycosyl donors

There are numerous glycosylation methods involving different glycosyl donors (Figure 1)[2]. The name of the glycosylation method generally reflects the functionality of the glycosyl donor except for the Fischer glycosylation that uses reducing sugars and the Köenigs-Knorr procedures that use glycosyl halides as donors.

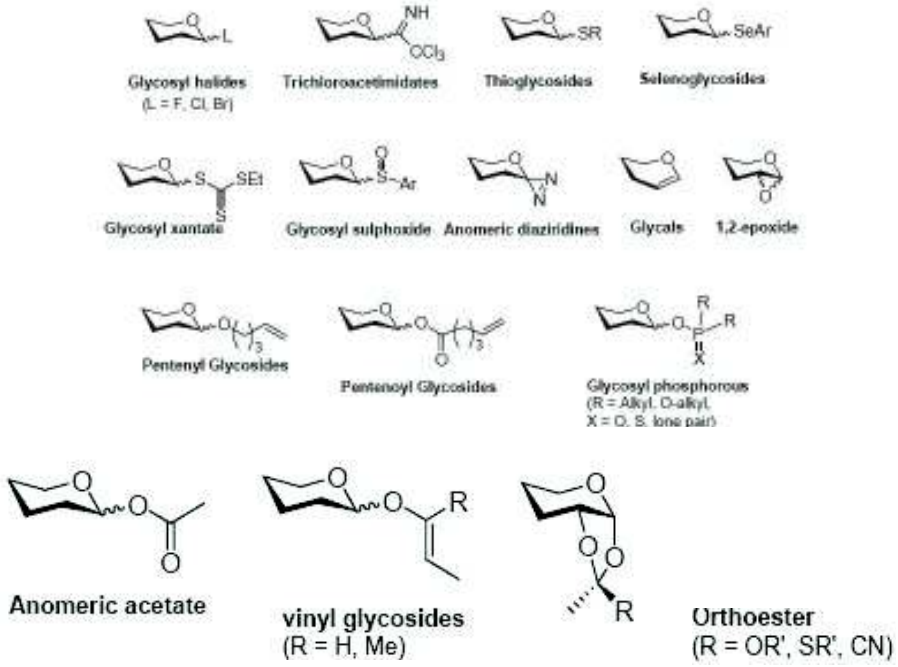


Figure 1 Structure of glycoside donors used in oligosaccharide synthesis

As a rule it is difficult to predict which glycosylation method will be the most suitable to solve a certain problem. Nevertheless, there are some factors influencing the reactivity of glycosyl donors that should be taken into account and that can be further used in the optimization of an oligosaccharide synthesis.

Reactivity of Glycosyl Donors

The reactivity at the anomeric center depends to a large degree on the choice of the protecting groups specially those on C-2. Glycosyl donors are then classified in two main groups: armed donors (with an ether group on C-2) more reactive than disarmed donors (with esters, amides on C-2)[2].

Ester groups induce some positive charge at the anomeric center making the formation of the oxonium ion a slower process.

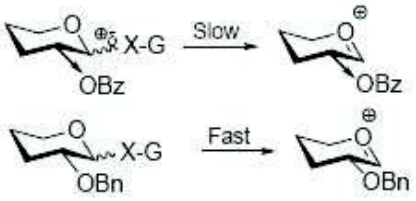


Figure 2

When identical protecting group's patterns are desired, reactivity may be controlled by different leaving groups. Both the nature of the heteroatom X and substituent G of the leaving group will affect the reactivity. The configuration of the glycoside also influences its reactivity. Another element of control occurs *via* the use of different promoters P for leaving groups activation. Finally, sterical/torsional factors also have an influence. Fused rings resist flattening of the pyranose ring during oxonium ion formation). As examples, butanodione and cyclohexane dioneacetals (BDA and CDA methodologies) on C-3 and C-4 also reduce reactivity.

A modern glycosyl donor must have the following characteristics:

Accessibility, high stability toward protecting group manipulations and mild activation conditions.

Reactivity of Glycosyl Acceptors

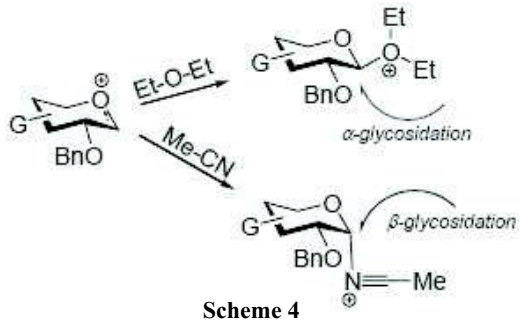
With regard to the reactivity of the acceptor, this depends on the nucleophilicity of the hydroxyl groups in partially protected carbohydrates that in turn depends on their nature (1º more reactive than 2º), their spatial orientation (equatorial more reactive than axial), the conformation of the sugar ring ($^4C_1$ or $^1C_4$) and the presence of other protecting groups in the molecule[3]. It can be generalised that electron-withdrawing groups diminish the reactivity of the acceptor. In addition, the steric hindrance of the groups has an influence i.e. bulky group at C-6 such as OTBDPS or OTBDMS or OPiv reduce the yield of a (1→4) glycosylation to a large extent.

5. Promoters, Solvents and Experimental Conditions.

The nature of the *promoter*, generally a Lewis acid, has an influence in the sense that it favours the departure of the leaving group. In addition, its nature classifies the reactions as homogenous and heterogeneous and this has implications for the stereochemistry.

The *solvent* also has an influence on the overall rate of the process and on the stereochemistry, especially in the case of non-participating glycosyl donors. Anhydrous solvents are required to avoid competition from water. Solvents of low polarity, such as dichloromethane or ether are frequently used. Sometimes polar aprotic solvent such as acetonitrile or nitromethane are used.

On the other hand, some solvents may also form complexes with the intermediate sugar oxonium cations affecting the orientation of the incoming *O*-nucleophile. For example, diethyl ether enhances the formation of α-glycosides while acetonitrile favours the accumulation of β-anomers. This is explained by the formation of an exocyclic complex with the solvents that hinder the β- and α-faces, respectively.



Scheme 4

Experimental Conditions

The experimental conditions are very critical for the success of the reaction. Generally, the use of extremely dry solvents, inert atmosphere and molecular sieves that can act as acid scavenger are needed. Sometimes a non-nucleophilic base is also needed. The order in which the reagents are added is also important in some cases.

The normal procedure (NP) of adding reagents is appropriate for less reactive disarmed donors. The promoter (P) is added over a mixture of acceptor (A) and donor (D). For highly reactive armed donors, the inverse procedure (IP) in which the donor is added over a mixture of acceptor and promoter is the most convenient.

This can be rationalized as follows:

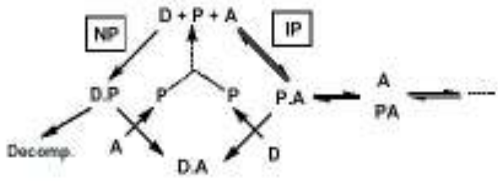
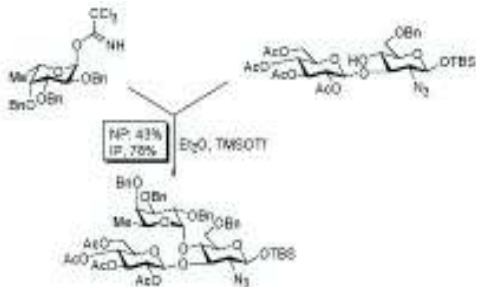


Figure 3

For a donor and acceptor with similar reactivities the NP is commonly used. For a ter-molecular reaction D + P +A, due to the nature of the reagents the reaction is expected to occur through an association D.P and then interaction with A to obtain disaccharide D.A. For highly reactive donors this strategy is less successful because the donor can decompose in the presence of P before interacting with A. The IP involves the complex A.P is first formed and then reacts with the donor sometimes solves the problem.



Scheme 5

6. Anomeric control in chemical glycosylation. Methods for stereoselective formation of glycosidic linkages

Types of anomeric linkages

The stereoselective introduction of the glycosidic linkage is one of the most challenging aspects in chemical oligosaccharide synthesis. The anomeric linkages can be classified according to the relative and absolute configuration at C-1 and C-2.

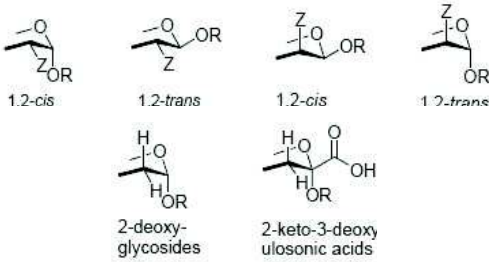


Figure 4

The 1,2-*cis*- and 1,2-*trans*-2-D-*glycero* series (allo-, gluco-, gulo- and galactopyranosides) and the 1,2-*cis* and 1,2-*trans*-2-L-*glycero* series (altro-, manno-, ido- and talopyranosides). In addition, some miscellaneous glycosidic linkages can be identified, including 2-deoxyglycosides and 3-deoxy-2-keto-ulo(pyranosylic) acids.

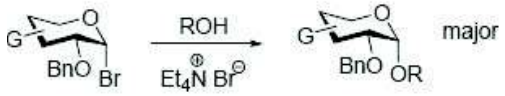
6.1. Preparation of 1,2-trans-*glycosides by neighbouring group participation*

The nature of the protecting group at C-2 of the glycosyl donor is a major determinant of the anomeric selectivity. A protecting group at C-2 that can perform neighbouring group participation (disarmed donors) during glycosylation will give 1,2-*trans* glycosidic linkages (Scheme 2).

Nucleophilic attack of the alcohol at the anomeric center of the more stable oxonium cation **3** originated by participation of the neighbouring after departure of the leaving group X, results in the formation of a 1,2-*trans*-glycoside (C-2 axial) **4**. Glucosyl type donors (C-2 equatorial) will give β-linked products while mannosides will give α-glycosides.

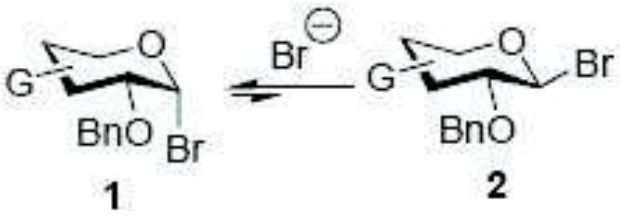
6.2. In situ anomerization for the synthesis of α-*glycosides (Lemieux)*

Lemieux etal[4] introduced this procedure as a way of controlling the anomeric selectivity in armed donors with non-assisting functionality at C-2. The reaction conditions (e.g. solvent, temperature, and promoter) will determine the anomeric selectivity. The *in situ anomerization procedure* results mainly in the formation of α-glycosides.



Scheme 6

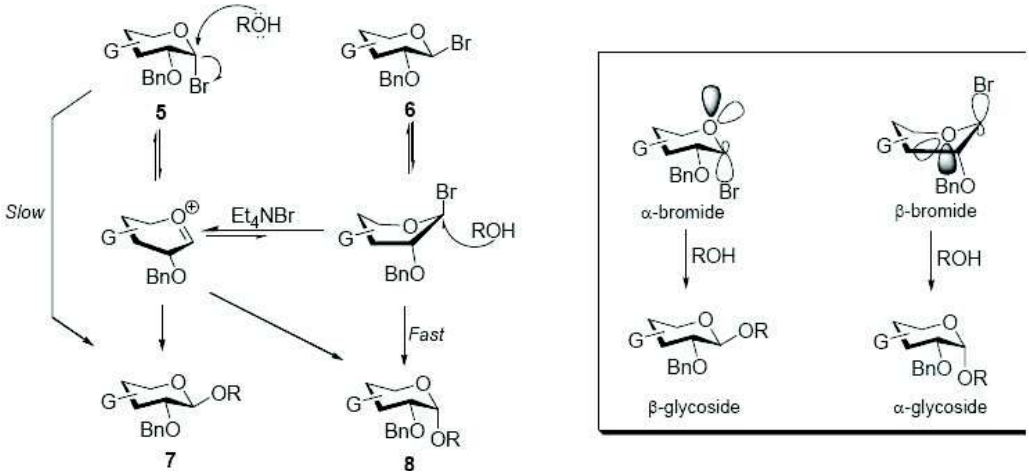
Lemieux discovered that the α-haloglucopyranoside is in equilibrium with the more reactive β-halide and that the equilibrium is catalysed by halide ions derived from tetraalkylammonium halides, and the reaction proceeds with inversion of a highly reactive β-halide with the alcohol component via nucleophilic substitution.



Scheme 7

This reaction is thought to proceed through several intermediates (Scheme 8). At equilibrium the proportion of the α-halide is relatively high. The β-halide is less stable because of the destabilization as a result of the anomeric effect but reacts more rapidly than the α-halide with an O-nucleophile.

To allow substitution of the β-halide, the C-1-halide bond, in order to be broken, must be antiperiplanar to the electron lone pair of the ring oxygen[5]. To establish such an arrangement, a conformational change to the highly reactive boat-like intermediate is required. This makes reaction of the β-halide fast. In the case of the α-halide a conformational change is not required since the C-1 halide bond is already anti-periplanar to the ring oxygen lone pair and the substitution of the α-halide is slow. It is clear that the equilibrium rate must be fast enough to ensure that sufficient β-halide is continuously present. If the difference in reaction rate between the α- and β-halides with the alcohol is large enough, α-linked O-glycosides are obtained as major compounds or exclusively.



Scheme 8 Preparation of glycoside by insitu anomerization

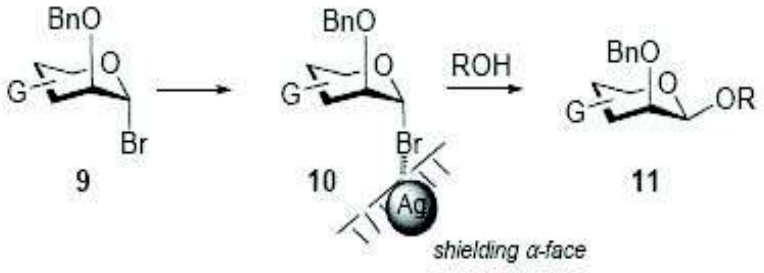
The reaction requires very reactive glycosyl halides (armed) and long reaction times, in particular when the originally tetra-alkyl ammonium bromides are used as catalysts.

The *in situ anomerization* procedure has proven to be very useful. The use of other hydrophilic promoters such as mercuric bromide, silver perchlorate and silver triflate make it possible to carry out the reaction with even less reactive halides. However, the stereoselective outcome of the glycosylations is very dependent not only on the reactivity of the catalyst, but also on the reactivity of both the halide and the acceptor. Careful adjustment of the reactivity of the two different components is essential in order to obtain satisfactory results.

