

# 1.06 Protecting Group Manipulations in Carbohydrate Synthesis

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## 1.06.1 Introduction

Carbohydrates play essential roles in a lot of diverse biological processes, whose survey, on a molecular level, necessitates the synthesis of various natural mono- and oligosaccharides, glycoconjugates (neoglycolipids, neoglycoproteins, neoglycopeptides), and their analogs. Since carbohydrates are polyfunctional compounds, the chemical synthesis – even of the most simple derivatives – requires the application of protecting groups, and this is more pronounced in the preparation of complex oligosaccharides and glycosaminoglycan fragments, which are considered the ‘non plus ultra’ of oligosaccharide syntheses.

Essentially, the protecting groups employed in the chemistry of carbohydrates are the same as those generally used in organic chemistry. However, the polyfunctionality, that is, the presence of a large number of the same functional group – which is mainly the hydroxyl group – at the carbohydrate skeletons, necessitates specific protecting group manipulations, including introduction of ester, ether, and acetal groups, their removal or occasional migration and various additional transformations. There are other, nonetheless important, but less frequently emerging groups to be used for the protection of nitrogen, carboxyl, and carbonyl functionalities.

The protecting groups inhibit the participation of the substituted hydroxyl, or other functional groups in certain chemical transformations. At the same time, it is important to consider the electronic and/or steric influence of these groups on the reactivity of the molecule, as a whole, and this is most particularly valid for the generation of the glycosidic linkages, namely, in glycosidation reactions tuning the reactivity of the reaction partners. Further, the stereochemical outcome can be highly influenced and regulated by the protecting groups incorporated into the donor and acceptor molecules.

This chapter is aimed at the discussion of the introduction and removal of the most frequently applied protecting groups in carbohydrate chemistry, as well as the art of protecting group strategies and manipulations. Since many of the aspects of the formation, stabilities, and splitting of the protecting groups in organic syntheses are comprehensively reviewed by excellent monographs,<sup>1,2</sup> the detailed description of these will not be highlighted here. At the same time, an emphasis will be made on the application of the protecting groups and manipulation with them in carbohydrate chemistry.

We are well aware that the chemistry of sugars is not limited to oligosaccharide syntheses. Nevertheless, a great majority of the examples has been taken from this latter particular field. The reason for this is quite obvious: the construction of certain complex structures requires the application of a wide variety of protecting group strategies, which expose and demonstrate the existing rules.

## 1.06.2 General Considerations

During the designing of a synthesis strategy, consideration of economical factors is very important. Consequently, application of the possibly least and less variety of protecting groups is desired. Application of a protecting group requires at least two synthetic steps: its introduction and removal. Therefore, regioselective processes offering acceptable preparative yields with polyhydroxy derivatives are very necessary. Related examples from the field of oligosaccharide syntheses are the ‘open glycosylations’,<sup>3,4</sup> for example, the regioselective glycosidation of unprotected allyl  $\alpha$ - or  $\beta$ -D-mannopyranosides at the primary hydroxyl group with a glycosyl bromide<sup>5</sup> or with glycosyl trichloroacetimidate.<sup>6</sup> Of the similarly regioselective reactions, oxidation of mono-, oligo-, and polysaccharides with TEMPO results in the oxidation of the primary hydroxyl groups exclusively.<sup>7–9</sup> However, such selective reactions are not frequent. In many cases only two hydroxyl groups remain free, for example, in the acceptor molecule, but there is such a great difference between the reactivity of these two groups that for a regioselective transformation no protection of the less-reactive hydroxyl is necessary, and thereby a few synthetic steps may be avoided. In general, the primary hydroxyl groups are much more reactive than the secondary hydroxyls and, due to steric or other factors, even two secondary hydroxyl functions may possess different reactivity. Utilization of the above observations considerably enhances the efficiency of the syntheses, but their applicability may be quite limited, most particularly in biologically

relevant cases. Thus, generally all of the functional groups (hydroxyl, amino, carbonyl, and carboxyl) must be protected – except the one to be involved in the reaction.

