2.1 Reactions at Oxygen Atoms

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Abstract

Synthetic protocols based on carbohydrates require the differentiation of their abundant hydroxyl groups, by and large, in order to expose just one single hydroxyl group to the selected reagent. This differentiation is usually carried out with the assistance of protecting groups that block the rest of the hydroxyl groups while being compatible with the given reaction conditions. By corollary, the knowledge and apt choice of the appropriate protecting groups is a key factor in successful synthetic endeavors. In this chapter, an overview of the most commonly employed protecting groups in carbohydrate chemistry is given. Alkyl ethers, being robust protecting groups, have a long history in synthetic carbohydrate chemistry and in related structural studies of polysaccharides. Acetals and ketals, which are of fundamental importance in carbohydrate chemistry, are then discussed. Acyl and silyl protecting groups, which also play an important role in modern monosaccharide transformations, are also presented. Finally, recent blocking strategies are described, including orthogonal strategies, by which the protecting groups are harmoniously combined in modern carbohydrate chemistry.

Keywords

Protecting groups; Alkylation; Acetalation; Acylation; Carbonylation; Silylation; Phosphorylation

Abbreviations

ADMB	4-acetoxy-2,2-dimethylbutanoyl
All	allyl
Alloc or Aloc	allyloxycarbonyl
APAC	2-(allyloxy) phenyl acetyl
BDA	butane 2,3-diacetals
Bn	benzyl
Bocdene	2-(*tert*-butoxycarbonyl)-ethylidene
BOM	benzyloxymethyl ether
Bz	benzoyl
BzOBT	1-*N*-benzyloxy-1,2,3-benzotriazol

Cac or ClAc	chloroacetyl
CAN	ceric ammonium nitrate
CBz	benzyloxycarbonyl
CDA	cyclo-hexane-1,2-diacetal
CSA	camphorsulfonic acid
CCL	*Candida cylindracea* lipase
CVL	*Chromobacterium viscosum* lipase
DABCO	diazabicyclo[2.2.2]octane
DBMP	ditertbutylmethylpyridine
DBU	1,8-diazabicyclo[5,4,0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	dichlorodicyanoquinone
DIB	(diacetoxyiodo)benzene
DISAL	3,5-dinitrosalicylate
Dispoke	dispiroketal
DMAP	4-(dimethylamino)pyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DMTr	dimethoxytriphenylmethyl
DMTST	dimethyl(methylthio)sulfonium trifluoromethane sulfonate
DTBMP	di-*tert*-butylmethylpyridine
DTBS	ditertbutylsilylene
EDAC	1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride
Fmoc	fluoren-9-ylmethoxycarbonyl
HATU	2-(7-aza-1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
IDCP	iodonium di-*sym*-collidine perchlorate
Lev	levulinoyl
MEM	methoxyethoxymethyl
MMTr	monomethoxytriphenylmethyl
Mocdene	2-(methoxycarbonyl)-ethylidene
MOM	methoxymethyl ether
NAP	2-naphthylmethyl
NBS	*N*-bromosuccinimide
NIS	*N*-iodosuccinimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
NPM	*p*-nitrophenylmethyl
PAB	pivaloylaminobenzyl
PBB	*p*-bromobenzyl
PCB	*p*-chlorobenzyl
PFL	*Pseudomonas fluorescens* lipase
Piv	pivaloyl
PIB	*p*-iodobenzyl

PLE	pig liver esterase
PMB	*p*-methoxybenzyl
PMBM	*p*-methoxybenzyloxymethyl
PN	protease *N*-neutral protease
Poc	propargyloxycarbonyl
PPL	lipase from porcine pancreas
PPTS	pyridinium *p*-toluenesulfonate
PSE	phenylsulfonylethylidene
RJL	*Rhizopus javanicus* lipase
SEE	1-[2-(trimethylsilyl)ethoxy]ethyl
SEM	trimethylsilylethoxymethyl ether
SET	single electron transfer
TBS or TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TES	triethylsilyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofurane
TIBAL	triisobutylaluminum
TIPDS	1,1,3,3-tetraisopropyldisiloxane
TIPS	trisopropylsilyl
TMEDA	tetramethylethylenediamine
TMS	trimethylsilyl
TMTr	trimethoxytriphenylmethyl
TPS	triphenylsilyl
Tr	trityl
Troc	2,2,2-trichloroethyloxycarbonyl
TBAF	tetrabutylammonium fluoride

1 Introduction

This chapter describes the chemical reactions at the oxygen atoms of carbohydrates along with some of their fundamental characteristics. The hydroxyl groups of carbohydrates display all the chemical properties associated with simple alcohols. The only difference is that carbohydrates contain many hydroxy groups with similar chemical character. Since the hydroxy groups in carbohydrates play different biological roles depending on their positions, the ability to perform chemical reactions on a particular hydroxy group is highly important. However, the regioselective transformation of one out of several hydroxy groups is far from being trivial. While the differentiation between the primary *versus* the secondary hydroxy groups is in general not too difficult, the discrimination between secondary hydroxy groups is a difficult task.

Usually, partially substituted derivatives are made with the aid of protecting groups. The protecting groups used in carbohydrate chemistry are the same as in any other area in organ-

ic chemistry [1,2,3,4]. In addition to this fact, it is important to point out that in carbohydrate derivatives protecting groups do more than protect; they also confer other effects to the molecule and can alter the course of a reaction. Important examples of such effects are the use of 2-*O*-participating groups in glycosyl donors [5] or the armed/disarmed concept for glycoside coupling [6].

This chapter aims to impart general synthetic strategies for most sugars and oligosaccharide structures through the use of some basic, well-proven protecting groups, coupled with general strategies towards regioselectivity. The discussion outlines frequently used protecting groups in carbohydrate chemistry, briefly surveying conditions for their introduction, stability, and removal. It should be noted at this stage that the hydroxyl group of the anomeric center, is unique in having two attached oxygen atoms and therefore it will be treated in a separated section.

2 Reactions at Non-Anomeric Hydroxyl Groups

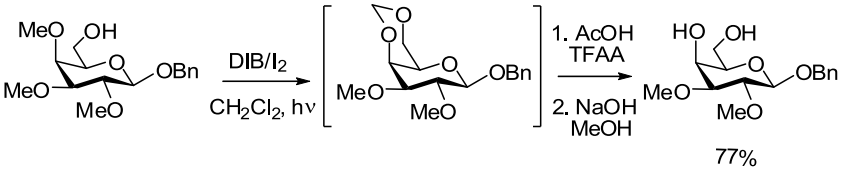
2.1 Alkylation Reactions: Ether-Type Protecting Groups

Alkyl and aryl ethers are relatively stable to acids and bases due to the high C–O bond energy and it is difficult to recover the parent alcohols from them; therefore, most useful ether-type protections utilize resonance stabilization (by delocalization) of the benzylic-type cation or radical to facilitate the cleavage.

2.1.1 Methyl Ethers

Conversion to methyl ethers of non-anomeric hydroxyl groups is a long-established procedure used, in conjunction with ethylation and deutero-methylation, for the analysis of glycosides, oligosaccharides, and polysaccharides.

Methyl ethers are not normally regarded as protecting groups (though they may be considered in special cases [7]) because the removal is difficult requiring conditions not compatible with other functional groups. A recent study has demonstrated a wide range of susceptibilities to methylation of the hydroxyls in various methyl pyranosides using diazomethane together with transition-metal chlorides and boric acid [8]. On the other hand, the selective removal of an

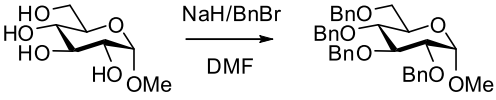


Scheme 1
Selective removal of methoxy protecting groups

ether adjacent to a hydroxyl group in carbohydrate substrates was accomplished with (diacetoxyiodo)benzene (DIB) and I_2 under irradiative conditions (Scheme 1). In this step, the methoxy protecting group was transformed into a mixture of acetals (methylenedioxy acetal or *O*-methyl acetate) which upon basic hydrolysis provides the diol [9,10].

2.1.2 Benzyl (Bn) Ethers

The classical permanent protecting group of carbohydrate hydroxyl functions is probably the benzyl ether. It is very stable and can be readily removed under essentially neutral conditions. For this reason, numerous benzylation and *O*-debenzylation procedures have been described. Benzyl ether formation is usually achieved by the reaction of alcohols and benzyl halides in the presence of a base such as sodium hydride in anhydrous DMF (Scheme 2) [11], or a mild base (Ag_2O) in THF using a phase-transfer catalyst [12]. Benzylation can also be accomplished by the use of an acidic catalyst with benzyltrichloroacetimidate as the reagent [13]. A method using the reductive etherification of TMS ethers under non-basic conditions has also been reported [14].



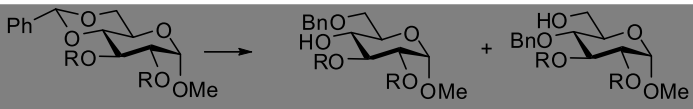
Scheme 2
Benzylation of methyl α-D-glucopyranoside

Benzyl ethers are highly stable to a wide range of reagents but are readily removed through catalytic reductive conditions [15]. Hydrogenolysis is commonly carried out using hydrogen gas with a palladium catalyst absorbed on charcoal although modifications involving hydrogen transfer have been used. A variety of alternative strategies include Na/liquid ammonia [16], anhydrous $FeCl_3$ [17,18], and $CrCl_2$/LiI [19].

Selective Benzylation Selective benzylation of carbohydrate hydroxyl functions by direct one-step protection is difficult to achieve. Therefore, several techniques for the selective protection have been developed over the years and the most common are discussed below.

Reductive Opening of Benzylidene Acetals. An attractive approach for the selective introduction of benzyl groups is provided by the regioselective opening of *O*-benzylidene acetals [20,21,22]. Generally, one of the two C–O bonds in benzylidene acetals can be selectively cleaved, and the direction of the cleavage is dependent on steric and electronic factors as well as, on the nature of the cleavage reagent. Reductive ring-opening of the 1,3-dioxane ring of 4,6-*O*-benzylidene-α-D-glucopyranosides gives the 6-*O*-benzyl and 4-*O*-benzyl ethers respectively in different ratios, depending on the combination of the reagent Lewis acid, solvent, and the substituent at C-3. Some examples are shown in Table 1.
4,6-*O*-Benzylidene-D-galactopyranosides behave in a similar manner to the D-gluco analogs in most cases [29,30]. In the ring opening of the dioxolane rings of 2,3-*O*-benzylidene-α-D-man-

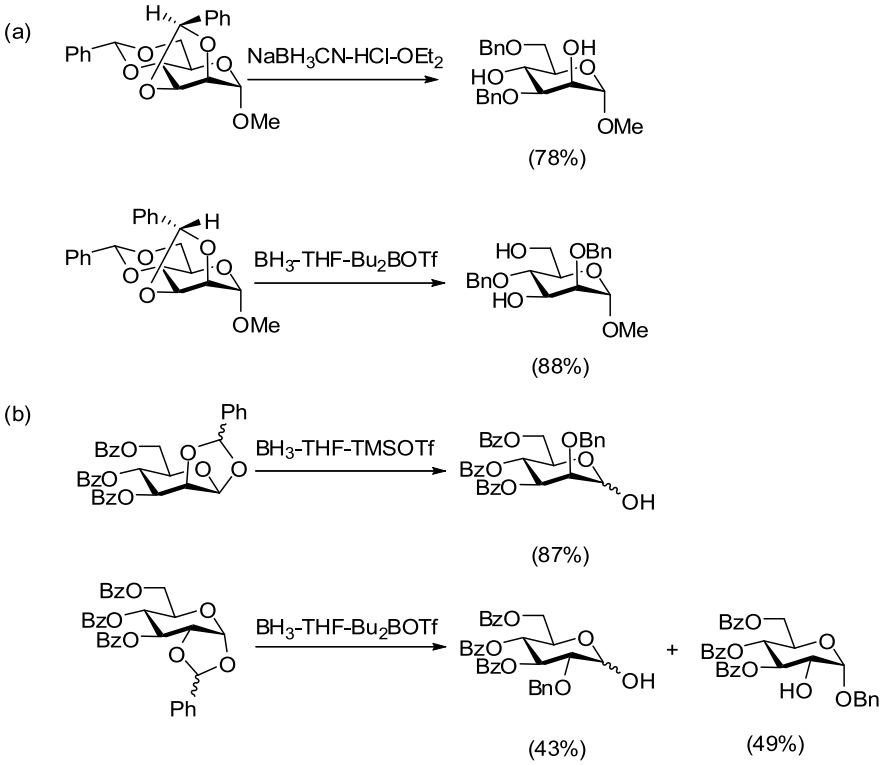
Table 1
Reductive opening of 4,6-*O*-benzylidene-α-D-glucopyranoside



Entry	Reagent	Solvent and temperature	R	Yield (%) 6-*O*-Bn	Yield (%) 4-*O*-Bn	References
1	$NaBH_3CN/HCl$	THF, 0 °C	Bn	81		[23]
2		THF, 0 °C	Bn	95		[23]
3		THF, rt	Bn (1-*O*-Allyl)	80		[24]
4		THF, rt	Bn (1-*O*-Allyl)	79	16	[25]
5	$Me_3N{\cdot}BH_3/AlCl_3$	THF, rt	Bn	71		[26]
6		THF, rt	Bz	74		[26]
7		Toluene, rt	Bn		50	[26]
8		Toluene, rt	Bz		40	[26]
9	$Me_3N{\cdot}BH_3/BF_3{\cdot}Et_2O$	MeCN, 0 °C	Bn	30	55	[27]
10		CH_2Cl_2, 0 °C	Bn	3	73	[27]
11	Et_3SiH/CF_3CO_2H	CH_2Cl_2	Bn	81	55	[28]
12		CH_2Cl_2	Ac	98		[28]
13	$BH_3{\cdot}THF/Bu_2BOTf$	CH_2Cl_2, 0 °C	Bn		87	[30]
14	$BH_3{\cdot}THF/Cu(OTf)_2$	CH_2Cl_2, rt	Bn		94	[31]
15	$Me_2EtSiH/Cu(OTf)_2$	CH_3CN, 0 °C	Bn	84		[31]

noside derivatives, the directions of the reaction are determined by the configuration of the benzylidene carbon (*Scheme 3a*). Regarding the reductive ring-opening of 1,2-*O*-benzylidene derivatives, in the case of *manno*-type derivative only a C–O1 bond was cleaved, whereas both the C–O1 and C–O2 bonds were cleaved in the case of the gluco-type compound (*Scheme 3b*) [32].
Benzylidene acetals can also be opened under oxidative conditions, typically NBS in CCl_4, to give benzoyl ester protected halogen derivatives, thereby providing an entry into deoxycarbohydrate compounds [33].