6.3. Heterogeneous catalysis (Paulsen).

Glycosylation of α-halides in the presence of an insoluble silver salt proceeds mainly with inversion of

configuration and formation of the β-glycoside. In this case, the equilibration between glycosyl halides is restricted because there is no nucleophile in the reaction mixture and the reaction will therefore proceed with inversion of configuration. Silver silicate and silversilicate-aluminate have often been used as the heterogeneous catalyst. These catalysts have proved to be valuable in the preparation of β-linked mannosides which can not be prepared by neighbouring group participation or *in situ anomerization*.



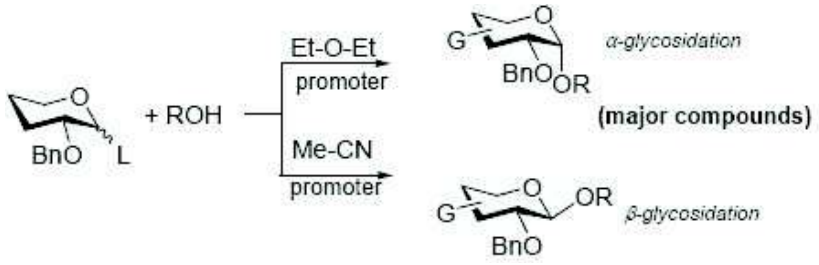
Scheme 9

However, the method only works well with very reactive halides and sufficient reactive alcohol components[6]. With less reactive components, significant proportions of the α-isomers are obtained. β-glycosides from glucose, galactose or fucose can also be prepared by the Paulsen method, but it is usually more convenient to come along with strategies involving neighbouring group participation.

6.4. Stereoselective preparation of α- *and* β-*glycosides by participation of the solvent*

The choice of the combination promoter/solvent plays a crucial role for the anomeric stereocontrol of a glycosylation, especially when a non-participating group is at C-2 position.

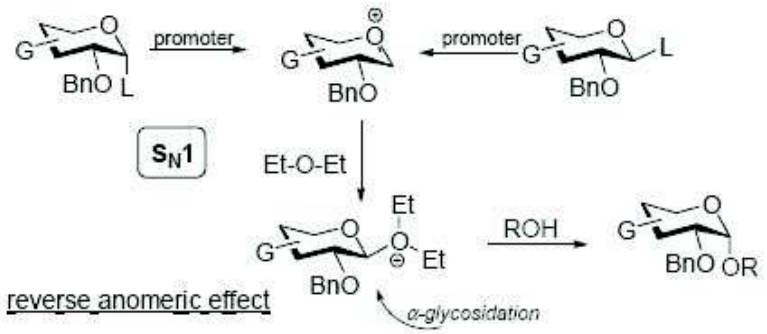
In general, if any participating group is present at C-2, the glycosylation reaction follows a SN^2 pathway in non-polar solvents. The influence of the solvent under SN^1-type conditions has been extensively studied for ethers and nitriles.



Scheme 10

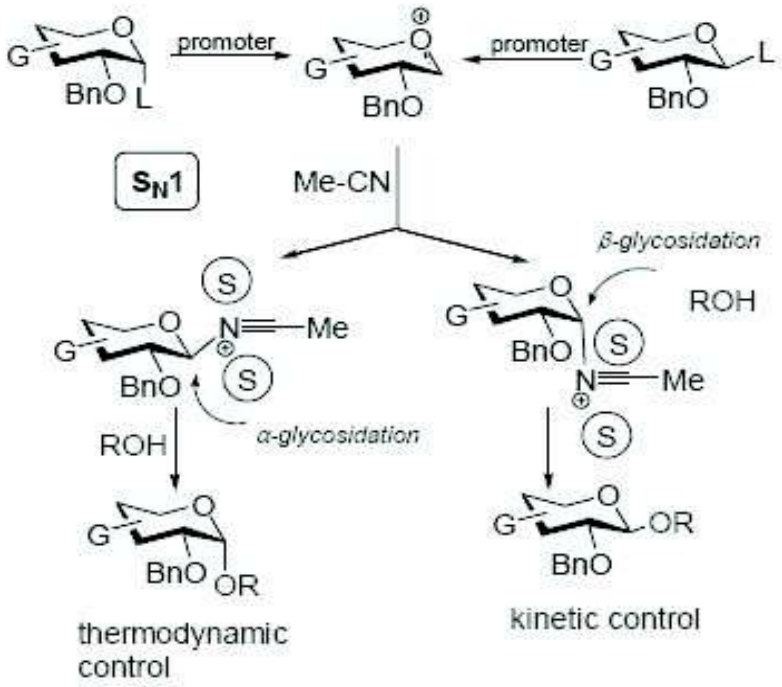
Ethers such as diethyl ether or THF favour the α-linkage while with acetonitrile, β-glycosides are commonly obtained.

In diethyl ether, using strong acid promoters, the SN^1-type reaction is favoured. Ethers participate in forming equatorial oxonium cations due to the reverse anomeric effect[7], sssssssssssssswhichfavours thermodynamically α-glycosides.The influence of nitriles, "The nitrile effect", is more complex [8]. Acetonitrile as polar solvent favours an SN^1 mechanism that implies the formation of an oxonium cation that is solvated with preference at the α-face forming the kinetically controlled α-nitrilium-nitrile complex. This complex finally renders the β-anomer by nucleophilic substitution by an alcohol.

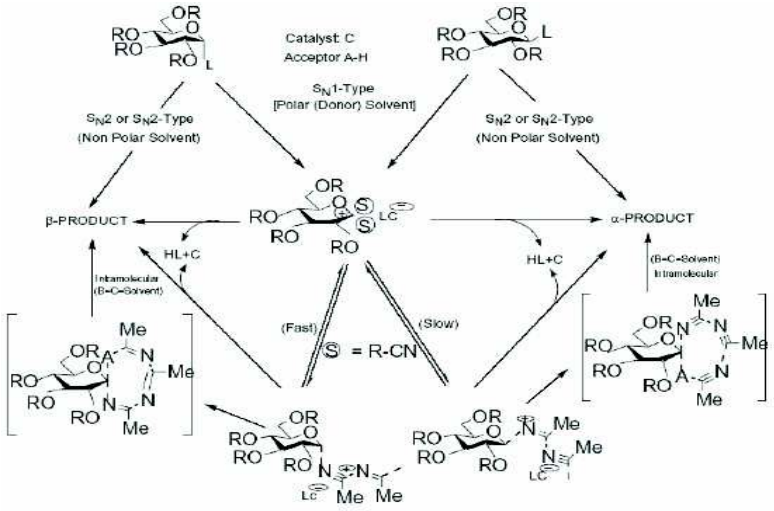


Scheme 11

On the other hand, the complex β-nitrilium-nitrile is thermodynamically more stable due to the reverse anomeric effect, favouring the α-anomer. In any case, the complexation with the nitrile increases the reactivity of the donor.

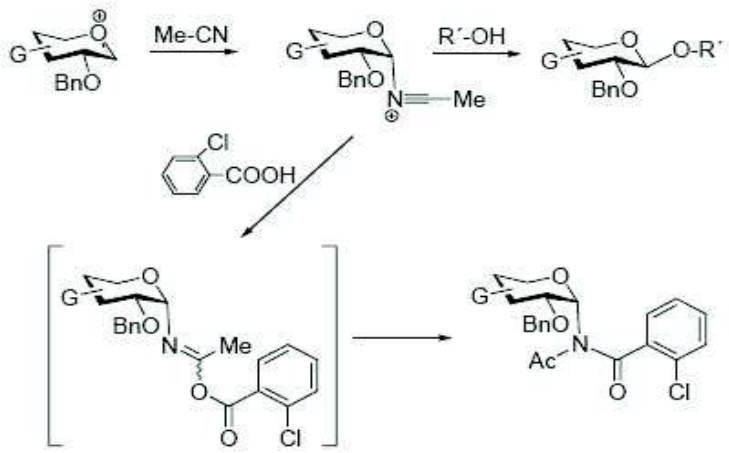


Scheme 12



Scheme 13 (Nitrile Effect)

For quite some time, there has been controversy with respect to the absolute configuration of the intermediate α-glycosyl nitrilium ion. Trapping the intermediate nitrilium ion by 2-chlorobenzoic acid gave the corresponding amide with α-configuration, thus confirming α-nitrilium ions [9].

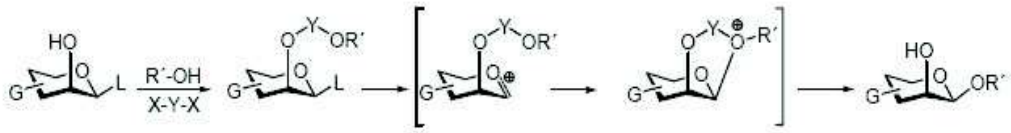


Scheme 14

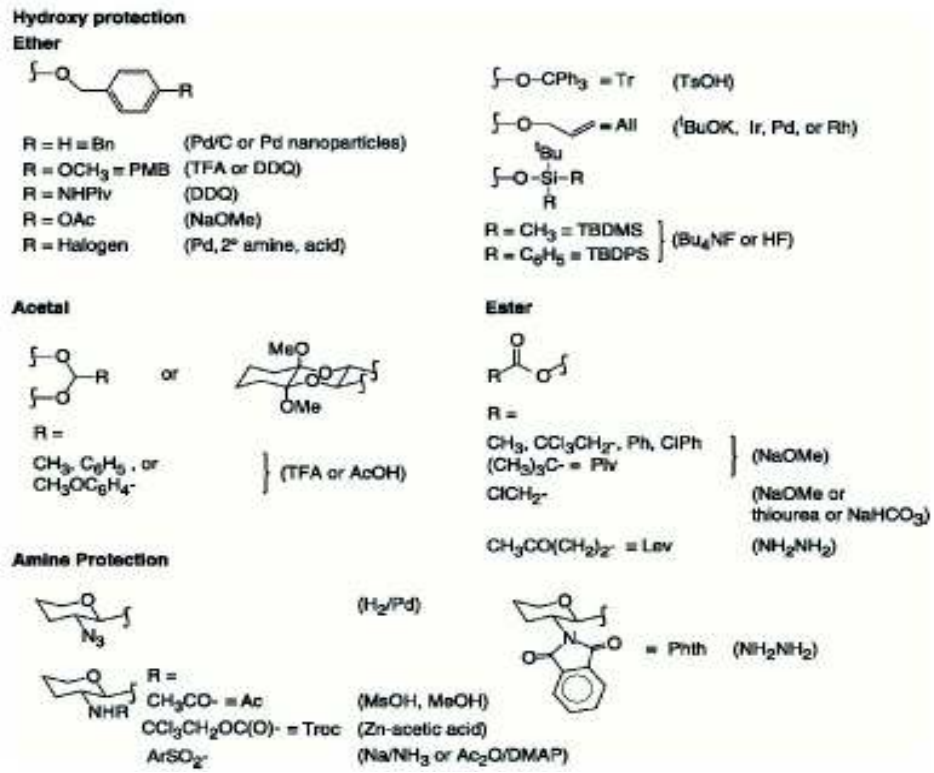
Unfortunately this method gives low β-selectivity for mannosidases.

6.5. *Intramolecular aglycon delivery approach*

This method has been applied with success to the synthesis of β-mannosides. In this method the sugar alcohol (ROH) is first non-permanently linked to the C-2 position of a suitable protected mannosyl donor via an acetal or silicon tether (Y = CH_2 or $SiMe_2$). Activation of the mannose donor results in an intramolecular delivery of the alcohol in a concerted reaction resulting in the formation of exclusively β-mannopyranosyl linkages[10].



Scheme 15



Common protecting groups used in oligosaccharide synthesis

It is important to note, that inspite of the general approaches discussed above for stereoselective control of the glycosidic linkage, other factors such as type of oligosaccharide, leaving group at the anomeric center, protection and substitution pattern, promoter, solvent, temperature, could have a major effect on the α/β selectivity.

It should be realized that there are no methods or strategies of general application for oligosaccharide synthesis, which is one of its greatest difficulties. Nevertheless, convergent multistep synthetic sequences that give complex oligosaccharides consisting of up to 20 monosaccharide units are currently feasible by applying different strategies.

Different procedures of glycosylation reactions by direct activation

1. Köenigs-Knorr method and related. Glycosyl Fluorides (Mukaiyama)
2. *n*-Pentenyl glycoside method (Fraser-Reid)
3. *S*-Glycoside methods (Lönn, Garegg, van Boom)
4. Phenylselenoglycosides
5. *O*-Alkylation and the trichloroacetimidate method (Schmidt)
6. Glycosylation with glycals (Lemieux, Thiem,

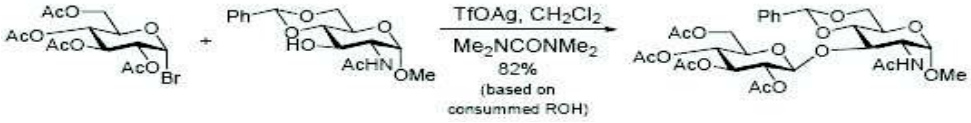
Danishefsky)

1. Köenigs-Knorr and related methods.

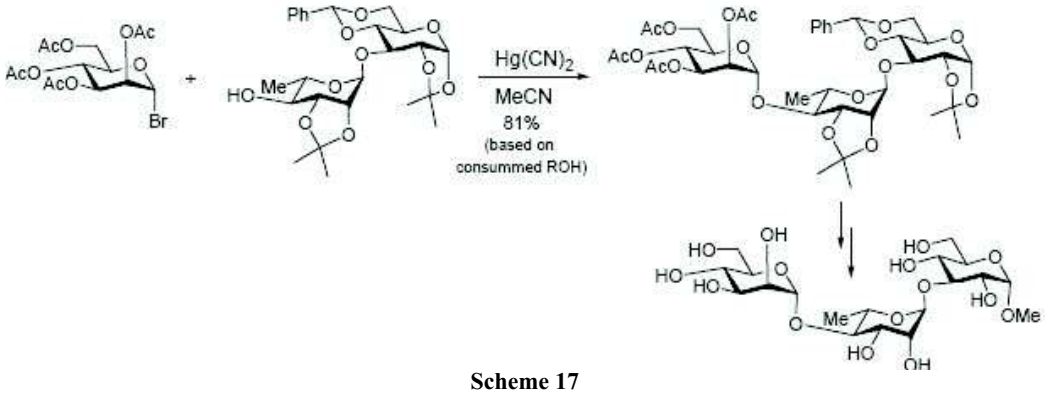
The Köenigs-Knorr method uses glycosyl bromides and chlorides as donors in the glycosylation reaction. It was first performed in 1901 and up until the mid 1980's, the method and its numerous variants have been extensively used to prepare a wide variety of O-glycosides.

Insoluble promoters such as Ag_2O and Ag_2CO_3 were initially used. Soluble catalysts including $HgBr_2$ and $Hg(CN)_2$ (Helferich-Weiss, 1956) and AgOTf (Hanessian-Banoub, 1977), were exploited as promoters. In the latter case, the reactions were sometimes performed in the presence of tetramethylurea as acid scavenger [12].