The required properties of an ideal protecting group are as follows: (1) readily available reagents are necessary for its introduction and removal; (2) it should be readily characterized, its introduction is not accompanied by the formation of a new asymmetric center, but if this cannot be avoided, only one stereoisomer must be present; (3) it should be stable in most of the chemical transformations; and (4) it should be compatible with the work-up conditions. A further advantage is that the resulting protected compound is highly hydrophobic, thus making extractive work-ups easier, and if the product is crystalline, so as to offer convenient purification.<sup>10</sup> An additional general requirement is that, upon removal, no problems occur with the separation from a residue due to the cleaved protecting group.<sup>11</sup> Still another advantage is that monitoring of the compound protected with the given group becomes easier,<sup>12</sup> and in certain cases additional practical factors can also be determined, for example, no heterogeneous catalyst is required upon removal which might be a problem in solid support syntheses.<sup>13</sup>

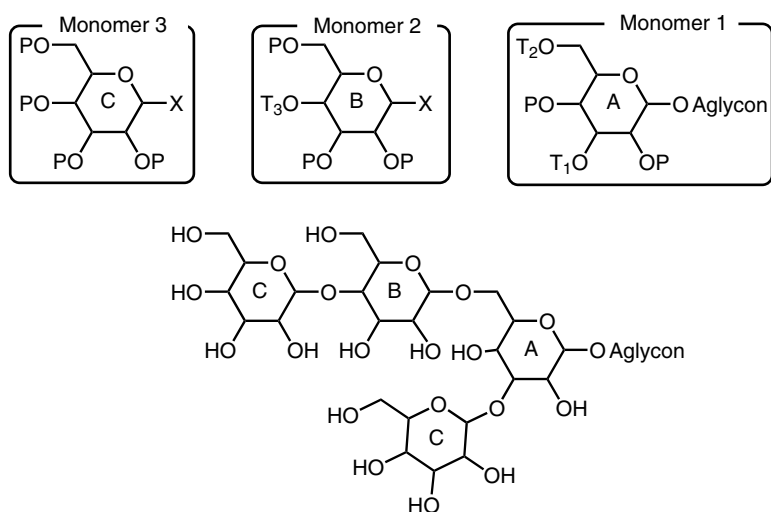
### 1.06.2.1 Protecting Group Strategy: Permanent, Temporary, and Unichemo Protection

In order to synthesize a complex oligosaccharide or glycoconjugate, the correct selection of the protecting group strategy/manipulation, namely the role of introduction and removal is of primary importance. The success of long, complicated synthetic routes may be disadvantageously influenced or even prevented by the decomposition of the product upon removal of an unfortunately selected protecting group. At the same time, a good manipulation with the protecting groups may significantly shorten the reaction sequence.

Carbohydrate chemists must consider that much more functional groups are to be protected than those required to carry out the desired transformations. For example, in a synthesis of a tetrasaccharide from monosaccharides three hydroxyl groups should be glycosylated and 13 hydroxyls should be protected. Obviously, it is quite advantageous to protect all of the 13 groups with the same (or that very similar in character) protecting group (e.g., acyl) to ensure removal in a single step. The groups staying in the target molecule until the penultimate step, involving their removal, are called permanent protecting groups. Other groups that are retained in the molecules only in one step, or in a few steps, and which can be selectively split (by distinguishing them from the permanent protecting groups), are the temporary protecting groups (**Figure 1**). The number and character of the temporary protecting groups are obviously determined by the structure of the target molecule.

In general, two types of permanent protecting groups are applied: (1) the benzyl, or benzyl-equivalent groups, if the target compound is sensitive to basic or alkaline deprotection (i.e., splits or migrates, such as the phosphate ester);<sup>14</sup> and (2) ester-type permanent protecting groups are used when the product carries, for example, an unsaturated aglycon<sup>15</sup> which changes upon hydrogenolysis of the benzyl groups.

After selection of the permanent protecting groups, the number of the temporary protecting groups is dependent on the structure of the target molecule. In the case of a branched oligosaccharide, or when other substituents (e.g., sulfate,

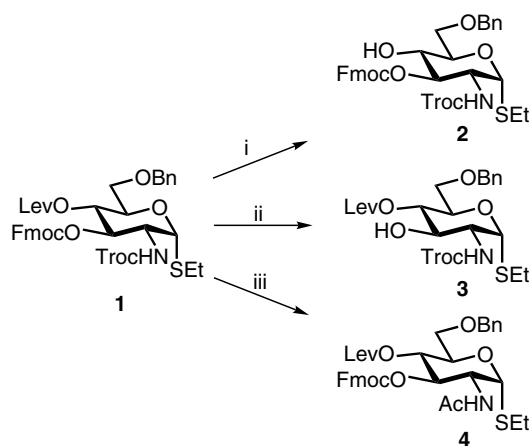


**Figure 1** Protecting group pattern of monomers for the synthesis of a tetrasaccharide. P=permanent protecting group; T<sub>1</sub>, T<sub>2</sub>, T<sub>3</sub>=temporary protecting groups.

