Synthesis of Oligosaccharides of 2-Amino-2-deoxy Sugars

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I. Introduction

The last 15 years have witnessed a burgeoning interest in the chemistry of glycoconjugates, which result from the covalent linkage of a sugar moiety called glycan with a protein (glycoprotein) or a lipid (glycolipid). Intensive research on the biomedical front is presently concerned with the various aspects of glycoconjugates such as the bacterial polysaccharides, cell surface glycoproteins and glycolipids, and other complex proteoglycans of immunological significance which are involved in a host of biological processes. The oligosaccharide parts of the glycolipids, glycoproteins, and bacterial lipopolysaccharides have received much attention and have acquired an importance as great as that of protein and nucleic acids. Their functions are less well understood, but it is clear that the oligosaccharide moieties of glycoproteins and other glycoconjugates of biological membranes play a key role in cell–cell and cell–virus recognition. This may be due to the fact that strongly hydrophilic glycan chains will normally be located at the outer surface of molecules in aqueous environments, which render them available for interaction with other molecules. Some important biological roles of the oligosaccharide moiety of glycoconjugates to be noted are as follows: (1) The differences in oligosaccharide structures are responsible for blood group activities and, more generally, are involved in ontogenesis and oncogenesis as differentiation antigens.[1,2] (2) The nature and extent of glycosylation of proteins determines the half-life of their survival in the blood streams. (3) The contact between the oligosaccharides initiates the invasion of cells by viruses and initiates the production of antibodies toward the invading virus. (4) The oligosaccharides may be involved in enzyme action.

The structural diversity of the complex carbohydrates of glycoconjugates has been much more appreciated over the past few years because, due to the vast improvements in analytical techniques, hundreds of complex carbohydrate structures have been determined. Synthetic studies of these complex molecules could not only provide chemical evidences for or against the proposed stereostructures but also be directed to supply enough of such synthetic oligosaccharides for the biological studies in medical and biotechnological research.

The aim of this review is to report the progress toward the establishment of reliable methods for the prepa-

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Paul Boullanger was born in 1947 in Lyon, France. He attended *the Ecole Supérieure de Chimie Industrielle de Lyon where he* received his chemical engineering degree in 1970. He obtained his Ph.D. (Thèse d'Etat) in Lyon in 1976, under the supervision of G. Descotes. After a 1 year post-doctoral stay with R. U. Lemieux (Edmonton, Alberta, Canada) he returned to the University Claude Bernard of Lyon where he is now a Research Director at the Centre National de la Recherche Scientifique (C.N.R.S.). His current field of research lies in oligosaccharide chemistry where, besides the synthetic point of view, he is interested in high molecular weight assemblies such as neoglycoproteins (artificial antigens), (co)-polymers, and tensioactive oligosaccharides and liposomes.

ration of 2-amino-2-deoxyglycopyranosides. This importance derives mainly from the natural occurrence of the numerous glycosides of *N*-acetylglucosamine which are widely distributed in living organisms where they constitute building blocks of glycoconjugates such as peptidoglycans, mucopolysaccharides (hyaluronic acids, keratan sulfates, and inner and outer core regions of glycoproteins). They are also encountered in the human milk, in blood group substances, in bacterial lipopolysaccharide antigens where they constitute part of the epitopes, and in plants. A sulfated and acetylated

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glucosamine oligosaccharide is recognized by root cells of leguminous plants and acts as a signal for symbiotic host-specificity of rhizobia bacteria.[3] This recent example shows that receptors for amino sugars are also present on plant cells.

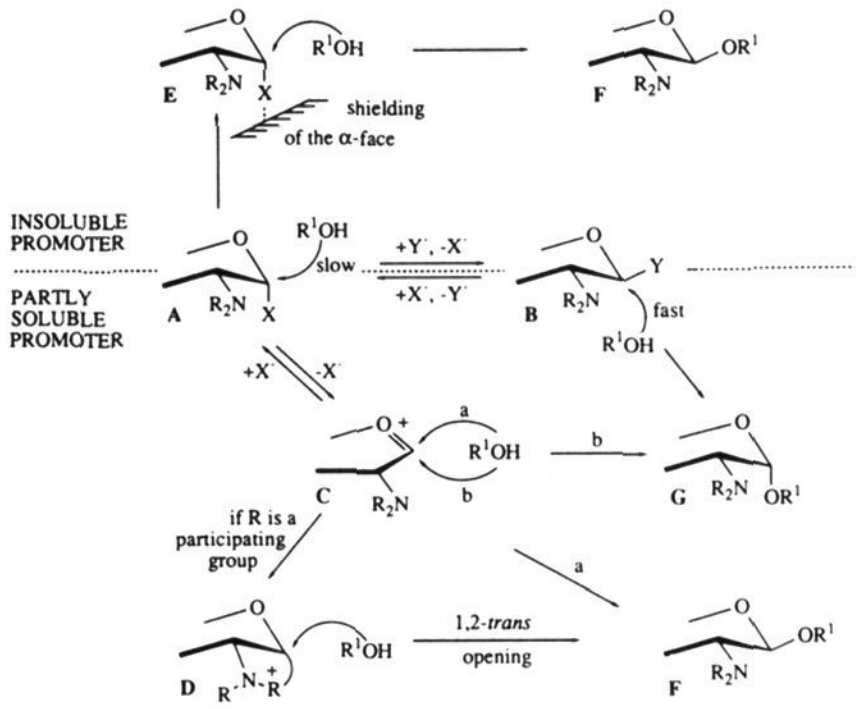
A great number of reviews or books devoted to the oligosaccharide synthesis have appeared in the literature.[4-20] In these articles, the part concerning the synthesis of 2-amino-2-deoxy sugars was most often restricted to a few paragraphs due to the enormous scope of the subject. Of course, the methods used for the glycosylation of the 2-amino-2-deoxy sugars were directly derived from that reported for "usual" carbohydrates. Nevertheless, some of these glycosylation methods were very specifically designed for the field of the 2-amino-2-deoxy carbohydrates. These methods take into account the differences of valences or nucleophilicities between oxygen and nitrogen atoms and are different from the methods already described in the general oligosaccharide synthesis. This is the reason why this review article will be focused exclusively on all the glycosylation aspects concerning the 2-amino-2-deoxy sugars. Other important aspects concerning the protective groups or the stereochemistry of the acceptor alcohols, will be mentioned in this article, but not treated with any more detail, in order to tightly restrict the field of this article to the glycosylation processes.

II. The General Reaction Mechanism

The glycosylation reaction is a very sophisticated procedure subject to many controversies and disputes. Recently, the use of very precise techniques (e.g. high-field ^{1}H and ^{13}C NMR, mass spectrometry, or high-pressure liquid chromatography) allowed a better knowledge of the glycosylation processes, but these methods also pointed out the high degree of complexity of a very simple reaction, such as the condensation of a glycopyranosyl bromide with an alcohol.

Despite this high complexity, some important features concerning the glycosylation process are now well

Scheme I

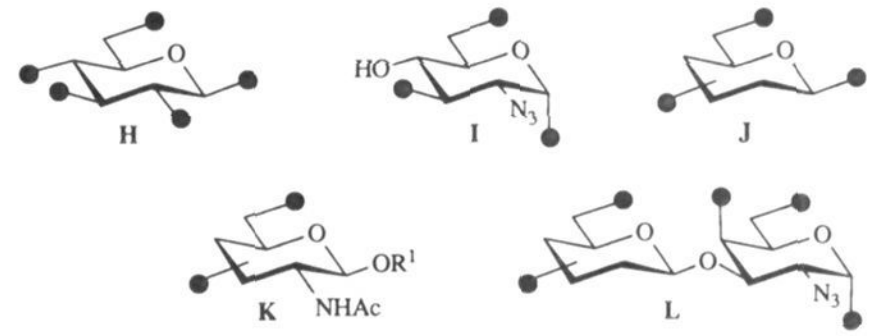


understood and these should be kept in mind in order to design a retrosynthetic scheme for the preparation of a given oligosaccharide. These features will be exemplified in the field of the 2-amino-2-deoxy carbohydrates.

The so-called glycosylation procedure is the creation of a carbon–oxygen bond via a nucleophilic substitution pattern. This substitution involves the anomeric position (C-1) of the carbohydrate containing the leaving group (X, Scheme I), which is often called the glycosylation donor A, with one hydroxyl group of the alcohol (R^1OH, called the glycosylation acceptor) which is often, itself, either a mono or oligosaccharide. The reaction usually is realized in the presence of an activator which also acts as an acid scavenger and which is called the *reaction promoter. The role of the promoter is to assist* the departure of the anomeric leaving group (X) in a way which avoids the formation of the oxocarbenium ion C resulting, most of the time, in a lack of stereoselectivity and affording mixtures of α- and β-glycosides (G and F, respectively). Promoters are often used in catalytic amounts (e.g. Lewis acids with oxygenated leaving groups X) but can also combine with X in stoichiometric proportions.

In order to achieve 1,2-trans-glycosylations, two approaches were reported to be of general use. The most widely used method involved a glycosylation donor containing a participating group as the amino protective function. The formation of a cyclic intermediate D by anchimeric assistance resulted in a shielding of the "α-face" of the donor allowing the reaction of the acceptor alcohol on the "β-face" only and thus affording the 1,2-*trans*-glycoside F with a high degree of stereoselectivity.[21] This approach has been used in the Koenigs–Knorr reactions, in the so-called "oxazoline" and "phthalimido" procedures and in other miscellaneous glycosylation reactions which will be detailed in this article. Another method reported for the synthesis of 1,2-*trans*-glycosides F involved the use of 1,2-*cis*-2-amino-2-deoxy-α-D-glycopyranosyl halides A (having an amino nonparticipating protective group) and an insoluble promoter able to shield the "α-face" of the donor during the substitution (E) with the acceptor alcohol. The above method was used mainly with 2-azido-2-deoxy donors and insoluble promoters, but

Scheme II



the reported 1,2-trans stereoselectivities were often lower than those observed with the donors containing C-2 participating groups.

Finally, the syntheses of 1,2-*cis*-glycosides G should fit two main requirements i.e., a nonparticipating group as amino protection and a leaving group which is in a 1,2-trans orientation with respect to the C-2 substituent (B). Due to the higher reactivities and lower stabilities of such donors B, the above derivatives were often prepared in situ by an exchange of leaving groups from the C-1 epimers A. In the cases where the attack of the acceptor alcohols (R^1OH) on the "α-face" of the donor were faster than the reverse epimerization process (leading back to A), good 1,2-*cis*-glycosylation stereoselectivities were achieved. In the field of the 2-amino-2-deoxy sugars, this procedure was applied with 2-azido-2-deoxyglycopyranosyl donors and soluble (or partly soluble) promoters.

III. Schematic Representation Used in This Article

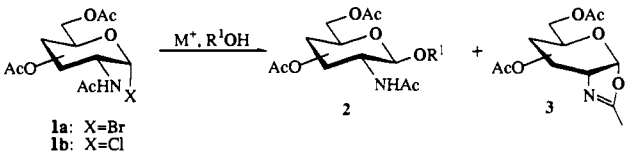
In order to avoid the multiplication of reaction schemes and formulae in this review article, we will use a simplified symbolism reported recently.[11]

Thus formula H (Scheme II) will represent any fully protected carbohydrates having the β-D-*gluco* configuration irrespective of the protective groups and/or the number of sugar residues glycosylated on this unit. Furthermore, formula I will represent any protected monosaccharide or oligosaccharide with the α-D-*gluco* configuration containing a free HO-4 group, and a 2-azido-2-deoxy function regardless of the other substituent units and/or protective groups. Formula J, will represent any mono- or oligosaccharide fully protected or substituted on the 2, 3, and 4 positions and having the β-D configuration. If necessary, formulae such a K and L will represent respectively any 2-acetamido-2-deoxy fully protected mono or oligoglycopyranoside of β-D anomeric configuration and any oligosaccharide in which a 2-azido-2-deoxy-β-D-galactopyranosyl unit is substituted on HO-3 by any fully protected β-D-mono- or β-D-oligosaccharide.

In several instances where the structures and configurations of the donors and/or acceptors are of crucial importance, the official symbolism will be used, but it should be understood that they will correspond to *protected* structures. For example a β-D-Gal*p*-1→4)-D-Glc*p*NPht donor will represent a fully protected (unless otherwise stated) lactosaminyl donor and not the free lactosamine disaccharide.

This simplified symbolism will be, of course, accompanied by complementary explanations in the text or on the formulae themselves. In certain unavoidable

Scheme III



circumstances, for the sake of clarity, the full structure of the glycosyl acceptors or donors will be reported as is.

IV. Koenigs–Knorr Reactions

The Koenigs–Knorr reaction is one of the oldest methods for the preparation of 1,2-*trans*-glycosides involving per-O-acetylated glycopyranosyl halides as donors and silver salts[22] as promoters.

In the 2-amino-2-deoxy series the 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glycopyranosyl halides **1a** and **1b** (Scheme III) possess different properties than the corresponding 2-*O*-acetyl derivatives. The glycopyranosyl bromides **1a** (D-*gluco* and D-*galacto* configurations) are unstable,[23–27] whereas the glycopyranosyl chlorides **1b** are more stable but less reactive.[28]

The glycopyranosyl halides **1a** and **1b** were used for the glycosylation of simple alcohols (which were used in excess) in the presence of mercuric cyanide as the promoter.[29–31] The 1,2-*trans*-glycosides **2** were obtained with a good degree of stereoselectivity in addition to the oxazoline side product **3**, which reduces the yield of the glycosylation reaction.

In addition to the 2-acetamidoglycopyranosyl donor derivatives **1a** and **1b**, other amides were used with participating protecting group at C-2; such as the 2-benzamido, 2-dichloroacetamido,[32,33] 2-trifluoroacetamido,[34,35] and 3-hydroxymyristic acid amides.[36,37]

In the synthesis of glycopeptides, Koenigs–Knorr glycosylation reaction permitted the preparation of the β-D-Glc*p*NAc-(1→O)-Ser and β-D-Gal*p*NAc-(1→O)-Ser glycoside derivatives in moderate yields.[38–41]

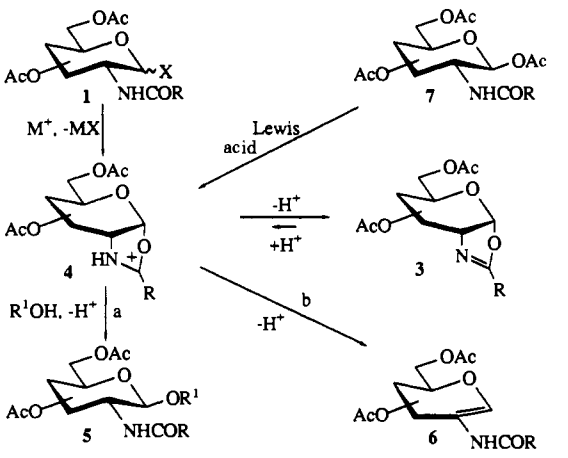
In the field of oligosaccharide synthesis, this glycosylation method has been restricted to the primary hydroxyl position at C-6; for example β-D-Glc*p*NR-(1→6)-D-Gal*p*,[42–44] β-D-Gal*p*NR-(1→6)-D-Gal*p*,[32,45] β-D-Glc*p*NR-(1→6)-D-Glc*p*NR (lipid A derivatives),[46–50] or more complex oligosaccharides[51] were synthesized in moderate yields.

Due to the low reactivities of the aforementioned glycopyranosyl donors, regioselective reactions have been achieved in the Koenigs–Knorr glycosylation of acceptors containing HO-4 (or HO-3) and HO-6 free diols[52–54] to afford the respective β-(1→6)-disaccharides.

Several improvements of the Koenigs–Knorr method for the synthesis of 2-amino-2-deoxyglycosides have been introduced to enhance the nucleophilicity of the acceptor moiety, as for example: tritylation according to the Bredereck's procedure,[47,55,56] the use of 1,6-anhydro derivatives,[57–60] and the use of open-chain carbohydrates.[61,62] Other improvements were also introduced using solid-phase synthesis,[63,64] cadmium carbonate[65] or tin(II) trifluoromethanesulfonate[66] as promoter.

In conclusion, the Koenigs–Knorr reaction in the series of the 2-amino-2-deoxy sugars is limited to the formation of simple 1,2-*trans*-glycosides of reactive acceptor alcohols possessing a primary hydroxyl group

Scheme IV



(which are generally used in excess), in the presence of mercuric cyanide as the promoter. When this method was extended to the glycosylation of secondary alcohol position of the various acceptors, the reported yields were usually very low.[65]

V. Oxazoline Method

The oxazoline method is an extension of the Koenigs-Knorr glycosylation method which was discussed in the previous section. The oxazolinium ion **4** (Scheme IV) formed by abstraction of the anomeric leaving group X from the glycopyranosyl donor **1**, can lose a proton to afford the oxazoline **3**. The latter is quite stable and can be used as a glycopyranosyl donor in further 1,2-trans-glycosylation reactions. In acidic medium, the protonation of the oxazoline **3** reforms the oxazolinium ion **4**, which either can be reacted with an acceptor alcohol to afford the expected 1,2-*trans*-glycoside **5** (pathway a) or eliminate the C-2 proton to afford the 2-acetamido glycal side product **6** (pathway b).[67]

A. Preparations of Oxazolines and Oxazolinium Ions

2-Methyl(3,4,6-tri-*O*-acetyl-1,2-dideoxy-α-D-glucopyrano)[2,1-*d*]-2-oxazoline **3** was prepared by Khorlin and Zurabyan[68–71] from 2-acetamido-3,4,6-tri-*O*-acetyl-2-deoxy-α-D-glucopyranosyl chloride (**1**, X = α-Cl, R = CH_3) in the presence of a silver salt and a base (pyridine or 2,4,6-trimethylpyridine). Preparations and reactivities of hexopyranose oxazolines and oxazolinium ions have been reviewed recently.[72] Numerous other glycosylation systems (leaving groups of donor/promoter/base) have been described in the literature. These systems operate according to the same reaction (Scheme IV).[73,74]

The oxazolinium ions **4** can be formed directly from the glycopyranosyl precursors **1** without isolation of the oxazoline donors **3**. Thus 1-O-acetylated derivatives (**1**, X = β-OAc) have been employed with various acids[75] and Lewis acids such as $ZnCl_2$,[76] $SnCl_4$,[77] $AlCl_3$,[78] TMSOTf,[79,80] $FeCl_2$,[81] and $FeCl_3$.[82–85] It is to be noted that 1,2-*trans*-glycopyranosyl donor precursors (**1**, X = β-OAc) are better models for the formation of the oxazolinium ions **4** than the corresponding 1,2-cis donors, because of the anchimeric assistance of the C-2 participating group.[86,87]

When the corresponding glycopyranosyl halide precursors (1, X = α-Br or α-Cl) are used for the formation of the oxazolinium ions, the 1,2-trans configuration is favored over the 1,2-cis orientation by addition of tetraalkylammonium halides.[88,89]

More drastic methods for the preparation of oxazoline 3 and oxazolinium ions 4 have been described in the literature, but unfortunately these are not applicable to oligosaccharide syntheses.[90-93] On the other hand, recent methods were reported for the preparation of the oxazolines 3, which were more compatible with oligosaccharide syntheses, such as the use of 1-propenyl β-D-glycosides (1, X = OCH=CHCH$_3$) and mercuric salts[94,95] or the use of anomeric phosphate (1, X = OPO(OH)$_2$) and triethylamine.[96]

The most commonly used oxazolines were the methyloxazolines 3 (R = CH$_3$), which after glycosylation, afforded the β-D-glycosides 5 possessing the natural *N*-acetyl function. Other alkyl oxazolines have been used as glycosylation donors in which R = phenyl,[68,83,84,97-100] R = CH$_2$Cl,[83,84,97,101] R = CH$_2$Ph or CH$_2$OMe,[83,97] and R = H.[102,103] Beside fully acetylated derivatives, partially O-benzylated oxazolines have also been reported.[104]

B. Glycosylation Reactions Using the Oxazoline Donors

Most of the glycosylation methods described in the literature deal with simple acceptor alcohols and the glycosylation yields are often difficult to compare as the stoichiometries of reactants used (donor/acid catalyst) are different. Generally in these cases the acceptors were used in excess.