Examples:



Scheme 16



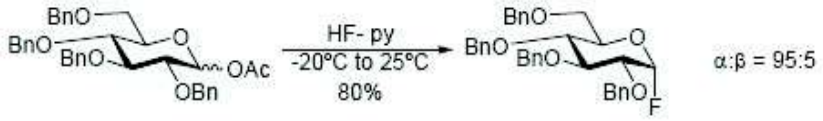
Scheme 17

In spite of the generality of the method there are several inconveniences that have limited its use. The intrinsic instability of glycosyl halides, the requirement of at least an equimolar amount (often up to 4 eq) of metal salts as promoters (frequently incorrectly termed as "catalyst") and problems concerning the disposal of waste material (e. g. mercury salts) have made the method become less popular nowadays [13].

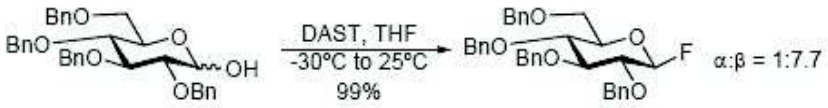
Other alternative methods of great interest have been developed.

1.1. Glycosyl fluorides[14]

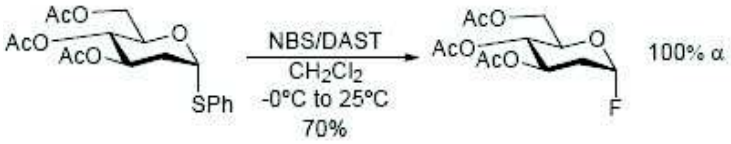
In 1981, Mukaiyama and co-workers [15] introduced anomeric fluorides for the preparation of *O*-glycosides.The introduction of fluorine as leaving group is a good alternative to the Köenings-Knorr method due to the stability of the C-F bond. Glycosyl fluorides are easier to handle than glycosyl chlorides or bromides. They are typically prepared from the anomeric acetates by reaction in HF/py[16], from hemiacetals by reaction with DAST[17] or from thioglycosides by reaction with NBS/DAST.[17] (Scheme 18, 19, 20)



Scheme 18



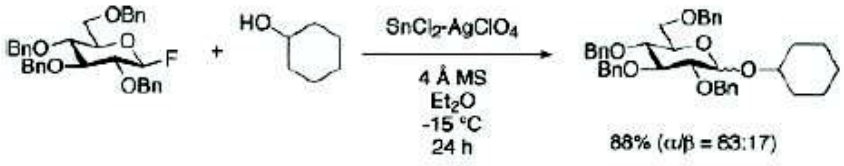
Scheme 19



Scheme 20

Because of the difference in halophilicity of this element compared with bromine and chlorine, the glycosylation reactions require the use of other promoter systems besides silver salts.

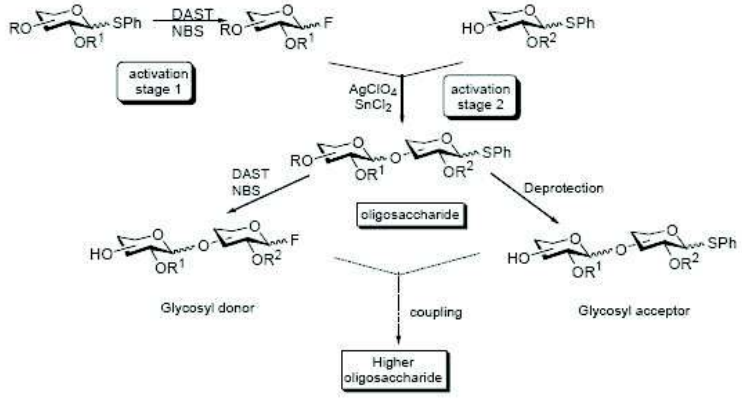
Mukaiyama and co-workers carried out the first reaction in 1981. In this case, 1,2-*cis*-α -glycosides were predominantly obtained in high yields due to the anomeric effect.



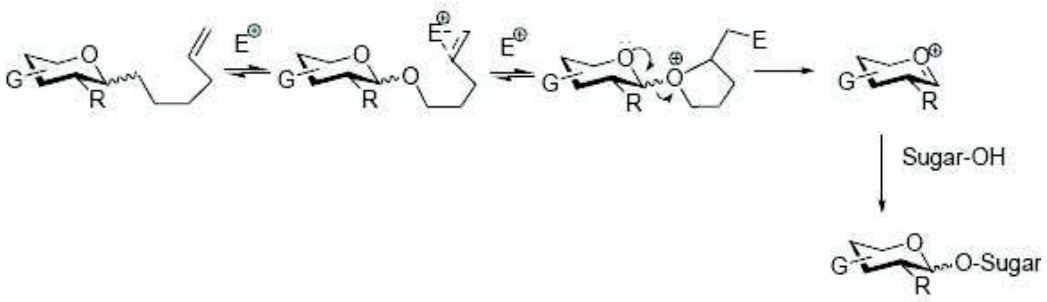
Scheme 21

Apart from $SnCl_2$-$AgClO_4$ (Mukaiyama *et al*), the following systems have been used: TMSOTf (Hashimoto *et al*), $BF_3.OEt_2$ (Kunz *et al*), Cp_2ZrCl_2-$AgBF_4$ and Cp_2HfCl_2- AgTfO/$AgClO_4$ (Suzuki *et al*, and Mattheu *et al*), Cp_2ZrCl_2-$AgClO_4$ (Matsumoto *etal*), $La(ClO_4)_3$ (Kim *et al* and $LiClO_4$ (Böhm and Waldmann *et al*). The promoters of wider application imply the use of lanthanide metals.

The glycosylations with anomeric fluorides follow the general principle as described for bromides and chlorides. Apart from their enhanced stability, anomeric fluorides have not proven to be superior to bromides or chlorides in terms of glycosylation efficacy. Glycosyl fluorides can also be used together with thioglycosides in selective and two stage activation and orthogonal glycosylation strategies.

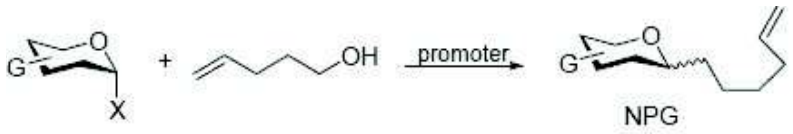


Scheme 22



Scheme 23

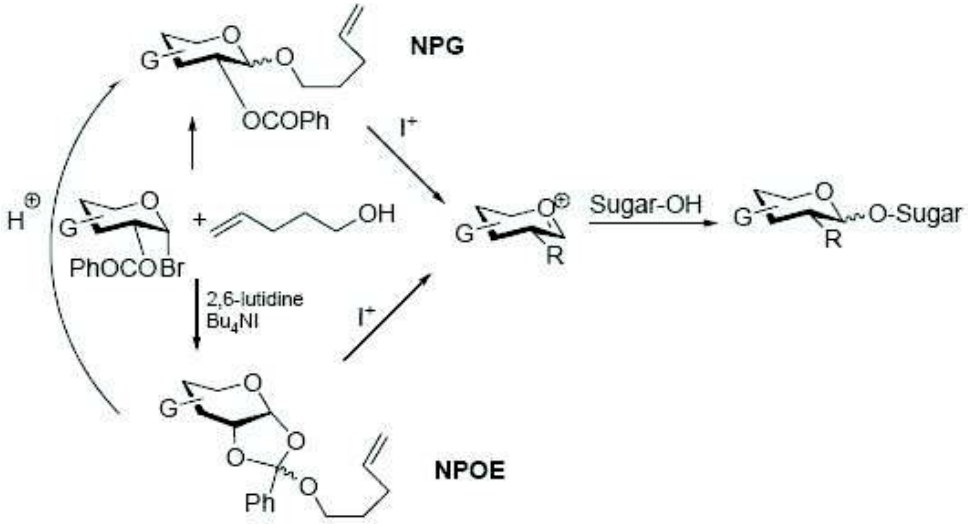
The promoter of choice is any source of halonium ion viz. NBS or NIS alone or activated by Lewis acid. NIS/Et_3SiOTf [20] or NIS/TfOH [21] are commonly used catalyst. When using halosuccinimides alone, the reaction is very slow, and often requires hours or days for completion. A promoter of intermediate potency is IDCP (iodonium dicollidone perchlorate).



Scheme 24

Preparation of *n*-pentenyl glycosides (NPGs) may be carried out following standard procedures for preparing alkyl glycosides, including Fischer or Koenigs-Knorr glycosylations with 4-pentenol.

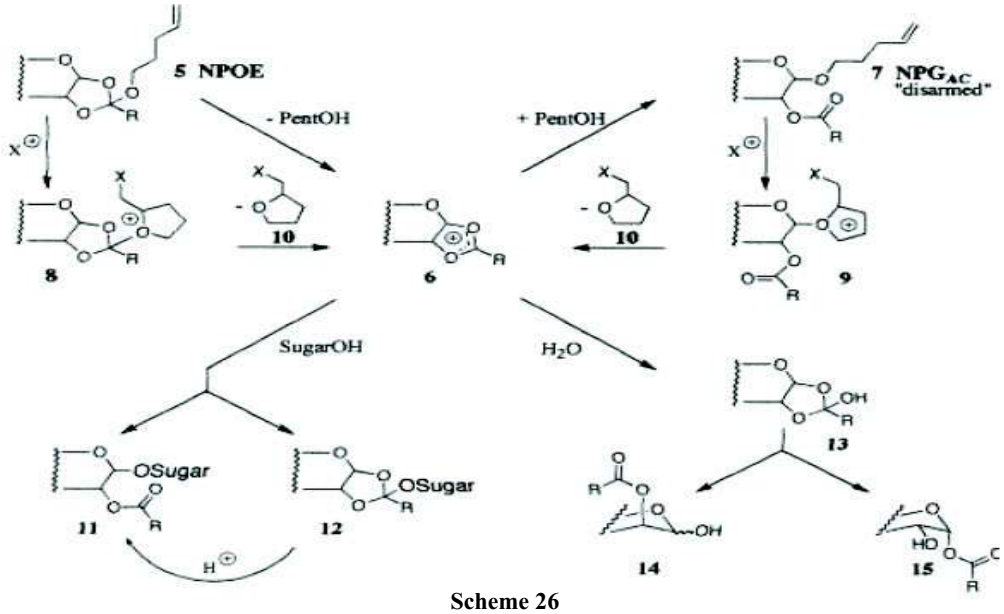
When using perbenzoylated glycosyl bromides, reaction with 4-pentenol gives *n*-pentenyl 1,2-orthoesters (NPOEs), which can also serve as glycosyl donors. NPOEs are transformed into NPGs through an acid-induced rearrangement. The promoter of choice is NIS. Recently,[22] an efficient activation of NPOEs with NIS and lanthanide triflates ($Yb(OTf)_3$) has been reported.



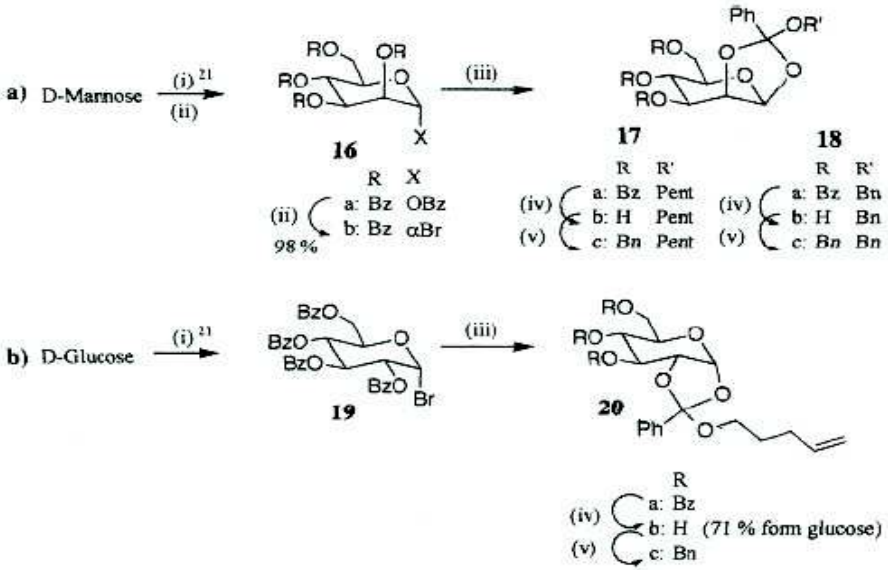
Scheme 25

The advantage of using orthoesters is that they are stable to bases and so, several base promoted protecting group transformations can be carried out before the acid-induced rearrangement that converts NPOE to NPG. Basically, both donors proceed mechanistically in the same way. They generate the same intermediate that leads to the oligosaccharide [23].

NPOEs have the advantage over NPGs of the high stereocontrol observed due to the effective shielding of the α-(for D-Man) and β-(for D-Glc) faces. Thus the reaction of benzoyl bromides with 4-pentenol gave the NPOEs that show a high stereocontrol in glycosidic linkage formation shielding the β- and α- faces of D-mannose and D-glucose that lead to α- and β-glycosides, respectively.



Scheme 26

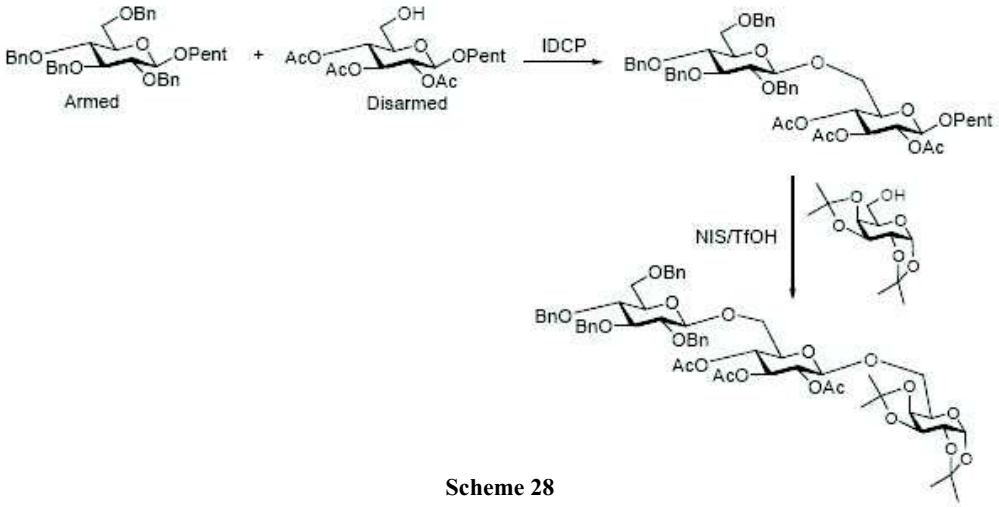


Scheme 27

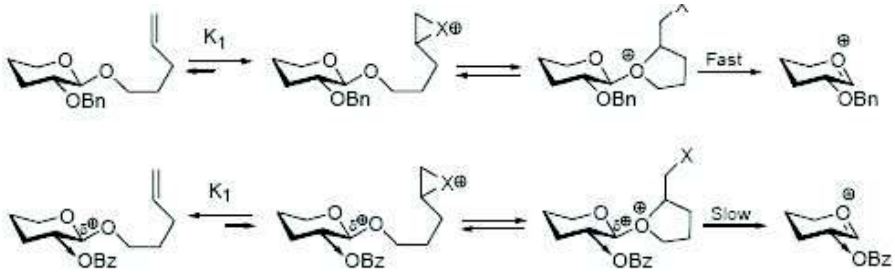
Protecting groups influence the reactivity of pentenyl glycosides as donors with so-called armed-disarmed strategy[20,21,24]. This difference makes the chemoselective glycosylation possible. This strategy has been applied to several glycosyl donors.