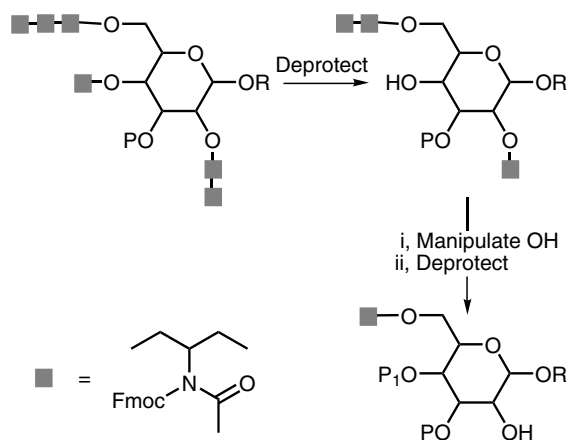
phosphate) are present, numerous temporary groups are necessary that must be selectively removable in the presence of each other (orthogonal). The permanent and temporary protecting groups are not necessarily the members of another type of compounds. In oligosaccharide syntheses,<sup>16</sup> benzoate esters are often used as permanent groups together with the selectively removable acetate or chloroacetate esters as temporary protecting groups. The pivaloyl, levulinoyl, or chloroacetyl groups can also be selectively removed in the presence of permanent acetate esters. A general practice is the application of ester in the presence of ethers or vice versa (Figure 2). The acetals are usually employed for the simultaneous temporary protection of two hydroxyl groups, and then they are cleaved or transformed in a selective manner.

In conclusion, in oligosaccharide syntheses either the representatives of one group of compounds are employed as permanent and temporary protecting groups, or these functions are selected from two or three types of organic substances.

An interesting alternative of the protecting group manipulations is the so-called unichemo strategy,<sup>17,18</sup> which was introduced, not very surprisingly, by a peptide chemist.<sup>17</sup> In this approach a single type of protecting group is used exclusively, which is an oligopeptide, and the only difference is in the polymerization degree of the individual protecting group. For cleavage the Edman-degradation is applied. The hydroxyl group which is protected by a monomer is liberated, and the oligomers protecting the other hydroxyls are degraded with one monomer. Following the manipulation of the hydroxyl, the repeated degradation cycle furnishes the next free hydroxyl group(s), and again, each of the unichemo-protected oligomers is shortened with one monomer unit (Figure 3).



**Figure 2** Conditions: (i)  $\text{H}_2\text{NNH}_2 \cdot \text{HOAc}$ ,  $\text{MeOH}:\text{DCM}$  (1:10), 99%; (ii)  $\text{Et}_3\text{N}$  (20%),  $\text{DCM}$ , 99%; (iii)  $\text{Zn}$ ,  $\text{HOAc}$ , then  $\text{Ac}_2\text{O}$ ,  $\text{Py}$ , 86%.