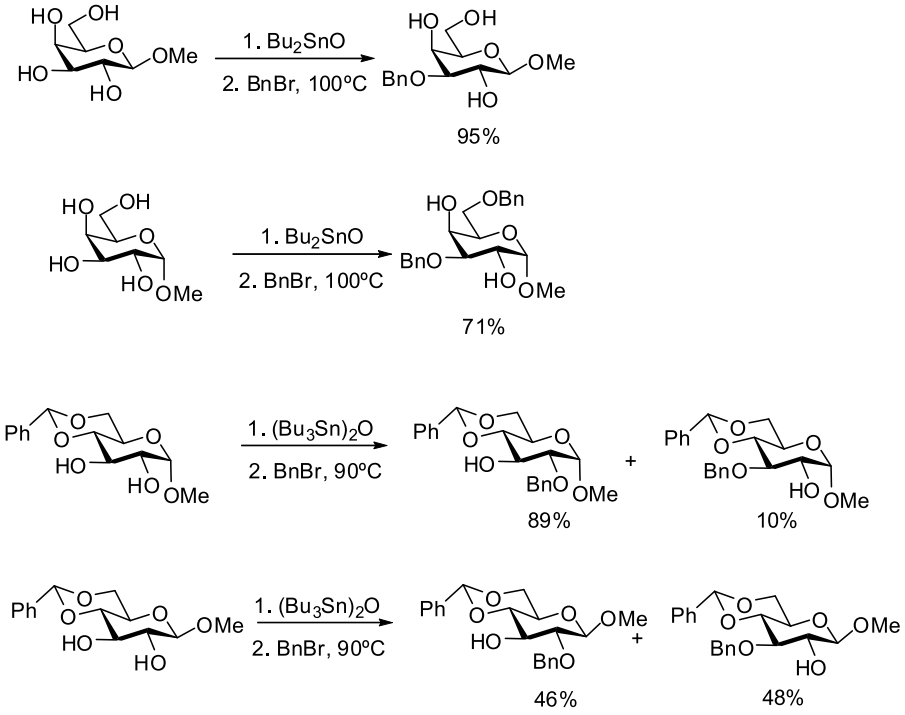
Formation of Organotin Intermediates. Another method for selective benzylation refers to the activation of the hydroxyl groups of saccharides by the formation of organotin intermediates such as trialkylstannyl ethers or dialkylstannylene acetals [34]. When the substrate is treated with the tin reagent, one or two Sn–O bonds are formed, enhancing the nucleophilicity of the oxygen atom in the stannyl ether or stannylene acetal. This effect is not identical for the two oxygen atoms of a Sn-acetal, resulting in a differential increase of their nucleophilicity and an ensuing higher regioselectivity.
The activation is carried out by reaction of the polyol with bis(trialkyltin) oxide or a dialkyltin oxide with heating and can be performed in various solvents, the most common being methanol



Scheme 3
Regioselective benzylation by reductive ring opening of benzylidene acetals

or toluene. Subsequent treatment of the preformed tin intermediates dissolved in a polar aprotic solvent with alkyl halides in the presence of added nucleophiles such as tetrabutylammonium halides [35] or CsF [36] yields the corresponding alkyl (benzyl) ethers. Regarding regioselectivity, this is much the same irrespective of which type of tin derivative is used, the primary hydroxyl group and equatorial hydroxyl group in a vicinal *cis*-dioxygen configuration are preferentially benzylated. As exemplified in *Scheme 4*, this rule is generally correct, but the degree of selectivity is also dependent on structural features and other factors such as the presence of additives.

Regioselective de-*O*-benzylation. An alternative strategy to partially benzylated carbohydrates has been accomplished by selective de-*O*-benzylation of easily available polybenzylated precursors. This has been achieved in limited cases by catalytic hydrogenolysis [37], catalytic hydrogen-transfer cleavage [38], acetolysis [39], hypoiodite fragmentation [40], iodine-mediated addition-elimination sequences [41], or use of Lewis acids [42].
Recently, isobutylalanes [43,44,45,46] or the combination $CrCl_2$/LiI [47] have been shown as efficient agents for the selective deprotection of poly-benzylated carbohydrates. The reaction with isobutylalanes is assumed to proceed through the formation of a penta-coordinated com-



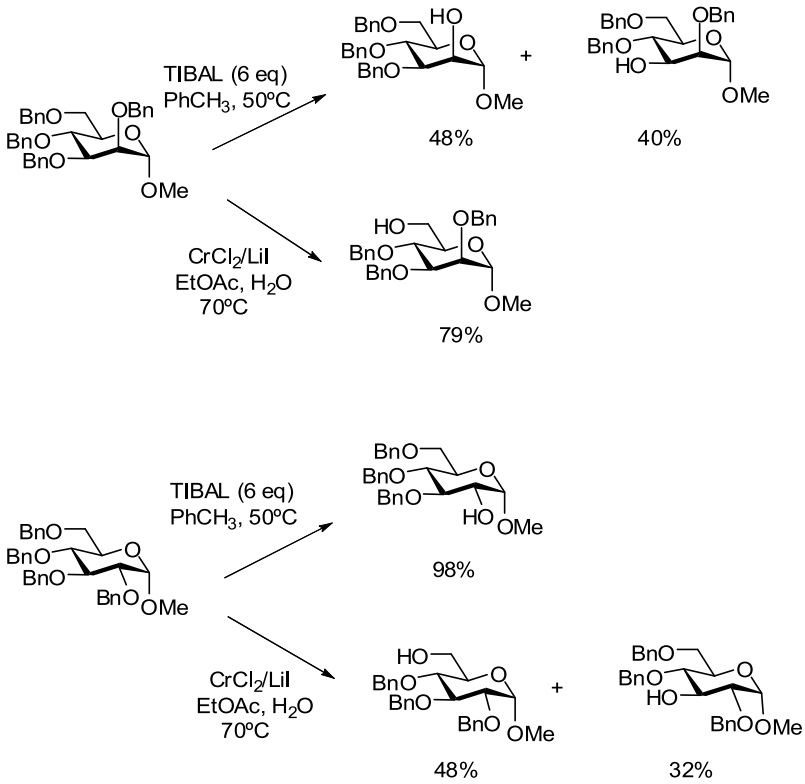
Scheme 4
Examples of stannyl mediated regioselective benzylation

plex between the aluminum reagent and a 1,2-*cis* oxygen pattern of the sugar. A second aluminum atom then selects the less hindered oxygen atom and directs the de-*O*-benzylation [46]. When one oxygen atom is clearly more accessible than the other the reaction is highly regioselective. In contrast, when the system $CrCl_2$/LiI is used, a three-point coordination model of the carbohydrate with Cr(II) or Cr(III) is needed for optimal selectivity [47] (*Scheme 5*).

2.1.3 Substituted Benzyl Ethers

To increase the scope of available hydroxyl protecting groups substituted benzyl ethers, which can be selectively removed in the presence of unsubstituted benzyl ethers have been developed. These substituted benzyl ethers are generally less stable to different reaction conditions than unsubstituted benzyl ethers and therefore are used as temporary protecting groups.

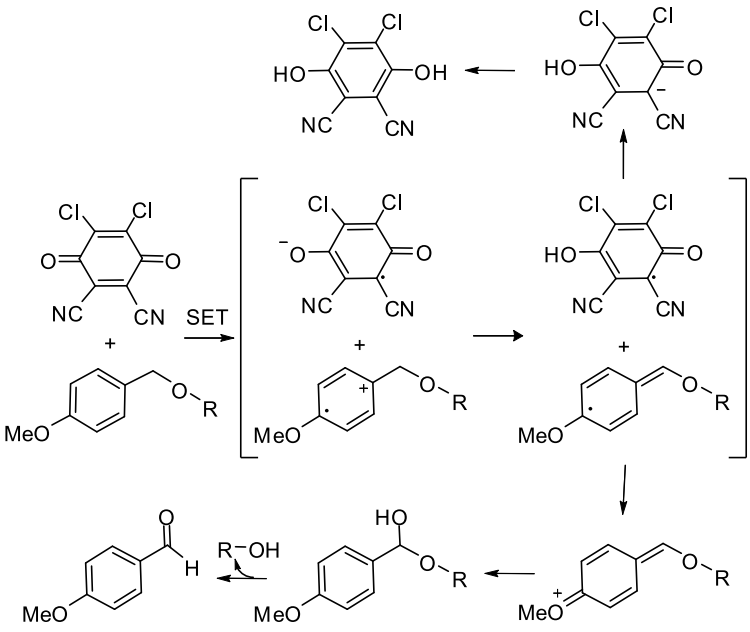
p-Methoxy Benzyl (PMB) Ethers Of the several benzyl ether-type protecting groups reported, *p*-methoxy benzyl (PMB) enjoys a unique position in carbohydrate chemistry due to the ease of its introduction and removal. PMB group demasking, in general, is mediated either by oxidizing agents or by Lewis acids. Thus, hydroxyl moieties protected as PMB ethers can be regenerated easily by oxidation with DDQ [48,49], DDQ-$FeCl_3$ [50], DDQ-$Mn(OAc)_3$ [51], or CAN [52,53]. In the case of DDQ, the *p*-methoxybenzyl group is cleaved selectively with-



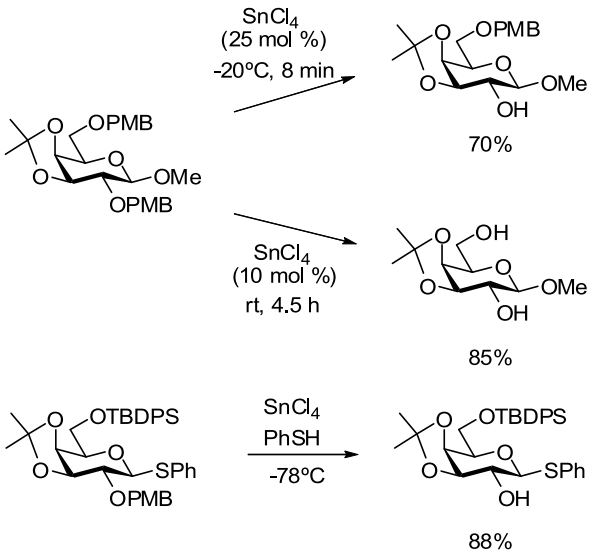
Scheme 5
Examples of regioselective de-*O*-benzylation

out affecting several other protecting groups, including benzyl ether. The reaction is assumed to proceed through an easy single electron transfer (SET) to DDQ to generate an oxonium ion which can be captured by water [48,49] (*Scheme 6*).

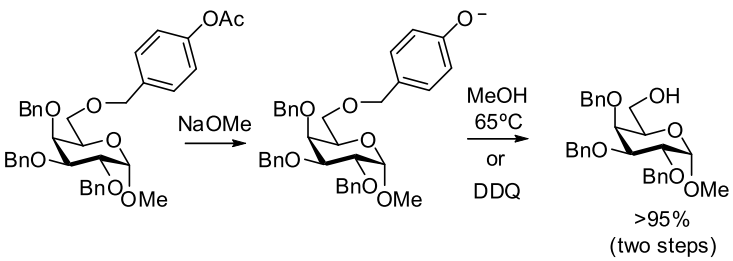
Deprotection of polyhydroxylated carbohydrate PMB ethers can also be accomplished with $SnCl_4$ [54]. The reaction is compatible with benzyl, TMS, isopropylidene acetal, or methoxy protecting groups. Sometimes the reaction results in unusual regioselectivity and partial deprotection is observed. Preferential mono or bis cleavage of PMB ethers was achieved with careful control of the reaction conditions. However, the general conditions fail in the case of thioglycosides, and a combination of $SnCl_4$/PhSH needs to be used [55] (*Scheme 7*). This combination is particularly useful in the cases where oxidative reagents such as DDQ or CAN need to be avoided. PMB ethers can also be cleaved with $ZrCl_4$ [56], $SnCl_2$/TMS-Cl/anisole [57], CF_3CO_2H in CH_2Cl_2 [58], $CeCl_3 \cdot 7H_2O$/NaI [59], or I_2/MeOH [60]. The PMB group has also been used as an in situ-removable protecting group for a reactive hydroxyl group in a one-pot reaction involving two sequential glycosilations. The deprotection was performed with *N*-iodosuccinimide-trifluoromethanesulfonic acid at 0 °C and the procedure was used in the synthesis of the globotetraose (Gb4) tetrasaccharide [61].