Armed disamed strategy with NPGs.

Benzylated pentenyl glycoside reacts faster than acylated ones.



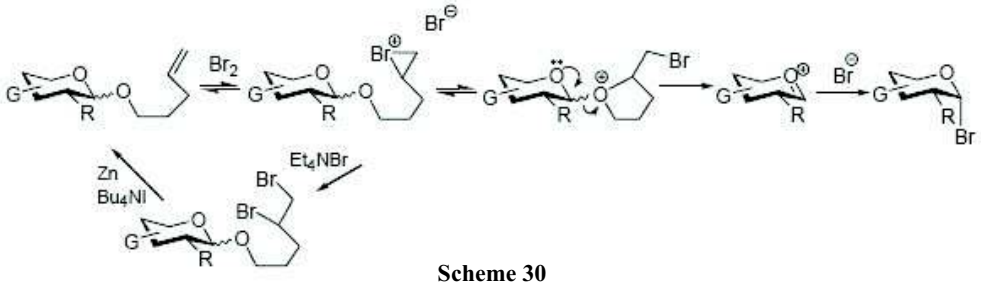
Scheme 28



Scheme 29

IDCP is appropriate for the coupling of some reactive (armed) NPGs but is not potent enough for use with unreactive (disarmed) NPGs. For this purpose, NIS/Et_3SiOTf or NIS/TfOH must be employed.

In the cases where the nature of the protecting groups does not allow the application of the armed disarmed strategy, two NPGs can still be coupled by use of an intermediate dibromination step (Scheme 30). Thus, depending on how the reaction is carried out, one can obtain either the glycosyl bromide or a vicinal bromide.

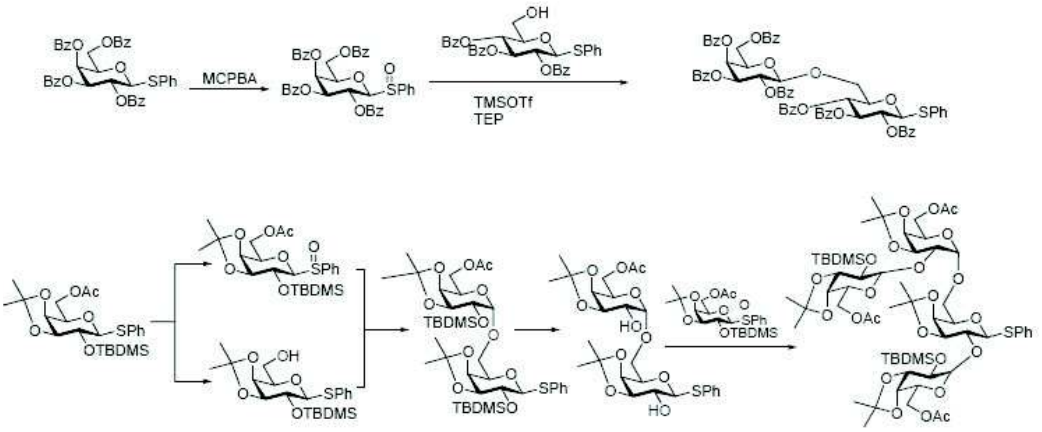


Scheme 30

3. S-Glycoside methods

There are several methods in which the anomeric carbon is activated by groups having sulphur in place of the exocyclic hemiacetal oxygen. The best known example of this type of protection/activation group is the alkyl(aryl)thio group (thioglycosides). Oxidized forms of thioglycosides, such as sulfoxides can act as glycosyl donors as well as other derivatives like S-xantates.

The two-stage activation strategy reported employs anomeric sulphoxides as donors and thioglycosides as acceptors. The latter can be converted into sulfinil glycosides by oxidation[25].



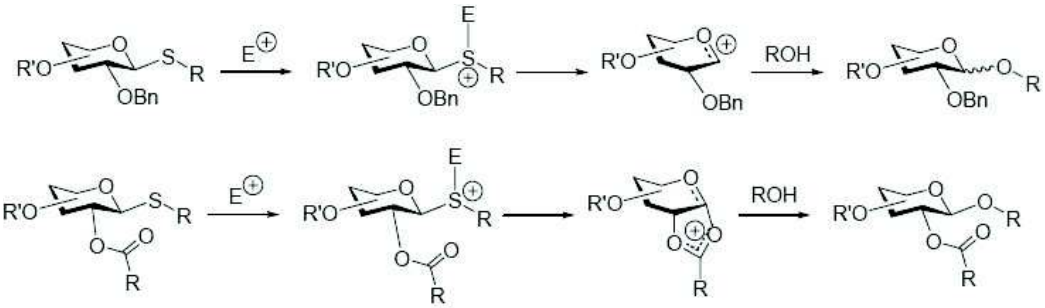
Scheme 31

3.1. *Thioglycosides*

The sulfur atom in a thioglycoside is a soft nucleophile and is able to react selectively with soft electrophiles such as heavy metal cations, halogens, and alkylating or acylating reagents.This fact make thioglycosides very versatile agents in carbohydrate chemistry. Additionally, the hydroxy and ring oxygen atoms of carbohydrates are hard nucleophiles, which can be functionalized with "hard" reagents, without affecting alkyl(aryl)thio function.

Scheme 32

An electrophile activates the thioglycoside by producing intermediate sulfonium ions, which then give rise to glycosylating carbocationic intermediates that react with the alcohol giving the glycoside.



Scheme 33

Although this possibility was known for a considerable time (Bonner, 1948; Ferrier, 1973), it has been since 1984 that it has been extensively explored. In 1984 Lönn first reported the use of methyl triflate as the first efficient general promoter for direct glycosylation with thioglycosides. MeOTf has disadvantages because it is toxic and in the presence of slow reacting glycosyl donors, it can give rise to methyl ethers in addition to glycosides. For this reason, other thiophilic promoters have been developed.

For example dimethyl(methylthio)sulfonium triflate, DMTST,[26] $NOFB_4$,[27] MeSOTf,[28] PhSeOTf,[29] MeI,[30] NIS, TfOH,[31,32,33] IDCP,[34] TBPA[35].

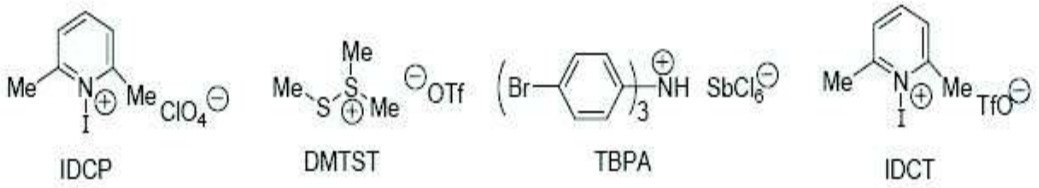


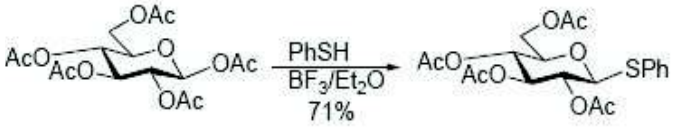
Figure 5

Iodonium dicollidine perchlorate (IDCP) is better replaced by iodonium dicollidine triflate (IDCT), which has similar reactivity and which does not require the use of $AgClO_4$ in its synthesis. MeOTf, DMTST, NIS-TfOH and in particular PhSeOTf are all most efficient promoters that produce fast reactions. Tris(4-bromophenyl)ammoniumyl hexachloroantimon-ate (TBPA) differs from others in that its cation is radical, and as such produces radical cationic sulfonium ions as glycosylating species from thioglycosides.

Regarding stereochemistry, the glycosylations with thioglycosides follow the general principle as described for bromides and chlorides.

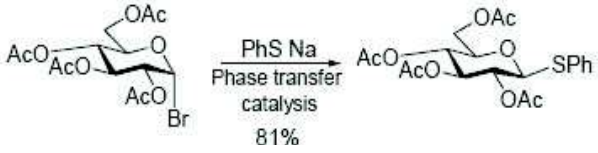
With regards to the preparation of thioglycosides, they can be grouped into three categories:

A. Acid-promoted Displacement at the anomeric center. This implies the synthesis from asugar derivative of a thiol in the presence of a Lewis acid[36].

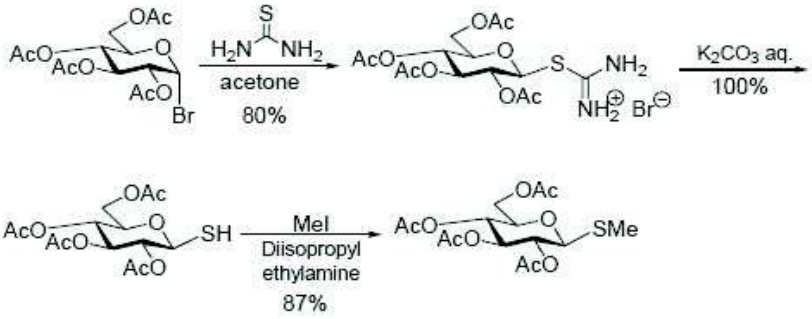


Scheme 34

B. Base-promoted Displacement at the Anomeric Center. This implies the synthesis by *S*-nucleophilic displacement at the Anomeric Center[37].



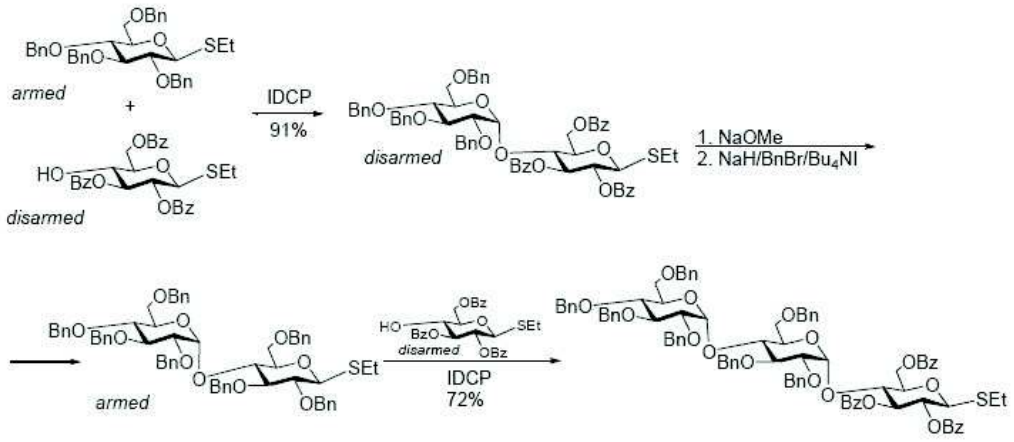
Scheme 35



Scheme 36

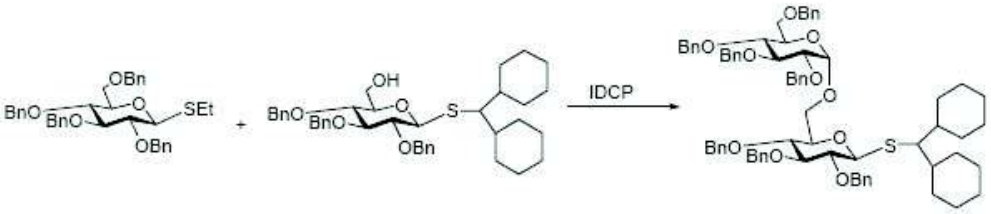
Synthesis by preparation of a 1-thioglycoside followed by S-alkylation[38] (Scheme 36). Once prepared the 1-thioglycoside, it is alkylated with an alkyl halide, often *in situ*. Although the total number of steps is higher, the reagents are cheap and the yields are high throughout.

Protecting groups influence the reactivity of thioglycosides[39].



Scheme 37

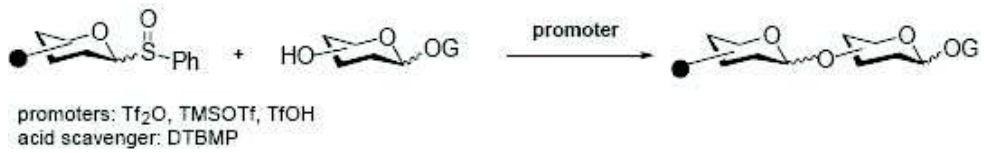
The anomeric thio substituent also has an influence. Simple alkyl substituents such as methyl, ethyl or isopropyl groups, show comparable reactivity towards thiophilic promoters. However, a bulky alkyl substituent such as dicyclohexylmethyl[40] is much less reactive. This allows the assembling of sugars in a chemoselective fashion.



Scheme 38

3.2. *Sulfinil glycosides: the sulfoxide method*

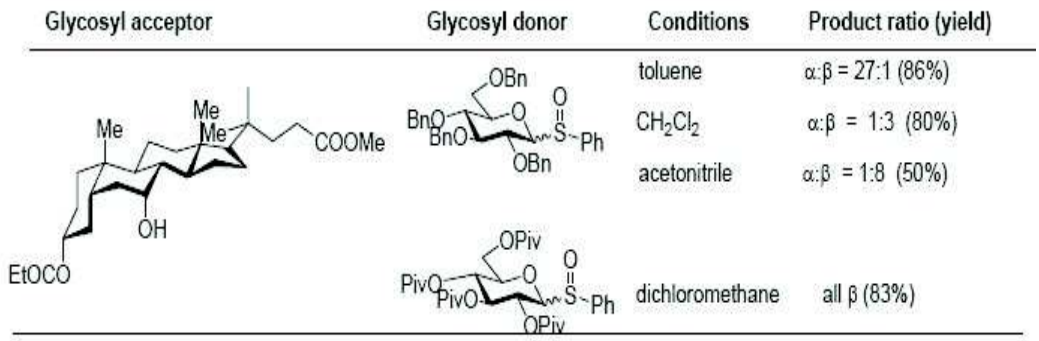
The use of glycosyl sulfoxides as glycosyl donors,[41] provides a new and powerful method for chemical glycosylations, where a glycosyl sulfoxide (also called sulfinil glycosides) reacts with a glycosyl acceptor in the presence of a promoter, to give a di- tri- or oligosaccharide.