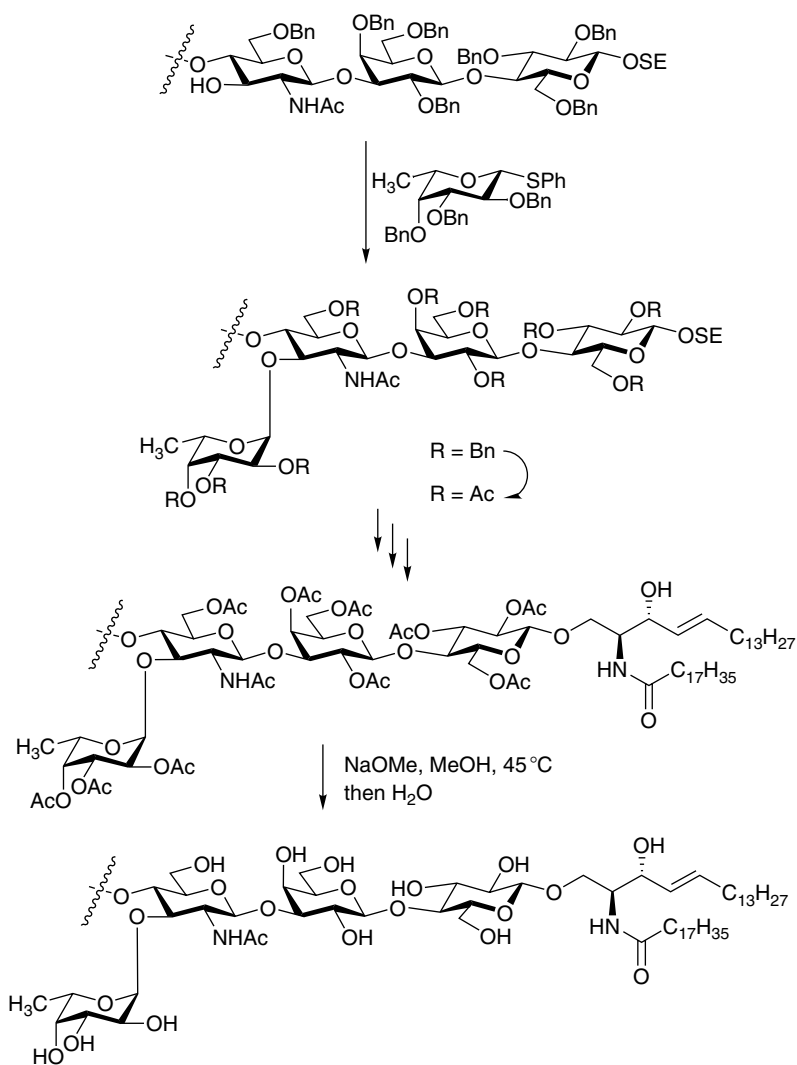


**Figure 3** The principle of the 'unichemo' protection.

When designing a protecting group strategy, it must be taken into account that the protecting groups modulate the properties of the whole molecule. The alkyl groups generally enhance<sup>19</sup> (sometimes even too much),<sup>20</sup> and the ester groups diminish,<sup>21–25</sup> respectively, the reactivity of the molecules. A number of protecting groups, first of all the acyl substituents influence the steric outcome of the glycosidation reactions by means of anchimeric assistance.<sup>23,26</sup> Due to steric reasons, other groups (generally the acetals) have effects on the reactivity and stereoselectivity,<sup>19,27,28</sup> or on the regioselectivity,<sup>29,30</sup> and bulky groups may change the conformation of the sugar skeleton.<sup>31–35</sup> Many examples have been reported on how to tone<sup>36</sup> the reactivity of the donor and acceptor molecules by choosing their appropriate protecting groups, so as to reach a good-yielding coupling with high selectivity, and to avoid undesired side reactions.<sup>37–39</sup>

In some longer reaction sequences, change of the protecting groups may also emerge. An example for this is the synthesis of the  $\alpha$ -L-fucopyranoside-containing oligosaccharides, where – in order to ensure  $\alpha$ -selectivity – application of fucopyranosyl donors carrying the so-called nonparticipating benzyl groups is desired. Since the generated bond in this case is rather sensitive, following glycosidation the benzyl groups are exchanged to esters (acetyl or benzoyl)<sup>15,40,41</sup> (Figure 4).

Apart from the influence on the reactivity and stereoselectivity of the selected number and type of the protecting groups, in an appropriate design of a synthesis strategy practical aspects have also to be considered. Sometimes it is



**Figure 4** Change of the protecting groups during a reaction sequence.

most advantageous if the protected saccharide is well-detectable and characterizable, as well as highly lipophilic that makes the work-up procedure more convenient.

In theory, in the case of all of the aldohexoses, three secondary and one primary hydroxyl groups have to be protected – except the anomeric center. However, it does not mean that an analogous protection scheme can be applied for all of the sugars, since the regioselective introduction, removal, and transformation of a given group is also dependent on the configurational properties of the individual sugar. Moreover, a successful manipulation with a monosaccharide cannot necessarily be transferred to a higher-membered oligomer, even in the most simple case, for example, for the removal of an acyl group.<sup>42</sup>

In conclusion, compilation of a successful protecting group strategy necessitates an excellent knowledge of the literature procedures, and to realize the plan good practice is needed besides a bit of luck pulling the strings from time to time.

### 1.06.3 Regioselective Formation of the Protecting Groups

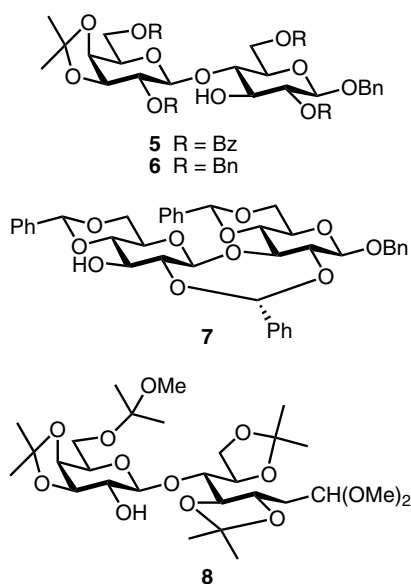
The synthesis of a synthon carrying free hydroxyl group(s) in the given position(s) can be accomplished by (1) protection of the hydroxyls of the polyol, which are not involved in the transformations, and needed to be free in the target molecule, or (2) the regioselective cleavage of the protecting groups of a fully protected derivative.