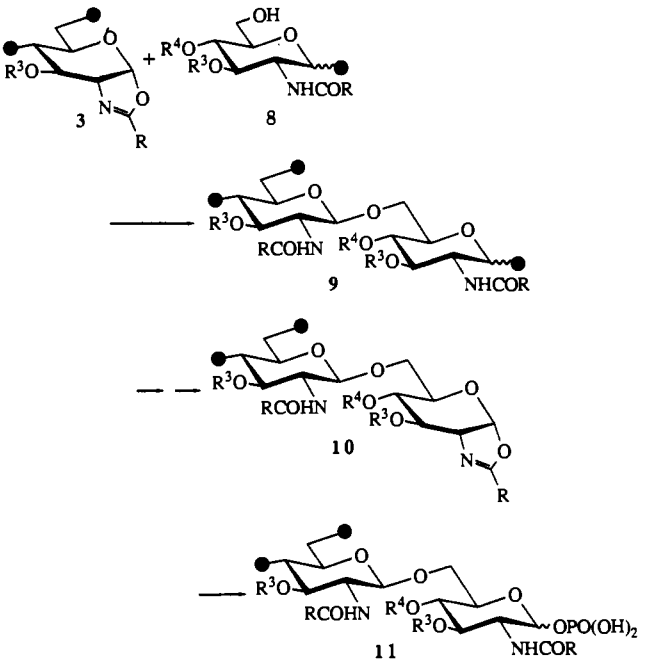
In the original procedure of Zurabyan and Khorlin,[68,69] *p*-toluenesulfonic acid was used as a catalyst for the glycosylation reactions which were performed in refluxing nitromethane and toluene as solvent. Good glycosylation yields (40–70%) were reported for reactive acceptor alcohols (methanol,[105] allyl alcohol,[36] benzyl alcohol,[87,106] phenol,[100,107,108] 2,2-bis(bromomethyl)ethanol[109]) and either monosaccharide or disaccharide glycopyranosyl donors.[87,110-112] This procedure has been exploited for the preparation of a novel series of 6-aminohexanol derivatives of D-glucosamine in yields varying from 47% to 62%.[90,111,113-115]

When acceptors containing secondary alcohols were used for this glycosylation method, byproducts, such as the 2-acetamido-D-glycal 6 (Scheme IV) were obtained.

Improvements to this glycosylation method have been introduced in order to overcome the harsh conditions used in the original procedure. Thus the use of 1,2-dichloroethane[116] and other chlorinated solvents[37,117,118] avoided the precipitation of the oxazolinium *p*-toluenesulfonate salts and allowed this reaction to be performed at a lower temperature. Also, the use of other acid catalysts increased the glycosylation yields.[98,99,119]

A more recent improvement for the formation of 1,2-*trans*-glycosides was introduced by Kiso and Anderson[83,84] which used the peracetylated β-D-glucosamine derivative 7 as the glycopyranosyl donor and stoichiometric amount of ferric chloride as the promoter. It should be mentioned that this glycosylation reaction may be performed at 60–80 °C in dichloroethane, and the media can be buffered by the addition of the base *N,N,N',N'*-tetramethylurea,[19] especially in the case of acceptors possessing acid labile protecting groups. In the Kiso–Anderson procedure the oxazolinium ions 4 are formed in situ and the β-glycosides 5 are obtained in better yields than with the original procedure of Zurabyan and Khorlin.[83-85,97,120,121]

Scheme V



The method was very recently studied in detail in the case of 1,3,4,6-tetra-*O*-acetyl-2-chloroacetamido-2-deoxy-β-D-glucopyranose (7, R = CH$_2$Cl) as the donor and several monosaccharidic acceptors. The reactions, performed in the presence of ferric chloride as the promoter, afforded the expected β-disaccharides with good stereoselectivities except with the allyl 2-acetamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside acceptor where the stereoselectivity was lost (α:β = 1:2).[122] It should be noted that a transglycosylation from the acceptor–aglycon to the donor was observed in two examples[122] which could constitute a limitation to the method.

Finally, it is important to note that the oxazoline glycosylation method has been employed successfully only in some cases for the field of oligosaccharide synthesis. In the case of disaccharidic oxazoline donors, the glycosylation yields were affected by their intrinsic molecular structures, thus lower yields were obtained for the β-D-Glc*p*NAc-(1→4)-D-Glc*p*N-oxazoline donor[123] and higher yield for β-D-Glc*p*NAc-(1→3)-D-Glc*p*N-oxazoline donor.[124] Selective β-(1→6) glycosylation of HO-4, HO-6 free diol containing acceptors were successfully achieved by several groups.[63,123,125,126] Some important examples will be discussed in the following sections.

1. Synthesis of Lipid A Analogues

Due to its biological importance, numerous approaches were developed for the synthesis of the lipid A[127] backbone 11 (Scheme V) which is a constituent part of bacterial lipopolysaccharides.

The oxazoline glycosylation procedure was extremely suitable for such syntheses, which involved the simultaneous creation of a β-(1→6) linkage and the amide function, which resulted from the direct opening of the oxazoline ring. Model disaccharides such as β-D-Glc*p*-NAc-(1→6)-D-Glc*p*NAc **9** (R = Me, $R^3 = R^4$ = Ac) were first studied, which did not involve the introduction of the fatty acids on the hydroxyl and amine functions (Scheme V). Better yields (50–70%)[101,117,123,128] for this glycosylation were obtained, when an excess of the oxazoline donor **3** (2–3 equiv with respect to the glycosyl acceptor **8**) rather than when stoichiometric amounts were used (yield 35–40%).[129]

For the proper synthesis of lipid A analogues, the oxazoline glycosylation method was used to afford the respective β-(1→6) glycosidic linkage followed by the introduction of the phosphoryl group on C-1 (Scheme V). Thus the oxazoline donor **3** (R = lipid chain) was used for the glycosylation of the free HO-6 D-Glc*p*NR acceptor **8** (R = lipid chain) to afford the β-(1→6) disaccharide **9** which was transformed into the phosphate disaccharide **11** via the intermediacy of the oxazoline disaccharide **10**.

An important feature of the oxazoline glycosylation method for the synthesis of the β-(1→6) disaccharide **9** worth mentioning is that good glycosylation yields were reported when glycopyranosyl donors **3** and acceptors **8** were used, in which R is a linear lipid chain.[120,130–132] When R was a branched chain (3-hydroxymyristic acid), β-elimination of the side chain of the lipid was observed during the glycosylation step.[36,37,120,133]

The difference in reactivity between the HO-4 secondary and HO-6 primary hydroxyl groups of the diol-glycosyl acceptor **8** (R^4 = H) was once again exploited for the regioselective synthesis of β-(1→6) glycosidic linkages.[37,120,131,132] The chemical transformation of disaccharide **9** into the disaccharide oxazoline donor **10** was achieved by the methods described in section A, and this latter compound **10** was reacted with phosphoric acid derivatives to afford the C-1 phosphorylated compound **11** in moderate yields (30–60%) and with a low stereoselectivity.[52,120,134–139]

2. Glycosylations Involving D-Galactose Acceptors

a. Creation of β-(1→6)-Linkages. Due to the widespread occurrence of β-D-Glc*p*NAc-(1→6)-D-Gal*p* and β-D-Gal*p*NAc-(1→6)-D-Gal*p* moieties in oligosaccharides of biological interest such as the proteoglycans, glycolipids, and blood groups substances,[140] the synthesis of these epimeric disaccharide units was achieved using the so-called oxazoline procedure. The syntheses of the aforementioned β-(1→6) disaccharides were achieved in good yields (60–80%) using an excess of the glycopyranosyl donors **3** having either the D-*gluco*[84,86,97,104,141–143] or D-*galacto* configuration[144,145] and the suitably protected D-Gal*p* acceptors. Similar yields were obtained for the syntheses of higher oligosaccharides containing the same β-(1→6) disaccharide units under the same conditions (excess of the glycopyranosyl donor **3**).[146–150]

β-(1→6) regioselective glycosylation reactions were also achieved with glycosyl acceptors containing diols located at either HO-3 and HO-6[54] or HO-4 and HO-6[144,151–153] in moderate yields (less than 50%).

b. Creation of β-(1→3)- and β-(1→4)-Linkages. In the case of galactosyl acceptors containing either a HO-3 or HO-4 free hydroxyl group, moderate yields of glycosylation were reported (20–65%) even when excess of the oxazoline donor **3** (2–4 equiv) was used.[104,146,154–160] These glycosylation yields were not drastically improved using Kiso and Anderson's modification.[84,97] When the galactosyl acceptor containing the vicinal HO-3 and HO-4 free diol was condensed with the oxazoline donor,[52] a weak regioselectivity was reported for the preferred HO-3 equatorial position,[151,154] affording a mixture of β-(1→3) and β-(1→4) disaccharides and also β-(1→3) and β-(1→4) branched trisaccharides.

3. Glycosylations Involving D-Mannose Acceptors

β-D-Glc*p*NAc-(1→*n*)-D-Man*p* disaccharide units are largely encountered in glycans of glycoproteins and their syntheses have been approached by the oxazoline procedure. Unfortunately, due to the low nucleophilicities of the secondary hydroxyl groups of D-mannose, the glycosylations using either the D-Glc*p*N-oxazoline **3** or β-D-Gal*p*-(1→4)-D-Glc*p*N-oxazoline (lactosamine) donors[161–165] were restricted only to the HO-6 primary hydroxyl group of the mannose acceptor.

As previously described, regioselective glycosylations were also achieved using mannose acceptor containing HO-4 and HO-6 free diol.[163,165] Here again β-(1→6) disaccharides were exclusively formed.

Glycosylation reaction involving a HO-2 hydroxyl group of various, open-chain mannose dimethyl acetal acceptors with the oxazoline donor **3**, afforded mediocre yields of the expected β-(1→2) disaccharide products.[166,167]

Glycosylations of HO-3 hydroxyl group of the mannose acceptor, with the lactosamine–oxazoline donor, afforded low yields of the corresponding β-(1→3) oligosaccharide,[168] whereas, by comparison, the glycosylation using the corresponding HO-3 free galactose acceptor afforded 84% yield of the expected β-(1→3) oligosaccharide.[146]

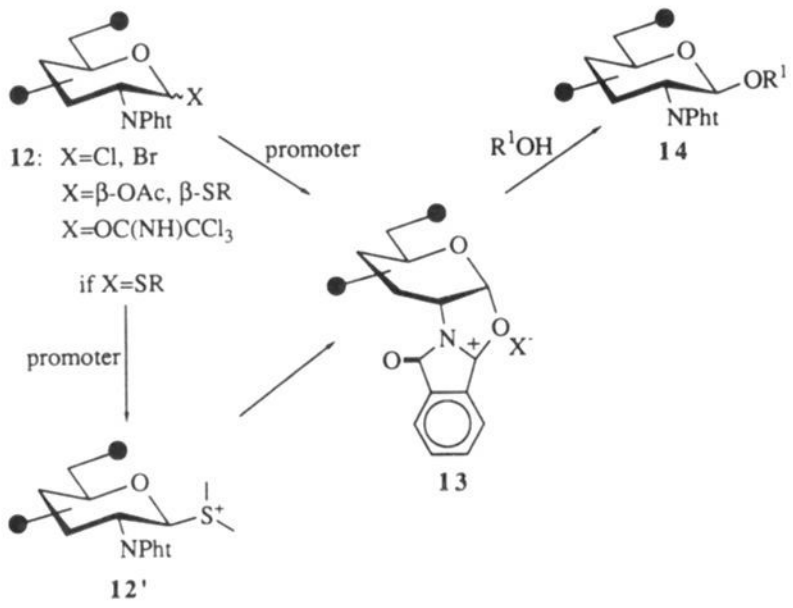
4. Glycosylations with Other Acceptors

Various syntheses have also been reported in low yields (20–43%) for the β-D-Glc*p*NAc-(1→4)-D-Glc*p*-NAc (chitobiose) disaccharide unit starting from the oxazoline donor **3** (used in large excess) and properly protected HO-4 free D-glucosamine acceptors.[116,104,169–173] It should be mentioned that, by comparison, the HO-6 position of D-glucosamine derivatives were glycosylated with good yields (82–86%) using the oxazoline approach.[174] Higher oligosaccharides of the type D-Man*p*-(1→4)-β-D-Glc*p*NAc-(1→4)-β-D-Glc*p*NAc were also synthesized starting from the same acceptors and D-Man*p*-(1→4)-D-Glc*p*N-oxazoline donors.[175–177]

In the field of glycopeptides the oxazoline glycosylation method showed some success with serine and threonine acceptors.[39,119,145,178]

The reaction of oxazoline donors with alditol open-chain acceptors afforded modest yields using *p*-toluenesulfonic acid as a catalyst.[124,179,180] These glycosylation yields were increased by using Kiso and Anderson's modification[179,181] or by using trimethylsilyl trifluoromethanesulfonate and tetramethylurea as acid catalyst.[162]

Scheme VI



Finally, the oxazoline glycosylation method has also been extended to the five-membered ring system in which either the glycosyl donors[98,99,105,182] or the acceptors[124,145] were furanoses.

C. Conclusion

The oxazoline procedure and its various improvements allowed the successful synthesis of 1,2-*trans*-glycosides and oligosaccharides. The main advantage of this method lies in the obtention of β-glycosides in their natural *N*-acetyl form, which most of the time is an extremely useful feature. The main limitation of this glycosylation procedure is due to the harsh conditions (high temperature and acidity) required for this condensation, which make it incompatible for the use of acceptors of low nucleophilicities needing prolonged reaction times. One drawback resulting from the above conditions is the partial anomerization of β-glycosidic bonds; another drawback is the possible migration of acid-sensitive protective groups such as acetals. Finally, the oxazoline glycosylation method seems to be restricted to the reactive free hydroxyl positions of the acceptors (mainly the primary alcoholic functions HO-6 of hexopyranose acceptors).

Better glycosylation methods (mostly the so-called phthalimido procedure) which are extremely more successful for the condensations of acceptors of low reactivities will be presented in the next section.

VI. Phthalimido Glycosylation Method

In 1976 Lemieux et al. introduced the use of 2-deoxy-2-phthalimidoglycosyl halides **12** in glycosylation reactions as an important and reliable method for the preparation of 2-amino-2-deoxy-β-D-glycopyranosides.[183] In the presence of the soluble silver trifluoromethanesulfonate–collidine complex, 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl bromide glycosylated simple alcohols or 2,2,2-trichloroethanol as well as monosaccharidic acceptors in excellent yields[183] (Scheme VI). The reaction can be conducted at room temperature or even below 0 °C.

The success of this method relied on the rapid abstraction of the halogen to liberate the strongly delocalized intermediate **13**, which has a pronounced tendency to form the 1,2-*trans*-glycoside **14**. The marked obstruction to the formation of 1,2-*cis*-glycosides was attributed to the evident steric hindrance arising from the phthalimido group.

After the glycosylation step, the deprotection of the phthalimido function into the free amino group could be achieved by subsequent hydrazinolysis using 85% hydrazine hydrate in 95% ethanol at reflux.[183] Dephthaloylation could also be performed with butylamine in refluxing methanol,[184-186] sodium borohydride,[187,188] hydrazine acetate,[189] or hydroxylamine[190] to afford the free amine.

The following sections will deal with the phthalimido method utilizing the various 2-deoxy-2-phthalimido glycopyranosyl halide donors and different promoters such as silver triflate, silver zeolite, silver salicylate, mercuric cyanide, mercuric cyanide–mercuric bromide, and silver perchlorate–silver carbonate.

The final part of this section will deal with the Lewis acid catalyzed glycosylation methods, which were derived from the original phthalimido procedure, in which the halide leaving group of the 2-deoxy-2-phthalimidoglycosyl donor has been replaced by an imidate, acetate, or a thioether according to Scheme VI (X = β-$OC(NH)CCl_3$, β-OAc, or β-SR).

A. Uses of 2-Deoxy-2-phthalimido-D-glycopyranosyl Halides as Donors

The usual preparation of 2-deoxy-2-phthalimidoglycopyranosyl halide donors involved the reaction of the 2-amino-2-deoxy sugar precursors with phthaloic anhydride in the presence of a base, followed by peracetylation and treatment with hydrogen halide[191,192] (closure of the phthalimido ring occurs during the acetylation step).

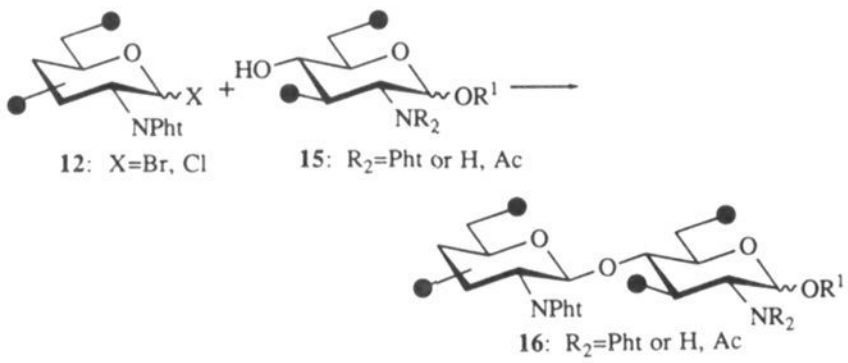
The chemical syntheses and properties of both the anomeric forms of 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-D-glucopyranosyl halides **12** (X = Br, Cl, I) have been described by Lemieux et al.,[183] and it was proven that the β-form is the more stable. It was also shown that, during glycoside synthesis with the "phthalimido method", there was little advantage in using the 2-deoxy-2-phthalimido-β-glycopyranosyl bromide donor instead of an anomeric mixture. Although all the glycosylations reported initially utilized the 2-deoxy-2-phthalimido-β-glycopyranosyl bromide, the β-chloride donor was more often used in view of its greater stability. A variety of properly protected 2-deoxy-2-phthalimido halide donors of D-glucosamine and D-galactosamine, and a multitude of disaccharides and trisaccharides of 2-deoxy-2-phthalimido halide donors have been used in diverse glycosylation reactions and will be described in the following section.