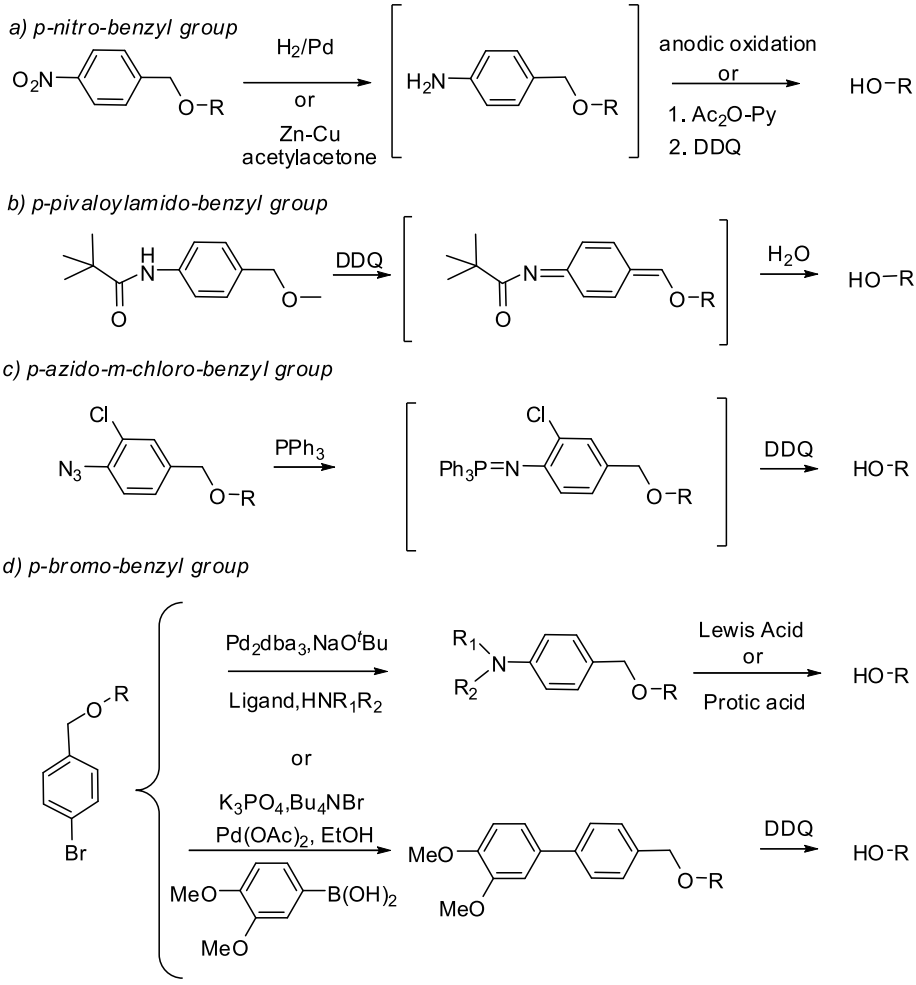
Scheme 6
Removal of *p*-methoxybenzyl ethers with DDQ



Scheme 7
Examples of deprotection of *p*-methoxybenzyl ethers with $SnCl_4$



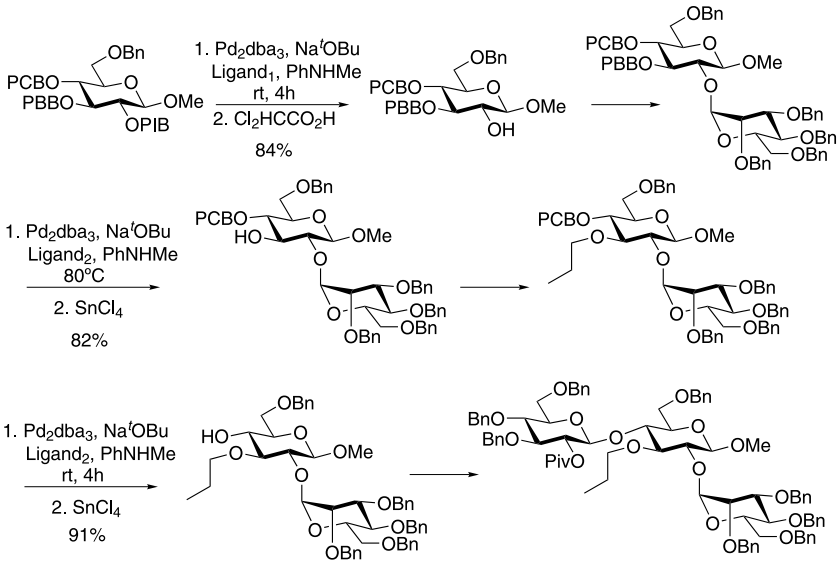
Scheme 8
Two-step deprotection of *p*-acetoxybenzyl protecting group



Scheme 9
Examples of *p*-substituted benzyl-type protecting groups

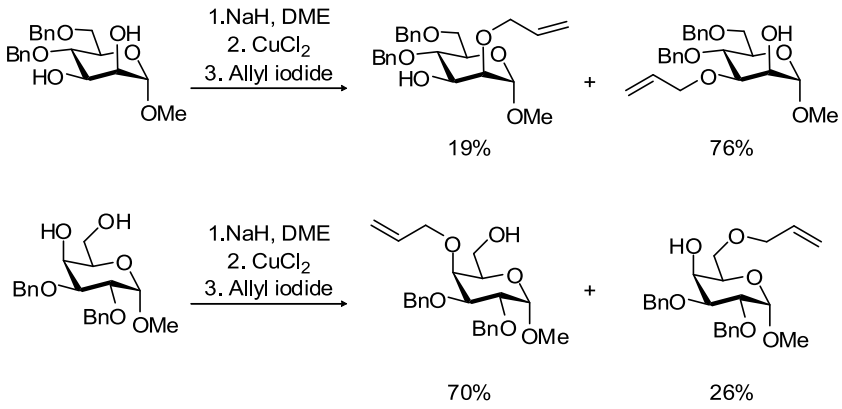
Other *p*-hydroxybenzyl-derived protecting groups include *p*-acetoxybenzyl ether and 2-(trimethylsilyl)ethoxymethoxybenzyl ether [62]. These groups require a two-stage deprotection strategy in which treatment with base or fluoride was followed by thermolysis or mild oxidation of the obtained *p*-phenoxybenzyl intermediate (*Scheme 8*). The conditions are compatible with many of the standard manipulations of oligosaccharide synthesis and with the presence of benzyl or PMB ethers.

Other p-Substituted Benzyl-Type Ethers Although the PMB protecting group has been extensively utilized in oligosaccharide synthesis, the acid sensitivity of this group sometimes restricts its synthetical application especially during glycosylations. Therefore, other *p*-substituted benzyl groups have been developed (*Scheme 9*). The *p*-nitrobenzyl (or *p*-nitrophenylmethyl NPM) group, which is acid-stable, is readily cleaved via a two-stage procedure involving reduction to an *p*-amino-benzyl ether followed by mild anodic oxidation [63]. *p*-Acetamidobenzyl and *p*-pivaloylaminobenzyl (PAB) derivatives are also used as protecting groups for hydroxyl groups [64,65]. These ethers are much more stable under acidic conditions than a PMB ether, can be obtained by direct alkylation of the hydroxyl group or by acylation of the corresponding *p*-aminobenzylether, and are deprotected by treatment with DDQ. The oxidation occurs at a rate comparable to PMB ethers, so that no preferential cleavage could be achieved with DDQ between these two groups. *p*-Azido benzyl groups are also useful as protecting groups of hydroxyl moieties [66,67]. They can be removed much



Ligand$_1$ = 1-(N,N-dimethylamino)-1´-(diciclohexylphosphino)biphenyl
Ligand$_2$ = (*o*-biphenyl)P(*t*Bu)$_2$

Scheme 10
Iterative deprotection of *p*-halobenzyl ether protecting groups



Scheme 11
Example of regioselective allylation from copper complexes

faster than the PMB group by DDQ oxidation after conversion of the azide group into the corresponding iminophosphorane. This group allowed for temporary protection of hydroxyl groups in solid-phase synthesis of oligosaccharides [68].

The chemically stable *p*-halobenzyl ethers (PIB = *p*-iodobenzyl, PBB = *p*-bromobenzyl; PCB = *p*-chlorobenzyl) are converted to labile arylamines via Pd-catalyzed amination [69]. Rapid deprotection of the amine benzyl ethers was observed under very mild Lewis acid conditions. Regarding compatibility of these novel protecting groups with others commonly used, selective cleavage was achieved in the presence of silyl ethers, PMB groups, and glycal double bonds. As shown in *Scheme 10*, the differences in the rates of reaction between aryl chlorides, bromides, and iodides in the Pd-catalyzed amination reactions allows for iterative deprotection. In a related method, the *p*-bromobenzyl group is converted to a DDQ-labile *p*-(3,4-dimethoxyphenyl)benzyl ether by a Suzuki–Miyaura coupling reaction. This protecting group played a key role in the access to the fully lipidated malarial GPI disaccharide [70].

2.1.4 Allyl and Related Ethers

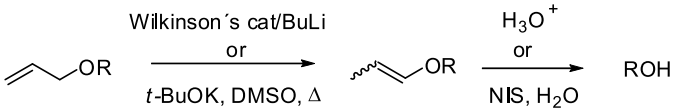
The protection of alcohols with allyl [71] and related (prenyl, methylallyl, cinnamyl, homoallyl) groups is of great importance in carbohydrate synthesis due to their stability under the conditions required for glycoside formation. These groups are moderately stable to acids and bases, and offer the potential for selective dealkylation of differentially protected sites.

The most general method of preparing allyl ethers is to react the alcohol with allyl bromide or iodide in the presence of sodium hydride. The reaction is best carried out in a polar solvent, usually DMF [72]. Alcohols may also be alkylated after conversion to their barium salts. This technique is employed in the case of *N*-acyl derivatives of aminosugars to avoid any risk of alkylation at nitrogen which would accompany the use of sodium hydride as the base [73,74]. Conversion of alcohols to allyl carbonates, followed by palladium-catalyzed extrusion of CO_2, constitutes a milder alternative to the classical Williamson-type pro-

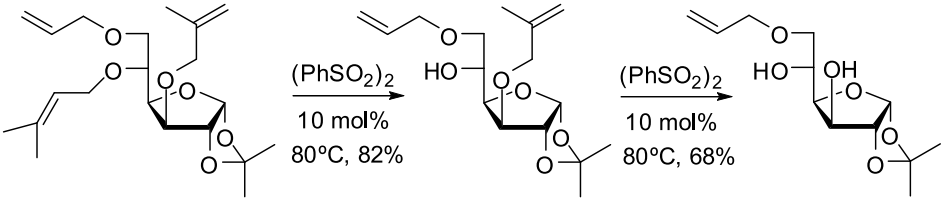
cedure [75,76]. Compounds containing base labile groups can also be allylated using allyl-trichloroacetimidate [77].

As in the case of benzylation, strategies used for selective allylation include prior conversion to organotin derivatives. When comparisons have been made, there does not seem to be significant differences in selectivities between benzylation and allylation [33,78]. Diols have also been selectively alkylated as their copper (II) salts. Under such conditions no disubstitution is observed and regioselectivity towards formation of a preferred monoallylated product (4,6-diols give mainly 4-substitution and 2,3-diols give mainly 3-substitution) is usually high (*Scheme 11*) [79].

Common allyl deprotection methods are two-stage procedures that include isomerization to the more labile 1-propenyl group with a variety of agents (*Scheme 12*). The most frequently employed conditions are treatment of the allyl ether with *t*-BuOK [80], Wilkinson catalyst [81], Pd/C [82], $PdCl_2$ [83], ruthenium(II) [84], and iridium(I) complexes [85] followed usually by acid hydrolysis or oxidation of the resulting enol ether. Also reported are methods including oxidative conditions such as DDQ [86], SeO_2 [87], NBS-*hv* [88], and OsO_4/NMO/$NaIO_4$ [89]. As a general rule substitution of the allylic framework either slows down or even inhibits the transition-metal catalyzed isomerization [71]. The crotyl and the prenyl groups are readily removed in DMSO/*t*-BuOK through γ-hydrogen elimination reactions. These processes are faster than the allyl to prop-1-enyl isomerization but the difference in rates does not appear to be sufficient to allow good selectivities [90]. $Yb(OTf)_3$ [91], I_2/CH_2Cl_2 [92], or DDQ [93] are mild and efficient methods to cleave prenyl ethers. Remarkable selectivity in the order methyl-prenyl > prenyl > mathallyl > allyl has been observed by using diphenyldisulfone in a sealed tube at 80 °C (*Scheme 13*) [94]. These reactions are initiated by the benzene-sulfonyl radical formed from thermal homolysis of $(PhSO_2)_2$. The reaction conditions are compatible with the presence of other protecting groups such as acetals and allyl, benzyl, or silyl ethers.



Scheme 12
Two-stage removal of allyl ether protecting groups



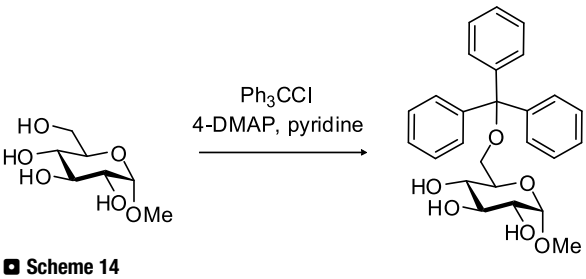
Scheme 13
Selective cleavage of branched allyl ethers

2.1.5 Trityl (Tr) Ethers

The usefulness of triphenylmethyl ethers as protecting groups in organic synthesis, in general, and in carbohydrate and nucleoside chemistry in particular is well documented. Its utility is attributed to the ease in preparing and removing them as well as to the high selectivity for primary positions observed in polyols. Tritylation of primary hydroxyl groups using trityl chloride in pyridine is one of the oldest selective alkylation processes described in carbohydrate chemistry (*Scheme 14*). Forcing conditions (trityl perchlorate and 2,4,6-tri-*tert*-butyl pyridine in dichloromethane) may cause etherification of secondary hydroxyl groups [95]. Alcohols can also be protected as triphenylmethyl ethers by treatment with p-methoxybenzyl trityl ether (PMBOTr) and DDQ under virtually neutral conditions [96].

Trityl ethers are generally cleaved under protic or Lewis acid conditions, such as formic acid [97], trifluoroacetic acid [98], BCl_3 [99], $Yb(OTf)_3$ [100], and $VO(OTf)_2$ [101]. Recently, supported-acids [102,103] or Nafion-H [104] have been found to be useful reagents for the removal of the triphenylmethyl group. Finally, trityl ethers are readily cleaved to the corresponding alcohols by using CBr_4/MeOH [105] or CBr_4-photoirradiation conditions [106].

Substituted trityl groups such as its mono- (MMTr), di- (DMTr) and trimethoxy- (TMTr) derivatives are also used for the protection of primary hydroxyls (*Fig. 1*). The MMTr and DMTr groups can be cleaved [107,108] under much weaker acidic conditions than the parent trityl ether due to the electron-releasing effect of their methoxy groups toward the benzene ring. None of these trityl ethers is stable enough to survive under normal glycosylation conditions, and therefore they are only used as intermediates to construct building blocks in carbohydrate chemistry. However, the use of DMTr as a protecting group is extremely widespread in oligonucleotide chemistry.



Scheme 14
Tritylation of methyl α-D-glucopyranoside

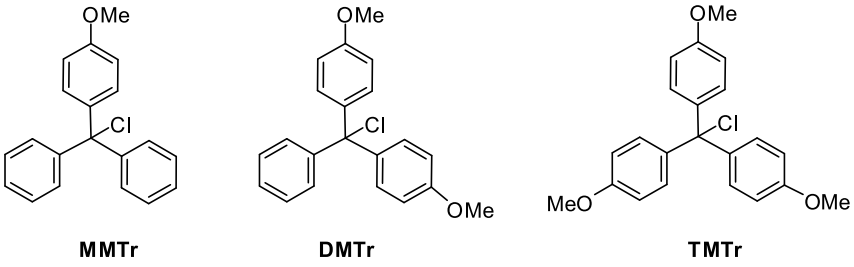
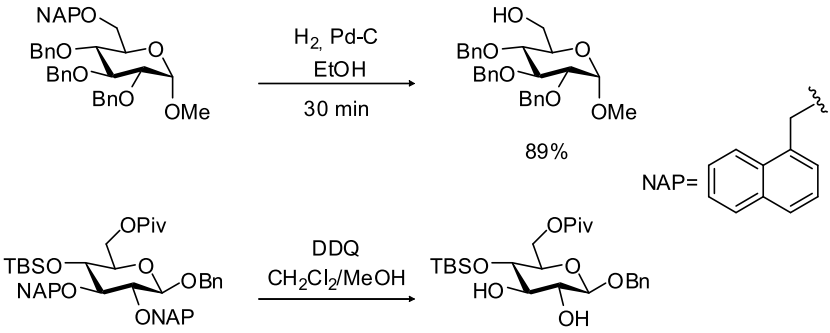


Figure 1
Substituted trityl protecting groups

2.1.6 2-Naphthylmethyl (NAP) Ethers

The 2-naphthylmethyl (NAP) group was introduced by Esko et al. [109] and Spencer et al. [110] as a protecting group for polyhydroxy systems. It is stable under conditions normally used for glycoside formation and offers the potential for selective cleavage by hydrogenolysis even in the presence of benzyl groups [110] (● *Scheme 15*). Standard conditions for introduction of the NAP group are, the alkylation with naphthyl bromide [110] or the hydrogenolysis of dioxolane-type (2-naphthyl)methylene acetals [111,112].