#### 1.06.3.1 Simultaneous Protection of Three or More Hydroxyl Groups

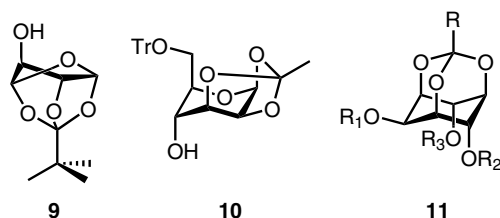
In a few cases there is a possibility for the protection of more hydroxyl groups in a single step so that one of the hydroxyls remains free. This strategy permits a significant reduction of the steps required, for example, for the preparation of 3-*O*-methyl-lactose, as well as allows the economical preparation of the oligosaccharide fragments of arabinogalactans.<sup>43,44</sup>

Such a substitution reaction in the monosaccharide field is quite rare. As an example, acetylation of benzyl  $\beta$ -D-glucopyranoside with NaOAc/Ac<sub>2</sub>O to result in the 2,4,6-tri-*O*-acetyl derivative can be mentioned.<sup>45</sup> Such functionalizations of disaccharides that are dependent on the configuration are often applied. Tsukida *et al.* studied the conditions of the benzylation of  $\beta$ -alkyl 3',4'-*O*-isopropylidene lactosides in detail, and following optimization, the 2,2',6,6'-tetrabenzoate **5** could be isolated with a good yield.<sup>46</sup> The lactosides can also be alkylated (**6**) at the same positions.<sup>47</sup>

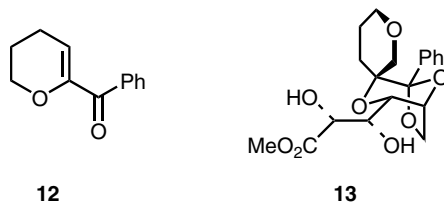
An acetal represents a most particularly useful protecting group to simultaneously substitute more hydroxyl groups of a saccharide derivative. For lactose and laminaribiose, the isopropylidene<sup>48</sup> and the benzylidene acetal, respectively, proved to be suitable;<sup>49,50</sup> thus, **8** and **7** were synthesized (Figure 5).



**Figure 5** Simultaneous protection of hydroxyls.



**Figure 6** Simultaneous protection of three hydroxyls by internal orthoester group.



**Figure 7** Simultaneous protection of three hydroxyls by the 6-benzoyl-3,4-dihydro-(2H) pyran reagent.

In the case of monosaccharides<sup>51</sup> and inositols,<sup>52–55</sup> an orthoester function offers the joint protection of three hydroxyl groups. Such tricyclic or internal orthoesters of carbohydrates are long known,<sup>56,57</sup> and prepared from sugars with *D-arabino*, *D-xylo*, *L-rhamno*, *D-gluco* and *D-manno* configurations from 1,2-orthoesters. The susceptibility of the hydroxyl groups to be included in an internal orthoester is dependent on the configuration. In *D-xylo* (**9**) or *D-gluco* sugars and *D-manno* derivatives (**10**), the 1,2,4- and 1,2,3-positions, respectively, can be simultaneously protected this way.<sup>58</sup> Internal orthoesters are not very often used as protecting groups, rather their capability for polymerization is utilized in syntheses of certain types of oligosaccharides (**Figure 6**).<sup>51</sup>

At the same time, in the inositol field the orthoformate (**11**, R=H) or orthoacetate (**11**, R=Me) protecting groups are routinely applied. Apart from incorporating three hydroxyl groups, a further advantage of such orthoesters is that they fix the ring-conformation, thus permitting further regioselective substitutions.<sup>52</sup>

A novel method for the protection of triols was worked out by Rawlings *et al.*,<sup>59</sup> by introducing the 6-benzoyl-3,4-dihydro-(2H)pyran reagent **12**. They combined the protecting capability of dihydropyran and a carbonyl group in a single molecule. The susceptibility of the procedure was demonstrated with sugar alcohols and  $\delta$ -gluconolactone **13** (**Figure 7**).