1. D-Glucose and D-Glucosamine Acceptors

Lipid A analogues β-D-Glc*p*NPht-(1→6)-D-Glc*p*NPht were synthesized by reaction of a 2-deoxy-2-phthalimidoglucopyranosyl donor **12** with either a free HO-6 and HO-4 Glc*p*NPht acceptor[120] or a 6-*O*-trityl-Glc*p*NPht acceptor[193] (**15**, Scheme VII).

The first chitobiose synthesis achieved by the phthalimido method was effected by condensation of stoichiometric amounts of both the glycosyl acceptor 2,2,2-trichloroethyl 3,6-di-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside[194] (**15**, R_2 = phthaloyl, Scheme VII) with the donor 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl bromide **12**, in the presence of

Scheme VII



silver triflate and collidine, to afford the corresponding 1,2-*trans*-chitobiose disaccharide **16** (R_2 = phthaloyl) in 51% yield.[183]

Similar glycosylation of 2,2,2-trichloroethyl 3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (**15**, R_2 = phthaloyl) with the β-phthalimido glycopyranosyl bromide donor **12** in the presence of silver triflate and a proton scavenger[195-197] afforded the chitobiose derivative in 61% yield. On the other hand, when the glycosylation was realized in the presence of silver zeolite as the promoter, similar β-(1→4) glycosylation yields were obtained.[198] The reported yields of glycosylations for differently protected phthalimido donors and HO-4 free D-glucosamine acceptors in the same conditions ranged from 22% to 94%.[184,185,189,199-202] A comparison of the glycosylation efficiencies of six standard 2-deoxy-2-phthalimidoglucopyranosyl donors toward HO-4 free glucosamine acceptors was recently published and constitutes a valuable tool for the synthesis of chitobiose derivatives.[203]

The total synthesis of the β-D-Glc*p*NAc-(1→4)-D-Mur*p*NAc constituent repeating unit of the glycan chain of the bacterial cell wall peptidoglycan was effected by reacting the β-phthalimidoglycosyl donor **12** with the acceptor benzyl 2-acetamido-6-*O*-benzyl-2-deoxy-3-*O*-[(*R*)-1-(methoxycarbonyl)ethyl]-α-D-glucopyranoside. This reaction was realized with a 3-fold excess of the glycosyl donor. It is interesting to mention that this reaction did not proceed below 0 °C and was totally inhibited by the presence of bases.[204] The same disaccharide was also synthesized in 85% yield with a 1,6-anhydro derivative of D-Mur*p*NAc as donor and silver triflate as the promoter.[205]

The syntheses of the trisaccharides β-D-Man*p*-(1→4)-β-D-Glc*p*NAc-(1→4)-D-Glc*p*NAc (representing a partial structure of the core region of the carbohydrate chain of *N*-glycoprotein)[206] and of β-D-Gal*p*NAc-(1→4)-β-D-Glc*p*NAc-(1→2)-D-Man*p*[207,208] (partial structure of lutropin carbohydrate chains) were realized in good yields, respectively, by reaction of the β-D-Man*p*-(1→4)-β-D-Glc*p*NPht or D-Gal*p*NPht donors and the appropriate HO-4 free D-glucosamine acceptors.

This method also allowed the synthesis of β-D-Gal*p*NAc-(1→4)-β-D-Glc*p*[209] from donors **12** (D-*galacto* series) and the properly protected acceptors.

2. D-Galactose and D-Galactosamine Acceptors

a. 2-Deoxy-2-phthalimido-D-glucopyranosyl Donors. β-D-Glc*p*NAc-(1→3)-D-Gal*p* (*lacto*-*N*-biose II disaccharide) which occurs as part of the structure of human blood groups A, B, H, and Le[a] substances was synthesized by the condensation of the β-phthalimidoglucosyl bromide **12** with the suitably protected free HO-3 acceptors in good yields[210-212] in the presence of silver triflate–collidine and molecular sieves. A yield of 78% was also reported for the synthesis of the same disaccharide using a 1,6-anhydro acceptor.[213]

The β-(1→2) disaccharide isomer β-D-Glc*p*NPht-(1→2)-D-Gal*p* was obtained under similar condensation conditions, using a free HO-2 acceptor in 80% yield.[210]

The glycosylation of the HO-3 acceptor trideuteriomethyl 2-*O*-benzoyl-4,6-*O*-benzylidene-β-D-galactopyranoside, with the phthalimido-β-D-glucopyranosyl bromide **12** in the presence of silver zeolite as the promoter gave a higher yield than when effected in the presence of silver triflate.[214] The glycosylation of the related HO-3 acceptors with the phthalimido-β-glucopyranosyl bromide **12** in the presence of silver zeolite and in the absence of a base afforded 80% of an α:β mixture of the corresponding (1→3)-linked disaccharides.[215] It is interesting to notice that addition of soluble bases such as collidine or tetramethylurea completely suppressed the disaccharide formation. The formation of the expected β-(1→3)-linked disaccharide β-D-Glc*p*-NPht-(1→3)-β-D-Gal*p*-OCD_3 was obtained in 75% yield, when silver triflate was used in conjunction with a nonnucleophilic base (2,6-di-*tert*-butyl-4-methylpyridine).[215] Similarly, free HO-3 D-galactose disaccharidic acceptors were used for the synthesis of a trisaccharide [β-D-Glc*p*NAc-(1→3)-α-D-Gal*p*-(1→4)-L-Rha*p*] related to the lipopolysaccharide of *Escherichia coli* O75[216] or a trisaccharide [β-D-Glc*p*NAc-(1→3)-β-D-Gal*p*-(1→4)-D-Glc*p*][217,218] intermediate in the synthesis of a sialyllactotetraosylceramide.

Condensations of the HO-6-containing acceptors 8-(methoxycarbonyl)octyl 2-(*N*-acetylbenzamido)-3,4-di-*O*-benzoyl-2-deoxy-α-D-galactopyranoside and 8-(methoxycarbonyl)octyl 2-acetamido-2-deoxy-3,4-*O*-isopropylidene-α-D-galactopyranoside were effected respectively with the donors phthalimido-β-D-glucopyranosyl chloride and phthalimido-β-D-lactosaminyl chloride to afford the corresponding β-(1→6) antigenic determinant oligosaccharides containing the β-D-Glc*p*-NAc-(1→6)-α-D-Gal*p*NAc unit.[219]

A series of core chain trisaccharides were synthesized by condensation of the peracetylated disaccharidic 2-phthalimido glycopyranosyl chlorides, derived from lactosamine and lacto-*N*-biose. Thus the reaction of the above donors with the primary hydroxyl of 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose proceeded in the presence of silver triflate–collidine to afford the corresponding trisaccharides β-D-Gal*p*-(1→4)-β-D-Glc*p*-NPht-(1→6)-D-Gal*p* and β-D-Gal*p*-(1→3)-β-D-Glc*p*N-Pht-(1→6)-D-Gal*p* in respectable yields (>75%).[220] Furthermore, the same donors were used with 7-deoxy-β-L-(and α-D)-*glycero*-D-galactoheptopyranose acceptors to afford the expected β-(1→6) trisaccharides in 36% and 65% yields, respectively.[221]

The tetrasaccharide repeating unit of the capsular polysaccharide of *Streptococcus pneumoniae* [β-D-Gal*p*-(1→4)-β-D-Glc*p*NAc-(1→3)-β-D-Gal*p*-(1→4)-β-D-Glc*p*] was prepared by the condensation of the appropriate donor, namely 6-*O*-acetyl-3-*O*-benzoyl-4-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-2-deoxy-2-phthalimido-D-glucopyranosyl bromide and the HO-3′ containing 1,2-*O*-(1-cyanoethylidene)-D-lactose acceptor.[222,223] Furthermore, the tetrasaccharide [β-D-Gal*p*-(1→4)-β-D-Glc*p*NPht-(1→3)-β-D-Gal*p*-(1→4)-

D-Glc*p*] related to paragloboside was prepared in 83% yield.[224]

The total stereo- and regiocontrolled synthesis of the ganglioside GM_2[225] **17** has been reported and the tetrasaccharide moiety was prepared by condensation of the donor phthalimido-β-D-glycopyranosyl bromide **12** with the HO-4′ galactose containing trisaccharide in the presence of silver triflate–molecular sieves 4A in dichloromethane in 60% yield.[226]

β-D-Gal*p*NAc-(1->4)-β-D-Gal*p*-(1->4)-β-D-Glc*p*-Cer
3
α-D-NeuAc-(2

17

The method was extended to the sequential synthesis of trisaccharide and branched pentasaccharide **18** by twice condensing a phthalimido-β-D-lactosaminyl donor with a galactose acceptor in respective yields of 72% [β-(1→3) trisaccharide] and 46% [β-(1→6) pentasaccharide].[227]

β-D-Gal*p*-(1->4)-β-D-Glc*p*NPht-(1
6
D-Gal*p*
3
β-D-Gal*p*-(1->4)-β-D-Glc*p*NPht-(1

18

b. 2-Deoxy-2-phthalimido-D-galactopyranosyl Donors. A terminal nonreducing precursor β-(1→3)-linked trisaccharide of the Forssman antigen [α-D-Gal*p*N_3-(1→3)-β-D-Gal*p*NPht-(1→3)-D-Gal*p*] was prepared by condensing the disaccharide glycosyl bromide 6-*O*-acetyl-3-*O*-[6-*O*-acetyl-2-azido-3,4-di-*O*-benzoyl-2-deoxy-α-D-galactopyranosyl]-4-*O*-benzyl-2-deoxy-2-phthalimido-D-galactopyranosyl bromide with the 1,6-anhydro-2,4-di-*O*-benzyl-β-D-galactopyranose in the presence of silver triflate–collidine in good yields.[228,229]

Glycosylation of an axial HO-4′ containing lactose acceptor with 4-*O*-acetyl-3,6-di-*O*-benzoyl-2-deoxy-2-phthalimido-D-galactopyranosyl bromide donor failed to occur under the standard conditions (silver triflate–collidine). This condensation was successful when silver perchlorate and silver carbonate were used as promoters and afforded the corresponding β-(1→4)-linked trisaccharide in 38% yield.[230] A better yield (82%) was obtained with 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-D-galactopyranosyl bromide as the donor, in the presence of silver perchlorate (or silver perchlorate–silver carbonate) as the promoter, and differently protected D-lactose acceptors.[231,232] Condensation of the phthalimido chloride **12** (X = α-Cl) with the same acceptor under the same conditions using silver perchlorate and silver carbonate as promoters afforded 54% of the expected β-(1→4)-linked trisaccharide.[230] It is interesting to note that when the acceptor was changed for another one having the 6′-*O*-benzoyl protective group, namely methyl 2,3,6-tri-*O*-benzoyl-4-*O*-(6-*O*-benzoyl-2,3-di-*O*-benzyl-β-D-galactopyranosyl)-β-D-glucopyranoside, only 8% of the β-(1→4)-linked trisaccharide was obtained.[230] The glycosylation on HO-4′ was also described for the synthesis of a constitutive trisaccharide derivative[233] of sialylpentaosylceramides[234] isolated from Tay-Sachs brains.

3. Regioselective Glycosylations

Regioselective glycosylation of a free HO-4 and HO-6 diol acceptor benzyl 3-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranoside with the phthalimido-β-D-glucopyranosyl bromide in the presence of silver triflate and tetramethylurea[120] afforded the corresponding β-(1→6) disaccharide in high yield which was used for the preparation of the phosphorylated disaccharide skeleton **11** of lipid A (Scheme V).

Also glycosylation of the trideuteriomethyl 2,3-di-*O*-benzoyl-β-D-galactopyranoside diol acceptor, with the phthalimido-β-D-glucopyranosyl bromide **12** (X = Br) in the presence of silver zeolite (and the absence of collidine) afforded the β-(1→6)-linked disaccharide in 79% yield.[215]

Regioselective glycosylations of the diol containing acceptor methyl 4,6-*O*-benzylidene-1-thio-β-D-galactopyranose with the α-phthalimidoglucosyl bromide **12** in the presence of silver triflate–collidine afforded 55% of the β-(1→3)-linked disaccharide, together with 12% of the β-(1→2)-linked isomer. The obtained β-(1→3)-linked disaccharide was used for the synthesis of the globotetraose P-antigen.[235]

The regioselective glycosylation of a free HO-3′ and HO-4′ D-lactose acceptor using different catalyst systems were described by Paulsen and co-workers.[236,237] Therefore, the acceptor benzyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,6-di-*O*-benzyl-β-D-galactopyranosyl)-β-D-glucopyranoside was condensed with the phthalimido-β-glycopyranosyl bromide **12** (X = Br) using various conditions. In the presence of silver triflate–collidine this homogenous glycosylation afforded 83% of the β-(1→3)-linked trisaccharide, together with the β-(1→4) trisaccharide (10%). When the same reaction was effected with silver silicate as the promoter and molecular sieves 4A under heterogenous catalysis mode, the glycosylation occurred mainly on the axial group HO-4′, affording the β-(1→4)-linked trisaccharide (86% yield), together with the β-(1→3)-linked isomer in 8% yield.[237]

Glycosylation of the same diol containing acceptor with hexa-*O*-acetyl-2-deoxy-2-phthalimido-β-D-lactosaminyl bromide under homogeneous catalysis (silver triflate) afforded the β-(1→3)-linked tetrasaccharide in 65% yield, whereas heterogeneous catalysis (silver silicate) afforded mainly the β-(1→4) tetrasaccharide.[238] When 4,6-di-*O*-acetyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-2-deoxy-2-phthalimido-D-galactopyranosyl bromide was reacted with the same diol acceptor under homogeneous catalysis using mercuric cyanide and mercuric bromide, the corresponding β-(1→3)-linked trisaccharide was obtained in 25% yield.[236,239] When 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-D-galactopyranosyl bromide was used as the donor, good yields but a poor regioselective glycosylation trend were observed.[239]

Also, glycosylation of the HO-3′ of the diol acceptor methyl 3,6-di-*O*-acetyl-4-*O*-(2,6-di-*O*-acetyl-β-D-galactopyranosyl)-2-deoxy-2-phthalimido-β-D-glucopyranoside (containing free HO-4′ and HO-3′ groups) with a disaccharidic β-phthalimido glucopyranosyl chloride donor **12** in the presence of silver triflate–collidine afforded the expected β-(1→3)-linked tetrasaccharide

in 64% yield.[240] The latter was further transformed into glycopyranosyl chloride and condensed again with the same acceptor to give the β-(1→3)-linked hexasaccharide.[241]

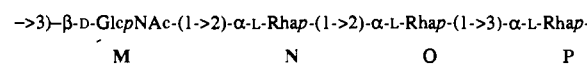
Actually, the regioselectivity in the glycosylation of diol acceptors seems to be affected not only by the nature of the promoter but also by the type of protective groups surrounding the diol system. Ester protective groups generally enhance the difference of reactivities between the hydroxyl functions, whereas ether protective groups may reduce their acceptor abilities.

Recently the synthesis of a tumor-associated Le^x glycosphingolipid was realized by stepwise glycosylation with a trisaccharide 2-phthalimidoglucopyranosyl fluoride donor with silver triflate and hafnium cyclopentadienyl chloride as the promoter.[242] The acceptors were HO-3 and HO-4 free diols on galactose units (di-, penta-, and octasaccharide) and regioselective glycosylations occurred on the HO-3 position with respective yields of 91%, 84%, and 79%.

During the synthesis of lacto-*N*-triosylceramide and related glycosphingolipid,[187] it was noticed that the regioselectivity outcome of the glycosylation of the diol acceptor benzyl 2,3,6-tri-*O*-benzyl-4-*O*-(2,6-di-*O*-benzyl-β-D-galactopyranosyl)-β-D-glucopyranoside with the donor β-phthalimido glucopyranosyl bromide **12** (X = Br) was affected by the polarity of the solvent used. Thus, in nonpolar solvents such as 1,2-dichloroethane or toluene, the glycosylation of the acceptor in the presence of silver triflate and molecular sieves afforded almost equal amounts of the β-(1→3)- and β-(1→4)-linked trisaccharides, whereas the β-(1→3)-linked trisaccharide was obtained as the major product, when the reaction was performed in nitromethane.