Scheme 39

The promoter systems for these sulfinil glycosides are triflic anhydride (Tf_2O) or trimethylsilyl triflates in stoichiometric amount or triflic acid in catalytic amount. The reaction is always carried out in the presence of an acid scavenger (di-tert -butyl methyl pyridine)[42].

Daniel Kahne first developed this method and was able to glycosylate very unreactive hydroxyl groups as the C-7 hydroxyl group in a deoxycholic acid derivative. He used two types of glycosyl donors with non-participant and participant protecting groups. Yields are good with non-polar solvents. In the absence of a neighbouring group, the stereochemical outcome of the reaction is strongly influenced by the solvent: The yield of the β-glycoside increases with the polarity of the solvent (nitrile effect). With a C-2 participating group, the final product is all β.



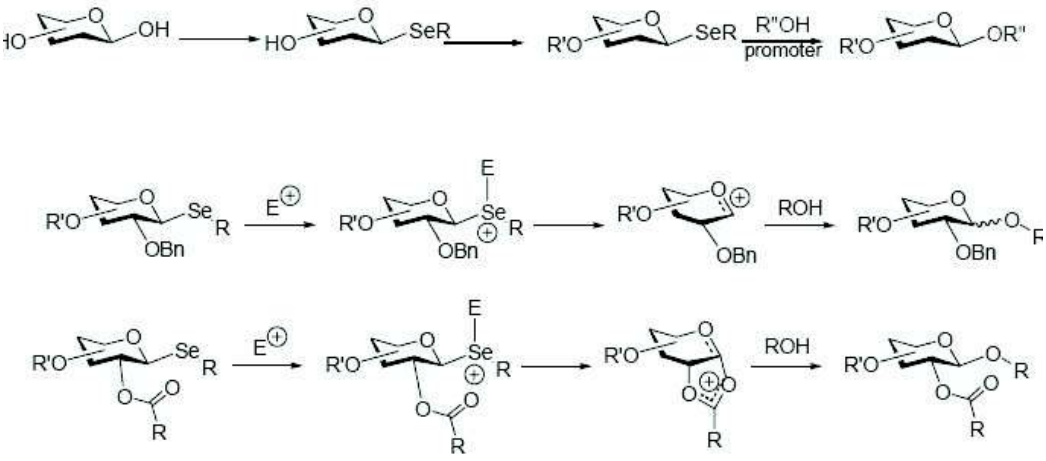
Scheme 40

The sulfoxide-glycosylation method is highly efficient with rather unreactive nucleophiles, has potential for chemoselective glycosylations and is applicable to the synthesis of oligosaccharides on solid supports. However, the highly reactive donors used in this method make it impractical in some cases due to their decomposition.

One advantage of the sulfoxide method is its flexibility and wide scope. It has been demostrated that using a standard set of conditions, it is possible to construct families of oligosaccharides.

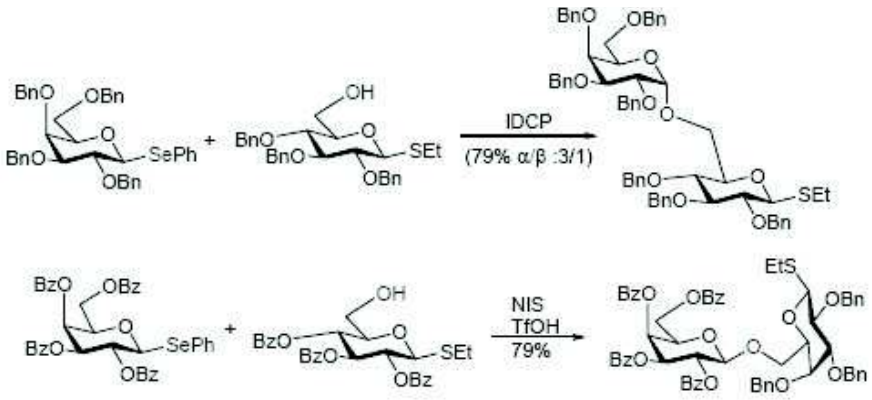
4. Phenylseleno glycosides

Anomeric phenylselenides are interesting glycosyl donors. The phenylseleno substituent behaves largely like thioglycosides with respect to stability towards protecting group manipulations and lability towards electrophilic reagents.



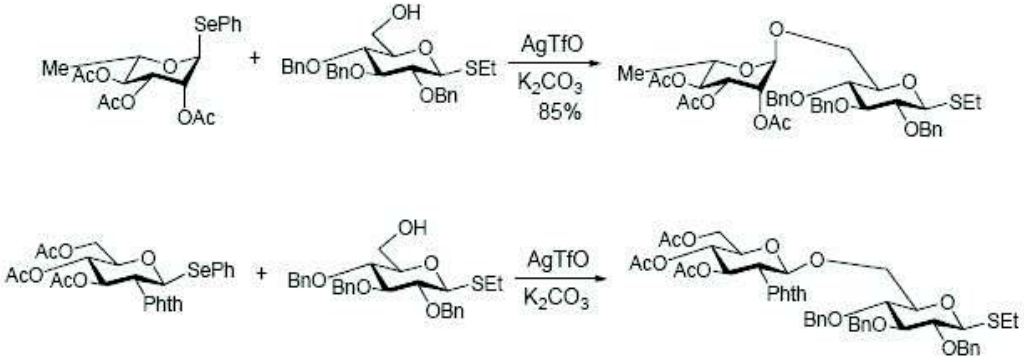
Scheme 41

Phenylseleno glycosides are more reactive than thioglycosides allowing chemoselective glycosylations[43].



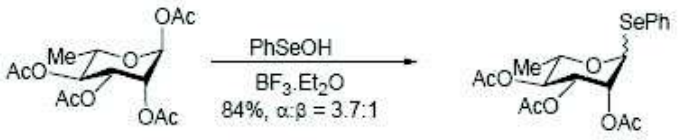
Scheme 42

Both C-2 acylated and benzylated glycosyl donors can be activated with AgTfO. The glycosylation is quenched with the presence of tetramethylurea or collidine. Thioglycosides are usually stable towards AgOTf, so orthogonal glycosylations[44] are feasible. As AgTfO and bases such as tetramethylurea or collidine are frequently employed in glycosylations with glycosyl halides, chemoselective glycosylations of glycosyl halides in the presence of selenoglycosides are also possible.

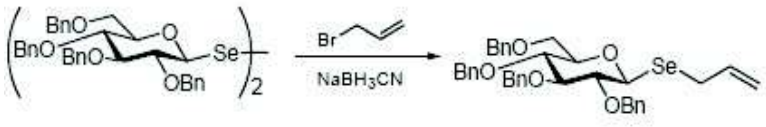


Scheme 43

Phenylseleno glycosides can be prepared from peracetylated sugars by reaction either with phenylselenol[45] or from glycosyl halides with potassium phenyl selenoates or from diglycopyranosyl diselenides by reaction with alkyl halides under reducing conditions[46].



Scheme 44

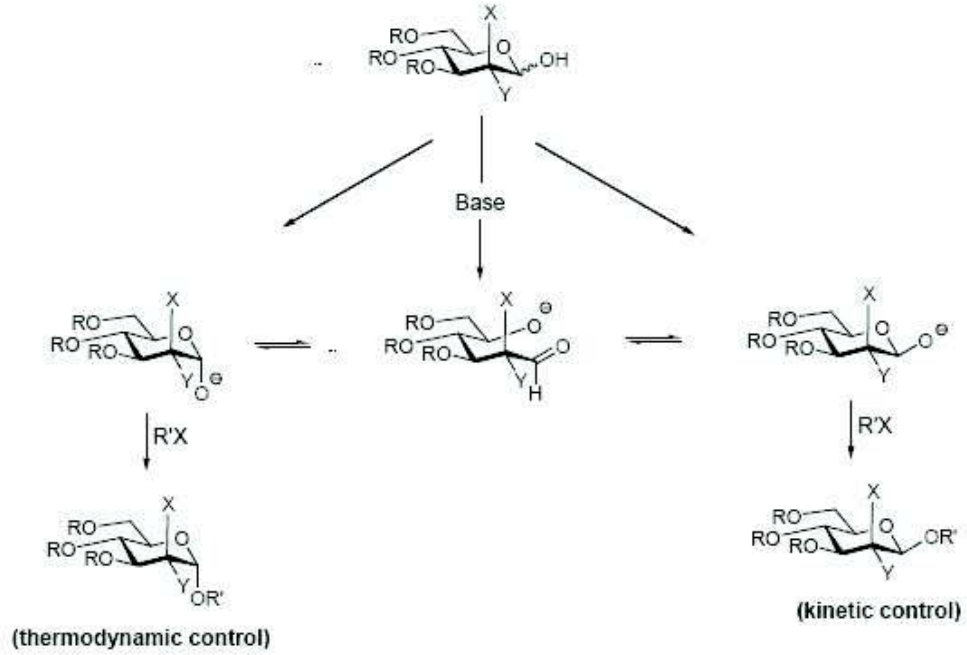


Scheme 45

4. O-Alkylation and the trichloroacetimidate method (Schmidt)

4.1. *O-Alkylation method*[47]

The anomeric oxygen of a sugar can be activated for a glycosylation not only by acids (Fischer glycosylation) but also by bases. Upon treatment a hemiacetalic sugar with a base, the generated anomeric oxide can be alkylated leading directly and irreversibly to a glycoside. This process is called anomeric O-alkylation.



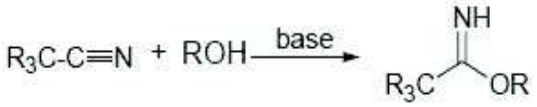
Scheme 46

In this procedure, some inconveniences should be considered: The equilibrium between the two anomeric forms and the open-chain form gives three sides of attack and also, a base catalysed elimination in the open chain form could become an important side reaction. Therefore, the yield, the regioselectivity and the stereoselectivity of the anomeric O-alkylation was not expected to be outstanding.

Chelation control[48] can also become a dominant factor in the determination of the α/β selectivity.

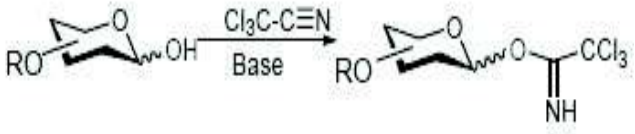
4.2. The trichloroacetimidate method

Electron deficient nitriles are known to undergo direct and reversible base-catalysed addition of alcohols to the triple bond system, providing O-alkyl imidates. The free imidates can be directly isolated as stable adducts..



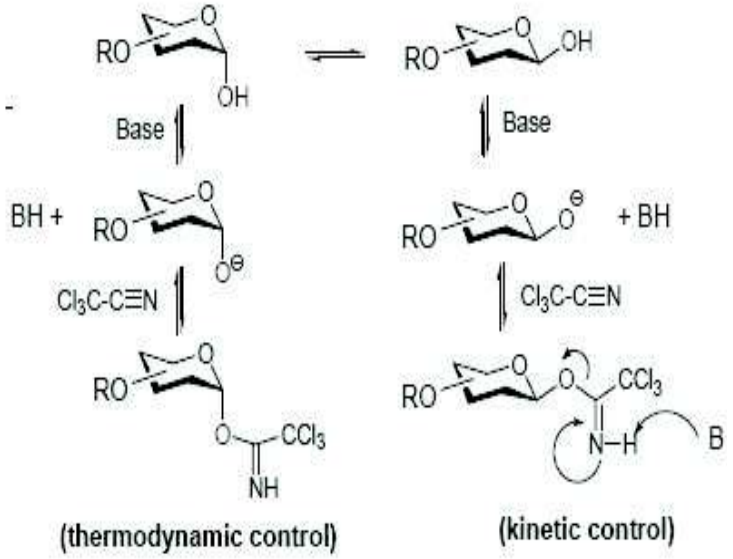
Scheme 47

The reaction of hemiacetalic sugars in the presence of a base with trichloroacetonitrile gives the anomeric trichloroacetimidates. In this way, the anomeric oxygen atom has been transformed into a good leaving group[49].



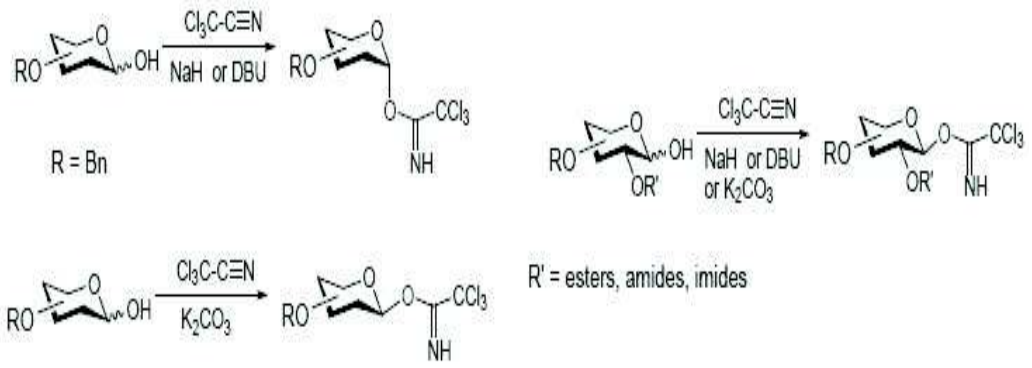
Scheme 48

Taking into account the equilibrium between both anomers and the enhanced nucleophilicity of equatorial oxygen atoms (owing to steric effects and to the stereoelectronic kinetic anomeric affect), the equatorial (β)-trichloroacetimidate is generated with preference or even exclusively in a very rapid and reversible reaction. However, this product anomerizes in a slow base catalysed reaction through retro-anomerization of the 1-oxide anion. Through a new trichloroacetonitrile addition, the thermodynamically more stable axial (α)-trichloroacetimidateis formed (thermodynamic anomeric effect).



Scheme 49

The equilibration between the two trichloroacetimidates can be speeded up by stronger bases.

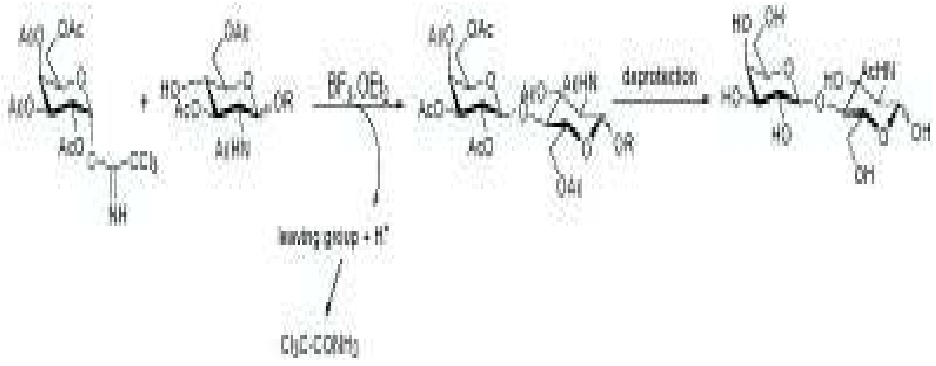


Scheme 50

Thus, with different bases both O-activated anomers can be obtained in pure form and high yield. However, NaH is appropriate for axial trichloroacetimidates while weaker bases such as K_2CO_3 is appropriate for equatorial trichloroacetimidates.