● Scheme 15
Selective removal of NAP ethers

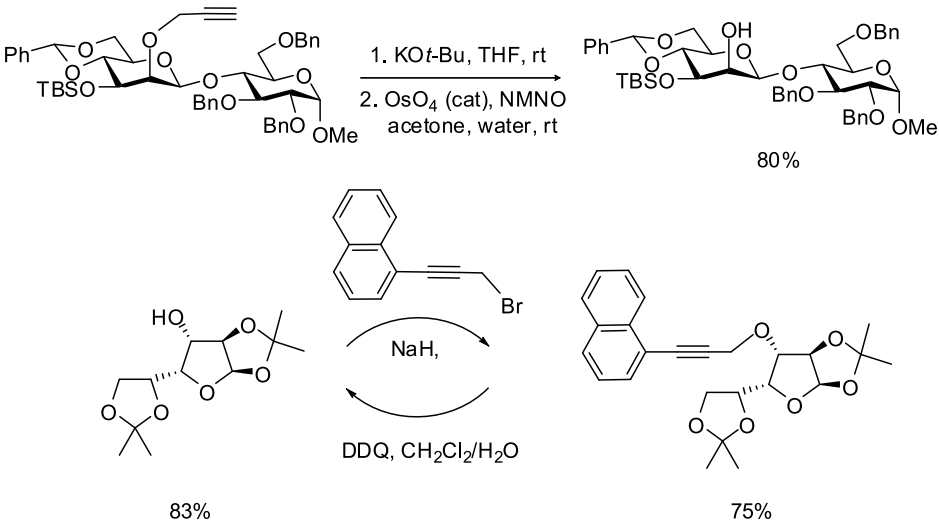
The NAP ethers can easily be removed by hydrogenolysis [110] or by DDQ oxidation under conditions which other usual protecting groups like acetyl, pivaloyl, phthalimido, benzyl, and benzylidene survive [113,114]. Recently some successful applications of sugar NAP ethers in the synthesis of complex oligosaccharides have been reported [115].

2.1.7 Propargyl Ethers

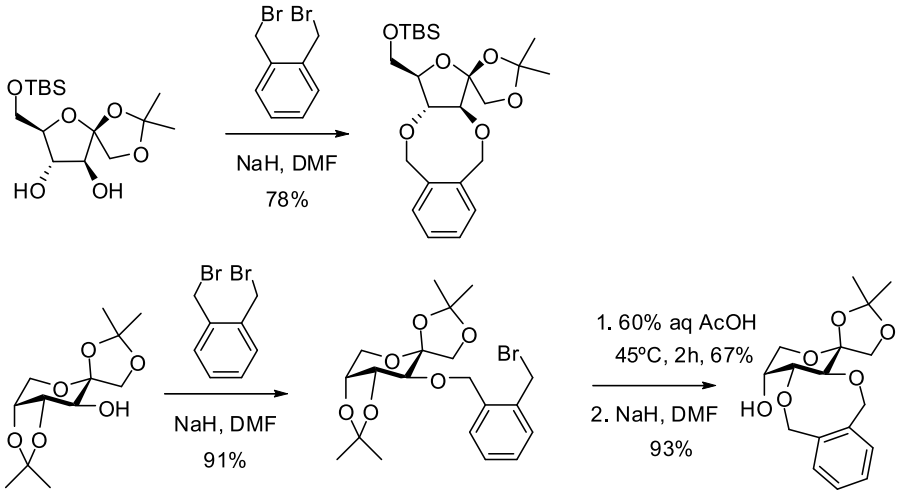
Crich and coworkers, have successfully used propargyl ethers as protecting groups in oligosaccharide synthesis [116,117]. Propargyl ethers are readily introduced under standard techniques and are cleaved by a two-set deprotection protocol: an initial treatment with base followed by catalytic osmylation of the resulting allenyl ether (● *Scheme 16*). The use of the (1-naphthyl)-propargyl group opens the possibility for its one-step cleavage with DDQ [117]. These two protecting groups, because of their minimal steric character, are useful for improving the diastereoselectivity of β-mannosylation reactions [116,117,118].

2.1.8 *o*-Xylylene Ethers

In contrast to all ether-type protecting groups so far mentioned, the *o*-xylylene group is a bifunctional protecting group devised for simultaneous protection of two vicinal hydroxyl groups of a carbohydrate molecule [119]. The *o*-xylylene group can be easily introduced by direct alkylation of the diol with α,α'-dibromoxylene or by a two-step process involving an initial alkylation of one hydroxyl function followed by an intramolecular ring-closing reaction (● *Scheme 17*). The *o*-xylylene protecting group has been successfully used as an element of conformational control of remote stereochemistry in the synthesis of spiroketals [120].



Scheme 16
Propargyl ethers as protecting groups



Scheme 17
The *o*-xylylene protecting group

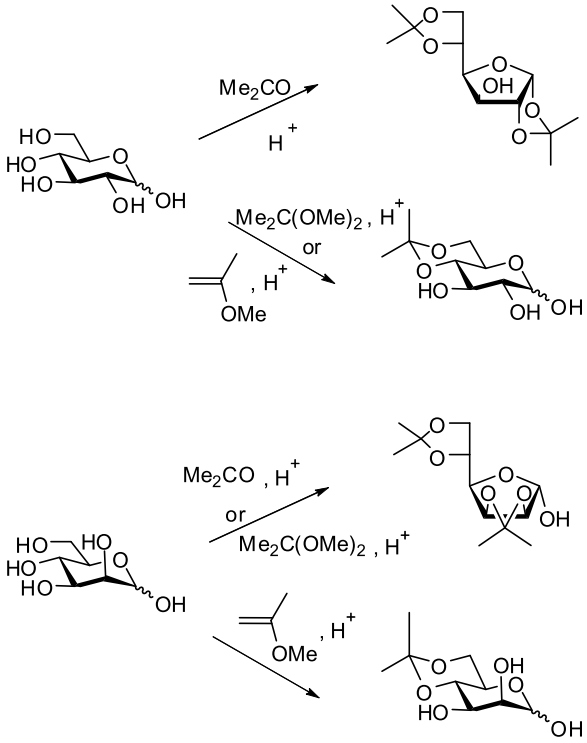
2.2 Acetalation Reactions: Acetal-Type Protecting Groups

Emil Fischer described as early as 1895 the formation of acetals of glycoses [121]. Since then, this type of protecting group has been extensively used in carbohydrate chemistry. Acetal protecting groups are readily available, easily introduced and removed, and stable to a good range of reactions. Standard conditions for the formation of acetals include treatment of a diol with a carbonyl reagent together with some acid catalyst.
Cyclic acetals such as benzylidene, isopropylidene, or 1,2-diacetals have been effectively used in the regioselective protection of diol systems. The ease of formation and the structures of products are a function of the regio- and stereochemistry of the hydroxyl groups and the properties of the employed carbonyl reagent. Acetals have been applied as protecting groups in many sugars including aminosugars and oligosaccharides. Exhaustive lists of catalyst and conditions can be found in reviews devoted to carbohydrates [122].

2.2.1 Cyclic Acetals

Isopropylidene (acetonides) and benzylidene derivatives are the most commonly used acetals for the simultaneous protection of 1,2- and 1,3-diols in carbohydrate and nucleoside chemistry [123]. Cyclohexylidene acetals are occasionally used, most often as an alternative to benzylidene acetals. Protection using cyclohexane-1,2-diacetals or the related butane-2,3-diacetals represents a new approach which has proved its value in complex oligosaccharide synthesis [124].
Besides being useful for selective protection of monosaccharides, cyclic acetals can display a number of interesting reactions, such as reductive or oxidative ring opening, that amplify the synthetic interest of these protecting groups [125].

Isopropylidene, Benzylidene, and Related Acetals Isopropylidene or benzylidene acetals are formed either by direct condensation of the diol with the appropriate carbonyl compound (acetone or benzaldehyde, respectively) or by transacetalation with the corresponding dimethoxy acetal. Both processes are carried out in acidic conditions [123].
One advantage of these acetals is their regioselective introduction. Benzylidene derivatives are formed preferentially with 1,3-diols of which anomeric or primary hydroxyl groups are a part. Therefore, they are generally used for 4,6-*O*-protection of pyranoses forming either *cis*- or *trans*-fused 1,3-dioxane rings. In these six-membered rings only the thermodynamically more stable [126] equatorial phenyl-substituted derivatives are observed. Formation of benzylidene acetals has also been achieved under basic conditions using α,α-dihalotoluenes in refluxing pyridine [127].
In contrast, isopropylidene acetals are more stable as five-membered 1,3-dioxane rings formed on *cis*-1,2-diols. Practically all examples in the literature show that, the use of acetone for the acetonation of sugars, leads to 1,3-dioxane rings, which are thermodynamically favored [128]. If 2-alkoxypropene is used as reagent, a reversal on the regioselectivity is observed, and the kinetic products (4,6-*O*-isopropylidene acetals) are preferentially formed [129]. An intermediate behavior is observed for the transacetalation process involving 2,2-dimethoxypropane which gives results either similar to those obtained with acetone or similar to those obtained with enol ethers (➤ *Scheme 18*) [130].

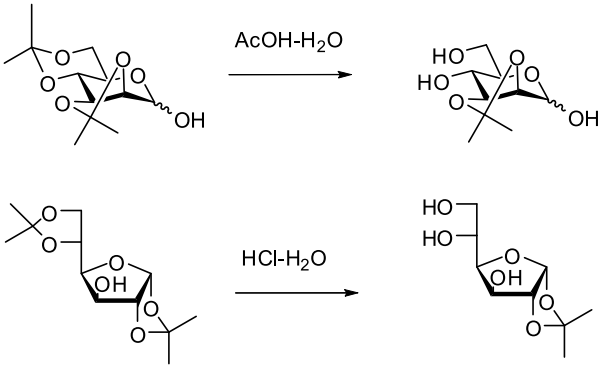


Scheme 18
Examples of isopropylidene formation on hexoses

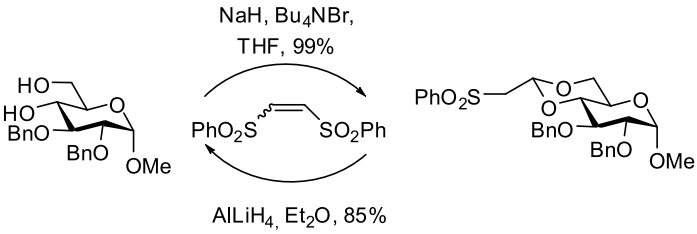
The most extensively adopted method for removal of these protecting groups involves the use of acidic conditions. There are various types of protic and Lewis acids that have been used for this purpose: aq. H_2SO_4 [131], Dowex acidic ion-exchange [132], trifluoroacetic acid [133], $Zn(NO_3)_2$ [134], supported $HClO_4 \cdot SiO_2$ [135] or recoverable $VO(OTf)_2$ [136]. Thiourea can also provoke the cleavage under essentially neutral conditions [137].

Relative to their deprotection, it should be emphasized, that the selective removal of one acetal in the presence of the same (or different) type of acetal, at distinct positions in the same molecule, is possible and has been observed quite often [138]. Several well-established observations can be summarized as follows (i) 1,3-dioxanes are hydrolyzed more easily than the corresponding 1,3-dioxolane, (ii) implication of the anomeric center renders the acetal function more stable, (iii) *cis*-fused 1,3-dioxolanes in a furanose or pyranose ring are more stable than the ones that involve a side chain, and (iv) *trans*-fused benzylidene acetals of hexopyranoses are hydrolyzed faster than the corresponding *cis*-fused acetals [123]. Some examples are shown in *Scheme 19*.

Some other alkyliden acetals with atypical properties have been used as protecting groups in carbohydrate chemistry. Thus, phenylsulfonylethylidene (PSE) acetals can be synthesized from glycosides under basic conditions. These derivatives are suitable for the protection of



Scheme 19
Examples of selective removal of acetal protecting groups



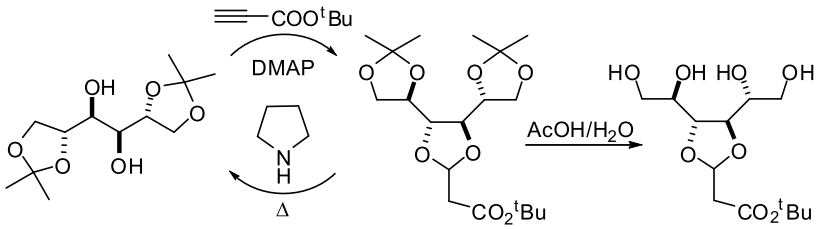
Scheme 20
Phenylsulfonylethylidene acetal as protecting group

1,2- and 1,3-diols. The equatorially configurated cyclic acetals are exclusively formed with 1,3-diols whereas the diastereoselectivity of the dioxolane-type acetals from 1,2-diols is quite poor. PSE acetals are deprotected to the corresponding diols under classical reductive conditions ($LiAlH_4$) (● *Scheme 20*) [139].

Vicinal diols in sugar substrates can also be protected as their 2-(*tert*-butoxycarbonyl)-ethylidene ("Bocdene") or 2-(methoxycarbonyl)-ethylidene ("Mocdene") derivatives in the reaction with *tert*-butyl or methyl propynoate. The acetal-like structures of these protecting groups is of interest because they are stable under acidic conditions, which allows their selective deprotection versus other acetals, and can be removed under basic conditions via an addition-elimination mechanism (● *Scheme 21*) [140]. The procedure is not suitable for 1,3- or 1,4 diols.

Diacetal Protecting Groups The pioneer work of Ley's group concerning the application of 1,2-diacetals such as the dispiroketal (dispoke) [141,142,143,144,145], the cyclo-hexane-1,2-diacetal (CDA) [146], and the butane 2,3-diacetals (BDA) [147] has found widespread application in carbohydrate chemistry (● *Fig. 2*) [148].