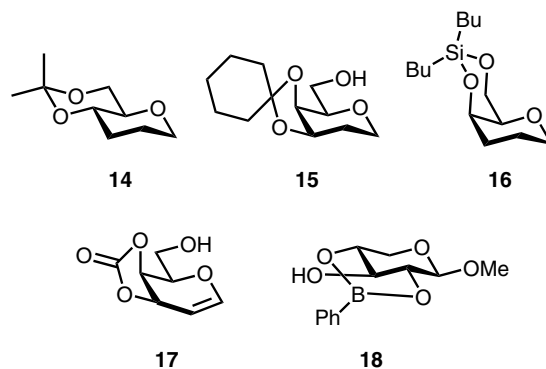
### 1.06.3.2 Simultaneous Protection of Two Hydroxyl Groups

Joint protection of the hydroxyls of carbohydrate 1,2- and 1,3-diols is very often accomplished with acetal (e.g., **14**, **15**, **16**),<sup>60</sup> orthoester (**26**),<sup>61–63</sup> cyclic carbonate (**17**),<sup>64–67</sup> or boronate (**18**)<sup>68</sup> functions (**Figure 8**).

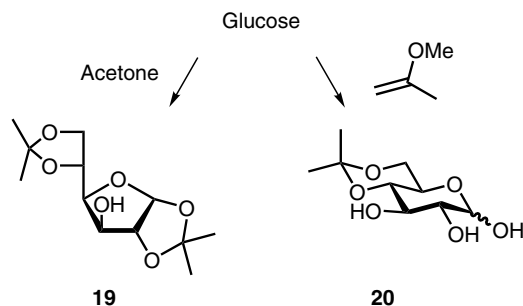
Various reasons contributed to the success of acetal protecting groups in carbohydrate chemistry. Thus, simple, readily available, cheap, and nontoxic reagents are used for their preparation, and the acetalation reactions are convenient to carry out with high yields. In addition, it is very important that by an adequate selection of the type of the acetal and of the reagents and conditions, the ring-size of the sugar can be influenced, and 1,2- and 1,3 diols can be distinguished. In the case of vicinal diols, selective protection of the *cis*- and *trans*-diols can be effected. Several review materials and book chapters deal with the preparation, transformation, migration, and cleavage of carbohydrate acetals.<sup>69–74</sup>

Of such acetals, the isopropylidene and benzylidene derivatives are by far the most frequently applied. Methoxybenzylidene,<sup>75,76</sup> diphenylmethylene, and cyclohexylidene<sup>77</sup> acetals are less often employed. Of the silylene acetals, the di-*t*-butylsilylene acetal<sup>78</sup> and the TIPDS group<sup>34,79</sup> are to be mentioned. A new and well-utilizable group of acetals is the 1,2-diacetals of carbohydrates.<sup>80</sup>

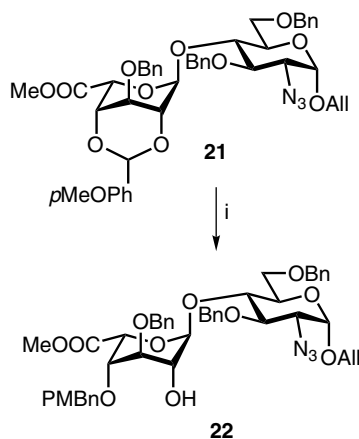
For demonstration, the application of the isopropylidene acetal (acetone) is shown on a sugar with *D-gluco*-configuration (**Figure 9**). Treatment with acetone, 1,2:5,6-di-*O*-isopropylidene-*D*-glucofuranose **19** can be obtained,<sup>81</sup> whereas with 2-methoxypropene the product is the 4,6-*O*-isopropylidene glucopyranose derivative **20**.<sup>82</sup> Acetalation of saccharides of *D-manno*-<sup>83</sup> and *D-galacto*-<sup>84</sup> configurations with 2-methoxypropene also results in good



**Figure 8** Possible protection of diols.



**Figure 9** Formation of different acetonides from glucose.



**Figure 10** Conditions: (i) PhBCl<sub>2</sub>, Et<sub>3</sub>SiH, Et<sub>2</sub>O, -78°C, 90%.

selectivity to furnish the 4,6-*O*-isopropylidene acetals. At the same time, for the synthesis of the 4,6-*O*-isopropylidene acetal of 2-deoxy-2-acetamido-D-glucopyranose, 2,2-dimethoxypropane was the best reagent for choice.<sup>85</sup>

A general way for the protection of 1,3-diols is the conversion into arylmethylenes acetals, by introducing, in a great majority of cases, benzylidene and methoxybenzylidene functions. This is a general way to protect the 4,6-positions in the case of *gluco*-, *manno*-, and *galacto*-configurations, and less trivial, but clever selective substitution of the 2,4-hydroxyl groups in *ido*-compound **21** (Figure 10).<sup>86</sup> Di-*t*-butylsilylene acetal is useful for the protection of 1,3-diols, which – apart from the selective protection – has a general role<sup>29</sup> in influencing the stereoselectivity of glycosidation reactions.