4. L-Rhamnose and L-Talose Acceptors

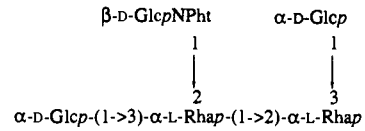
Great strides in the investigation of the immunodeterminant region of the O-specific polysaccharide **19** of *Shigella flexneri* serotype Y[243-247] were achieved by the use of artificial antigens synthesized by the phthalimido method. The disaccharide MN was prepared by the condensation of 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-D-glucopyranosyl bromide with the HO-2 acceptor 8-(methoxycarbonyl)octyl 3,4-di-*O*-benzyl-α-L-rhamnopyranoside in the presence of silver triflate–collidine to afford the corresponding β-(1→2) disaccharide in good yields.[248,249] Glycosylation of a similar free HO-2 acceptor with $Hg(CN)_2$–$HgBr_2$ as promoter and the donor 3-*O*-acetyl-4,6-di-*O*-benzoyl-2-deoxy-2-phthalimido-D-glucopyranosyl bromide afforded the β-(1→2)-linked disaccharide MN in good yields.[250,251]



19

Other preparations of the MN disaccharide[252,253] were reported for the synthesis of *S. flexneri* building blocks and effective use was then made of oligosaccharide block synthesis. Thus the syntheses of trisaccharide MNO[254] and of tetrasaccharide MNOP were achieved in high yields,[255] often in the form of 8-(methoxycarbonyl)octyl glycoside.[249,250,256,257]

Glycosylation of a free HO-2′ rhamnose containing tetrasaccharide acceptor with 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl bromide using mercuric cyanide and mercuric bromide as promoters in acetonitrile using the so-called "vacuum technique" afforded the expected branched pentasaccharide **20** in 69% yield.[258] It should be noted that silver triflate assisted glycosylations afforded very low yields of this pentasaccharide, in agreement with similar reactions reported by Wessel and Bundle.[249,259]



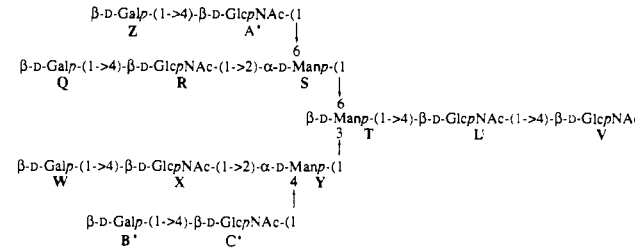
20

Glycosylation of the acceptor 4-*O*-benzyl-1,2-*O*-benzylidene-α-L-rhamnopyranoside with the 2-deoxy-2-phthalimido-α-D-glucopyranosyl bromide donor **12** in the presence of silver triflate–collidine afforded the desired β-(1→3) disaccharide in addition to a β-(1→1) trehalose type disaccharide due to a migration of 1,2-*O*-benzylidene group.[260] The same disaccharide fragment [β-D-GlcpNAc-(1→3)-L-Rhap] of *Streptococcus* group A polysaccharide was prepared in 64% yield from donor **12** and a HO-3 free *p*-nitrophenyl L-rhamnopyranoside acceptor.[261]

The backbone disaccharide of the main heteropolymeric chain of the O-specific polysaccharide of *Pseudomonas maltophilia* [β-D-GlcpNAc-(1→3)-α-L-Talp] was also synthesized by glycosylation of the HO-3 free containing L-talose acceptor with a phthalimidoglucopyranosyl bromide donor in the presence of mercuric cyanide and mercuric bromide.[262]

5. D-Mannose Acceptors

The phthalimido method has been employed for the synthesis of the various β-glycosidic fragments present as building blocks in the complex fundamental structures of the carbohydrate chain of *N*-glycoproteins of the lactosamine type structure **21**. For example, the simplest disaccharide RS was obtained in 88% yield from a 2-deoxy-2-phthalimido-D-glucopyranosyl bromide donor and silver triflate–collidine as the promoter.[263,264]



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The synthesis of the reducing trisaccharide [β-D-Galp-(1→4)-β-D-GlcpNPht-(1→2)-α-D-Manp] (QRS) which is a precursor of the partial structure of fetuin glycoprotein was achieved by the condensation of phthalimido β-D-lactosaminyl bromide donor with a free axial

HO-2 mannose acceptor either in the presence of silver triflate–collidine in good yields,[265-267] or in the presence of silver triflate and molecular sieves 4A (94% yield).[268] Glycosylation of the acceptor *p*-nitrophenyl 3-*O*-benzyl-4,6-*O*-benzylidene-α-D-mannopyranoside with phthalimido-β-lactosaminyl bromide was reported not to proceed in the presence of silver triflate–collidine but to occur under the Helferich modification in dry acetonitrile and in the presence of mercuric cyanide in 31% yield.[269]

Glycosylation of the HO-2′ axial group of the mannose disaccharide acceptor 8-(methoxycarbonyl)octyl 3-*O*-allyl-2,4-di-*O*-benzyl-6-*O*-(3,4,6-tri-*O*-benzyl-α-D-mannopyranosyl)-β-D-mannopyranoside with the phthalimido-β-glucopyranosyl bromide **12** in the presence of silver triflate–collidine afforded 78% of the trisaccharide β-D-Glc*p*NPht-(1→2)-α-D-Man*p*-(1→6)-β-D-Man*p* (RST).[270] Analogues of the latter synthetic trisaccharide (RST) were used as specific substrates for the enzyme assay for GnT-V activity which measures the transfer of radiolabeled Glc*p*NAc from UDP-Glc*p*NAc.[271,272]

Other oligosaccharides related to the *N*-glycoprotein structure **21** were prepared by this method; for example R(A′)S was synthesized in high yields (78–94%) by reaction of two 2-deoxy-2-phthalimido-β-D-glucopyranosyl donors with a free HO-2 and HO-6 D-mannose acceptor.[273,274] Furthermore, structures (A′ST) or [R(A′)ST] were prepared by the condensation of the free HO-2′ and HO-6′ mannopyranoside disaccharide acceptors and the phthalimido-β-glucopyranosyl bromide (or chloride) **12** in the presence of silver triflate.[275] The protected tetrasaccharide R(A′)ST was obtained in 26% yield when the reaction was performed in acetonitrile and molecular sieves 4A. On the other hand, when the same reaction partners were reacted in dichloromethane, the β-(1→6) trisaccharide A′ST only was formed in 71% yield.[276] Nevertheless, the tetrasaccharide R(A′)ST was obtained in 53% yield when the complex silver triflate–collidine was used as the promoter in dichloromethane.[277] This latter compound was used as a selective substrate for the enzyme *N*-acetylglucosaminyl transferase V(GnT-V).[277]

The core pentasaccharide [RS(XY)T] was prepared by condensation of 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-D-glucopyranosyl chloride and a free HO-2′ and HO-2″ α-D-Man*p*-(1→3)-[α-D-Man*p*-(1→6)]-α-D-Man*p* acceptor in 44% yield.[278]

In 1982 Paulsen and Lebuhn[279] were the first to prepare two basic sequences [QRSTU and QRS(WXY)-TU] as building blocks in *N*-glycoproteins, which both contained the β-D-Glc*p*NAc-(1→2)-D-Man*p* disaccharide residues. Furthermore, HO-2″ mannose containing trisaccharide acceptors were condensed with the phthalimido-β-lactosaminyl bromide in the presence of silver triflate–collidine to afford, in high yields, the isomeric blocked pentasaccharides QRSTU and WX-YTU.[280]

Two other isomeric pentasaccharides representing unsymmetrical sequences of the carbohydrate chain of the *N*-glycoproteins of the lactosamine types were synthesized. Thus, the condensation of the HO-2″ mannose tetrasaccharide acceptor with the phthalimido-β-glucopyranosyl bromide in the presence of silver triflate–collidine afforded 61% of the phthalimido pentasaccharide XY(S)TU.[281] Similarly, when the same glycosylation was effected with an isomeric HO-2″ mannose tetrasaccharide acceptor, a yield of 73% of the phthalimido pentasaccharide RS(Y)TU was obtained.[281]

A reducing pentasaccharide WX(B′C′)Y was prepared by the condensation of the diol acceptor benzyl 3,6-di-*O*-benzyl-α-D-mannopyranoside with a phthalimido-β-lactosaminyl bromide in the presence of silver triflate and collidine in good yields (72%).[265,266] Similar condensation was effected on the allyl 3,6-di-*O*-benzyl-α-D-mannopyranoside acceptor, with phthalimido-β-lactosaminyl bromide which afforded the desired pentasaccharide WX(B′C′)Y in 57% yield together with 42% of trisaccharide B′C′Y.[282] The same methodology, starting from benzyl 2,4-di-*O*-benzyl-α-D-mannopyranoside as the acceptor, and the same donor afforded the QR(ZA′)S fragment in 52% yield.[283] A hexasaccharide fragment of a complex type of glycan chain in glycoproteins was also synthesized from 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-α-D-glucopyranosyl chloride and the branched S(Y)T D-mannose acceptor.[284]

The glycosylation of a free HO-2′ and HO-4′ S(Y)T acceptor with a phthalimido-β-lactosaminyl bromide donor in presence of silver triflate–collidine afforded a mixture of the β-(1→4) pentasaccharide B′C′Y(S)T (33% yield) and the expected heptasaccharide [WX-(B′C′)Y](S)T (37% yield).[285]

Other heptasaccharides [QRS(WXY)T] representing portions of the glycan chains of fetal calf serum fetuin[265,266] or octasaccharides from *N*-glycoproteins of the lactosaminic type[280] [QRS(WXY)TU] were also prepared in high yields by the phthalimido method as well as an isomeric hexasaccharide with a different branching mode.[286] The nonasaccharide {QRS[WX-(B′C′)Y]T} was also synthesized from a trimannoside acceptor [S(Y)T] and a 2-deoxy-2-phthalimido-D-lactosaminyl bromide donor in 19% yield only.[287]

Indeed, the phthalimido method allowed the preparation of sophisticated structures such as the highly branched nona- or undecasaccharide portions of complex types of orosomucoid α_1-acid glycoprotein present in human serum.[288]

Finally, the well-established phthalimido method successfully met the challenge of synthesizing most of the 2-amino-2-deoxy-β-D-glycopyranosides. Thus, the condensation of the HO-2 monosaccharide acceptor 8-(methoxycarbonyl)octyl 3,4,6-tri-*O*-benzyl-β-D-mannopyranoside with the different donors 4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl chloride and 3,6-di-*O*-benzyl-4-*O*-(4-*O*-acetyl-3,6-di-*O*-benzyl-2-deoxy-2-phthalimido-β-D-galactopyranosyl)-2-deoxy-2-phthalimido-D-glucopyranosyl chloride afforded the corresponding β-(1→2)-linked disaccharide and trisaccharide, in the presence of silver triflate–collidine, in high yield.[207] It should be mentioned that this latter trisaccharide contains the unusual sequence [D-Gal*p*NAc-(1→4)-β-D-Glc*p*NAc-(1→2)-α-D-Man*p*] which seems to be unique to the pituitary glycoprotein hormone lutropin when sulfated on HO-4″ position.[207]

A trisaccharide related to the complex glycan chains [β-D-Glc*p*NPht-(1→4)-β-D-Man*p*-(1→4)-β-D-Glc*p*N_3] was synthesized in good yield (78%) by the phthalimido procedure.[267,289] This trisaccharide intermediate was further used for the synthesis of a highly branched

nonasaccharide which represented the carbohydrate chain of the "bisected" structure of lactosamine-type *N*-glycoproteins.[267]

Another synthetic approach to the latter fragment involved the glycosylation of an HO-2 mannose acceptor with a 2-phthalimidochitobiosyl bromide donor, followed by inversion of HO-4″ of the nonreducing terminal unit (conversion of D-*gluco* into D-*galacto* configuration).[290]

B. Lewis Acid Catalyzed Glycosylations by 1-*O*-Acetate and 1-Thioglycosides of 2-Deoxy-2-phthalimido-β-D-glycopyranosyl Donors

Different conceptual approaches to oligosaccharide synthesis were also developed using either 2-deoxy-2-phthalimidoglycopyranosyl acetates or thioglycosides as potential donors. Lewis acid catalyzed glycosylations have been previously employed for the activation of the C–O bond at the anomeric carbon atom in the synthesis of 1,2-*trans*-glycosides.[291]

1. *O*-Acetyl Leaving Groups

Treatment of 1,3,4,6-tetra-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranose[192] (**12**, X = β-OAc, Scheme VI) with equimolar amounts of allyl or benzyl alcohol activated by stannylation and a Lewis acid (equimolar amounts) afforded high yields of the corresonding β-glycosides.[292]

Several Lewis acids such as tin tetrachloride,[190,293,294] boron trifluoride etherate,[295] or trimethylsilyl trifluoromethanesulfonate[240,296] were used successfully to activate the β-anomeric *O*-acetyl group to afford the 1,2-*trans*-2-deoxy-2-phthalimidoglycosides.

Lewis acid catalyzed condensation of a β-acetate of 2-deoxy-2-phthalimidoglucopyranose with the HO-4 acceptor methyl 2-acetoamido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranoside (in the presence of trimethylsilyl trifluoromethanesulfonate) afforded the chitobiose disaccharide in good yield.[297]

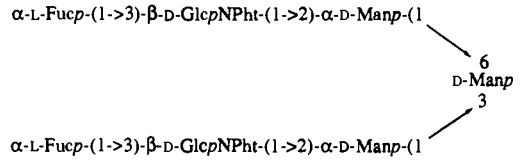
Paulsen and Tietz used the oligosaccharide building block formed of *N*-acetylneuraminic acid and lactosamine as glycopyranosyl donor. The suitably protected β-acetate trisaccharide donor [β-D-Neu*p*5Ac-(2→6)-β-D-Gal*p*-(1→4)-β-D-Glc*p*NPht-OAc] was condensed, in the presence of trimethylsilyl trifluoromethanesulfonate, with either D-mannose acceptors: benzyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside or benzyl 6-*O*-acetyl-3,4-di-*O*-benzyl-α-D-mannopyranoside to afford the blocked tetrasaccharide β-D-Neu*p*5Ac-(2→6)-β-D-Gal*p*-(1→4)-β-D-Glc*p*NPht-(1→2)-D-Man*p* in good yields.[298,299]

Glycosylation of an HO-2 and HO-3 free diol 1,6-anhydro-D-mannopyranose acceptor with the β-acetate of 2-deoxy-2-phthalimidoglucopyranose in the presence of trimethylsilyl trifluoromethanesulfonate as the promoter afforded a mixture of β-(1→2) and β-(1→3) disaccharides in 9% and 7% yields, respectively.[300] Note that the above β-(1→2) disaccharide was synthesized in 86% yield from a 2-deoxy-2-phthalimidoglucopyranosyl bromide donor and a $^4C_1$ D-mannose acceptor.[300]

2. *S*-Alkyl Leaving Groups

Glycosylation reactions based on the activation of 1-thio-β-D-glycosides, for the synthesis of complex oligosaccharides, have an obvious advantage over other methods because of their stability under a variety of conditions commonly encountered during the various manipulations of the carbohydrates. The use of stable *S*-glycosides such as glycopyranosyl is dependent on the nucleophilicity of the bivalent sulfur atom to electrophilic reagents such as *N*-bromosuccinimide (NBS),[301] *N*-iodosuccinimide in conjunction with triflic acid,[302,303] or methyl trifluoromethanesulfonate (methyl triflate),[304,307] which generate from the respective *S*-glycosides (**12**, X = β-SR), a highly reactive sulfonium leaving group (**12′**, Scheme VI). This latter is displaced by anchimeric assistance of the participating group at C-2 to form the carbenium cation **13** which is attacked by the acceptor at C-1 to form the corresponding 1,2-*trans*-glycoside **14** (Scheme VI).

In 1985, Lönn reported that the glycosylation reaction effected between a thioglycoside donor and an acceptor in the presence of methyl triflate was an efficient route for 1,2-*trans*-glycosides.[304] Thus ethyl 3-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-4,6-*O*-benzylidene-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside was reacted with the HO-2 free D-mannose acceptor benzyl 3,4,6-tri-*O*-benzyl-α-D-mannopyranoside in the presence of methyl triflate to afford 72% of β-(1→2)-linked trisaccharide. Similarly, condensation of an HO-2′ and HO-2″ free diol D-mannose trisaccharide acceptor with the same thioglycoside afforded the heptasaccharide **22**.



22

Methyl triflate condensation at room temperature of the trisaccharide donor ethyl 4-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-6-*O*-benzyl-3-*O*-(2,3,4-tri-*O*-benzyl-α-L-fucopyranosyl)-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside with an HO-2 D-mannose acceptor afforded the expected tetrasaccharide together with small amounts of the glycal derived from the donor.[305] The same tetrasaccharide was also prepared in 83% yield from the related phenyl thioglycoside donor and *N*-iodosuccinimide in conjunction with triflic acid as the promoter.[303]

Other Lewis acids were used successfully to activate the 1-thioglycosides such as dimethyl(methylthio)sulfonium trifluoromethanesulfonate (DMTST),[308-313] nitrosyl tetrafluoroborate,[314,315] phenylselenenyl triflate,[316-318] or a mixture of copper(II) bromide, tetrabutylammonium bromide, and silver trifluoromethanesulfonate.[319,320]

Alkenyl sulfenyl halides such as methylsulfenyl bromide (MSB) and *o*-nitrobenzenesulfenyl chloride (NSC), in the presence of silver triflate, were used to activate a thioglycoside donor with the acceptor methyl 2-*O*-benzyl-4,6-*O*-benzylidene-α-D-glucopyranoside to afford the corresponding β-(1→3)-linked disaccharide in 95% and 64% yields using MSB or NSC, respectively.[321]

Another mode of activation of 1-thio-β-glycosides involved the use of silver triflate and bromine. The

latter promoter was shown to give a high yield of β-D-GlcpNPht-(1→2)-L-Rhap without using highly toxic promoters such as methyl triflate or DMTST.[322]

Self-condensation of ethyl 6-O-acetyl-3-O-benzyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside in the presence of methyl triflate afforded 70% of an oligomeric mixture containing the chitobiose unit.[323]

The total syntheses of the Forssman and Para Forssman antigens were achieved respectively by condensation of the disaccharides [α-D-GalpNPht-(1→3)-β-D-GalpNPht] or [β-D-GalpNPht-(1→3)-β-D-GalpNPht] thioglycosides with the same HO-3″ trisaccharide acceptor [α-D-Galp-(1→4)-β-D-Galp-(1→4)-β-D-Glcp] in nitromethane in the presence of Bu_4NBr–$CuBr_2$–silver triflate. Mixtures of pentasaccharides were obtained in 78% yield (α:β = 1:10) and 65% yield (α:β = 1:8) which were further transformed into the Forssman antigen target compound **23**[324] and the Para Forssman epimer.[325]

α-D-GalpNAc-(1->3)-β-D-GalpNAc-(1->3)-α-D-Galp-(1->4)-β-D-Galp-(1->4)-β-D-Glcp

23

Other compounds of biological interest were synthesized using the 1-thio activation procedure. Thus the condensation of a GlcpNPht 1-thio donor with a HO-3 (or HO-4) free D-mannosamine acceptor allowed the preparation of β-D-GlcpNPht-(1→3) or (1→4)-D-ManpN_3 related to the repetitive unit of *Haemophilus influenzae* type D[326] or type e,[327] respectively.

Furthermore, the condensation of a 1-thio disaccharidic phthalimido donor with a HO-3 free D-Galp acceptor gave rise to the α-L-Fucp-(1→3)-β-D-GalpNPht-(1→3)-β-D-Galp related to the Le^x tumor associated antigen.[310]

Finally, a β-(1→3)-D-lactosamine dimer was prepared in 88% yield by reaction of an ethyl 2-deoxy-2-phthalimido-1-thio-β-D-glycopyranoside donor and a free HO-3′ D-lactosamine acceptor in the presence of DMTST and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as the promoter.[328] The latter tetrasaccharide was used as an intermediate in the synthesis of a monofucosyl heptasaccharide corresponding to a tumor-associated glycolipid.[328]

C. Uses of 2-Deoxy-2-phthalimido Glycopyranosyl Trichloroacetimidates as Glycosylation Donors

In 1983, Schmidt et al. introduced the use of 2-deoxy-2-phthalimidoglycopyranosyl imidates as glycosyl donors for the preparation of 2-amino-2-deoxy-β-D-glycopyranosides.[329] The β-imidates **12** [Scheme VI, X = β-OC(NH)CCl_3] were obtained by reaction of carbohydrate hemiacetals with trichloroacetonitrile in the presence of a base. The glycosylation reactions were then conducted in dichloromethane or 1,2-dichloroethane, at low temperature (−20 °C/−40 °C) with either boron trifluoride etherate or trimethylsilyl trifluoromethanesulfonate as the catalyst.