1,2-Diacetals are highly selective protecting agents which are able to discriminate di-equatorial diols in many carbohydrate derivatives [148]. These protecting groups are stable to functional group manipulation, glycosidation, and are easily removed at the end of a synthetic sequence



Scheme 21
2-(*tert*-Butoxylcarbonyl)-ethylidene acetal as protecting group

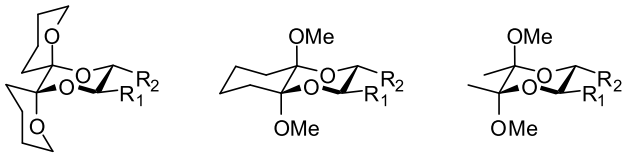


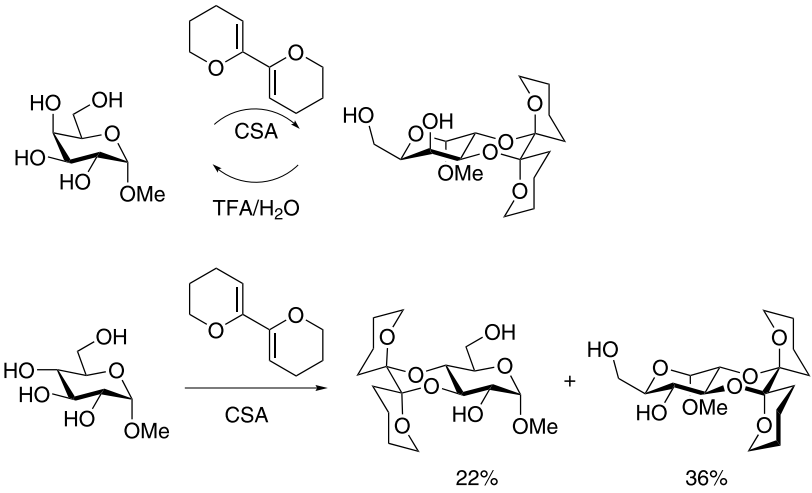
Figure 2
Diacetal protecting groups

by aqueous trifluoroacetic acid [149]. Furthermore, 1,2-diacetal protected substrates present a rigid structural architecture that is able to effect reactivity-tuning during glycosidation reactions. This property has been successfully used in oligosaccharide synthesis [150].

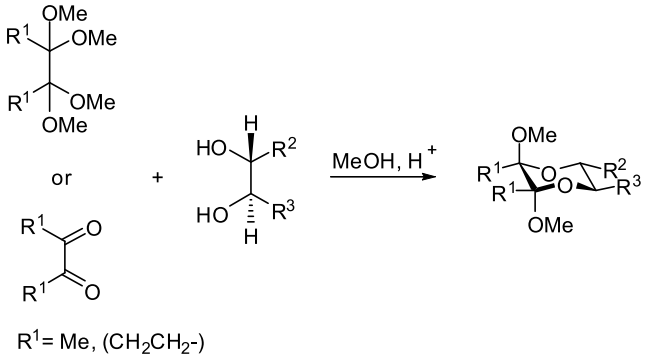
The dispiroketal protection of monosaccharides is controlled by the stabilizing influence of multiple anomeric effects leading to a single diastereomeric derivative. In certain examples, where there is more than one diequatorial diol pair present in the molecule, as for example in D-glucose derivatives, reaction affords a mixture of diacetals (*Scheme 22*). The reaction, often giving crystalline compounds, is carried out by treatment of the polyol with 3,4,3′,4′-tetrahydro-6,6′-bis-2H-pyran in chloroform at reflux in the presence of a catalytic amount of CSA [151].

Cyclohexane-1,2-diacetals (CDA) are, however, a better alternative for application to highly polar derivatives within the carbohydrate area. The cyclohexane-1,2-diacetals are formed by reacting 1,1,2,2-tetramethoxycyclohexane [146] or 1,2-cyclohexanedione [152] in boiling methanol containing a catalytic amount of CSA (*Scheme 23*). The corresponding 1,4-dioxane products are formed with high stereoselective control owing to favorable anomeric effects and equatorial placement of functionality around the periphery of the 1,4-dioxane ring. The CDA derivatives are often highly crystalline and usually do not require chromatography. They are stable but can be deprotected readily. They are also able to withstand a wide variety of reaction types such as iodination, reduction, oxidation, Wittig coupling, silylation, and glycosidation reactions.

Likewise, butane-2,3-diacetals (BDA) are good protecting groups for vicinal diequatorial diols. They are prepared either from butane-2,3-dione [153] or from the tetramethoxy butane-2,3-diacetal [147] (*Scheme 23*). BDA derivatives are usually isolated as solids rather than



Scheme 22
Examples of protection of diequatorial vicinal diols with dispiroketals



Scheme 23
Acid-catalyzed formation of 1,2-diacetals from 1,2–*trans*-diols

highly crystalline materials but they have very desirable NMR features that help analysis of the products since the methyl groups act as useful diagnostic markers. As with CDA, BDA groups are readily removed at the end of the synthetic sequence.

Pyruvate Acetals Pyruvate ketals are present in many lipopolysaccharides of bacterial origin, in capsular polysaccharides (*Fig. 3*) [154], and also in glycolipids isolated from fish nerve fibers [155]. As a result of the unique structural features including the presence of a negative charge on the carboxyl functional group and the chiral center, pyruvate ketals influence immunological specificity and patterns of immunological cross reactivity and therefore play an important role in cell–cell recognition processes [156]. Hexopyranosides containing pyru-

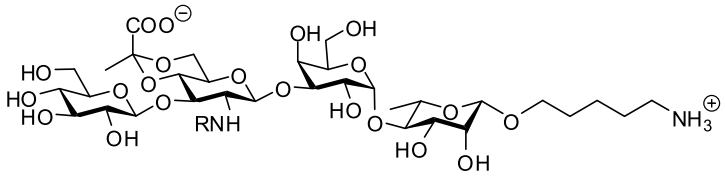
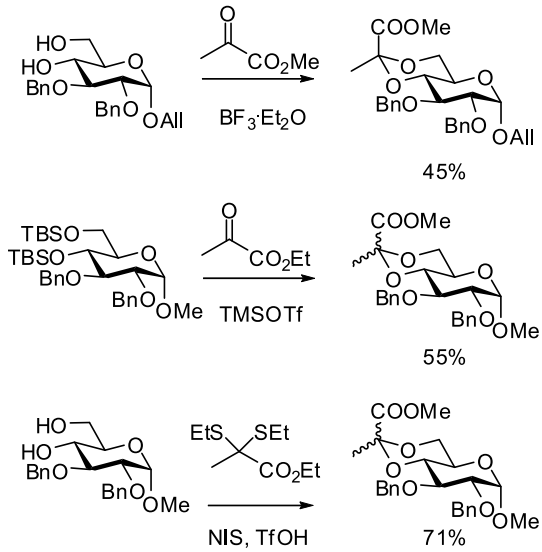


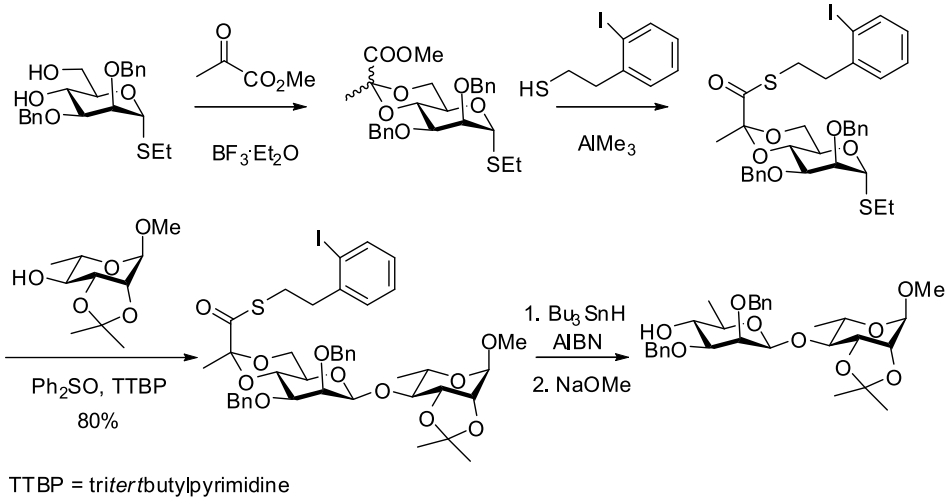
Figure 3
Pyruvated tetrasaccharide related to *Streptococcus pneumoniae* Type 27

vic acid ketals are also useful tools for immunochemical studies of *Klebsiella* polysaccharides [157]. Most commonly, pyruvate ketals are present as 4,6-ketals of hexose residues [158]. However, they also occur as 1,4-dioxolanes formed either from *cis*-axial-equatorial [159] or *trans*-diequatorial hydroxyl groups [160].

Pyruvate ketals can be synthesized [161] by direct condensation of a pyruvate ester with a diol in the presence of a Lewis acid, but this is less preferred because of the electron-withdrawing effect of the adjacent carboxylate group [162,163]. Therefore, several indirect methods for the acetalization have been introduced including condensation with pyruvate derivatives [164,165] or generation of the carboxylate group by oxidation of a suitable precursor [166,167,168,169]. A more efficient route to pyruvic acid acetals starts from silylated diols [170] or by the reaction between diols and methyl pyruvate dialkyl dithioacetal [171,172] activated by methyl triflate, dimethyl(methylthio)sulfonium trifluoromethane sulfonate (DMTST), nitroso tetrafluoroborate ($NOBF_4$), SO_2Cl_2-trifluoromethanesulfonic acid, or *N*-Iodosuccinimide (NIS) and trifluoromethanesulfonic acid [173] (*Scheme 24*).



Scheme 24
Examples of synthesis of pyruvate acetals of carbohydrates



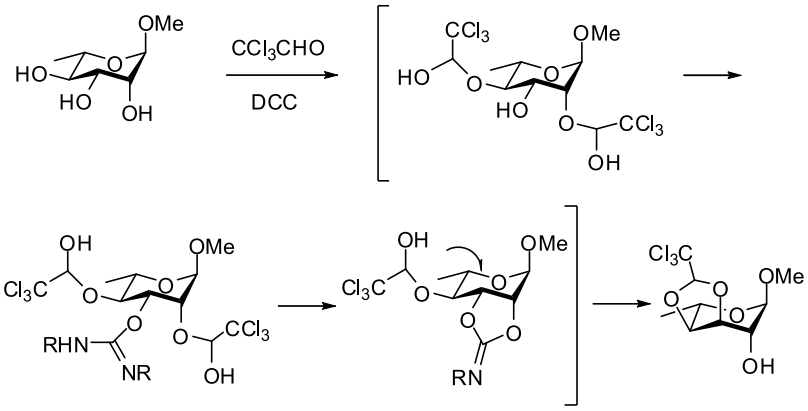
Scheme 25
Pyruvate acetals for stereoselective formation of β-D-mannopyranosides

Pyruvate-related acetals have been introduced by Crich as new protecting groups for carbohydrate thioglycoside donors [174]. The group conveys strong β-selectivity with thiomannoside donors and undergoes a tin-mediated radical fragmentation to provide high yields of the synthetically challenging β-rhamnopyranosides (*Scheme 25*) [174]. Besides this protecting group, it has been shown that this approach can also be applied to other related cyclic acetals [175,176,177].

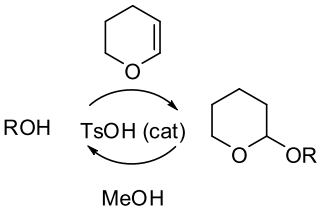
2,2,2-Trihaloethylidene Acetals In 1992 it was found that the reaction of hexafluoroacetone or chloral and dicyclohexylcarbodiimide (DCC) with bis-vicinal triols having a *cis-trans* sequence of hydroxyl groups resulted in the formation of cyclic acetals in which the central carbon of the triol had the inverted configuration [178,179]. In this acetalization the oxygen atom of the carbonyl compound (but not that of the alcoholic component) is inserted into the acetal moiety. As shown in *Scheme 26*, this non-classical pathway involves the in situ formation of a cyclic imidocarbonic ester intermediate, followed by an intramolecular S_N2-attack by a deprotonated neighboring hemiacetal moiety [180,181]. The resulting cyclic acetals are acid-stable but can be converted into the acid-labile ethylidene acetals by treatment with Raney Ni or Bu_3SnH.

2.2.2 Acyclic Acetals

Acyclic *O,O*-acetals are used for the temporary protection of mono-alcohols. Most commonly used are the tetrahydropyranyl (THP), the methoxymethyl (MOM), the benzyloxymethyl (BOM), or the methoxyethoxymethyl (MEM) protecting groups.



Scheme 26
Example of epimerization by non-classical acetalization



Scheme 27
Tetrahydropyranyl protecting group

Tetrahydropyranyl Ether The tetrahydropyranyl ether is one of the most frequently used protecting groups for alcohols during multi-step organic synthesis. It is usually introduced by treatment of the corresponding alcohol with 3,4-dihydro-2H-pyran in the presence of an acid catalyst (*p*-toluenesulfonic acid, PPTS, $BF_3 \cdot OEt_2$, or cation-exchange resins) (*Scheme 27*). Several other methods aiming to introduce the THP group under neutral conditions have been reported [182,183,184,185,186,187]. The resulting tetrahydropyranyl ethers offer stability towards strongly basic reaction conditions, organometallics, hydrides, acylating reagents, and alkylation reagents and the deprotection is usually performed as an acidic hydrolysis or alcoholysis.

In spite of the stability of THP ethers, its use in carbohydrate chemistry is currently limited due to the resulting diastereomeric mixtures obtained by the introduction of an additional stereocenter. This fact makes chromatographic separation and characterization of the products difficult and therefore their use will probably decrease in the future.

Alkoxymethyl Ethers The principal members of this set of protecting groups are: methoxymethyl ether (MOM) [188], methoxyethoxymethyl ether (MEM) [189], benzyloxymethyl ether (BOM) [190], *p*-methoxybenzyloxymethyl ether (PMBM) [191], and trimethylsilylethoxymethyl ether (SEM) [192] (*Fig. 4*). Since these protecting units are devoid of chirality, their use introduces no stereochemical complications.