Protection of *cis*-vicinal diols is not a problem: most of the acetalation reagents are suitable for this purpose.<sup>87</sup> However, this is not the case with the *trans*-vicinal diols. Although not directly from the polyol, 2,3-*O*-isopropylidene derivatives from *gluco*-compounds can be prepared, these are rather unstable.<sup>75,88</sup> One of the procedures to achieve protection of *trans*-diols was elaborated by van Boeckel by applying the TIPDS acetal.<sup>79,89</sup> Actually, this method also involves two steps; by acid-catalyzed migration of the initially formed 4,6-*O*-acetal the 3,4-protected derivative can be prepared (**24**, Figure 11).

Protection of *trans*-vicinal diols was worked out by Ley by introducing dispiroketal and butane-1,2-diacetals.<sup>80,90</sup>

Simultaneous protection of the anomeric and O2 hydroxyl groups can be achieved by utilizing an allyl aglycon. By means of isomerization of this latter function, a 1,2-ethylidene acetal can be constructed that can be cleaved with acid hydrolysis following the required transformations at other positions of the molecule.<sup>91</sup>

The benefit of acetals for protection of diols is not just in that two hydroxyl groups can be simultaneously substituted and liberated in single step. The arylmethylene acetals can be selectively cleaved into the respective substances carrying one of the previously protected hydroxyl groups free, and leaving the other substituted with an alkyl (or acyl) function. The regularity and conditions of such kinds of ring cleavages are discussed in detail in Section 1.06.4.3.

A practical methodology of simultaneous protection of the anomeric- and O2 hydroxyl group is the incorporation in orthoesters,<sup>92</sup> which are important for the substitution of diol-systems. The orthoesters **26** are easy to prepare (however, many carbohydrate chemists are not really happy with them when appearing as the by-products of glycosidations in some cases<sup>6,23,62,86,93–95</sup>) from glycosyl halides **25** and simple alcohols (MeOH, EtOH, PentOH) in the presence of an N-base. The reaction of the 1-OH derivatives of carbohydrates **27** with 1-chloro-2,*N,N*-trimethylpropenylamine, followed by treatment with an alcohol and triethylamine, also affords 1,2-orthoesters (Figure 12).<sup>96</sup>

No matter whatever they are called, orthoesters are resistant to bases and to alkaline conditions; therefore, removal of ester groups and regioselective or exhaustive alkylations can be readily accomplished with carbohydrates protected with orthoesters.<sup>38,62,63,97–100</sup>

The outstanding utility of protection in the form of orthoesters is manifested in their manifold chemical transformations as shown in Figure 13. Orthoesters can be hydrolyzed with dilute trifluoroacetic acid to yield the free reducing sugars **27**, or the glycosyl acetates<sup>38,62,101,102</sup> carrying a free C2 hydroxyl group **30**, can be rearranged<sup>67,94,103–105</sup> into 1,2-*trans* glycosides **29** with protic or Lewis acids. Orthoesters are ready to transform into glycosyl chlorides **28** directly by treatment with chlorotrimethylsilane,<sup>63</sup> and can be reduced into 1,2-ethylidene acetals **31**.<sup>106</sup>

Cyclic carbonates have long been known for the protection of vicinal diols.<sup>66</sup> Recently, such compounds are shown to enhance the reactivity of ethylthio glycosyl donors,<sup>64</sup> and used in certain solid support oligosaccharide syntheses.<sup>107</sup> Also, cyclic carbonates ensure to fix the conformation of the substrate, thus greatly contributing to the success of structural investigations. In general, cyclic carbonates can be produced from *trans*- and *cis*-vicinal diols, but the application of ethylene carbonate has opened a convenient route for the selective substitution of the *cis*-diol function of inositols (**33**, Figure 14).<sup>67</sup>

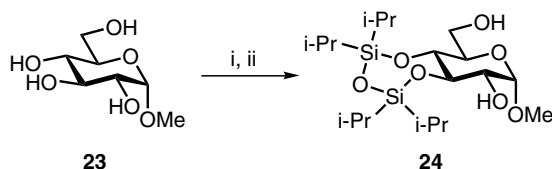


Figure 11 Conditions: (i) TIPDSCI, Py, r.t.; (ii) TsOH, DMF, r.t., 80%.