The tetrasaccharide β-D-Galp-(1→4)-β-D-GlcpNPht-(1→6)-[β-D-GlcpNPht-(1→3)]-β-D-GalpN_3-OR occurring as part of the O-glycoproteins was thus synthesized by a stepwise condensation of two different 2-deoxy-2-phthalimido-β-D-glucopyranosyl imidate donors on the same 2-azido-2-deoxy-β-D-galactopyranoside acceptor.[329,330]

The phthalimido imidate procedure has been used with D-glucosamine or D-lactosamine donors for the glycosylation of the HO-2[186,331] or HO-4[332–334] of the D-mannosamine moiety of oligosaccharides in order to create the β-D-GlcpNPht-(1→2)-D-Manp and β-D-GlcpNPht-(1→4)-D-Manp linkages found in the glycan chain of glycoproteins.

This method was also used for the creation of β-D-GlcpNPht-(1→n)-D-Galp linkages involving the HO-4[226] or HO-6[335] position of the D-galactose acceptor. Furthermore, 2-deoxy-2-phthalimido-β-D-glucopyranosyl imidate was reacted, in the presence of boron trifluoride etherate, with the HO-3 position of D-*galacto*-monosaccharide,[336] -disaccharide,[335] or -trisaccharide[336,337] acceptors, with high yields (over 70%).

2-Deoxy-2-phthalimido-β-D-lactosyl imidates were also used for the preparation of more complex oligosaccharides. For example, Ogawa et al. prepared tetrasaccharide (E′F′G′H′) and hexasaccharide (E′F′E′F′G′H′) derivatives in a stereocontrolled total synthesis of a sulfated heptaosylceramide **24** (D′E′F′E′F′G′H′). The synthesis of compound **24** was achieved by glycosylation of HO-3′ of β-D-Galp-(1→4)-β-D-Glcp (G′H′) acceptor with a lactosaminyl donor (E′F′), catalyzed by trimethylsilyl trifluoromethanesulfonate in 86% yield.[338] After deprotection of the HO-3‴ of the terminal galactose unit of the intermediate E′F′G′H′, a new glycosylation with the same donor then afforded the expected hexasaccharide E′F′E′F′G′H′ in 81% yield.[339]

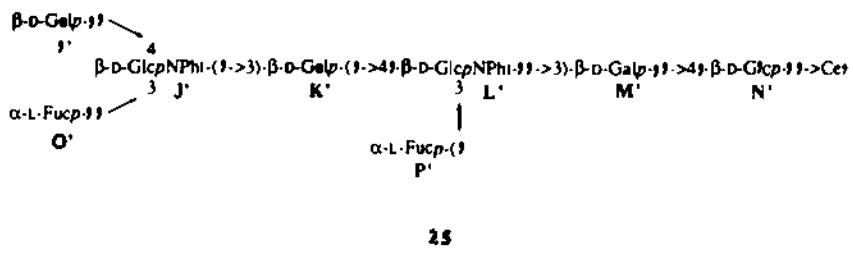
SO_3->3)-β-D-GlcpA-(1->3)-[β-D-Galp-(1->4)-β-D-GlcpNPht-(1->3)]$_n$-β-D-Galp-(1->4)-β-D-Glcp-(1->Cer
D′ E′ F′ G′ H′

24

By using the difference in reactivities of HO-3 and HO-4 in the D-galactose series, Veyrières et al. were able to synthesize polylactosamine fragments [β-D-Galp-(1→4)-β-D-GlcpNPht-(1→3)]$_n$ (n = 2, 4) by a blockwise synthesis approach[240,340] with a lactosaminyl donor and a lactosamine acceptor containing free HO-3′ and HO-4′.

The same difference in reactivities of HO-3 and HO-4 of a D-galactose unit was also exploited for the synthesis of oligosaccharides related to the structure of glycosylceramides **25**. The glycoheptaosyl derivative of a stage-specific embryonic antigen SSEA 1 [I′(O′)J′K′L′M′N′] was prepared by a regiospecific β-(1→3) condensation of the β-imidate donor I′(O′)J′ with a K′L′M′N′ acceptor (containing free HO-3‴ and HO-4‴) in 79% yield.[341] The octasaccharide portion of the Le^x octaosylceramide [I′(O′)J′K′(P′)L′M′N′] was also synthesized stepwise from the free HO-3′ D-galactose acceptor M′N′ and the same donor to afford the pentasaccharide K′(P′)L′M′N′ in 53% yield. After deprotection of HO-3‴ and HO-4‴ of the latter intermediate pentasaccharide, glycosylation with the same donor afforded the aforementioned octasaccharide in 78% yield.[342]

It was established that the glycosylation of HO-3′ of the M′N′ acceptor with the I′(O′)J′ donor was realized in higher yields when the HO-4′ position of the acceptor was also free.[342,343] This observation was confirmed by the low yield of coupling (22%) of a β-D-Galp-(1→3)-



25

β-D-Gal*p*NPht imidate donor with a free HO-3″ α-D-Gal*p*-(1→4)-β-D-Gal*p*-(1→4)-β-D-Glc*p*-OBn acceptor to afford a pentasaccharide related to a stage-specific embryonic antigen SSEA 3.[343]

A low yield (31%) was also reported for the glycosylation of the same trisaccharidic acceptor with a β-D-Gal*p*NPht-(1→3)-β-D-Gal*p*NPht imidate as the donor thus affording the pentasaccharide moiety of the Para Forssman antigen.[325] In this latter case, an increase of the glycosylation yield (58%) was reported when using a β-thioglycoside as the donor.[325]

Very recently, a synthesis of allosamidine was described from a 2-deoxy-2-phthalimidoallopyranosyl imidate donor and a 2-deoxy-2-phthalimidoallopyranoside acceptor in the presence of trimethylsilyl trifluoromethanesulfonate as the promoter. The β-D-All*p*-NPht-(1→4)-D-All*p*NPht disaccharide thus obtained in 80% yield was further reacted with racemic allosamizoline to afford the expected allosamidine.[344]

D. Other Modes of Anomeric Activation

4-Pentenyl 3-*O*-benzyl-2-deoxy-4,6-*O*-isopropylidene-2-phthalimido-β-D-glucopyranoside was shown to undergo iodonium ion induced coupling with a variety of sugar alcohols to give β-disaccharides in very good yields. Several linkages were thus created stereospecifically such as β-D-Glc*p*NPht-(1→*n*)-D-Glc*p* (*n* = 3, 4, 6).[190]

2-Deoxy-2-phthalimido-D-glucopyranosyl 4-pentenoates were also used as glucosylation donors, through an electrophile-induced lactonization with [(*s*-collidine)$_2$I]$^+$ClO$_4^-$, to afford stereospecifically the 1,2-*trans*-glucoside in good yield.[345]

Phenyl selenoglycosides were very recently reported as novel versatile glycosylation donors. A selective activation of the phenylseleno leaving group could be achieved in the presence of an ethyl thioglycosidic function (silver trifluoromethane sulfonate/potassium carbonate as the promoter).[346]

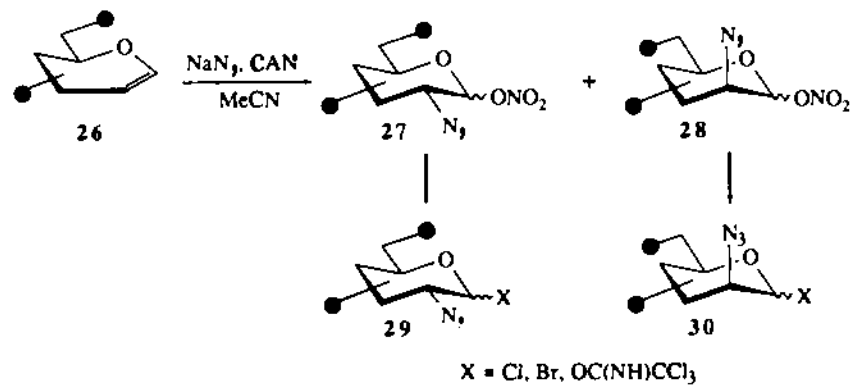
The efficiencies of six standard 2-deoxy-2-phthalimidoglucopyranosyl donors toward the same acceptors were recently reported. A very valuable comparison between various leaving groups could, therefore, be obtained for the synthesis of 2-deoxy-2-phthalimidoglucopyranosides.[203]

E. Conclusion

Since its introduction in the field of oligosaccharide synthesis, the so-called "phthalimido procedure" has found a wide range of applications for the preparation of complex molecules.

Most of the time, the glycosylations effected with 2-deoxy-2-phthalimido donors were found to show a complete 1,2-trans stereospecificity. Yields were generally high, even with unreactive alcohols and, furthermore, the method has been recently improved by the use of various leaving groups such as trichloroacetimidates or 1-thioalkyl groups.

Scheme VIII



X = Cl, Br, OC(NH)CCl$_3$

Very sophisticated oligosaccharides, including uronic acid acceptors[347] were built up using the phthalimido procedure in key steps. This method can, presently, be considered as the method of choice for the synthesis of 1,2-*trans*-glycosides of the 2-amino-2-deoxy sugars.

It could be pointed out, nevertheless, that the cleavage of the amino protective group requires alkaline conditions which could constitute a drawback to the method in a few instances.[348]

VII. Glycosylations Using 2-Azido-2-deoxy Donors

The azido function was shown to be a nonparticipating group which did not cause steric hindrance and, therefore, could possibly be used as the amino protective group of donors for 1,2-*cis*-glycosylation reactions. Furthermore, reduction of the azido group could afford the free amino group.

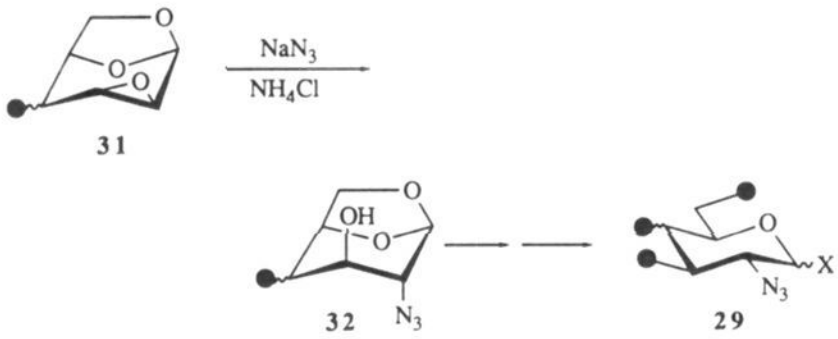
A. Preparations of 2-Azido-2-deoxy Sugar Donors

The most widely used reaction for the preparation of the 2-azido analogues was the azidonitration of glycals developed by Lemieux and co-workers[349,350] in 1979. This reaction occurred by the addition of ceric ammonium nitrate and sodium azide on protected glycals **26**, to afford epimeric mixtures of 2-azido-2-deoxy-1-*O*-nitropyranoses **27** and **28** (Scheme VIII). The stereochemistry of the addition favored the formation of the equatorial 2-azido derivative **27** with respect to the axial 2-epimer **28**. It should be mentioned that this addition reaction is regiospecific with all glycals and stereoselective mostly in the cases of acetylated D-galactal derivatives.[349] Besides D-glucal[351,352] and D-galactal, these reactions have also been extended to other peracetylated monosaccharidic glycals,[353,354] disaccharidic glycals,[266,355-358] and glycals derived from glycuronic acids.[359]

When protective groups other than acetates were used,[360-362] the stereoselectivity of this addition reaction sometimes exhibited some differences[363-366] which favored the formation of the 2-axial azido epimer **38**.[351] Finally, the epimeric 2-azido-1-*O*-nitro derivatives **27** and **28** were transformed into the corresponding 2-azidoglycopyranosyl halide (or trichloroacetimidate) donors **29** and **30** which were used for further glycosylation reactions. More recently, an anomeric *S*-xanthate was obtained from the epimeric mixture of **27** and **28** and used as a glycosylation donor.[367]

Another method for the preparation of 2-azido sugars involved the opening of 1,6:2,3-dianhydrohexopyranose derivatives **31** (Scheme IX) with sodium azide to afford,

Scheme IX



regio- and stereoselectively, the corresponding 2,3-trans diaxial 2-azido derivative **32**. This latter compound was transformed into the corresponding 2-azidoglycopyranosyl halide donor **29** via the opening of the 1,6-anhydro ring. This method has been successfully applied to the syntheses of 2-azido monosaccharidic glycopyranosyl halide donors[194,368-374] as well as to the syntheses of 2-azido disaccharidic glycopyranosyl halide donors.[375-377]

Preparation of the 1,6-anhydro-2-azido-2-deoxy intermediates **32** has been improved using more reactive nucleophiles[378,379] and using these intermediates **32** as acceptors in glycosylation reactions.[369,370,380]

Other methods were reported for the preparation of the 2-azido-2-deoxyglycopyranosyl donors which were not of general use but, nevertheless, should be mentioned in this rationale. Thus the addition of halogeno azides on suitably protected glycals[381,382] afforded, regioselectively, 2-azido-2-deoxyglycopyranosyl halides. The nucleophilic substitutions of the 2-sulfonate derivatives with azides were also reported to afford the 2-azido derivatives in good yields.[383-387] The diazo transfer on 2-amino-2-deoxyaldoses was also reported to give an easy access to 2-azido-2-deoxy sugars.[388] Finally, the opening of 2,3-cyclic sulfates,[389] the synthesis of 2-azido-2-deoxy-D-glucopyranose in eight steps from D-glucosamine[390] and the migration of the azido function from C-1 to C-2 with (dimethylamido)sulfur trifluoride (DAST)[391] were also reported.

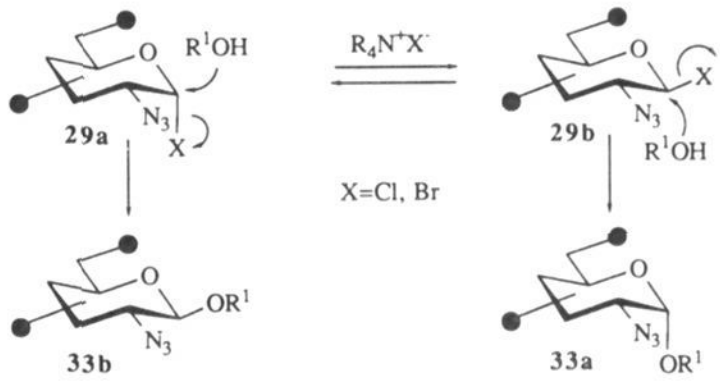
B. Glycosylation Reactions Using 2-Azido-2-deoxy Sugar Donors

Preparation of 1,2-*cis*- and 1,2-*trans*-glycosides of 2-azido-2-deoxy sugars from the various 2-azido-2-deoxy glycopyranosyl donors was affected by the nature of the anomeric leaving groups and the promoters used in these glycosylations. The glycopyranosyl halides were the most commonly used donors in such condensations, and the stereoselectivities of these glycosylation reactions, were strongly dependent on the nature of the promoters (soluble or insoluble). On the other hand, the stereochemistry of the glycosylation reactions using imidates as leaving groups of the 2-azido-2-deoxy donors was shown to be strongly dependent not only on the promoters used, but also on the nature of the acceptor and the orientation of the leaving groups (i.e., α or β).

Also, a free HO-1 reducing 2-azido-2-deoxy-D-galactose was used as the donor with serine or threonine acceptors in the presence of triflic anhydride in acetonitrile to afford the glycopeptides α-D-Gal*p*N_3-(1→0)-Ser (or Thr).[392,393]

More recently, the thioglycosides were introduced as

Scheme X



glycosyl donors which were used for various successful glycosylations. Each of the above methods will be discussed separately in the following sections.

1. Anomeric Halide Leaving Groups

a. Soluble Promoters Leading to the Synthesis of 1,2-*cis*-Glycosides. As was discussed in the general reaction (Scheme I) for the glycosylation reaction, the ideal formation of the 1,2-*cis*-glycosides required the presence of a nonparticipating amino protective group. The approach of the acceptor alcohol should be directed on the same side as the C-2 substituent. Also, the amino protective group should not be bulky, and the leaving group must be situated in a 1,2-trans relationship. This ideal situation was met in the syntheses of oligosaccharides of biological interest using glycopyranosyl donors (e.g. D-glucosamine or D-galactosamine) in which the nitrogen atom and the anomeric leaving group were in the equatorial orientation. Thus, in the case of glycopyranosyl halides, this preferred situation was attained either by the use of β-anomeric halides **29b** (Scheme X) or by the use of the so-called in situ anomerization of halide anomeric mixtures.[88]

Due to the instability of the β-anomeric glycopyranosyl bromides, only β-chlorides **29b** (X = Cl) were used as glycopyranosyl donors in the D-*gluco*[368,369,394-400] and D-*galacto*[370,401-405] series, whereas the anomeric glycopyranosyl bromides **29a** (X = Br) were involved in the in situ anomerization process.

Several glycosides and oligosaccharides **33** were prepared using the 2-azido-2-deoxy-β-D-glycopyranosyl chlorides as donors, in the presence of silver salts as promoters but, unfortunately, this method was restricted to reactive alcohol acceptors[402,406] due to the weak leaving group properties of the anomeric chloride ion. Nevertheless, this reaction was successfully applied to the syntheses of 2-azido-2-deoxy-α-D-galactopyranosides of L-serine and L-threonine.[407-416]

It should be mentioned that the unstable and more reactive 2-azido-2-deoxy-β-D-glycopyranosyl bromides **29b** (X = Br) were prepared in situ by equilibration of the stable α-bromide anomer **29a** and engaged in a one-pot reaction in the presence of both the acceptor alcohol and the promoter. The in situ anomerization using the so-called "common ion method"[88] was achieved using tetraethylammonium bromide.[5,417] The fundamental mechanism of this reaction has already been described by Lemieux et al.,[88] and it was shown that the rate of anomerization of bromide **29a** to **29b** was faster than the glycosylation reaction leading from **29a** to the β-glycoside **33b**. Also, it was demonstrated that the rate of conversion of the β-bromide **29b** into the α-glycoside **33a** was faster than the rate of reverse anomeric epimerization (**29b** into **29a**).