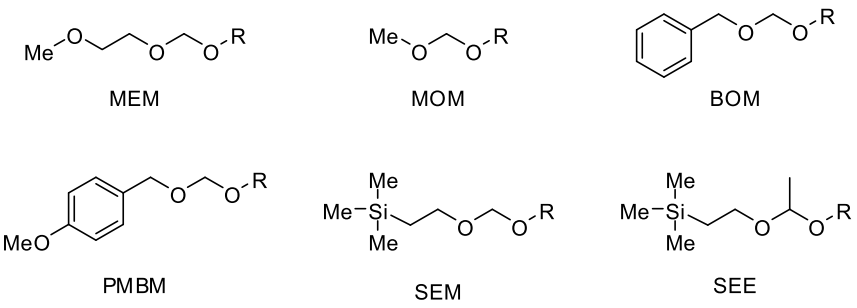


Figure 4
Principal members of the alkoxymethyl ether family

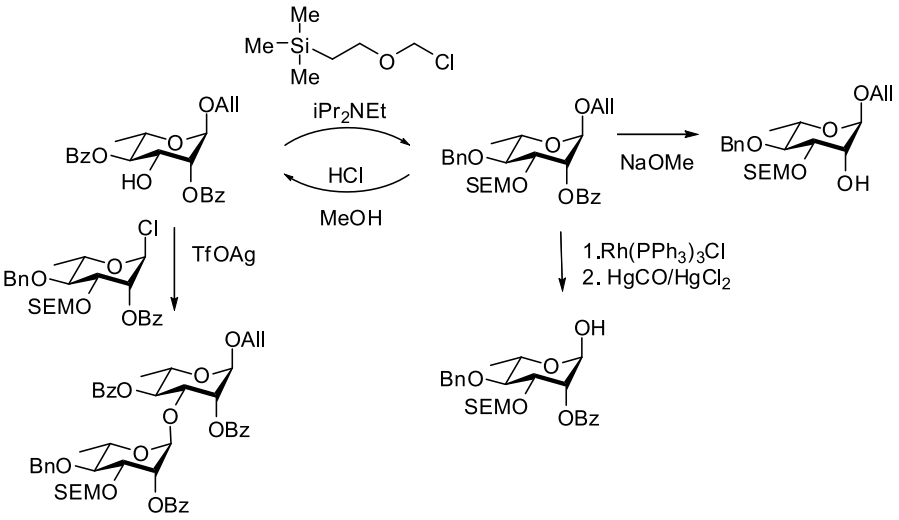
Usually, the formation of the alkoxymethyl ethers is effected by reaction of the corresponding chloride with either the sodium or lithium salt of the alcohol to be protected. The resulting ethers are stable to a wide variety of conditions including many organometallic reagents, reducing conditions, oxidizing agents, and mild acids. Indeed a number of the alkoxymethyl ethers are orthogonal to each other and can be used strategically in multistep syntheses. For example, SEM, BOM, and PMBM ethers are cleaved using a fluoride source, hydrogenolysis and oxidation, respectively. The alkoxymethyl ethers also vary in their degree of lability to Brønsted acids with MOM ether being the most robust.

The SEM group can be removed under milder reaction conditions than the MEM or MOM analogs. As shown in *Scheme 28*, the compatibility of this group with the conditions required for other selective functional group transformation, together with its stability under glycosylation conditions, allowed the preparation of rhamnopyranosyl synthons for the elaboration of higher order oligosaccharides (*Scheme 28*) [193].

The 1-[2-(trimethylsilyl)ethoxy]ethyl (SEE) group closely resembles the SEM group and can be introduced to alcohols with 2-(trimethylsilyl)ethyl vinyl ether in the presence of a catalytic amount of PPTS under neutral or slightly acidic conditions [194]. The SEE group can be removed with TBAF in THF (24 h, rt. to 45 °C).

2.3 Acylation Reactions: Ester-Type Protecting Groups

Acylation of hydroxyl groups of carbohydrates is one of the most commonly used functional group protection techniques in the synthesis of oligosaccharides. Acyl groups are readily introduced with many acylating agents of different reactivity. They are easily removed under basic (aqueous or non-aqueous) conditions, but are fairly stable under acidic conditions. The main drawback of esters as protecting groups is that they have a tendency to migrate (especially acetates), both under acidic and basic conditions. This is a concern in partially protected derivatives, and results in a mixture with the most stable compound preponderant. Thus, in *cis*-hydroxyls, there is normally a preferred migration from the axial position to the equatorial one and in 4,6-diols the migration goes from *O*-4 to *O*-6 preferentially [195].



Scheme 28
Example of use of SEM protecting group

There is a very large number of different ester protecting groups available and only the more common representatives in carbohydrate chemistry will be treated here. This includes acetate and substituted acetates such as chloroacetate, pivaloate, and levulinate groups. Aroyl groups are frequently used, such as benzoyl and substituted benzoyl e. g. p-phenylbenzoyl and 2,4,6-trimethylbenzoyl groups.

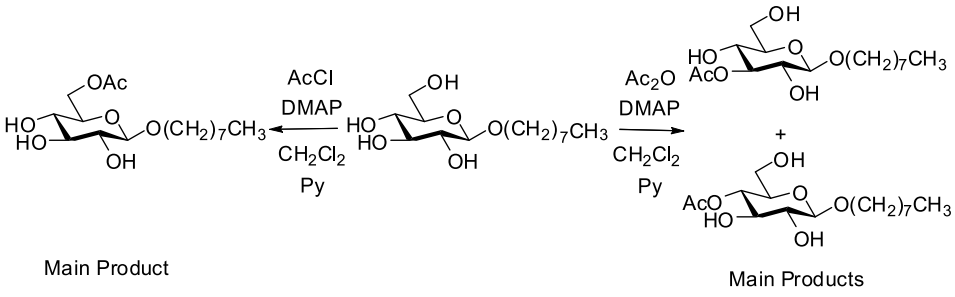
2.3.1 Acetyl (Ac) and Benzoyl (Bz) Esters

General Aspects In carbohydrate chemistry, per-*O*-acetylated sugars are inexpensive and useful intermediates for the synthesis of several natural products containing glycosides, oligosaccharides, and other glycoconjugates [196]. The acetylation reaction has also been employed for structural elucidation of many natural products containing carbohydrates. Acetylation of sugar alcohols is often carried out using a large excess of acetic anhydride or, more rarely, acetyl chloride, in the presence of pyridine (or other tertiary amine). Pyridine derivatives, such as 4-(dimethylamino)pyridine and 4-(pyrrolidino)pyridine have been added to the reaction as co-catalyst to speed up the acetylation reaction [197,198]. Similar considerations are valid for the *O*-benzoylation with the exception that benzoyl chloride rather than the anhydride is used.

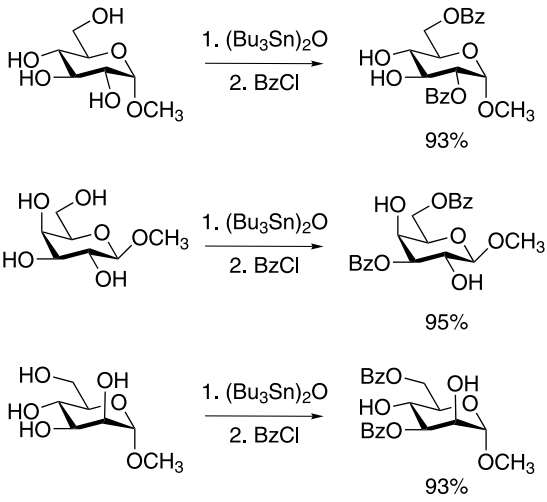
Recently, imidazole has been successfully applied as a catalyst for the acetylation of carbohydrates in acetonitrile [199]. A variety of other catalysts in combination with excess of acetic anhydride and solvent includes sodium acetate [200], sulfuric acid [201], perchloric acid [202], and a number of Lewis acid catalysts such as, iodine [203], $Sc(OTf)_3$ [204], $Cu(OTf)_2$ [205], $CoCl_2$ [206], $BiOCl\text{-}SOCl_2$ [207], $LiClO_4$ [208], $FeCl_3$ [209], $BiCl_3$ [210], and a series of heterogeneous catalysts such as, montmorillonite K-10 [211], zeolites [212], nafion-H [213], $HClO_4\text{-}SiO_2$ [214], or molecular sieves [215]. Recently, a $ZnCl_2$–sodium acetate combina-

tion [216] or $InCl_3$ [217] with acetic anhydride under microwave conditions has been reported for the acetylation of carbohydrates. A few reports have also appeared on the acetylation of carbohydrates using ionic liquids as solvents and catalysts [218,219].
Zemplén deacylation is the most commonly used deblocking reaction for the removal of ester protecting groups [220]. Using this transesterification reaction, OH-functions can be regenerated under mild conditions, in methanol with a catalytic amount of sodium methoxide at room temperature. The difference in the rate of benzoate and acetate solvolysis is sufficient to enable removal of acetates in the presence of benzoates. Typical conditions for this selective cleavage include ammonia in MeOH.

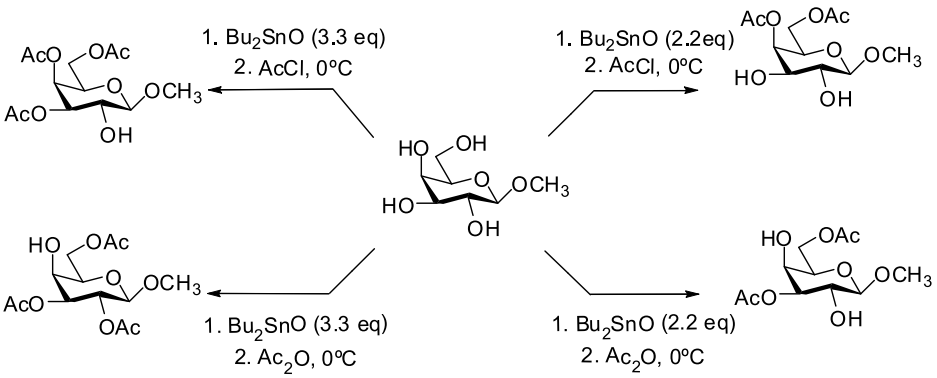
Regioselective Acylation Regioselective esterification of carbohydrates may be achieved in part by making use of the differing reactivities of hydroxyl groups. While the selective protection of primary hydroxy groups with sterically demanding acyl residues (e. g. by pivaloylation) is rather easily achieved, it is more difficult to protect one of a number of secondary hydroxy groups. Factors determining the regioselectivity of the acylation of secondary hydroxy groups in carbohydrates have been studied [221]; the most important ones being steric hindrance, intramolecular hydrogen bonding, and the configuration of the hydroxy groups. For instance, the presence of vicinal axial heteroatoms, such as O and S, enhances the nucleophilicity of the corresponding vicinal equatorial OH.
Regioselective acetylations have been promoted by different reagents such as alumina in refluxing ethyl acetate [222,223], silica gel-supported lanthanide chlorides and methylorthoacetate [224], a hindered base and acetyl chloride at low temperature [225], iminophosphorane bases and vinylacetate [226], NaH and 3-acetyl-thiazolidine-2-thiones [227], PPh_3/CBr_4 in ethyl acetate at high temperatures [228]. Recently, it has been shown that the rate and the selectivity of an acetylation reaction can be controlled by the counterion of the acetylating agent under nucleophilic catalysis. The team play of reagent, catalyst, and auxiliary base is responsible for the outcome of the reaction [229]. Thus, octyl β-D-glucopyranoside can be acetylated with high selectivity either on the primary or on secondary OH groups by using different acetylation agents under otherwise identical conditions (● *Scheme 29*).
The use of organotin reagents (● *Sect. 2.1.2* under ● *"Formation of Organotin Intermediates"*) provides a useful means of efficient regioselective acylations. There does not seem to be significant differences in selectivities between alkylation and acylation although forma-



Scheme 29
Counterion-directed regioselective acetylation of octyl β-D-glucopyranoside



Scheme 30
Examples of stannyl mediated regioselective benzoylation



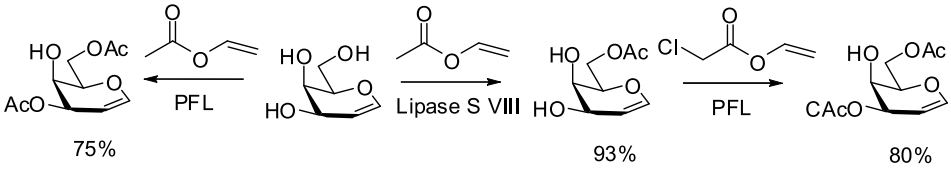
Scheme 31
Reagent-dependent multiprotection of methyl β-D-galactopyranoside

tion of *O*-acyl derivatives is a much faster reaction in any solvent, and it does not require heating or the presence of an additional nucleophile. Thus, treating methyl α-D-glucopyranoside with $(Bu_3Sn)_2O$ and then with BzCl gave the 2,6-di-*O*-benzoate, while the 3,6-di-*O*-benzoates were obtained upon analogous benzoylation of methyl β-D-galactopyranoside and methyl α-D-mannopyranoside, respectively (*Scheme 30*) [230].

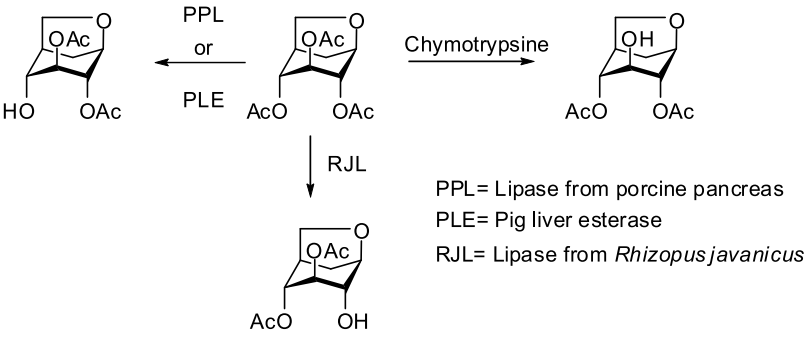
An extension of this tin chemistry to the regioselective acylation of unprotected sugars bound to a resin shows the possibility of using solid-phase techniques for the preparation of *O*-acyl derivatives of carbohydrates [231]. Very recently, it has been reported that organotin-mediated multiple carbohydrate esterifications can be controlled by the acylating reagent and the solvent polarity. When acetyl chloride is used, the reactions are under thermodynamic control, whereas when acetic anhydride is employed, kinetic control takes place (*Scheme 31*) [232].