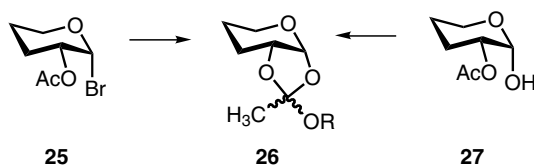
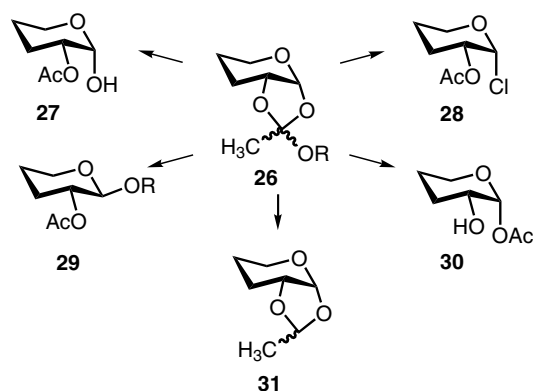
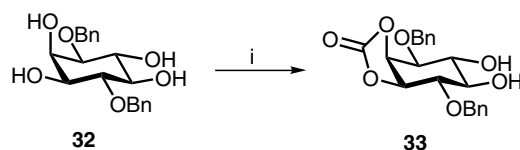


Figure 12 Formation of 1,2-orthoesters.



**Figure 13** Possible transformations of 1,2-orthoesters.



**Figure 14** Conditions: (i) ethylene carbonate,  $\text{NaHCO}_3$ ,  $120^\circ\text{C}$ , 30 min, 80%.

The chemistry of cyclic boronates has been reviewed by Ferrier<sup>108</sup> and Duggan.<sup>68</sup> Such derivatives are also useful for the protection of vicinal diols. In synthetic works they are not applied very often, but their utility as the recognizing elements of various sensors is rather important.<sup>68</sup>

### 1.06.3.3 Internal Protecting Groups

A clever, economical way for the protection of carbohydrates is to appropriately manage the substituents of the molecule: internal acetals (1,6-anhydro derivatives), lactones (in the case of uronic acids), or lactams (in the syntheses of NeuAc derivatives).

The 1,6-anhydro sugars **35** are successfully applied as synthons for the preparation of oligosaccharides and glycoconjugates (**Figure 15**).<sup>109–111</sup> Such compounds are readily available from aryl-*O*- and thioglycosides,<sup>112</sup> 6-*O*-benzylated glycosyl halides,<sup>113</sup> or from other 6-*O*-benzyl (or *p*-methoxybenzyl) derivatives.<sup>114–117</sup> Following manipulations at the other hydroxyl groups of the molecule, cleavage of the [3.2.1] bicyclic skeleton can be accomplished. For this, acetolysis is rather useful to furnish 1,6-di-*O*-acetyl derivatives **36**,<sup>16,42,109</sup> whose anomeric acetyl group is further transformed into, for example, a glycosyl bromide **38**, or glycosyl trichloroacetamide (by means of the selective cleavage of the anomeric acetyl group **37**). Splitting of the ring can also be performed to provide a glycosyl donor, namely a thioglycoside **34**.<sup>118</sup> The examples shown above demonstrate that the 1,6-anhydro derivatives can be most successfully utilized in the syntheses of oligosaccharides linked with a 1-6 bond.

In the case of uronic acids, a lactone ring incorporating the carboxyl group and one of the hydroxyl groups may temporarily protect these two functions.<sup>119</sup> By an appropriate selection of the reaction conditions, the readily available glucono-3,6-lactone can be acylated in a regioselective manner at the C4 hydroxyl group (**40**), and under more vigorous conditions the product is the 2,4-di-*O*-acyl derivative. Opening of the lactone ring then provides either the 2,3-di-OH (**41**, **42**), or 3-OH derivative with a good yield (**Figure 16**)<sup>120</sup> and this strategy can also be transferred to the oligosaccharide syntheses.<sup>121</sup> The 1,7-lactones of sialic acids were used by Schmidt *et al.* as acceptors in glycosidations.<sup>122</sup>

Recently, Ando *et al.* protected the carboxyl and amino functions at the sialyl acceptor in form of a 1,5-lactam (**44**, **Figure 17**).<sup>123,124</sup> Apart from selective protection, such a substitution was found to be advantageous with regard to the reactivity of the C4 and C8 hydroxyl groups in glycosidation reactions.