The yields and stereoselectivities of the glycosylation products obtained while using 2-azido-2-deoxy-D-glycopyranosyl halides as donors were shown to be strongly dependent on several parameters, such as the donor, the acceptor alcohol, and the promoter which often precluded any prediction concerning the stereoselectivity of the glycosylation reaction. Nevertheless, some general principles can be drawn from the literature for the synthesis of 2-azido-2-deoxy-1,2-*cis*-glycosides. Thus, with reactive acceptors, the donors of low reactivities (e.g. 2-azido-2-deoxy-β-D-glycopyranosyl chlorides) can be used in the presence of promoters of low reactivity (e.g. Ag_2O, Ag_2CO_3, $CdCO_3$)[406] or medium reactivity [e.g. $Hg(CN)_2$]. With unreactive acceptors, the donors of higher reactivities (e.g. 2-azido-2-deoxy-α-D-glycopyranosyl bromides) should be used in the presence of a reactive promoter allowing the in situ formation of a β-anomeric reactive species [e.g. $Hg(CN)_2$–$HgBr_2$, silver triflate, or $AgClO_4$–Ag_2CO_3].

The reactivities of the various promoters or mixtures of promoters have often been discussed.[402,406,417,418] The choice of the appropriate promoter should actually be made not only with respect to its involvement in the glycosylation procedure itself, but also with respect to the stabilities of the protective groups of both the donor and the acceptor in its presence.[380,419]

More recently, 2-azido-2-deoxy-D-glycopyranosyl fluorides were also used as donors with some success.[420–422]

On the other hand, the reactivities of the 2-azido-2-deoxyglycopyranosyl donors were shown to be strongly dependent on their protective groups and configurations. Thus, it was often reported that the reactivity of the donor increased with the increasing number of ether protective groups (mainly benzyl) and decreased with the increasing number of ester protective groups (mainly acetates).[380,402,411,418,423,424] Furthermore, the reactivity is most often higher with donors in the D-*galacto* than in the D-*gluco* configuration.[5,7,373] The aforementioned general principles were applied for the synthesis of various glycosides and oligosaccharides of biological interest.

i. Simple Alcohol Acceptors. The glycosylations of simple alcohols (methanol, allyl, benzyl, or cyclohexyl alcohols) were studied in the 2-azido-2-deoxy-D-glucose series[356,358,395,425,426] as well as in the 2-azido-2-deoxy-D-galactose[349,402,427] or -D-mannose[428] series. The glycosylations were usually in favor of the 1,2-cis isomer, but due to the high reactivity of the aforementioned acceptor alcohols, the stereoselectivities were often reported to be poor and strongly dependent on the promoter and solvent used.[402] Several acceptor alcohols having bridging arm properties such as functionalized phenols[356,429,430] or functionalized alkyl chains[411,431,432] were used as linear acceptor alcohols. Also, glycosylations of partly protected inositols were reported.[420,433] The stereoselectivities were acceptable in these latter examples but the yields were sometimes low.

ii. Glycopeptides. Syntheses of glycopeptides involving an α-linkage between D-galactosamine and L-serine or L-threonine have been widely used. Thus, the reaction of 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranosyl bromide with suitably protected L-serine or L-threonine in the presence of mercuric bromide–mercuric cyanide as the promoters, afforded the expected glycopeptide with a medium stereoselectivity (α:β = 5:1),[410,411] mainly due to the high reactivity of the donor. Recently better stereoselectivities were reported with the same donor by using $AgClO_4$–Ag_2CO_3 as the promoters.[415,416,434] The reaction of the corresponding 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-β-D-glucopyranosyl chloride as a donor of lower reactivity was proven to be more favorable for such glycosylations,[407,412] mainly in the presence of Ag_2CO_3–$AgClO_4$ as promoters.[410,414]

In the case of disaccharidic donors,[282,407,412,434,435] the reactivity was shown to be strongly dependent on the number of acetyl functions present on the latter.[416] Thus, the reaction of 4,6-di-*O*-acetyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-2-azido-2-deoxy-α-D-galactopyranosyl bromide with properly protected serine or threonine was realized with a medium stereoselectivity (α:β = 6:1) while the reaction performed with the corresponding 4,6-di-*O*-benzoyl donor afforded the expected glycopeptide with good yields and stereoselectivities in the presence of $AgClO_4$–Ag_2CO_3 as the promoters.[411,436] When $AgClO_4$ only was used as the promoter, some stereospecific glycosylations were reported,[415,437] but it should be mentioned that lower stereoselectivities (α:β = 6:1 to 3:1) were also obtained with the same promoter.[414,438]

It should be noted that the amino acid protective groups were also shown to interfere with the course of the glycosylation reactions.[413] These side reactions will not be detailed in this review article, which is devoted to the glycosylation aspects only. In conjunction with the methods already described in this rationale, glycosylations using 2-azido-2-deoxy sugar halides allowed the preparation of products of very high biological importance such as asialoglycophorin A fragments[437,438] or interleukin II fragments.[414]

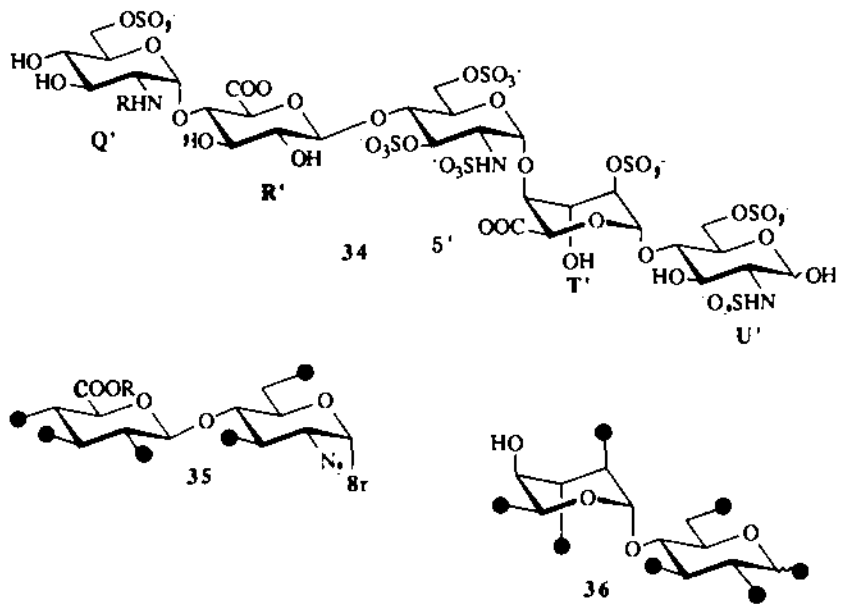
iii. Selected Oligosaccharides. The 1,2-cis glycosylation procedure using 2-azido-2-deoxyglycopyranosyl halides as donors and promoters allowing the in situ formation of 1,2-trans leaving groups has been well documented in the field of disaccharides.

Donors possessing the D-*galacto* configuration were reported to afford good yields and good stereoselectivities by reaction with various D-galactose acceptors (HO-3,[228,370,400,403,405,417,439] HO-6[406]), D-glucose (HO-4,[380,440] HO-6[406,411]), D-galactosamine (HO-3[228,229,324,370,379,400,404,423,440]), D-glucosamine (HO-3[370]), or with L-fucose acceptors (HO-3[363]).

The synthesis of the blood group substance A type 2, α-D-Gal*p*NAc-(1→3)-[α-L-Fuc*p*-(1→2)]-β-D-Gal*p*-(1→4)-D-Glc*p*NAc was realized with 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranosyl bromide as a donor and the properly protected trisaccharidic acceptor. Due to the low reactivity of the acceptor, several promoters were tested and the yields were shown to increase with the addition of increasing amounts of $HgBr_2$ to the $Hg(CN)_2$ promoter or by the use of silver triflate at low temperature in order to keep a good 1,2-cis stereoselectivity to the glycosylation process.[417,439]

Good results, with respect to yields and 1,2-cis stereoselectivities, were also reported from donors having the D-*gluco* configuration and acceptors of the D-galactose series (HO-3,[213,441,442] HO-4[237,419]), D-glucosamine (HO-3,[369,395,399,419] HO-6[443]) as well as D-fucose,[444] or L-*glycero*-D-*manno*-heptose[445] series.

Scheme XI



A good 1,2-cis stereoselectivity was also reported with a 2-azido-2-deoxy-L-idopyranosyl donor[446] whereas a lower stereoselectivity was observed when 2-azido-2-deoxy-D-xylopyranosyl donors were used.[447]

It should be mentioned that 1,6-anhydro derivatives of D-galactose and D-galactosamine were often used as acceptors in the above glycosylation reactions in order to increase the reactivity of the free hydroxyl groups. Such an approach constituted, for example, the key steps of the synthesis of the repeating unit of *Streptococcus pneumoniae* type I.[379]

iv. Regioselective Glycosylations. Regioselective glycosylations were attempted on benzylated lactose acceptor diols [β-D-Gal*p*-(1→4)-D-Glc*p*] having free HO-3′ and HO-4′, with 2-azido-2-deoxy-D-glycopyranosyl bromides. In the presence of promoters allowing the formation of equatorial leaving groups, no regioselectivity has been observed, and both 1,2-cis regioisomers were recovered in comparable yields.[236-239] Nevertheless, the glycosylation of the same acceptor diol with a donor of low reactivity, afforded a better regioselectivity of the 1,2-cis glycosylation (toward the HO-3′ position) but the yields were drastically affected (29% yield only) by this change.[238]

v. Synthesis of Heparin Fragments. Very recently, 2-azido-2-deoxy-α-D-glucopyranosyl bromides have been used in the synthesis of heparin fragments. Heparin **34** is a sulfated oligosaccharide which exhibits antithrombin activity[448,449] and contains two 1,2-*cis*-glucosaminyl linkages (e.g. Q′R′ and S′T′ in Scheme XI).

Nonsulfated oligosaccharidic fragments S′T′,[450] S′T′U′,[451] and Q′R′S′[452] were synthesized from a properly protected 2-azido-2-deoxy-α-D-glucopyranosyl bromide and the appropriate acceptor derivatives of D-glucuronic (R′) or L-iduronic (T′) acid and in the presence of reactive promoters such as silver triflate–collidine or $HgBr_2$. The nonsulfated tetrasaccharide (R′S′T′U′) was mostly prepared by reaction of the fully protected donor **35** (fragment R′S′) with the acceptor **36** (fragment T′U′) in the presence of silver triflate–collidine as the promoter but also with silver triflate only (which afforded a better 1,2-cis stereoselectivity of the glycosylation, but also a lower yield with protective groups fragile in acidic medium)[377] or Ag_2CO_3–$AgClO_4$.[453] After removal of the HO-4 protective group from the D-glucuronic acid moiety (fragment R′), the fully protected fragment R′S′T′U′ was used as the acceptor with 6-*O*-acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α-D-glucopyranosyl bromide as the donor[453-456] under the same conditions reported for the condensation of fragment R′S′ with T′U′. The stereoselectivities of these latter steps of 1,2-cis glycosylation were reported to be high (70–81%),[425,457,458] and their yields could be almost quantitative (96%).[377]

Similar syntheses were also reported for sulfated heparin fragments[459] or for fragments in which the L-iduronic acid moiety (T′) has been replaced by L-idopyranose,[460,461] D-xylopyranose,[462] (*R*)-glyceric acid,[463] or D-glucuronic acid.[464] All of these syntheses involved the same approach with a few modifications due only to the nature of the acceptor (mono- or oligosaccharide).

b. Insoluble Promoters Leading to the Synthesis of 2-Azido-2-deoxy-β-D-glycopyranosides. The methods already discussed in the preceding sections were not useful for the synthesis of the 1,2-*cis*-glycosides of D-mannosamine. In effect, a 2-amino participating group should lead to 1,2-*trans*-glycosides and the use of a soluble promoter with a 2-azido-2-deoxy-D-mannopyranosyl halide as donor should lead to the same α-anomeric 2-azido-2-deoxy-D-mannopyranoside.

As was seen in the general glycosylation mechanism (Scheme I), the 1,2-*cis*-glycosides of D-mannosamine might be formed starting from a donor containing a nonparticipating group on the C-2 (E with axial NR_2) position and an insoluble catalyst able to shield the "α-face" of the donor to favor the approach of the acceptor alcohol on the "β-face" and avoid the formation of an oxocarbenium intermediate (C) which would result in a loss of stereocontrol. Silver carbonate was the first insoluble promoter used in the synthesis of 1,2-*trans*-β-glycosides of the 2-azido-2-deoxy-D-*gluco*[357,368,395,443,465] and D-*galacto*[370] series, and the method was then extended to the synthesis of 1,2-*cis*-glycosides of D-mannosamine. Further improvements were realized later by the use of silver zeolites[466] or supported silver salts (silica gel,[467] silica/alumina[468]). In order to achieve the best β-stereoselectivity, it was reported that the reaction should be performed in solvents of low polarity (toluene) and by using the most reactive donors[351,444,469] and acceptor alcohols.[428]

The reactivities of the donors were shown to be strongly dependent on their protective groups.[470] Thus ether protection of HO-3 and HO-6 as well as ester protection of HO-4 seemed to favor the β-glycosylation by comparison with ester protection of HO-3 and HO-6 and ether protection of HO-4.[471-473] Furthermore, it was demonstrated that the β-stereocontrol of the reaction with 2-azido-2-deoxy-α-D-glycopyranosyl halides was better with donors having the D-*galacto* or D-*manno* configuration than with the corresponding D-*gluco* epimers.[471,472]

i. Simple Alcohol Acceptors. The glycosylations of simple primary alcohols were generally reported to afford the expected β-glycosides in high yields and with good stereoselectivities in the D-*gluco*[118,299,474-477] as well as in the D-*manno*[428] series, except with donors of lower reactivities.[478,479]

ii. Selected Oligosaccharides. A wide range of applications of the method were reported in the field of β-(1→6) oligosaccharides involving a 2-azido-2-deoxy-α-D-glycopyranosyl bromide as the glycosylation donor and the HO-6 primary and reactive hydroxyl group of

the acceptor. Thus the following linkages were created with a good stereoselectivity: β-D-Glc*p*N$_3$-(1→6)-D-Glc*p*N,[474,475,480] β-D-Glc*p*N$_3$-(1→6)-D-Gal*p*,[476] and β-D-Man*p*N$_3$-(1→6)-D-Glc*p*.[481]

The most important improvements in the synthesis of 1,2-*trans*-β-oligosaccharides with respect to the so-called oxazoline or phthalimido procedures were found in the preparation of compounds of biological interest containing functions which are labile in alkaline and/or acidic medium and could not survive drastic conditions. An antigenic fragment related to *S. pneumoniae* type I[378,379] was thus synthesized from 3,6-di-*O*-acetyl-2-azido-4-*O*-benzyl-2-deoxy-α-D-galactopyranosyl bromide as the donor with the properly protected ribitol receptor (HO-1 free) in the presence of silver silicate at −20 °C with a good yield (61%) and a good β-stereoselectivity. A phosphodiester function was further introduced on the above prepared fully protected disaccharide and the amino-free antigen could subsequently be recovered without cleavage of the fragile phosphodiester bond.

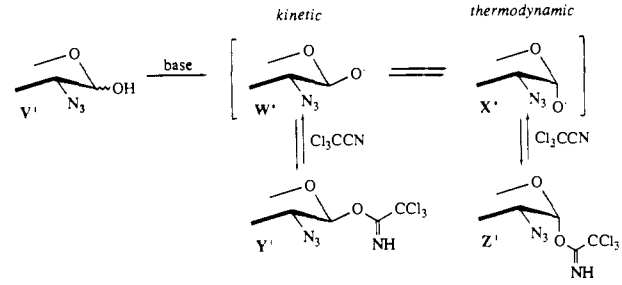
Another interesting example was reported by Paulsen et al.[445] in the field of lipopolysaccharidic antigens. The reaction of 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-glucopyranosyl bromide with benzyl 2,3,5,6-tetra-*O*-benzyl-α-L-*glycero*-D-*manno*-heptopyranoside as the acceptor in the presence of silver silicate at −50 °C afforded mainly the β-disaccharide (93%, α:β = 1:14) related to the core lipopolysaccharide of *Vibrio ordalii*. Glycosylation of the same acceptor and donor in the presence of silver triflate (soluble promoter) afforded the α-disaccharide (76%, α:β = 7.5:1) related to the core lipopolysaccharide of *Aeromonas hydrophila* and *Bordetella pertussis*.

Glycosylations using various monosaccharide acceptors containing free HO-4, HO-3, or HO-2 and promoted by insoluble silver salts were reported in the literature thus affording the following linkages respectively: β-D-Gal*p*N$_3$-(1→4)-D-Gal*p*,[482] β-D-Man*p*N$_3$-(1→4)-D-Glc*p*,[371,483] β-D-Man*p*N$_3$-(1→4)-D-Glc*p*N,[351,444,469] β-D-Man*p*N$_3$-(1→4)-L-Rha*p*,[478] β-D-Gal*p*N$_3$-(1→3)-D-Gal*p*,[370,484] β-D-Glc*p*N$_3$-(1→3)-D-Gal*p*,[476] β-D-Man*p*N$_3$-(1→3)-L-Fuc*p*N,[485] β-D-Gal*p*N$_3$-(1→2)-L-Rha*p*.[467,486]

iii. Regioselective Glycosylations. Selective glycosylations involving the HO-3′ and HO-4′ of lactose acceptors were studied in detail because of their involvements in the field of gangliosides and blood group substances. Thus, 6-*O*-acetyl-2-azido-3,4-di-*O*-benzyl-2-deoxy-α-D-glucopyranosyl bromide was regio- and stereoselectively condensed on the HO-4′ position of a properly protected lactoside acceptor (HO-3′ and HO-4′ free) in the presence of silver silicate as the promoter.[236,237] Condensation of the less reactive homologous 2-azido-2-deoxylactosaminyl donor with the same acceptor afforded the four possible regio- and stereoisomers[238] under the same reaction conditions.

The reactions of 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-D-galactopyranosyl bromide or 4,6-di-*O*-acetyl-3-*O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)-2-azido-2-deoxy-α-D-galactopyranosyl bromide with a benzylated lactoside acceptor (HO-3′ and HO-4′ free) in the presence of an insoluble catalyst afforded the β-(1→4) tri- or tetrasaccharide respectively in a regio- and stereoselective manner.[239] This regioselectivity toward HO-4 with respect to HO-3 was also reported with benzyl 2,6-di-*O*-benzyl-β-D-galactopyranoside[482] or a 2-azido-2-deoxy properly protected lactoside[487] as the acceptor diol and was attributed to a masking complexation of the promoter with the more reactive HO-3 position.

Scheme XII



It is interesting to mention, at this point, that the corresponding 2-deoxy-2-phthalimidoglycopyranosyl donors were reported to afford preferentially the β-(1→3) glycosides with the same acceptor diols[236-239] in the presence of a soluble promoter, which complements the scope of the 2-azido-2-deoxyglycosylation approach.

In summary, the 2-azido-2-deoxy-D-glycopyranosyl halides (possessing an equatorial C-2 substituent) could afford the 1,2-*cis*-glycopyranosides in the presence of soluble promoters allowing the in situ formation of a β-leaving group of high reactivity. On the other hand, the use of insoluble promoters with 2-azido-2-deoxy donors (irrespective of the orientation of the C-2 substituent) gave rise to β-D-glycopyranosides with various acceptor alcohols; this approach was especially relevant in the case of D-mannosamine donors.