Concerning the glycosylation step, reaction of donor and acceptor under very mild acid conditions leads to the corresponding glycoside in an irreversible manner. Acids, such as $BF_3.OEt_2$ or TMSOTf are used in catalytic amounts. The proton liberated on the glycoside bond formation reacts with the forming leaving group. This leads to a stable, non-basic trichloroacetamide that provides the driving force of the reaction.

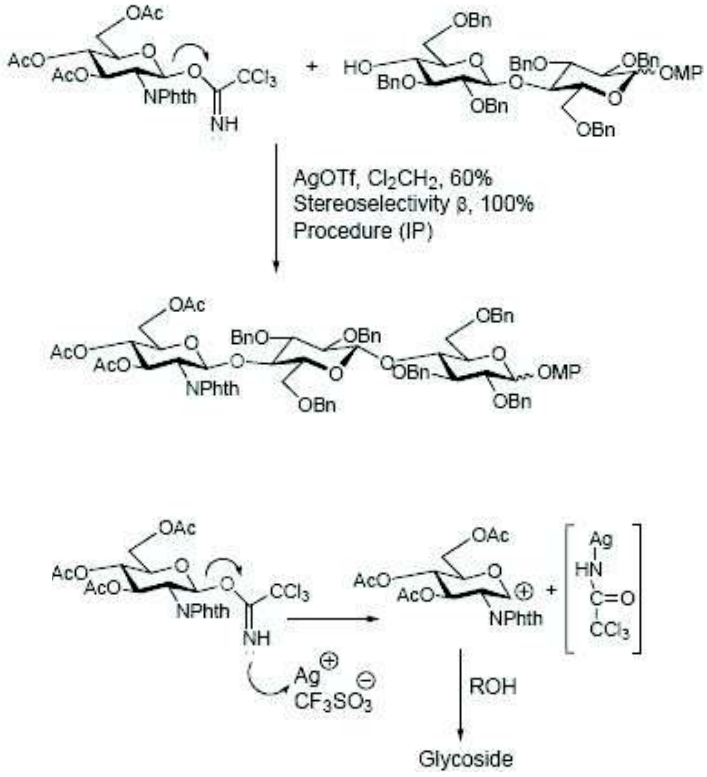
Example: Synthesis of lactosamine[50].



Scheme 51

The stereochemical requirements are the same as in other glycosylation methods.

Other mild activating species, such as, AgOTf, have also been used[51].



Scheme 52

For the synthesis of a tetrasaccharide derived from GlcNAc where the difference in reactivity between donor and acceptor is high, AgOTf has proved to be convenient because it activates the departure of the leaving group more slowly, thus minimizing decomposition of the donor.

Summary

Activation of the anomeric center with trichloroacetonitrile

- Convenient Base Catalyzed Trichloroacetimidate Formation
- Controlled acces to α- and β-compounds by choice of the Base
- Thermal stability of α- and β-trichloroacetimidates up to room temperature
- If required, silica gel chromatography can be performed

Glycosyl transfer

- Catalysis by acids (mainly Lewis acids) under very mild conditions
- Irreversible reaction
- Other Glycosidic bonds are not affected
- Usually High Chemical yield
- Reactivity corresponds to the halogenose/silver triflate system.
- Stereocontrol of Glycoside Bond Formation is Mainly Good to Excellent:
- Protecting groups with Neighbouring Group
- Participation: 1,2-*trans*-Glycopyranoside β-Glycosides of: Glc, GlcN, Gal, GalN, Xyl, Mur, 2-deoxy-Glc α-Glycosides of :Man, Rha.
- Protecting groups without Neighbouring Group Participation:
- Catalyst $BF_3.OEt_2$: Inversion of anomer configuration β-Glycosides of: Glc, GlcN, Gal, GalN, Xyl, Mur, GlcUA α-Glycosides of: Man, Rha
- Catalyst TMSOTf : Thermodynamically more stable anomer α-Glycosides of: Glc, GlcN, Gal, GalN, Man, Fuc, Mur.

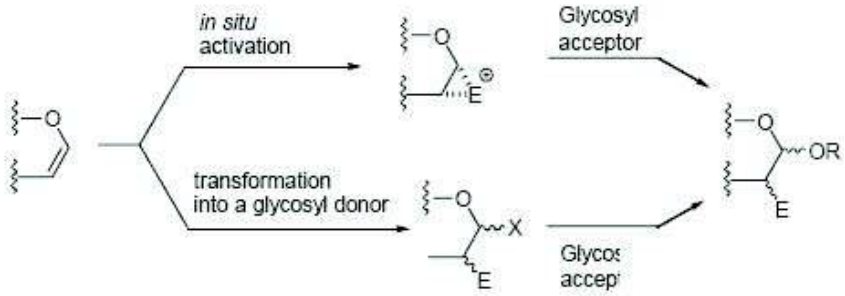
The outstanding significance of the

trichloroacetimidate method lies in the ability of glycosyl trichloroacetimidates to act as strong glycosyl donors under relatively mild acid catalysis. This has been demonstrated by its use in many laboratories all around the world. The efficiency of the method makes it appropriate for use in solid-phase.

6. Glycosylation with glycals (Lemieux, Thiem, Danishefsky)

Glycals in oligosaccharide synthesis were first used by Lemieux in 1960s,[52] by Thiem in 1980s [53] and since then, by Danishefsky and co-workers [54].

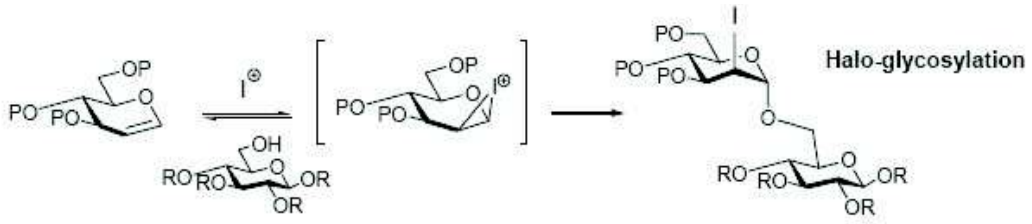
Glycals can be used as glycosyl donors in two modalities.



Scheme 53

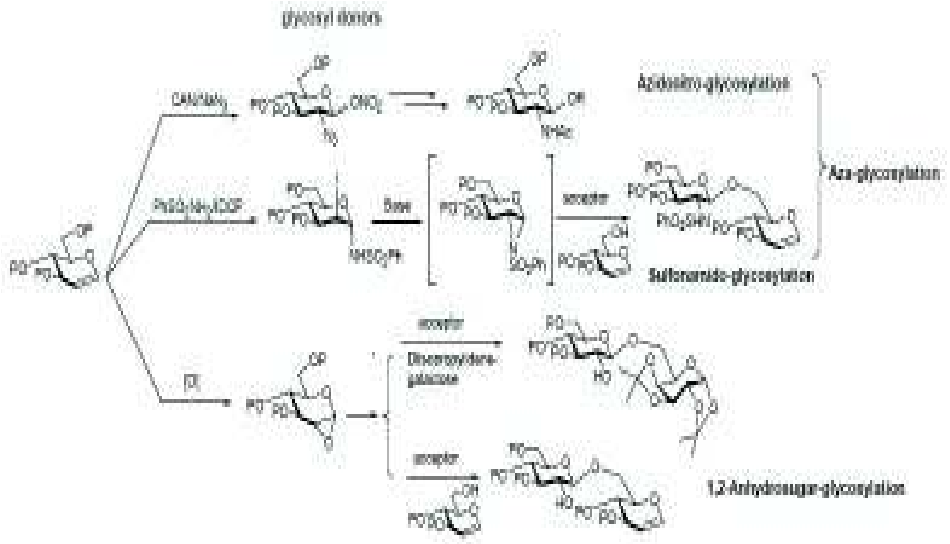
In the 1st motif, *in situ* activation makes the glycal act as glycosyl donor by forming a nonisolable intermediate. In the 2nd motif, the glycal is first converted into a glycosyl donor through different types of reactions (epoxidation, azidonitration or sulfonamide glycosylation). That is, the glycal is precursor of a defined glycosyl donor.

The pioneer experiments that used glycals as glycosyl donors, were done by Lemieux and Thiem who used halonium-mediated coupling to suitable acceptors. This particular reaction has the tendency to give a trans-diaxial addition and provides a crucial route to α-linked disaccharides having an axial 2-iodo function at the non-reducing end.



Scheme 54

Because the displacement of an axial iodine atom has proven to be very difficult, azaglycosylation of glycals has been investigated with the idea of preparing glycosides of 2- acylaminosugars.



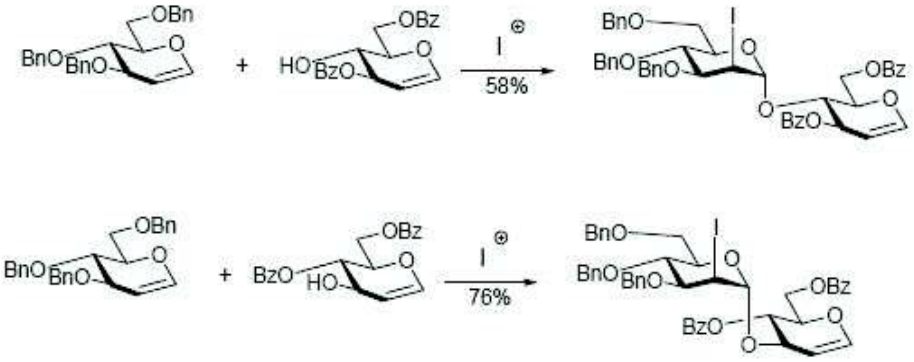
Scheme 55

Azidonitration with CAN/NaN_3 was studied by Lemieux and constituted an important advance at the time, nevertheless the conversion of the nitro-azido compounds into oligosaccharides has not been fully optimized with regards to the yield and stereoselectivity.

Other procedures, such as iodo-sulfonamidation developed by Danishefsky, have been used with more success for the synthesis of 2-acylamino oligosaccharides [55]. This method implies a *trans*-diaxial addition of an *N*-halobenzene sulfonamide to a glycal followed by a base treatment that gives an intermediate that reacts with any acceptor, for instance, another glycal, furnishing glycosides of benzenesulfonyl glucosamine derivatives: sulfonamido-glycosylation[56].

While iodo-glycosylation and sulfonamido-glycosylation are rather good methods for the conversion of glycals in various glycosides, the 1,2-anhydro sugar glycosylation provides a general method for converting glycals into common oligosaccharides of glucose, mannose and galactose in a high stereocontrolled manner. Once the glycal is converted into the 1,2-oxirane, it may react with several acceptors leading to disaccharides. This method has been the most widely used for the rapid assembly of oligosaccharides, and is appropriate for solid-phase synthesis.

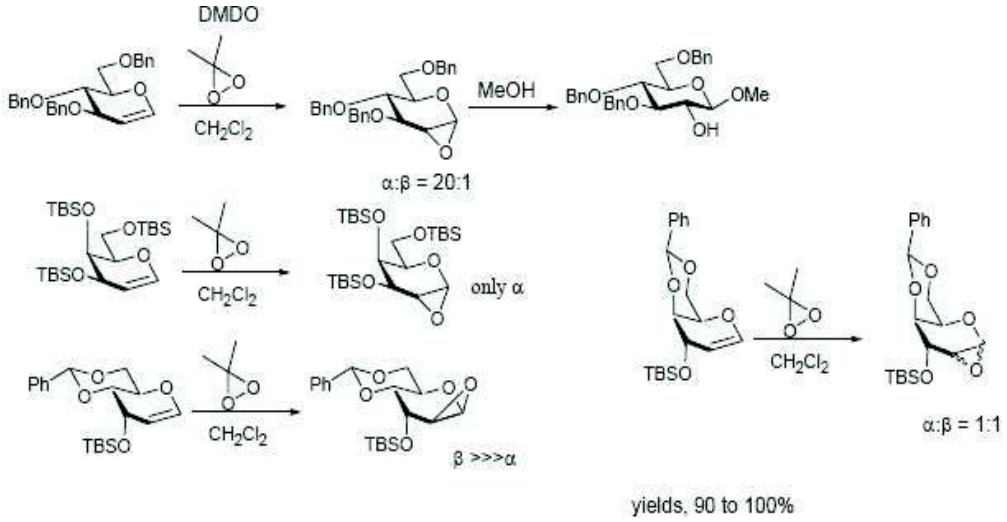
Protecting groups influence the reactivity of glycals as donors[56]. The armed-disarmed concept that prevails in pentenyl glycosides and thioglycosides is also applied here.



Scheme 56

When a benzylated glycal is made to react with benzoylated glycal no self-condensation is observed and only one product is obtained derived from the more reactive glycal acting as donor. With regards to 1,2-anhydro sugars, the method was able to be applied when it was discovered that glycals react smoothly with 2,2-dimethyldioxirane[57] prepared as a solution in dichloromethane, giving 1,2-anhydro sugars in good yields. The stereoselectivity of the epoxidation highly depends on the type of protecting groups and on the steric hindrance of the substituents.

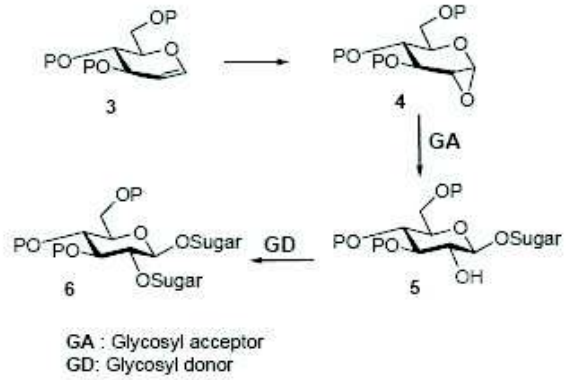
The 3,4,6-tri-*O*-benzyl-D-glucal gives the epoxide in quantitative yield. Its solvolysis gave the corresponding methyl glycoside with a stereoselectivity of 20:1 in favour of the α-isomer. With resident acetyl protecting groups, the stereoselectivity of the epoxidation is much reduced.



Scheme 57

TBS protecting groups or acetals also give high stereoselective epoxidations. Steric hindrance also has an influence. Reaction of TBS-protected galactal gives stereoselectively the α-epoxide, while the presence of an axial substituent at C-3 on the glycal promotes a quite selective epoxidation from its β-face. On the other hand, the gulal configurated glycal with hindering substituents on both faces of the double bond gave a 1:1 mixture of epoxides.