Enzymatic regioselective protection techniques are also an interesting and useful method for the protection of hydroxyl groups [233]. Such techniques are exclusively directed at regioselective acylation and deacylation, mostly by using different lipases [234] or proteases [235], which can catalyze acyl transfer reactions from activated esters to suitable acceptors. The most frequently used enzymes are *Porcine pancreatic lipase* (PPL), *Protease N-neutral protease* (PN), *Pseudomonas fluorescens lipase* (PFL), *Chromobacterium viscosum lipase* (CVL), and *Candida cylindracea lipase* (CCL). The results of the enzymatic acylation of several pyranoses and furanoses have been reviewed [236]. Almost all combinations of enzymes and substrates lead to acylation of the primary hydroxy group. The regioselectivities are usually higher than 70%, and the conversions between 40 and 100%. However, if the 6-OH groups are protected first or deoxygenated, in the corresponding enzymatic reactions, selectivities on the acylation of secondary hydroxyl groups are observed. An example is shown in *Scheme 32*, where enzymatic acyl transfer reactions turned out to be a viable method for the complete differentiation of the hydroxyl groups of glycal derivatives [237].

Enzymes are not only capable of introducing but also of removing acyl groups into carbohydrates [233]. For example, each of the three OH groups in 1,6-anhydroglucopyranose can be liberated selectively making use of enzymatic reactions (*Scheme 33*) [238,239,240]. The lipase-mediated hydrolysis proceeds with higher velocity and, in many cases with better selectivity, if butanoates or pentanoates are employed as substrates instead of acetates. In all cases the reaction conditions are so mild that the acid sensitive structures remain unaffected.



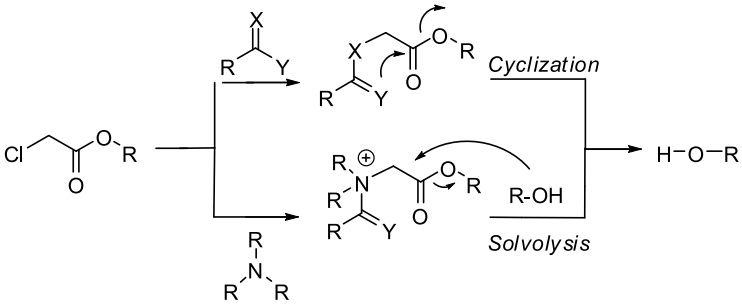
Scheme 32
Examples of enzymic regioselective acylation



Scheme 33
Examples of enzymic regioselective deacylation

2.3.2 Substituted Acetyl Esters

The lability of acetates is enhanced by introducing chlorine atoms in the α-position. Thus, chloroacetates (Cac or ClAc) hydrolyze faster than acetates and trichloroacetates are so reactive that they are rarely used in synthesis. Thus far, thiourea [241], hydrazine dithiocarbonate [242], pyridine [243] and diazabicyclo[2.2.2] octane (DABCO) [244] are representative of dechloroacetylation reagents. 1-Selenocarbamoylpiperidine also deprotects the *O*-chloroacetyl group with high chemoselectivity in the presence of other acyl groups such as acetyl, pivaloyl, and Fmoc without the assistance of a base [245]. Thiourea, hydrazine dithiocarbonate, or 1-selenocarbamoylpiperidine are believed to deprotect the ClAc group by following a cyclization mechanism. This mechanism is illustrated in *Scheme 34*: the nucleophilic atom (X) of the reagent replaces the chlorine atom of the ClAc group, and then another nucleophilic atom (Y) attacks the carbonyl carbon to break the C–O bond, thereby resulting in the production of free hydroxyl. In contrast, tertiary-amine-containing reagents such as pyridine and DABCO presumably attack the α-carbon to form onium salt, which is then solvolyzed by water, MeOH, or EtOH to produce naked hydroxyl group.



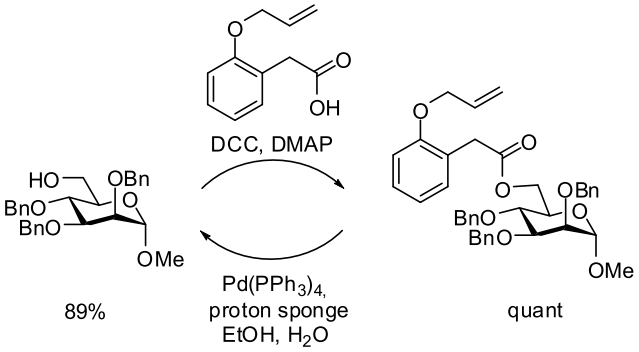
Scheme 34
Plausible mechanisms of removal of chloroacetyl groups

The chemoselective deprotection of the CAc group does not affect other protecting groups such as acyl derivatives (acetyl, benzoyl, or levulinoyl groups), carbonates, *p*-methoxybenzyl or silyl ethers and therefore has been included in sets of orthogonal protecting groups. However, the sensitivity of the chloroacetyl group may impose limitations for its application in the synthesis of complex oligosaccharides.

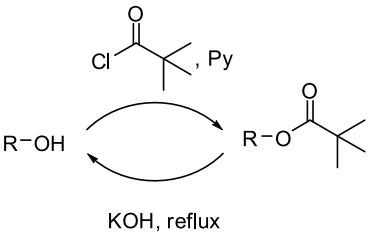
The 2-(allyloxy) phenyl acetyl (APAC) group has been proposed as a new robust acyl-type protecting group for hydroxyl groups [246]. It can be removed under mild conditions by relay deprotection whereby the phenolic allyl ether is cleaved by treatment with a transition metal followed by intramolecular ester cleavage by nucleophilic attack of the revealed hydroxyl (*Scheme 35*). It is compatible with glycosylations and can perform efficiently neighboring group participation leading to the exclusive formation of 1,2-*trans* glycosides.

2.3.3 Pivaloyl (Piv) Esters

The bulky pivaloyl group has been used as a protecting group in the synthesis of acylated nucleosides [247], monosaccharides, and disaccharides [248]. The pivaloyl esters are usually highly crystalline compounds, its position in a molecule is easily detectable by ^{1}H NMR, and it can be



Scheme 35
The 2-(allyloxy)phenyl acetyl protecting group



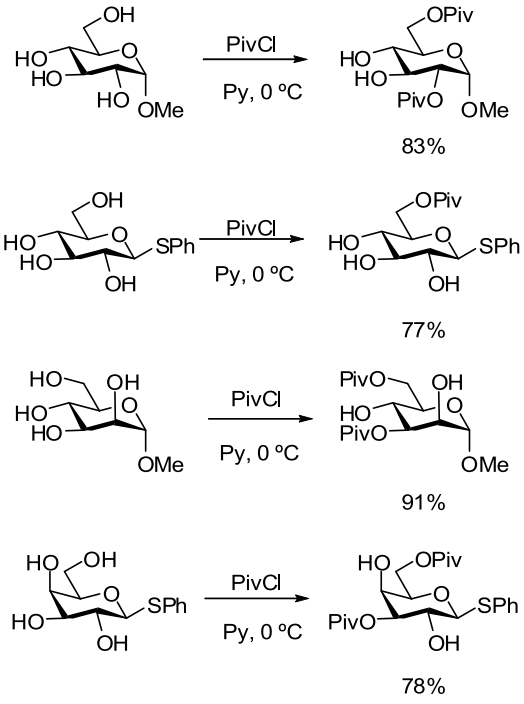
Scheme 36
The pivaloyl protecting group

removed totally or selectively by esterases from mammalian sera [249]. Furthermore, the use of pivaloate esters is advantageous in the stereoselective preparation of β-glycosidic linkages because they inhibit the sometimes competitive process of orthoester formation [250,251].

Pivaloylation of sugar alcohols is carried out using pivaloyl chloride in the presence of pyridine or with *N*-pivaloyl imidazole [252] in DMF. Pivaloyl esters are typically cleaved by base-catalyzed solvolysis (*Scheme 36*). Their greater steric hindrance makes them react slower than other acyl groups and some selectivity in the hydrolysis of different ester protecting groups may be observed.

A systematic study in the selective pivaloylation of various pyranosides and oligosaccharides [253] has shown that, in the absence of adjacent axial alcoxy groups, pivaloylation preferentially occurs at the primary hydroxyl groups. However, in the presence of an adjacent axial function, the reactivity of the vicinal secondary hydroxyl group is as high as that of the primary group towards pivaloylation (*Scheme 37*).

A limitation in the use of pivaloyl esters as protecting groups in a polyfunctional system is the harsh condition required for its cleavage (especially at sterically hindered secondary centers). The 4-acetoxy-2,2-dimethylbutanoyl (ADMB) esters have been proposed as an alternative because they are easily prepared, show similar reactivity in carbohydrate acylations, and are removed under much milder conditions (catalytic quantity of DBU at room temperature) [254].

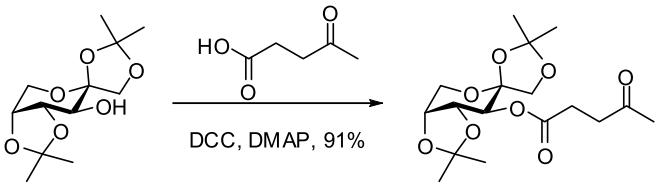


Scheme 37
Regioselective pivaloylation of hexopyranosides

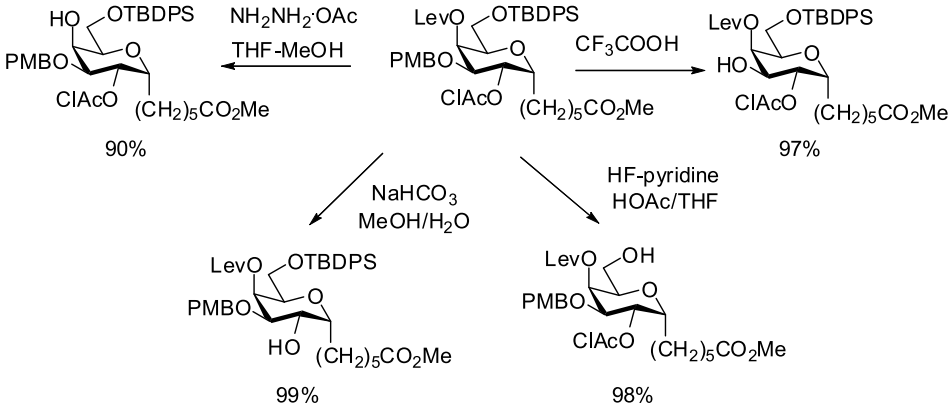
2.3.4 Levulinoyl (Lev) Esters

The levulinoyl (4-oxopentanoyl) moiety is a very useful temporary protecting group in nucleotide, polysaccharide, and glycolipid synthesis.

The levulinoyl esters are prepared from the free hydroxyl group by treatment of levulinic acid with DCC [255,256] or 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDAC) [257] in the presence of DMAP (*Scheme 38*). Additionally, 3′- and 5′-*O*-levulinyl protected derivatives of 2′-deoxy nucleosides have been prepared by regioselective enzymatic acylation using a variety of lipases and acetonoxime levulinate as acylating agent [258]. In contrast to other ester substituents, the *O*-levulinoyl group is far less prone to migration [259].



Scheme 38
Example of introduction of levulinoyl protecting group



Scheme 39
Example of orthogonal hydroxyl protecting groups

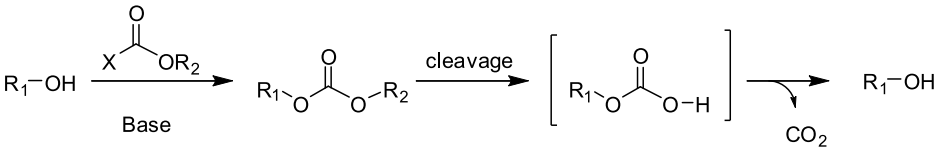
Levulinates are stable during coupling reactions and can be selectively cleaved without affecting other protecting groups in the same molecule. Actually, levulinoyl esters can be removed with hydrazine acetate under conditions that do not harm other acyl groups such as acetates, benzoates, or even chloroacetates [255]. This selectivity has allowed the levulinoyl group to be included in a number of orthogonal sets designed for the synthesis of collections of oligosaccharides. For example, Wong and coworkers showed that chloroacetyl, *p*-methoxybenzyl, levulinoyl, and *tert*-butyldiphenylsilyl groups can each be removed selectively and the freed hydroxyl group employed in glycosylation reactions (*Scheme 39*) [260]. Zhu and Boons showed that Fmoc, Lev, and diethylisopropylsilyl are another attractive set of orthogonal hydroxyl protecting groups for aminosugars [261].

2.4 Carbonylation Reactions: Carbonate-Type Protecting Groups

Carbonates represent an important family of protecting groups of hydroxyl groups. All of the members of the carbonate family are easy to introduce by reaction of the free alcohol with chloroformates or mixed carbonate esters. In general, carbonates are less reactive than esters towards basic hydrolysis owing to the reduced electrophilicity of the carbonyl afforded by the resonance deactivation by two oxygens. However, the conditions that attack esters may also attack carbonates.

Besides simple alkoxycarbonyl groups which are usually removed under basic hydrolysis, more sophisticated groups have been designed which are removed under milder and more specific conditions. In general, all the carbonate protecting groups are close relatives to the most important carboxyl protecting groups. The adaptation works because *O*-alkyl cleavage releases an unstable intermediate which decomposes with loss of carbon dioxide to give the free alcohol (*Scheme 40*).

The most commonly installed carbonates on carbohydrate derivatives include CBz, Troc, Aloc, Poc, and Fmoc groups.



Scheme 40
Formation and cleavage of carbonate-type protecting groups

2.4.1 Benzyl Carbonates (Cbz)

The benzyloxycarbonyl group (Cbz or Z) is useful in carbohydrate synthesis, not only for *N*-protection of amino sugars, but also to protect alcohols [262,263]. The main advantage of this group is that it is cleaved by hydrogenolysis, and when compared to benzyl ethers, benzyl carbonates are not only removed more readily [264] but also allow hydroxyl group protection under softer conditions than those employed for benzylation.