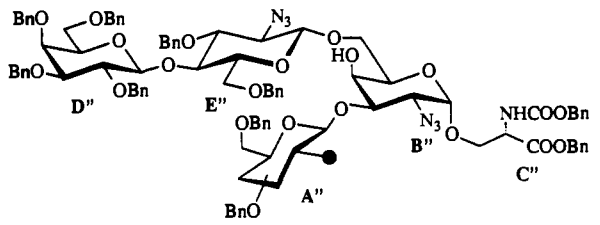
In both cases (soluble or insoluble promoter) the yields and stereoselectivities were strongly dependent on the relative reactivities of both the donors and the acceptors. A tight compromise should be found in each case with respect to the nature of the donor, the acceptor and the promoter, since yields and stereoselectivities were often opposed.[476]

2. Anomeric Imidate Leaving Groups

This method developed by Schmidt and co-workers[6] was first used in the D-glucose series[488] and then applied to other structures[489] and also to the 2-azido-2-deoxy-D-glucose and -D-galactose.[360] The trichloroacetimidate leaving group was introduced on the anomeric position from a reducing carbohydrate precursor V′ (Scheme XII) and trichloroacetonitrile in alkaline medium, via the alkoxy intermediates W′ and X′.

With a weak base (e.g. potassium carbonate), the kinetically favored β-anomer (Y′) was formed predominantly.[488] Alternately the use of a strong base (e.g. sodium hydride) allowed the formation of the thermodynamically stable α-anomer (Z′) in high yield. The aforementioned trichloroacetimidates Y′ and Z′ were used as glycosylation donors with Lewis acids as promoters. Starting from the α-imidates Z′ the glycosylation of alcohols promoted by boron trifluoride etherate proved to be highly stereoselective,[361,362,364,365,490-492] thus affording mainly the β-glycosides in good yields, whereas the promotion by trimethylsilyl trifluoromethanesulfonate exhibited a lower stereoselectivity.[360,493] Nevertheless, this latter Lewis acid was used successfully in the promotion of the gly-

Scheme XIII



37

cosylation reactions using the β-imidate Y′ as donor, which afforded, stereoselectively, the α-glycosides.[360,493]

Many examples have been reported concerning the synthesis of 2-azido-2-deoxy-β-D-glycopyranosides from 2-azido-2-deoxy-α-D-glycopyranosyl trichloracetimidates and BF_3·Et_2O as the promoter. The following linkages involving either mono- or oligosaccharide donors and acceptors were created: β-D-Glc*p*N_3-(1→6)-D-Gal*p*N and β-D-Glc*p*N_3-(1→3)-D-Gal*p*N,[362,491] β-D-Glc*p*N_3-(1→3)-D-Glc*p*N,[361] β-D-Glc*p*N_3-(1→6)-D-Glc*p*,[364] β-D-Glc*p*N_3-(1→3)-D-Gal*p*,[492,494,495] β-D-Gal*p*N_3-(1→4)-D-Glc*p*[365] and β-D-Gal*p*N_3-(1→3)-D-Gal*p*.[496] The reported yields and stereoselectivities were generally high except in the latter example[496] involving a tetrasaccharidic donor, a disaccharidic acceptor and zinc chloride as the promoter (α:β = 1:1.7).

4-*O*-Allyl-(or benzyl)-2-azido-3,6-di-*O*-benzyl-2-deoxy-α-D-glucopyranosyl trichloroacetimidates were also used as donors with a properly protected muramic acid acceptor to afford the expected β-(1→4) disaccharides related to the bacterial peptidoglycans. The reported yields and stereoselectivities were high when BF_3·Et_2O[497] was used as the promoter, whereas the stereoselectivities were lower in the presence of trimethylsilyl trifluoromethanesulfonate as the promoter (α:β = 1:1.6).[490] The other glycosidic linkage found in the bacterial peptidoglycan [β-D-Mur*p*NAc-(1→4)-D-Glc*p*NAc] was obtained in moderate yield (38%) using the same methodology, starting from an α-D-Mur*p*N_3 donor and a D-Glc*p*N_3 acceptor.[498]

The syntheses of glycopeptides using 2-azido-2-deoxy-D-glycopyranosyl trichloroacetimidates have been well documented. The simplest glycopeptide α-D-Gal*p*NAc-(1→0)-Ser was prepared from the α-trichloroacetimidate of the 2-azido-2-deoxy-D-galactopyranose.[360,499] The glycosylation of a properly protected hydroxyproline acceptor by the 2-azido-2-deoxy-α-D-glucopyranosyl trichloroacetimidate afforded, in the presence of BF_3·Et_2O, a β-glycopeptide intermediate in the synthesis of Bulgecinine and Bulgecin C.[500]

The synthesis of the main mucin fragments **37** involved a multistage process (Scheme XIII).

Thus various α-trichloroacetimidate donors A″B″ (A″ = D-Gal*p* or D-Glc*p*N_3) were reacted with the properly protected L-serine in the presence of trimethylsilyl trifluoromethanesulfonate as the promoter to afford the expected α-glycopyranosyl serine derivatives A″B″C″ with weak selectivities.[362,491] On the other hand, the use of the β-anomeric imidate of the donor A″B″ afforded the α-glycopyranosyl serine fragment A″B″C″ with a high degree of stereoselectivity using the same promoter.[491] After removal of protective groups on the B″ part, both HO-4 and HO-6 free diols A″B″C″ (A″ = D-Gal*p* or D-Glc*p*N_3) were separately glycosylated with the α-imidate donor D″E″ in the presence of BF_3·Et_2O as the promoter. A new β-(1→6) glycosidic bond was thus created in a stereoselective and regioselective manner to afford tetrasaccharides A″(D″E″)-B″C″ with high yields (81% and 80% yield, respectively).[360,491] This elegant synthesis of main mucin fragments illustrated the scope and limitations of this method.

2-Azido-2-deoxyglycopyranosyl imidates could be used for the synthesis of α- as well as β-oligosaccharides depending on the anomeric orientation of the leaving group and on the promoter used. However, the high stereo- and regioselectivities reported above were not reproducible with similar acceptor diols containing an anomeric β-*tert*-butyldimethylsilyl)oxy group. Another strategy for the preparation of sialooligosaccharides related to mucin fragments, in which the serine moiety was introduced at the last stage, exhibited lower stereoselectivities and yields.[501-503]

3. Use of Thioglycosides and S-Xanthates as Glycosylation Donors

As already mentioned in the sections devoted to the phthalimido procedure, β-thioalkyl glycosides could be used as glycosylation donors in the presence of various promoters such as methyl triflate,[304,305] dimethyl(methylthio)sulfonium triflate (DMTST),[308,504] or tetrafluoroborate (DMTSB),[505] alkyl sulfenyl triflates,[321] phenylselenenyl triflate,[316] nitrosyl tetrafluoroborate,[314] or halonium-forming species.[301,432,506] This activation of the anomeric center was extended to the 2-azido-2-deoxyglycosylation donors. In these reactions the β-anomeric leaving groups were reported to be sulfonium ions formed by reaction of the thioether with the promoters, the reaction of which afforded mainly the α-glycosides.[507,508] The α-stereoselectivities of the reactions were reported to be favored in solvents of low polarity, avoiding the loss of stereocontrol due to the formation of the oxocarbenium intermediate C (Scheme I).

A few examples only have been reported to date[147,504,508] using this strategy. Paulsen and coworkers[147] thus described the synthesis of the main mucin fragments (Scheme XIII) via this glycosylation approach. Several methyl (or ethyl) 2-azido-2-deoxy-1-thio-β-D-galactopyranosides (mono- or oligosaccharides) were reacted with the properly protected serine acceptors in the presence of methyl triflate or DMTST as the promoters in solvents of low polarities (ether and dichloromethane/toluene respectively).[509] The reported yields were generally good (70–94%) but the α-stereoselectivities were shown to be strongly dependent on the promoter (usually better with DMTST than with methyl triflate) and on the protective groups (better with *O*-benzyl than with *O*-acetyl groups). The yields, and especially stereoselectivities, decreased drastically when the sizes of the oligosaccharides involved in the reactions increased. The cleavage of β-(1→6) glycosidic bonds was also reported in such glycosylation conditions.[147]

The aforementioned inconveniences reduce the field of application of this method which is much more valuable for the synthesis of 1,2-*trans*-glycosides (with amino protective group participation) than for the preparation of 1,2-*cis*-glycosides of the 2-azido-2-deoxyglycopyranosyl donors.

Very recently, 2-azido-2-deoxy-β-*S*-xanthates were introduced as efficient glycosylation donors. The aforementioned donors were obtained in two steps by azidoxanthation of protected D-galactal and the glycosylations were realized in the presence of a thiophilic promoter. The stereoselectivities of the glycosylation steps were shown to be strongly dependent on the solvent used. Thus, when the reaction was carried out in dichloromethane, the 1,2-cis orientation was observed with DMTST or Cu(II) triflate as the promoter,[367,510] whereas in acetonitrile, the 1,2-trans glycosylation was observed with both preceding promoters[367,510] and also with tris(4-bromophenyl)ammonium hexachloroantimonate[511] which acts by one-electron oxidation of the sulfur atom.

C. Conclusion

Due to the small size of the azido protective group, 2-azido-2-deoxyglycopyranosyl donors constitute reactive intermediates of general use.

Several anomeric leaving groups (halides, trichloroacetimidates, 1-thioalkyl) can be used thus opening the scope of the reaction.

Depending on the leaving group and the promoter used, 2-azido-2-deoxyglycopyranosyl donors can induce either a 1,2-cis or a 1,2-trans stereochemistry. In 1,2-trans glycosylations, the above method is preferable to the oxazoline or phthalimido procedure for the deprotection of compounds which is otherwise impossible in an acidic or alkaline medium. Nevertheless, the 2-azido-2-deoxyglycopyranosyl derivatives constitute, in proper conditions, the donors of choice for the synthesis of 1,2-*cis*-glycosides of the 2-amino-2-deoxy sugars.

VIII. Miscellaneous Methods

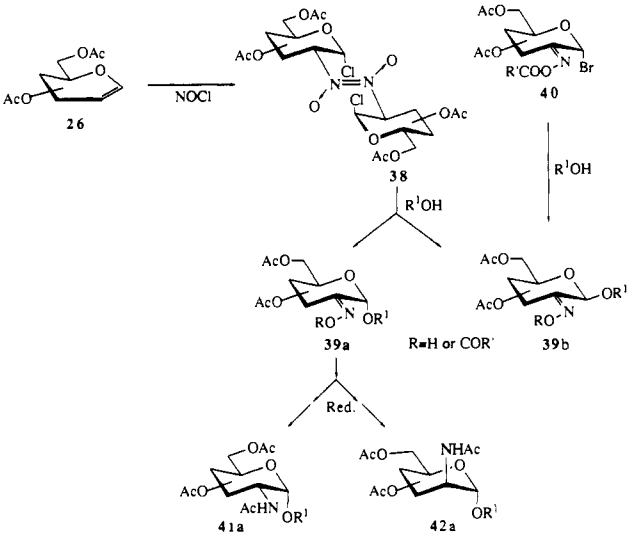
Several other glycosylation methods have been reported in the literature (although not fundamentally different from those previously described) which circumvent some of the inconveniences encountered during the glycosylation step and/or during the removal of the amino-protecting group of the glycosylated product.

A. Glycosylations Using Oximino Intermediates

Lemieux et al. introduced the nitrosyl chloride method in the 1970s. The addition of nitrosyl chloride to an acetylated glycal **26** led to the formation of a dimer adduct **38** (Scheme XIV) which reacted with the acceptor alcohol to afford an oximino intermediate **39**, which usually had the α-anomeric configuration.[512,513] The α-stereoselectivity and the yields were very good with simple acceptor alcohols[514] or monosaccharides,[515] but significant amounts of the glycosylated β-anomer were observed, or yields were shown to be strongly decreasing, with more sophisticated donors or acceptors.[42,515-518] In the case of diol acceptors, the reaction can also be regioselective.[398,519]

The syntheses of 2-oximino glycoside derivatives **39**[520-522] were also reported starting from a 2-keto intermediate treated with hydroxylamine or starting from a glycopyranosyl bromide possessing a C-2 oximino ester function **40** and alcohol acceptors in the presence of heavy metal salts.[523-525] The stereoselectivity of the aforementioned reaction was found to be

Scheme XIV



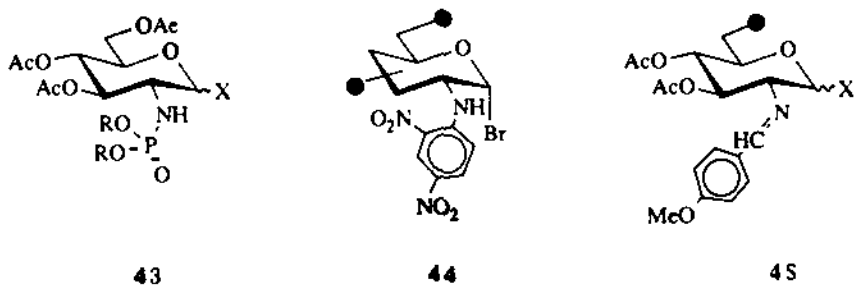
sensitive to the nature of the different promoters used. Thus the condensation of 3,6-di-*O*-benzoyl-4-*O*-(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyl)-2-*O*-(benzoyloximino)-2-deoxy-α-D-glucopyranosyl bromide and 1,2:3,4-di-*O*-isopropylidene-α-D-galactose afforded the β-trisaccharide (81% yield) in the presence of silver carbonate and iodine as promoter,[524] whereas the α-trisaccharide was obtained in 77% yield when silver triflate, iodine, and collidine were used as promoters.[524] Nevertheless, the β-stereoselectivity for this type of glycosylation reaction has been indicated to prevail most of the time as opposed to when the reaction is carried out from the dimer adduct.[523]

The reduction of the aforementioned oximino glycoside derivatives **39** could result in the formation of the two C-2 epimers of the 2-amino-2-deoxyglycosides **41** and **42**. Thus the hydrogenation with palladium and charcoal was reported to show a very low stereoselectivity affording the respective epimers **41** and **42** in the ratios ranging from 1:1 to 1:2.5.[526] Similarly, the reduction with lithium aluminum hydride was reported to show low stereoselectivities and low yields.[42,527] It was found that the best stereoselective reduction was obtained, after acetylation of the oximino intermediate, with diborane in oxolane. When the reduction of the free oximino derivative **39** was performed in the above conditions, the yields of the 2-amino products were high, whereas, the stereoselectivity remained low.[527] Also, it was reported that such reductions could lead to the corresponding 2-hydroxyamino derivatives of the parent oxime **39**.[517]

When the above reductions were effected after acetylation of the oximino function (i.e. on the N-acetylated oximino function), the stereoselectivity was drastically increased and favored the formation of the 1,2-*cis*-2-amino-2-deoxyglycoside **41** (Scheme XIV).

The enhancement of this stereoselectivity was more evident with the acetylated derivative **39** having the D-*arabino* configuration rather than with the corresponding D-*lyxo* epimer. Thus the D-*arabino*-oximino intermediate **39** was shown to afford preferentially the amino derivative with the D-*gluco* configuration over the D-*manno* epimer, whereas the D-*lyxo*-oximino intermediate **39** afforded a mixture of D-*galacto* and D-*talo* epimers in similar quantities.[527-529] An improve-

Scheme XV



43 44 45

ment in 1,2-cis stereoselectivity was also shown during the reduction of 2-(benzoyloximino)-β-D-arabinopyranosides affording β-D-mannopyranosides.[523] The above strategy (addition of nitrosyl chloride to glycals and subsequent reduction) was successfully applied to the syntheses of 1,2-*cis*-oligosaccharides of immunological interest[517] and 1,2-*cis*-aminoglycosides containing antibiotics such as streptomycin[519] and gentamycins.[530-532]

It should be noted that the reduction of the ketone derived from the oximino intermediate **39** with sodium borohydride constitutes also a viable route for the formation of 2-hydroxylated-1,2-cis-glycoside.[533]

B. Glycosylations Using 2-Dialkylphosphoramidate Donors

3,4,6-Tri-*O*-acetyl-2-(dialkylphosphoramido)-2-deoxy-α-D-glucopyranosyl halides **43** (R = Ph, Bn, 4-NO_2-Ph, 4-I-Bn; X = α-Cl, α-Br; Scheme XV) have been reported as glycosylation donors.[534] When simple alcohol acceptors (MeOH, BnOH) were used in excess with silver carbonate as promoter, β-glycosides were obtained in good yields (75–86%) and with a good stereocontrol.[534] In the case of monosaccharide acceptors possessing a free HO-6 primary hydroxyl group[54,535,536] or a reactive secondary position (i.e. glycerol[537]), glycosylation reactions using mercuric cyanide as the promoter afforded the β-glycosides with good stereoselectivities and moderate yields. With less reactive acceptors low yields and low stereoselectivities were observed, leading to α:β anomeric mixtures[538-541] and to side products such as the 1-cyano derivatives **43** (X = β-CN) and the phenyl glycoside **43** (X = β-OPh) resulting from the partial hydrolysis of the phosphoramidate function.[539]

After the glycosylation step the diphenylphosphoramidates could be deprotected chemioselectively by catalytic hydrogenation over Adam's catalyst.[534,535,538] Furthermore, the deprotection of all of the alkylphosphoramidates could usually be achieved through transesterification with benzyl alcohol and ammonia, followed by the hydrogenolysis over palladium on charcoal of the so-formed dibenzylphosphoramidates.[534,537,540]

C. Glycosylations Using 2-[(2,4-Dinitrophenyl)amino] Donors

The donors **44** (Scheme XV) were prepared by the action of 1-fluoro-2,4-dinitrobenzene on 2-amino-2-deoxy sugars followed by acylation and treatment with hydrogen bromide.[542,543]

The aforementioned amino protective group was supposedly nonparticipating and was expected to be 1,2-*cis*-glycoside producing. However, the steric hindrance of this participating group led mainly to the formation of anomeric glycosylation mixtures. Some examples of reactions giving rise to 1,2-*cis*-glycosides as the major derivatives were reported when the acceptor alcohol was used as the solvent (i.e. solvolysis).[544] Poor stereoselectivities were obtained when the reaction was performed in tetrahydrofuran, where the tetrahydrofuranyl oxonium ion intermediates should act as good leaving groups.[545,546] With monosaccharide acceptors the stereochemistry of the glycosylation reaction was rather unpredictable. When insoluble promoters were used such as Ag_2CO_3,[547] $AgClO_4$–Bu_3N,[548] and $AgClO_4$–Ag_2CO_3–collidine,[549] the stereoselectivity was mainly oriented in favor of the 1,2-cis anomers (α:β ratio varying from 2.5 to 4.0) in moderate yields (30–60%). When soluble promoters were used (mercuric salts) the stereoselectivity of the glycosylation was mainly in favor of the 1,2-trans isomers[546,550,551] in the D-*gluco* series but a 1,2-*cis* glycoside was reported in the D-*galacto* series.[552]