The strategy consists on the preparation of a glycal epoxide that reacts as donor with a glycosyl acceptor leading to a C(1)-O-sugar, with one hydroxyl group at C-2. This derivative acts as glycosyl acceptor when it reacts with a glycosyl donor furnishing a branched trisaccharide.



Scheme 58

Synthetic Strategies for the Assembly of Oligosaccharides

1. The pioneer linear glycosylation strategy
2. Convergent block synthesis
3. Selective and two-Stage Activation and Orthogonal Glycosylation strategy
4. Chemoselective Glycosylation Reactions
5. One-pot multistep glycosylations
6. Solid-phase oligosaccharide synthesis

1. *The pioneer linear glycosylation strategy*

In the pioneer linear glycosylation strategy, monomeric glycosyl donors have to be added to a growing saccharide chain. Each step requires manipulation of protecting and leaving groups which increases the number of reaction steps considerably. This fact, together with its low convergence, makes this linear strategy the least efficient for the synthesis of complex oligosaccharides. It has been used with glycosyl halides that require drastic reaction conditions for their preparation and, in consequence, is incompatible with complex oligosaccharides.

2. *Convergent block synthesis*

It is applicable for glycosylation methods in which the donors are formed under mild conditions, are stable enough to be purified and stored for a considerable period of time, and are able to undergo the glycosylation step also under mild conditions with high yield and high α/β stereoselectivity. Trichloroacetimidates, thioglycosides, glycosyl fluorides and glycals have been extensively used in block synthesis because they fulfil these requirements.

In a convergent glycosylation strategy most of the synthetic effort is directed towards the preparation of monomeric glycosyl donors and acceptors. The assembly of these units to an oligomer should involve the minimum number of synthetic steps and each synthetic step should proceed with high stereoselectivity and high yield. Furthermore, an efficient synthetic convergent strategy should make optimal use of common intermediates and oligosaccharide building blocks.

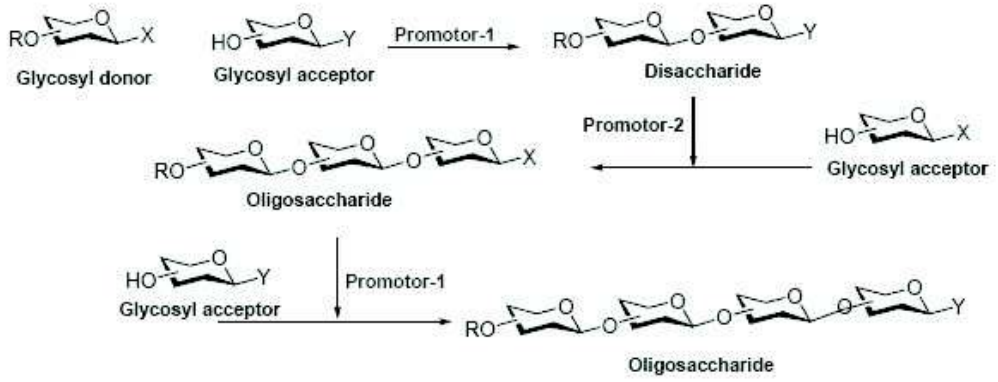
3. *Selective and Two-Stage Activation and Orthogonal Glycosylation strategies*

Notwithstanding the attractive features of the above mentioned block synthesis, the conversion of a common building block into a glycosyl donor requires several manipulations at the anomeric center presenting the drawback of the removal of the anomeric protecting group followed by the introduction of a leaving group, which can be a serious problem when performed on larger fragments. *The selective and two-stage activation strategy* solves this problem. In it, two types of anomeric leaving groups one obtained from the others, and one type of activation is used.

In 1984, Nicolaou and co-workers described the glycosylation strategy that is outlined in (Scheme 22). Glycosylfluorides and thioglycosides are used. This two-stage strategy is convergent and minimizes the number of manipulations, which have to be executed at the oligosaccharide stage. Attractive features of the strategy are:

The stability of thioglycosides under many different chemical conditions,their ease of activation by conversion into glycosyl fluorides their, the high efficiency of glycosyl fluorides in glycosidic bond formation and the excellent behaviour of thioglycosides as glycosyl acceptors.

An *orthogonal glycosylation strategy* uses two set of chemically distinct (orthogonal) glycosyl donors activated under different conditions.e.g anomeric sulphoxides as donors and thioglycosides as acceptors.(Scheme 31)



Scheme 59

In 1994, Ogawa and co-workers proposed this strategy that reduces the manipulation at the oligosaccharide stage. In this approach two anomeric leaving groups (X and Y) are used acting either as anomeric protecting group or as leaving group, depending on the activation conditions (Scheme 59).

4. *Chemoselective Glycosylation Reactions*

This strategy uses the influence of the nature of the protecting groups on the reactivity of donors and acceptors.

With respect to glycosyl donors, benzylated glycosyl donors (armed) are much more reactive than acylated ones (disarmed). This difference makes chemoselective glycosylations possible, the so-called *Armed-Disarmed strategy*. This strategy has been applied to several glycosyl donors. (Scheme 28, 29, 30 for pentenyl glycosides), (Scheme 37, 38 for thio glycosides) and (41 for seleno glycosides).

Tuning the glycosyl donor leaving group ability with a set of two groups, increases the versatility of the armeddisarmed glycosylation strategy.

Donors and acceptors are grouped into four levels of reactivity (Fig. 7):

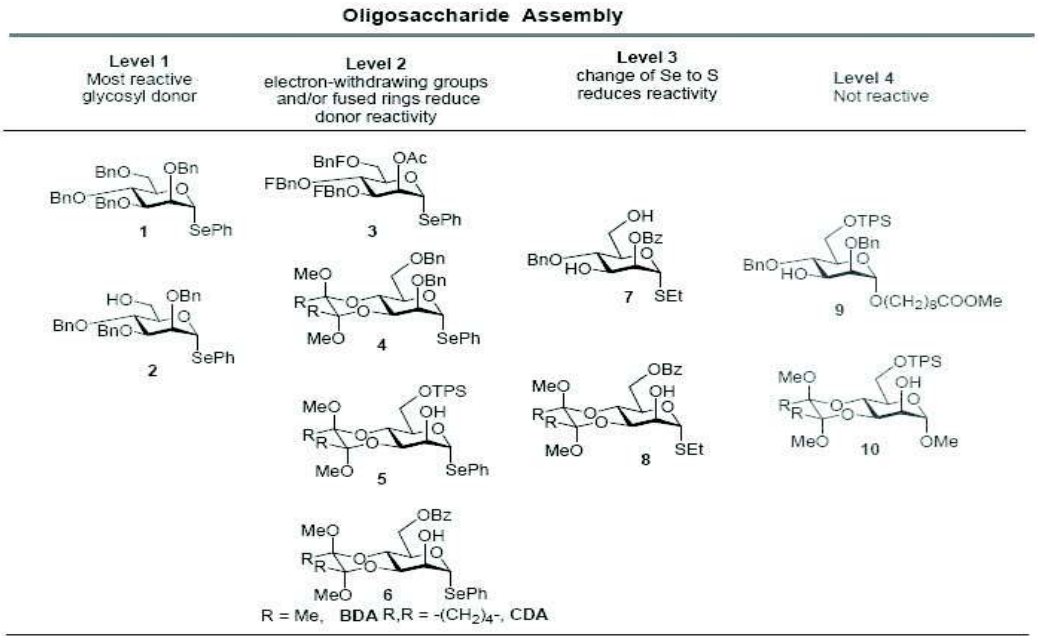
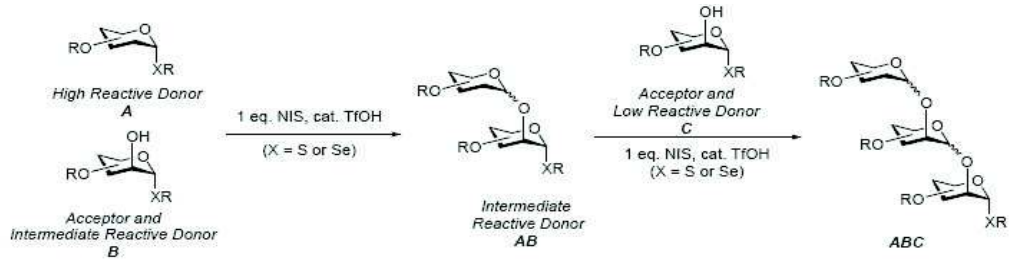


Figure 6

The general approach to the chemoselective synthesis of a trisaccharide by careful tuning of glycosyl donor and glycosyl acceptor reactivity is outlined in (Scheme 60).



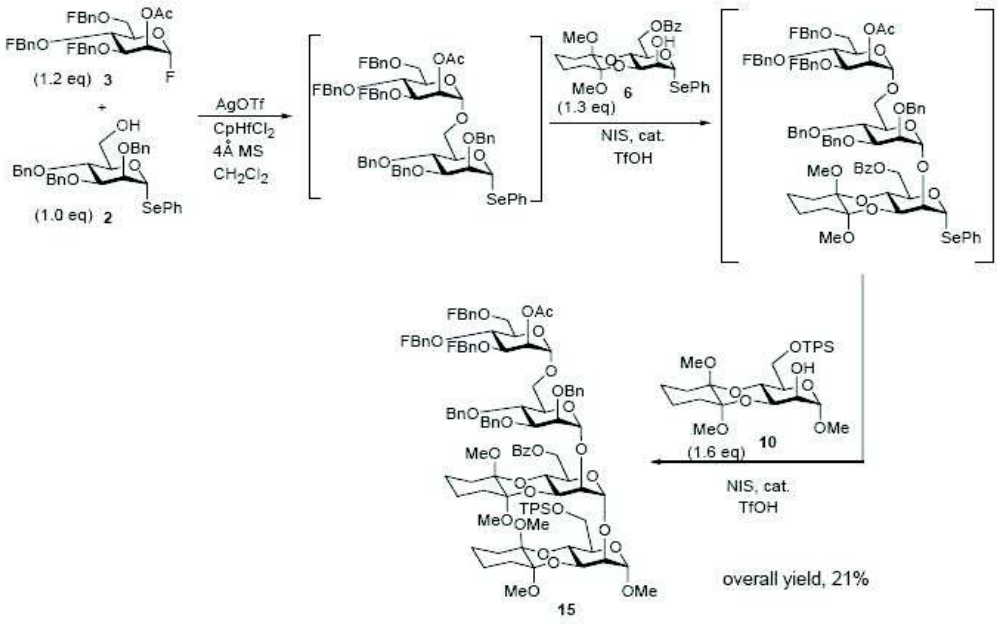
Scheme 60

5. *One-pot multistep glycosylations*

One-pot synthesis of oligosaccharides is often referred as a reactivity-based one-pot method in which glycosyl donors with decreasing anomeric reactivities are allowed to react sequentially in the same flask. This procedure, although is highly convenient because reduces the number of steps considerably, has the inconvenience that the donor reactivities have to be carefully adjusted which implies extensive protecting group manipulations.

Reactivity-based one-pot method

Tuning the reactivity of glycosyl donors by the influence of leaving and protecting groups, together with the principle of orthogonal activation enabled a highly efficient tetrasaccharide one pot - synthesis[58].

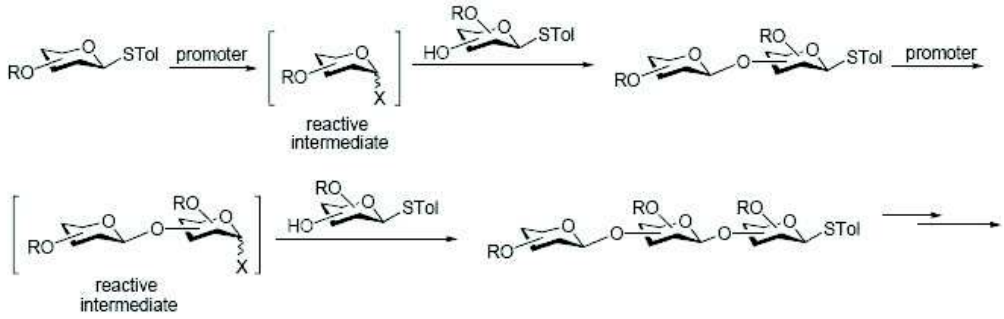


Scheme 61

Non-reactivity-based one-pot method

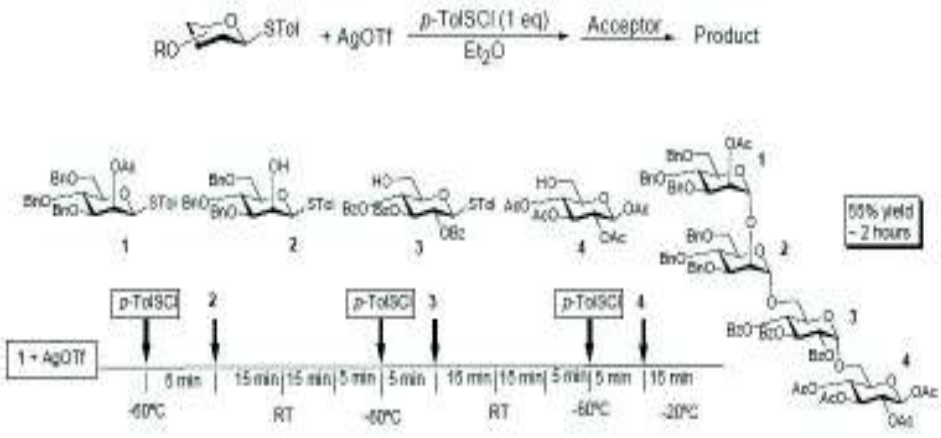
Recently Huang, Ye and co-workers have designed a general one-pot method independent of differential glycosyl donors[59].

The method is achieved by pre-activating the donor, that generates a reactive intermediate that reacts with the acceptor that contains the same reactive leaving group. The process can be repeated in the same vessel allowing the rapid assembly of oligosaccharides (Scheme 62).



Scheme 62

The general conditions were established by using *p*-tolyl thioglycosides as building blocks, and as the stoichiometric promoter, *p*-toluenesulfenyl triflate (*p*-TolSOTf) formed *in situ* from *p*-toluenesulfenyl chloride (*p*-TolSCl) and AgOTf.



Scheme 63

The tetrasaccharide Man-α-(1,2)-Man-α-(1,6)-Glc-α-(1,6)-Glc was assembled in this way in 55% overall yield and in less that two hours.

6. *Solid-phase oligosaccharide synthesis*

The solid-phase synthesis SPS (also called SPOS: Solid-Phase Organic Synthesis) is a methodology that performs the synthesis of a target compound on insoluble supports.

It offers several **advantages** over solution phase reactions:

- **Increased yields**, because excess reagents can be used to drive the reaction to completion.
- **Easy and simple purification processes**, because removal of the by-products and excess of reagents can be done by simply washing the resin.
- **Rapid overall process**, purification of the reaction products is made at the end of the synthesis minimizing the number of chromatographic steps required

It is becoming a valuable alternative to traditional synthesis.

Bruce Merrifield was the chemist that in 1963, pioneered solid phase synthesis. For this contribution, he earned the Nobel Prize of Chemistry in 1984. The use of solid support for organic synthesis relies on three interconnected requirements:

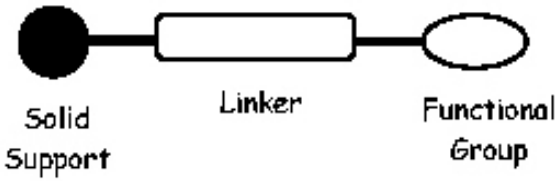
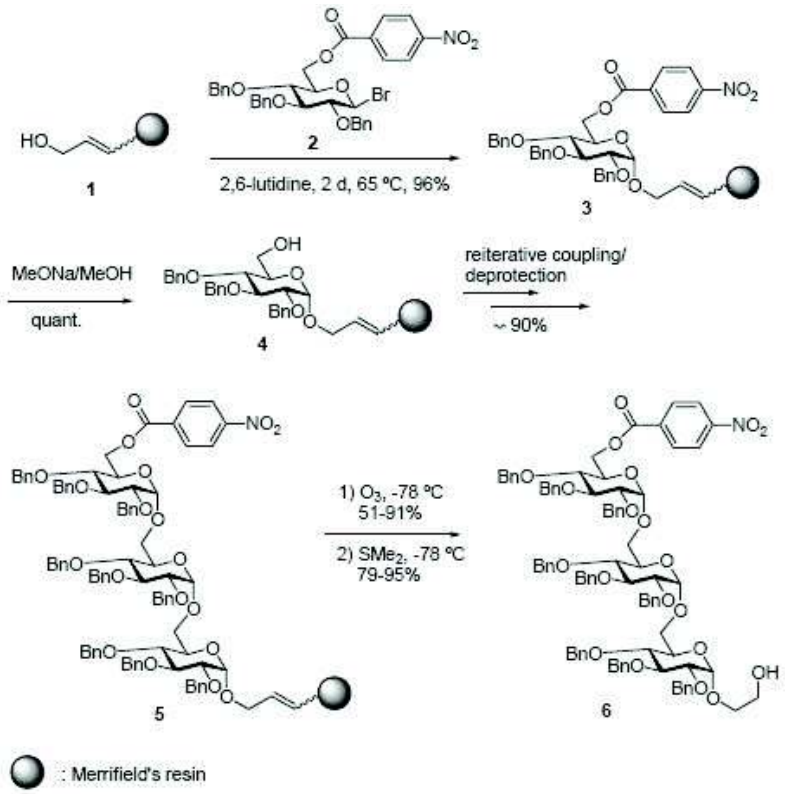


Figure 8

1. Solid support: A cross linked insoluble polymeric material that is inert to the conditions of synthesis.
2. Linker: Some means of linking the functional group of the substrate to the solid phase that permits selective cleavage of some or the entire product from the solid support during synthesis to control the extent of the reaction, and finally, gives the desired product.
3. Functional group: that requires a chemical protection/ deprotection strategy of the reactive groups.

Merrifield [60] originally developed this methodology. This methodology facilitates the generation of the products that are physically separated by attachment to the resin, thus facilitating the removal of the reagents and side products by simple filteration and washing. Besides the convenience of purification, solid phase support, also allow the use of excess phase reagents, to drive reaction to completion, since they can easily be removed (Scheme 64).



Scheme 63

Unfortunately, the limited capacity of solid supports has restricted the exploitation of solid phase methodology in the glycosylation reactions. Work continues to increase the loading levels obtainable to make solid phase synthesis more useful for commercial purpose.

References

1. Barresi, F.; Hindsgaul, O. *"Glycosylation methods in oligosaccharide synthesis"* Modern Synthetic Methods, 1995, *7*, 281-330.
2. (a) Toshima, K.; Tatsuta, K. *Chem. Rev.*, 1993, 93, 1503;
   (b) Sinay. P. *Pure App. Chem.*, 1991, 63, 519;
   (c) Fraser Reid, B.; Wu, Z.; Udodong, U.; Uttosson, H.; *J. Org. Chem.*, 1990, 55, 6068.
   (d) Pellissier, H. *Tetrahedron*, 2005, 61, 2947.
3. (a) Haines, A. H. "*Relative reactivities of hydroxy groups in carbohydrates"*, *Adv. Carbohydr. Chem Biochem.*, 1976, *33*, 11.
   (b)Moitessier, N.; Chapleur, Y "*Modulation of the relative reactivities of carbohydrate secondary hydroxyl groups Modification of the hydrogen bond network"*, *Tetrahedron Lett.*, 2003*, 44*, 1731.
   (c) Schmidt, R. R.; Toepfer, A. *Tetrahedron Lett.*, 1991, *32*, 3353.
4. (a) Lemieux, R. U.; Hendriks, K. B.; Stick, R. V.; James, K. *J. Am. Chem. Soc*., 1975, 97, 4056.
   (b) Lemieux, R. U.; Driguez, H. J.. *J. Am. Chem. Soc.*, 1975, 97, 4063.
   (c) Lemieux, R. U.; Driguez, H. J. *J. Am. Chem. Soc.*, 1975, 97, 4069.
   (d) Lemieux, R. U.; Bundle, D. R.; Baker, D. A. *J. Am. Chem. Soc.*, 1975, 97, 4076.
5. Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*. Springer Verlag, Berlin, 1983
6. Paulsen, H.; Lockhoff, O. *Chem. Ber.*, 1981, 114, 3102.
7. Lemieux, R. U. *Pure. Appl. Chem.*, 1971*, 25*, 527.
8. Vankar, D.; Vankar, P. S.; Behrendt, M.; Schmidt, R. R. *Tetrahedron*, 1992*, 47*, 9985
9. Ratcliffe, A. J.; Fraser-Raid, B. S. *J. Chem. Soc., Perkin Trans I*, 1990*,* 747.
10. Stork , G. and La Clair, J. J. *J. Am. Chem. Soc*., 1996, *118*, 247.
11. Barresi, F. Hindsgaul, O. *J. Am. Chem. Soc*., 1991,*113*, 9367 and *Synlett*, 1992, 759.
12. Hanessian, H.; Banoub, J. *Methods in Carbohydr. Chem*. *Vol. 8*, Whistler, R. L.; BeMiller, J.N. Eds. Academic Press, New York, 1980, 247
13. Betaneli, V.; Ovchinnikov, M. V.; Backinowsky, Kotchekov, N. K., *Carbohydr. Res.*, 1980, *84,* 211-214
14. Toshima, K. *Carbohydr. Res.*, 2000*, 327*, 15-26.
15. Mukaiyama, T.; Murai, Y.; Shoda, S. *Chem. Lett.*, 1981, 431.
16. Hayashi, M.; Hashimoto, S.; Noyori, S. *Chem. Lett.*, 1984, 1747.
17. Posner, G. H. Haines, S. R. *Tetrahedron Lett.*, 1985, *26*, 5-9.
18. Nicolaou, K. C.; Dolle, R. E.; Papahatjis, D. P.; Randall, J. L. *J.*

Am. Chem. Soc., 1984*, 106,* 4189
19. Fraser-Reid, B.; Konradsson, P.; Mootoo, D. R.; Udodong, U. *J. Chem. Soc. Chem. Commum.*, 1988, 823.
20. Mootoo, D. R.; Konradsson, P.; Fraser-Reid, B. *J. Am. Chem. Soc.*, 1989, 111, 8540.
21. Konradsson, P.; Mootoo, D. R.; McDevitt, R. E.; Fraser-Reid, B. *J. Chem. Soc. Chem. Commum.*, 1990, 270.
22. Jayaprakash, K. N.; Radhakrishnan, K. V.; Fraser-Reid, B. *Tetrahedron Lett.*, 2002, *43*, 6953.
23. Macha, M.; Schlueter, U.; Mathew, F.; Fraser-Reid, B.; Hazen, K.C. *Tetrahedron.* 2002, *58*, 7345.
24. (a) Mootoo, D. R.; Konradsson, P.; Udodong, U.; .; Fraser-Reid, B. *J. Am. Chem.*, *Soc.* 1988, 110, 5583.
(b) Mootoo, D. R.; Fraser-Reid, B. *Tetrahedron Lett.*, 1989, 30, 2363.
25. Khiar N.; Martin-Lomas, M. *J. Org. Chem.*, 1995, *60*, 7017.
26. (a) Fugedi, P.; Garegg, P. J. *Carbohydr. Res.*, 1986, 149, C9.
(b) Andersson, F.; Fugedi, P.; Garegg, P. J. *Tetrahedron Lett.*, 1986, 27, 3919.
27. (a) Pozsgay, V.; Jennings, H. J. *J. Org. Chem.*, 1987, 52, 4335.
(b) Pozsgay, V.; Jennings, H. J. *J. Org. Chem.*, 1988, 53, 4042.
28. (a) Dasgupta, F.; Garegg, P. J. *Carbohydr. Res.*, 1988, 177, C13.
(b) Dasgupta, F.; Garegg, P. J. *Carbohydr. Res.*, 1990, 202, 225.
29. (a) Ito, Y.; Ogawa, T. *Tetrahedron Lett.*, 1988, 29, 1061.
(b) Ito, Y.; Ogawa, T.; Numata, M.; Sugimoto, M. *Carbohydr. Res.*, 1990, 202, 165.
(c) Mori, M.; Ito, Y.; Ogawa, T. *Tetrahedron Lett.*, 1989, 30, 1273.
(d) Mori, M.; Ito, Y.; Uzawa, J.; Ogawa, T. *Tetrahedron Lett.*, 1990, 31, 3191.
30. (a) Reddy, G. V.; Kulkarni, V. R.; Mereyala, H. B. *Tetrahedron Lett.*, 1989, 30, 4283.
(b) Ravi. D.; Kulkarni, V. R.; Mereyala, H. B. *Tetrahedron Lett.*, 1989, 30, 4287.
(c) Mereyala, H. B.; Reddy, G. V. *Tetrahedron*, 1991, 47, 6435.
(d) Mereyala, H. B.; Reddy, G. V. *Tetrahedron*, 1991, 47, 9721.
(e) Mereyala, H. B.; Kulkarni, V. R.; Ravi. D.; Sharma, G. V. M.; Rao, B. V.; Reddy, G. V. *Tetrahedron*, 1992, 48, 645.
31. (a) Konradsson, P.; Udodong, U. E.; Fraser-Reid, B. *Tetrahedron Lett.*, 1990, 31, 4313.
(b) Konradsson, P.; Mootoo, D. R.; McDevitt, R. E.; Fraser-Reid, B. *J. Chem. Soc.Chem. Commun.*, 1990, 270.
32. Veeneman, G. H.; van Leeuwen, S. H.; van Boom, J. H. *Tetrahedron Lett.*, 1990, 31, 1331.
33. Sasaki, M.; Tachibana, K. *Tetrahedron Lett.*, 1991, 32, 6873.
34. (a) Veeneman, G. H.; van Boom, J. H. *Tetrahedron Lett.*, 1990, 31, 275.
(b) Veeneman, G. H.; van Leeuwen, S. H.; Zuurmond, H.; van Boom, J. H. *J. Carbohydr. Chem.*, 1990, 9, 783.
(c) Zuurmond, H. M.; van der Laan, S. C.; van der Marel, G. A.; van Boom, J. H. *Carbohydr. Res.*, 1991, 215, C1.
(d) Smid, P.; de Ruiter, G. A.; van der Marel, G. A.; Rombouts, F. M.; van Boom, J.H. *J. Carbohyd. Chem.*, 1991, 10, 833.
35. Marra, A.; Mallet, J. M.; Amatore, C.; Sinay, P. *Synlett.*, 1990, 572.
36. Ferrier, R.; Furneaux, R. *Methods, Carbohydr. Chem.*, 1980, *8*, 251.
37. Tropper, F.; Andersson, F.; Grandmaitre, C.; Roy, R. *Synthesis*, 1991, 734.
38. Horton, D. Methods in *Carbohydr. Chem.*, 1963, *2*, 433.
39. Veeneman, G. H.; van Boom, J. H. *Tetrahedron Lett.*, 1990, *31*, 275
40. Boons, G. J.; Geurtsen, R.; Holmes, D. R. *Tetrahedron Lett.*, 1995, 36, 6325.
41. Kahne. D.; Walker. S.; Chang.Y.; Van Engen. D. *J. Am. Chem. Soc.*, 1989, *111*, 6881.
42. Yan, L.; Kahne, D. *J. Am. Chem. Soc.*, 1996, 118, 9239.
43. Mehta, S.; Pinto, B. M. *J. Org. Chem.*, 1993, 58, 3269.
44. Mehta, S.; Pinto, B. M. *J. Org. Chem.*, 1993, 58, 3269.
45. Mehta, S.; Pinto, B. M. *J. Org. Chem.*, 1993, *58*, 3269.
46. Benhaddou, R.; Czernecki, S.; Randriamandimby, D. *Synlett,* 1992, 967.
47. Schmidt, R. *Angew. Chem. Int. Ed. Engl.*, 1986, *25*, 212.
48. Rembold, H.; Schmidt, R. R. *Carbohydr. Res.*, 1993, *246*, 137-159.
49. Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.*, 1994, 50, 21-123.
50. Schmidt, R. R. University of Konstanz, unpublished results.
51. Robina, I.; López-Barba, E; Fuentes, J. *Tetrahedron*, 1996, *52*, 10771-10784.
52. Lemieux, R. U.; Levine, S. *Can. J. Chem.*, 1964, 42, 1473.
53. (a) Thiem, J.; Karl, H.; Schwentner, J. *Synthesis*, 1978, 696.
(b) Thiem, J.; Karl, H. *Tetrahedron Lett.*, 1978, 4999.
54. (a) Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.*, 1989, 111, 6656.
(b) Suzuki, K.; Sulikowski, G. A.; Friesen, R. W.; Danishefsky, S. J. *J. Am. Chem. Soc.*, 1990, 112, 8895.
(c) Friesen, R. W.; Danishefsky, S. J. *Tetrahedron*, 1990, 46, 103.
55. (a) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.*, 1990, 112, 5811.
(b) Griffith, D. A.; Danishefsky, S. J. *J. Am. Chem. Soc.*, 1991, 113, 5863.
56. Friesen, R. W.; Danishefsky, S. J. *Tetrahedron*, 1990, *112*, 8895
57. Danishefsky, S. J. ; Halcomb, R. I. *J. Am. Chem. Soc.*, 1989, *111*, 6661.
58. Cheung, M.-K.; Douglas, N. L.; Berthold, H.; Ley, S. V.; Pannecoucke, X. M. *Synlett*, 1997, 257.
59. Huang, X.; Huang, L.; Wang, H.; Ye, X.-S. *Angew. Chem. Int. Ed.*, 2004, *43*, 5221- 5224.
60. Merrifield, R. B. *J. Am. Chem. Soc.*, 1963, 85 , 2149.