D. Glycosylations Using 2-[(4-Methoxybenzylidene)amino] Donors

Another nonparticipating amino protective group used in glycosylation reactions was the 4-methoxybenzylidene group. The glycopyranosyl donors **45** (X = α-Br, Scheme XV) were prepared from D-glucosamine and 4-methoxybenzaldehyde, followed by conventional acetylation and treatment with hydrogen bromide.[534]

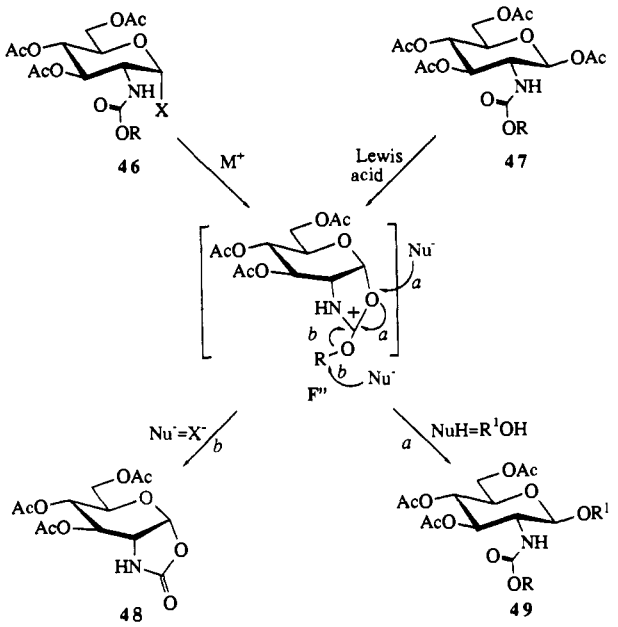
When Ag_2CO_3 was used as the glycosylation promoter with simple acceptor alcohols (MeOH, BnOH), 1,2-*trans*-glycosides were obtained in good yields (55–60%).[534] With monosaccharides[537,553,554] or L-serine[555] acceptors the glycosylation reactions using the same promoter afforded mixtures of anomeric glycosides with a low stereoselectivity and very poor yields. When mercuric cyanide was used as the promoter with aminoinositol acceptors, the corresponding α-glycosides were obtained in good yields (>50%), thus affording a good method for preparation of aminoglycoside antibiotics such as neamine[556,557] and lividomycin B.[558,559] A synthesis of dihydrostreptobiosamine fragment was realized by condensation of the enantiomeric L-*gluco* form of donor **45** with a free HO-2 isopropylidene derivative of benzyl dihydrostreptoside as the acceptor.[560]

Recently it was shown by Marra and Sinaÿ that the *N*-(4-methoxybenzylidene) group had participating tendencies in the glycosylation reactions.[561] These authors showed that when an *O*-benzyl-protected α-D-glucopyranoside acceptor with a free HO-6 was glycosylated with compound **45** as the donor, in the presence of silver triflate and collidine as the promoter, the β-(1→6) disaccharide was obtained in good yields (79%, β:α = 9:1).[561] Also, they showed that, when the free HO-4 isomeric acceptor was glycosylated under the same conditions, an anomeric mixture of the corresponding (1→4)-disacchardies was obtained in moderate yield (47%, α:β = 1:1).

When the same glycosylation reaction was performed in the presence of mercuric cyanide as the promoter, it was shown that the corresponding β-glycoside **45** (X = β-OR) was obtained together with the α-glycoside **45** (X = α-OR) in which addition of HCN had occurred on the double bond of the amino protecting group.

A new mode for activating the anomeric position of *N*-(4-methoxybenzylidene) derivatives has been recently reported in which a 4-pentenyl glycoside (**45**, X

Scheme XVI



= β-*O*-Pent) led to the formation of the corresponding 1,2-*cis*-glycosides. The promoter used for such glycosylation reactions, was the complex collidine–iodinium perchlorate, and the corresponding 1,2-*cis*-glycosides were obtained in good yields (60–68%) and stereoselectivities.[190]

In summary, the above mentioned results involving glycosylation reactions using 2-[(4-methoxybenzylidene)amino] donors showed contradictory results with regard to the various stereoselectivities of the products and no rationale can be made for their use in glycosylation reactions.

E. Glycosylations Using 2-(Alkoxycarbonylamino) Donors

N-(Alkoxycarbonyl) derivatives of 2-amino-2-deoxy sugars **46** and **47** (Scheme XVI) have been used as valuable glycosylation donors since they allowed chemioselective preferential deprotection of the amino protective group. It was anticipated that the carbamate protective group could be involved in C-2 anchimeric assistance to afford the cyclic azadioxocarbenium intermediate F″ the formation of which should be more favored than the corresponding oxazolinium ion[562] which was already described in the oxazoline procedure (section V).

The first example reported in the literature involved a glycosylation using the 3,4,6-tri-*O*-acetyl-2-(benzyloxycarbonylamino)-2-deoxy-α-D-glucopyranosyl bromide (**46**; X = α-Br, R = Bn) as donor and methanol in excess as acceptor, in the presence of Ag_2CO_3 as promoter,[534] to afford the corresponding β-methyl glycoside in moderate yield. It was shown that using the same donor and benzyl 2-acetamido-4,6-*O*-benzylidene-2-deoxy-α-D-glucopyranoside as acceptor, in the presence of mercuric cyanide as the promoter, the oxazolidinone **48** was obtained in almost quantitative yield together with the 3-*O*-benzyl ether derivative (8%) of the acceptor alcohol.[540] Nevertheless, when a 2-(benzyloxycarbonylamino)cyclohexanol acceptor was used in the same conditions, the expected β-glycoside was obtained.[563] The aforementioned oxazolidinone was reported to be formed in 40% yield from the corresponding β-acetylated compound **47** (R = Bn) in the presence of a Lewis acid.[98]

Other 1,2-trans glycosylations were also reported in moderate yields (42–46%), using similar donors (**46**, X = Cl, R = Et, Bn, CH_2CH_2Cl) and methanol or benzyl alcohol as the acceptor, in the presence of silver salts as promoters.[564]

As far as we are concerned, we have recently reported the glycosylation of model alcohols (isopropyl alcohol, cyclohexanol, *tert*-butyl alcohol, and 2,2,2-trichloroethanol) by several donors **46** (X = α-Br, R = Me, Et, All,[565] Bn, CH_2CCl_3, and *p*-nitrobenzyl) and **47** (R = Me, Et, All, Bn, CH_2CCl_3, *p*-nitrobenzyl, and *tert*-butyl),[566] in the presence of different promoters. Thus in the presence of mercuric cyanide all of the glycopyranosyl bromide donors **46** afforded the expected 1,2-*trans*-glycosides in good yields except in the case of the weakly nucleophilic trichloroethanol. It is to be mentioned that when the alkyl group of the carbamate function was able to accommodate a positive charge (R = All, Bn, or *p*-NO_2Bn) the oxazolidinone **48**, already reported by Paulsen and co-workers,[540] was obtained as a side product[566] in addition to the expected β-glycosides **49**. It is important to mention that this elimination reaction (Scheme XVI, pathway b), affording the oxazolidinone **48** from the ambident azadioxocarbenium ion F″, has never been observed in our hands when the β-acetate **47** was used as the glycosylation donor and trimethylsilyl trifluoromethanesulfonate as the promoter. In this latter Lewis acid catalyzed glycosylation method, all of the donors **47** (except when R = *t*-Bu) reacted with the same four acceptor alcohols already mentioned, to afford the expected β-glycosides in good to very good yields (50–95%).[566]

The 2-(allyloxycarbonylamino) derivative **47** (R = All) was studied in more details for the Lewis acid catalyzed glycosylation reactions.[567] The amino function of the so-formed β-glycosides could be easily deprotected in a chemiospecific manner [Pd(0) complexes] after the glycosylation step to afford the free amino group containing glycosides.[567] Thus, following the 2-(allyloxycarbonyl) procedure several monosaccharide or oligosaccharide acceptors were efficiently glycosylated to afford structural units of antigenic fragments, glycans building blocks[567–570] or glycopeptides.[571]

The alkoxycarbonyl approach has been successfully applied for the syntheses of lipid A intermediates. Thus the donors **46** (X = Br, Cl; R = CH_2CCl_3, Bn) were reacted with D-glucosamine acceptors (with free HO-6 or free HO-6 and HO-4) in the presence of mercuric cyanide as the promoter to afford the expected β-(1→6) disaccharides in good to very good yields (40–94%).[572–578]

Compound **46** (X = α-Br; R = CH_2CCl_3) was shown to be a 1,2-trans and a 1,2-cis glycosylation donor as well, depending on the promoter used. Thus, when zinc chloride (1 equiv) combined with trityl chloride (1 equiv) was used as a promoter, very good yields and high β-stereoselectivities (β:α = 99:1) were observed. In contrast, when zinc chloride (or bromide) only was used as the promoter, the α-glycosides were obtained stereoselectively (α:β = 99.1) in good yields.[579]

Recently, various anomeric activations were de-

scribed in the literature. Thus the dimethylphosphinothioate has been proposed as a good anomeric leaving group. The 3,4,6-tri-*O*-benzyl glycopyranosyl donor related to **46** [X = $OP(Me)_2S$, R = Bn] was prepared and reacted with various alcohol acceptors in the presence of iodine as an activator and triphenylmethyl perchlorate as a catalyst.[580] In this method the reported yields were good with reactive alcohols only (45–72%), whereas with unreactive acceptors the main product was the 3,4,6-tri-*O*-benzyl oxazolidinone related to **48**.[581]

3,4,6-Tri-*O*-benzyl-2-(benzyloxycarbonylamino)-2-deoxy-α-D-glucopyranosyl bis(dimethylamino) phosphate was used as glycosylation donor with an epipodophyllotoxin alcohol derivative as the acceptor and boron trifluoride etherate as the promoter to afford a 2-(benzyloxycarbonylamino)-2-deoxy-β-D-glucopyranoside in 74% yield.[582] It should be mentioned that the same acceptor alcohol was also reacted separately with both anomers of 3,4,6-tri-*O*-benzyl-2-(benzyloxycarbonylamino)-2-deoxy-D-glucopyranose in the presence of boron trifluoride etherate. Starting from the β-anomer, the β-glucoside, obtained in 72% yield, contained traces only of the isomeric α-glucoside, whereas starting from the α-donor, the stereoselectivity of the reaction was somewhat lower (80% yield, α:β = 17:1).[583]

3,4,6-Tri-*O*-acetyl-2-deoxy-2-(trichloroethoxycarbonylamino)-α-D-glucopyranosyl trichloroacetimidate [**46**, X = $OC(NH)CCl_3$; R = CH_2CCl_3] was also used recently as a donor in the presence of trimethylsilyl trifluoromethanesulfonate for the glycosylation of a free HO-2 D-mannose acceptor.[273]

In summary the 2-(alkoxycarbonylamino) approach for the synthesis of 1,2-*trans*-glycosides of 2-amino-2-deoxy sugars seems an alternative to the well-known glycosylation methods. In addition to good glycosylation yields, the stability of the amino protective group (except in strong alkaline medium) and the possibility of a chemioselective or chemiospecific cleavage of the latter into the free amino group offer viable routes to a wide variety of new oligosaccharides.

F. Other Glycosylation Methods

Several other glycosylation methods will be mentioned in the following section.

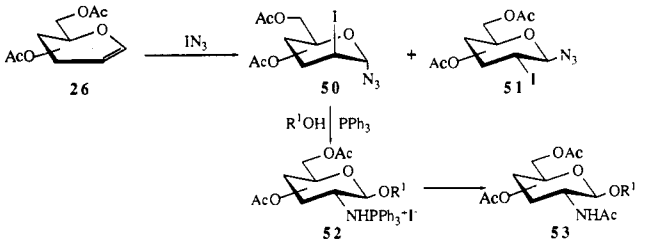
β-Phenyl glycosides were prepared by reaction of the 2-alkylamidoglycopyranosyl chlorides with the sodium salt of phenol.[100,107,165]

Alkyl glycosides of the 2-amino-2-deoxy sugars were prepared by solvolysis of anomeric esters.[584]

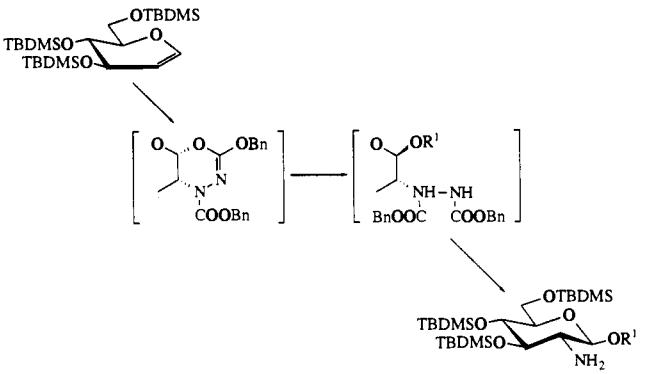
The Fisher method using 2-alkylamido-2-deoxy-D-glucopyranose donors and boron trifluoride etherate,[30] hydrochloric acid,[585] or triflic acid[586] as catalyst afforded the 1,2-*cis*-glycosides in moderate yields (30–67%), whereas when hydrogen fluoride was used, 1,2-*trans*-glycosides were obtained in good yields.[587]

Several other protecting groups of the amino function have also been reported. For example, β-carbonyl enamines (the deprotection of which could be achieved with either chlorine or bromine[588]) and benzyl sulfonamides (which could be deprotected by catalytic hydrogenation[589]) were shown to be participating groups in glycosylation reactions promoted by silver salts. Derivatives of urea,[590] 2,2,2-trichloro-1,1-dimethylethyl carbamates,[591,592] *N*-acylphenyloxazoline,[593] and *N*-formyl derivatives of D-glucosamine[102,103] were also used for 1,2-trans glycosylation reactions. The applicability

Scheme XVII



Scheme XVIII



of these glycosylation methods were nevertheless restricted to a few examples. It could be mentioned that an NMR study on several of the above donors and their 1,2-trans glycosylation products was reported in the literature.[594]

The recent introduction of the thioalkyl leaving group of some of the aforementioned glycopyranosyl donors afforded better 1,2-trans glycosylation yields.[595]

Finally, we would like to report on two recent methods of 1,2-trans glycosylation of 2-amino-2-deoxy sugars starting from glycals.

The addition of iodoazide IN_3 on 3,4,6-tri-*O*-acetyl-D-glucal or D-galactal **26** afforded mixtures of 1,2-*trans*-2-deoxy-2-iodo-D-glycopyranosyl azides **50** and **51**, in which the α-anomer **50** was more predominant (i.e. D-*manno* and D-*talo* configurations, Scheme XVII).[596,597]

Both 2-iodo azide compounds derived from D-glucal (**50** and **51**) were separately treated with triphenylphosphine in the presence of alcohol to afford 2-amino phosphonium salts of 1,2-*trans*-glycosides in good yields. The removal of the phosphonium protective group, without isolation of the intermediate **52**, followed by acetylation of the amino function, afforded the respective 1,2-*trans*-2-acetamidoglycosides **53** in overall yields of 40–80%.[597]

Similarly, 2-iodoglycopyranosyl azides were transformed into 2-iodoglycopyranosyl phosphoramidates[596] and used as glycosylation donors to afford 1,2-*trans*-glycosides.[598] The same approach was used in the synthesis of 1,2-*trans*-2-halo-1-sulfonamido hexoses from glycals and subsequent reaction with alcohols to afford 1,2-*trans*-glycosides.[599] This latter methodology was applied recently to the synthesis of the chitinase inhibitor allosamidine.[600]

The [4+2] cycloaddition of dibenzylazodicarboxylate on per-(*tert*-butyldimethylsilyl)ated D-glycals were reported to give dihydraoxadiazine intermediates (Scheme XVIII) which could react in acidic medium to afford 1,2-*trans*-glycosides. The cycloaddition yields (70–80%) and the yields of the opening of the cycloadducts (80–90%) were high with primary alcohols.[601,602]

The deprotection of the amino function by hydrogenation over Raney nickel afforded the free amino containing 1,2-*trans*-glycoside in very good yields (73–98%). Unfortunately an important limitation of the method is that it could not be extended to acetylated glycals.[602]

IX. Conclusion

Interest in the glycosylation reactions has witnessed an increase in importance in the last two decades. This renewal of interest can be attributed to the discovery of the role played by oligosaccharides in recognition phenomena which greatly benefitted the field of glycosylation of the above derivatives. We believe that this review article is a complete and accurate representation of the various syntheses of the 2-amino-2-deoxy carbohydrates.

In conclusion, the syntheses of 1,2-*trans*-glycosides of the 2-amino-2-deoxy carbohydrates were derived from the pioneering work of Koenigs and Knorr.

The oxazoline procedure which can be considered a logical application of this pioneering work remains an up-to-date method for the glycosylation of reactive acceptors, since the 1,2-*trans*-glycosides were obtained in their natural 2-acetamido form. Nowadays, more sophisticated procedures allow the synthesis of almost any oligosaccharide containing this 1,2-trans linkage irrespective of the reactivity of the acceptor alcohol. The phthalimido procedure constitutes the method of choice for the synthesis of 1,2-*trans*-glycosides of the 2-amino-2-deoxy sugars. Other methods described in this rationale, including the use of 2-azido-2-deoxyglycopyranosyl donors and the use of 2-alkoxycarbonyl derivatives of the 2-amino-2-deoxy carbohydrates, show some promise in this field. They allow the cleavage of the amino protective group (after the glycosylation step) in various, and sometimes neutral, conditions.

The synthesis of 1,2-*cis*-glycosides of the 2-amino-2-deoxy carbohydrates are less numerous but the recent introduction of the azido group as a small nonparticipating protective group for the amino function, greatly enhanced progress in the field. A complete knowledge of the reaction mechanisms was necessary for the successful design of 1,2-cis glycosylations. The role of the solubility of the promoter in the reaction solvent, the in situ anomerization of the leaving group, the reactivity of the acceptor, and the nature and orientation of the leaving group constitute the main controlling factors for such stereoselective reactions.

Finally, progress has been made in oligosaccharide synthesis due to the introduction of imidates as glycosylation donors and very recently of 1-thioglycosides in the presence of thiophilic promoters. These stable but, nevertheless, very reactive derivatives will probably open new prospects in the field of the 2-amino-2-deoxy carbohydrates.

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