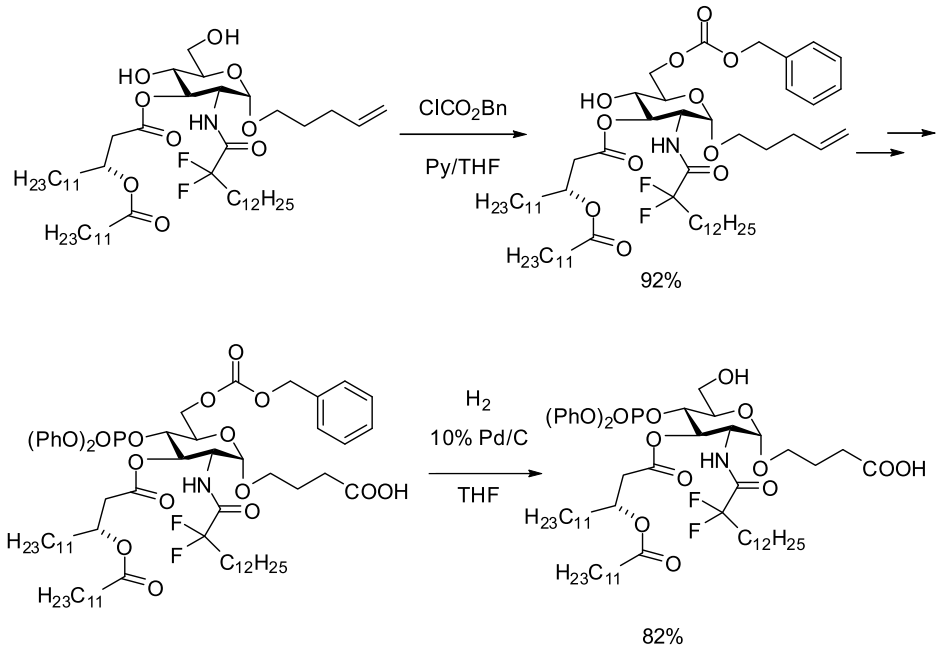
The benzyloxycarbonates are usually prepared by treatment of the alcohol with benzyloxycarbonyl chloride in the presence of a base (DMAP or *N*-ethyldiisopropylamine). Aqueous basic medium has to be avoided in polyol systems since these conditions favor the obtention of cyclic carbonates [265].

The benzyloxycarbonyl group has been used for the selective protection of monosaccharides. For instance, in the synthesis of a 1-*O*-carboxyalkyl GLA-60 analogue, a primary alcohol was selectively protected with benzylchloroformate and pyridine (◉ *Scheme 41*) [266]. Furthermore, Gotor and Pulido showed that the reaction of D-glucose, D-mannose, and D-galactose with acetone *O*-(benzyloxycarbonyl)oxime in dioxane in the presence of a lipase from *Candida antarctica* allowed the selective benzyloxycarbonylation of the primary hydroxyl group [267]. On the other hand, the regioselective protection of secondary alcohols in pyranosides has also been achieved in high yields [268]. Thus, in the α-D-mannopyranoside series the 3-OH is the more reactive secondary alcohol whereas in the α-D-gluco and α-D-galacto series, the 2-OH is the more reactive group.

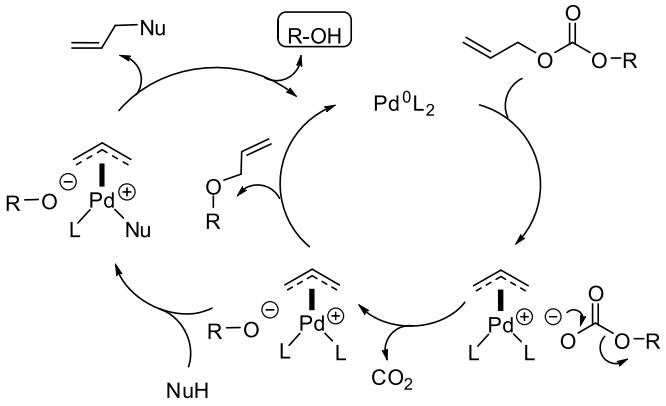
2.4.2 Allyl Carbonates (Aloc or Alloc)

The allyloxycarbonyl group [269] has shown a wide application in organic synthesis, especially in the fields of peptides, nucleotides, and carbohydrates. Allyloxycarbonyl derivatives are more easily prepared than the corresponding allyl ethers and they are more stable than ester protecting groups which find frequent use in carbohydrate chemistry.

Allyloxycarbonyl groups have been conveniently installed on primary and secondary hydroxyl groups of carbohydrate derivatives by reaction with allylchloroformate in the presence of TMEDA [270]. On the other hand, the Alloc group can be cleaved by transition-metal catalysts under conditions that are specific and with a high tolerance of other functional groups. As depicted in ◉ *Scheme 42*, allyl carbonates undergo facile oxidative addition with palladium(0) catalyst to afford π-allyl palladium complexes, which eject CO_2 to give, initially, allylpalladium alkoxides. Depending on the conditions, these intermediates either collapse to the allyl ether (◉ *Sect. 2.1.4*) or are intercepted by an external nucleophile to give the free alcohol [271].

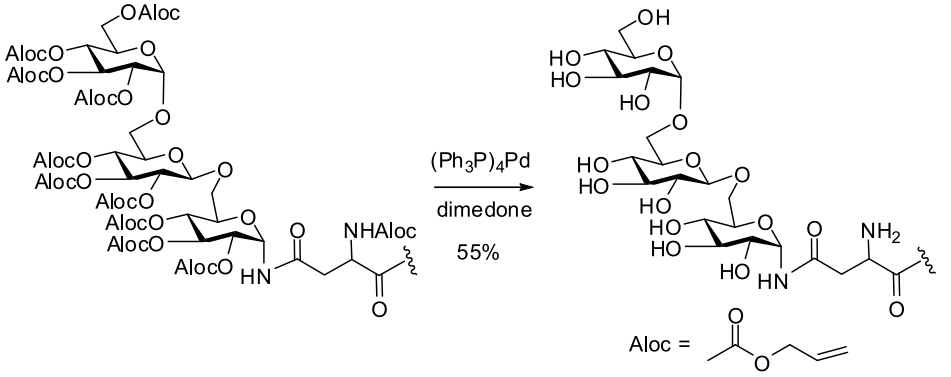


Scheme 41
Use of benzyloxycarbonyl group in the synthesis of a 1-*O*-carboxyalkyl GLA-60 analogue



Scheme 42
Palladium (0)-mediated cleavage of allyloxycarbonyl groups

An impressive example of how this protecting group has become a powerful tool for the construction of glycopeptides and oligosaccharides comes from the first synthesis of the glycopeptide nephritogenoside [272]. Its structure shows a trisaccharide composed of three glucose moieties linked to a peptide of 21 aminoacids. Taking into account the instability of the



Scheme 43
Aloc as a powerful tool for the construction of glycopeptides

molecule under acidic and basic conditions, the Aloc group was chosen as the final protecting group of amino and hydroxyl groups. Removal of a total of 11 allyl carbonates was carried out in one single step by treatment with palladium(0) and dimedone to give free nephritogenoside (*Scheme 43*).

2.4.3 Propargyl Carbonates (POC)

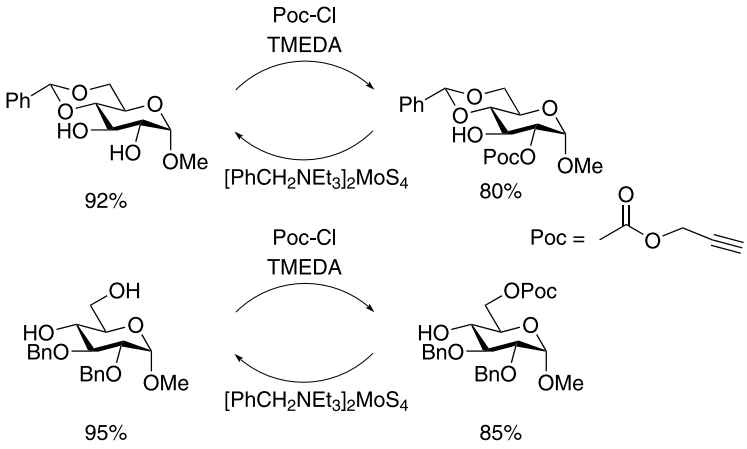
Recently, it has been shown that the propargyloxycarbonyl (Poc) group can be used for the protection of the hydroxyl function in carbohydrates [273]. The protection is achieved by treating the alcohol with propargyloxycarbonyl chloride (PocCl) in the presence of a suitable base. The mild reaction conditions can be modulated to attain regioselective protections (*Scheme 44*). The resulting propargyl carbonates are compatible with acidic, basic, and also glycosylation conditions.

Propargyl esters are deprotected effectively using benzyltriethylammonium tetrathiomolybdate $[PhCH_2Net_3]_2MoS_4$. The deprotected products usually can be isolated by simple filtration. Under the conditions of deprotection benzylidene acetals, benzyl ethers, acetyl and levulinoyl esters, and allyl and benzyl carbonates are left untouched and therefore can be used effectively for orthogonal protection in carbohydrate chemistry.

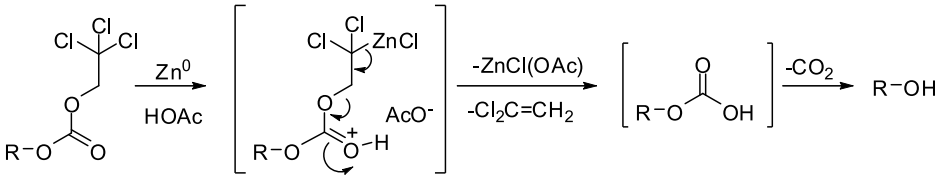
The utility of propargyloxycarbonyl chloride in simultaneous protection of alcohols and amines has been explored and it is possible to deblock propargyl carbonates leaving propargyl carbamates untouched [274].

2.4.4 2,2,2-Trichloroethyl Carbonate (TrOC)

Although very popular as an amino protecting group in peptide and glycopeptide chemistry, only a few reports deal with the trichloroethoxycarbonyl group as a hydroxyl protecting group in carbohydrate derivatives. The selective deprotection is carried out by treatment with zinc in acetic acid to give 1,1-dichloroethylene [275] (*Scheme 45*).

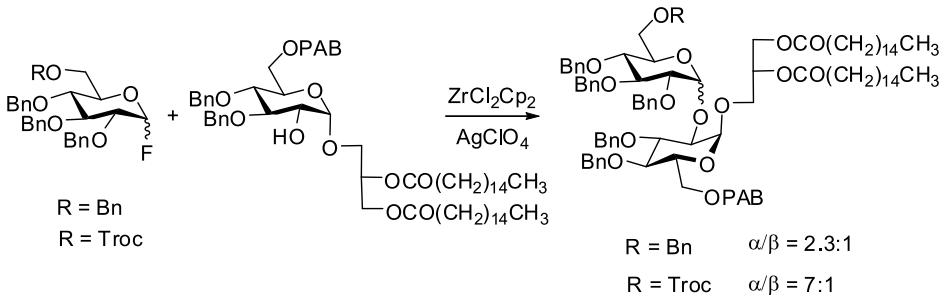


Scheme 44
Propargyloxycarbonyl as a protective group in carbohydrates



Scheme 45
Selective deprotection of 2,2,2-trichloroethoxycarbonyl group

Trichloroethoxycarbonyl groups have been installed on primary and secondary hydroxyl groups of carbohydrate derivatives by standard coupling with 2,2,2-trichloroethyl chloroformate. It has been shown that a Troc group in the primary position of a glycosyl donor reduces its reactivity but enhances α-selectivity in glycosylation couplings (*Scheme 46*) [276].



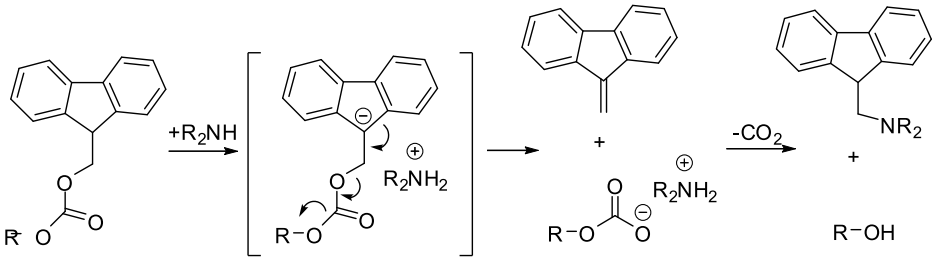
Scheme 46
Example of the α-orienting effect of the 6-*O*-Troc group

2.4.5 Fluoren-9-ylmethoxycarbonyl (Fmoc) Group

The Fmoc group is a well-established amino-protecting group [277] often used in peptide synthesis, but only recently has been recognized as a temporary hydroxyl protecting group for oligosaccharide synthesis [277,278,279,280].

The Fmoc group is readily introduced under standard conditions using FmocCl and a catalytic amount of DMAP in pyridine. The resulting carbonates are exceptionally stable under acidic conditions and therefore survive glycosylation reactions.

The Fmoc group can be removed with mild bases such as ammonia, piperidine, or morpholine [281]. The cleavage goes through a rapid deprotonation of the fluorene group to generate an aromatic dibenzocyclopentadienide anion. In a subsequent slower step, elimination generates dibenzofulvene (itself an unstable species that rapidly adds nucleophiles) and a carbonate residue, which then decomposes with loss of carbon dioxide to release the free alcohol (*Scheme 47*).



Scheme 47
Selective deprotection of fluoren-9-ylmethoxycarbonyl group

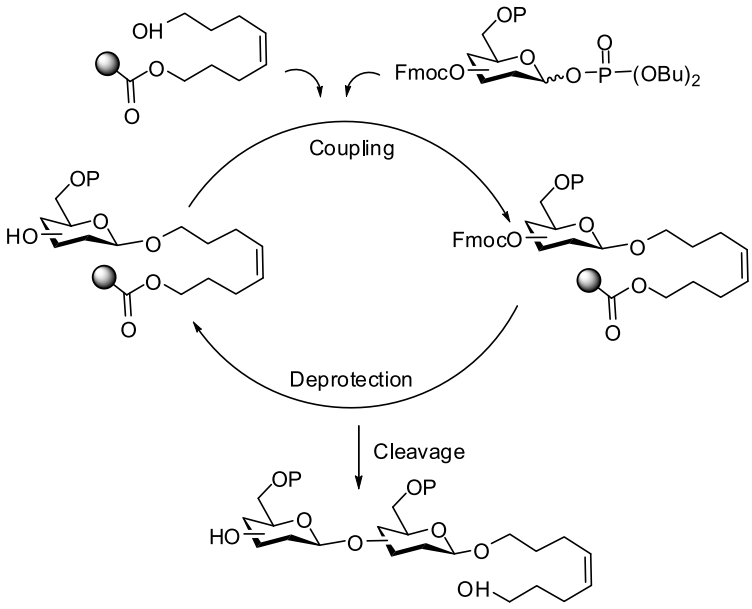
Recently, several groups have reported the use of glycosyl donors bearing Fmoc-protected hydroxyl groups for the solid-phase synthesis of saccharide libraries. Thus, a lactosyl donor, bearing an Fmoc-protected hydroxyl group, has permitted the effective construction of lactose-containing oligosaccharides in a solid-phase system [282,283].

The Fmoc group has also been used as a temporary protecting group in the automated synthesis of Lewis antigens. The UV active dibenzofulvene moiety released after Fmoc cleavage allowed for real-time monitoring of the reaction progress and provided a qualitative assay for the efficiency of each glycosylation and deprotection cycle during automated assembly (*Scheme 48*) [284].

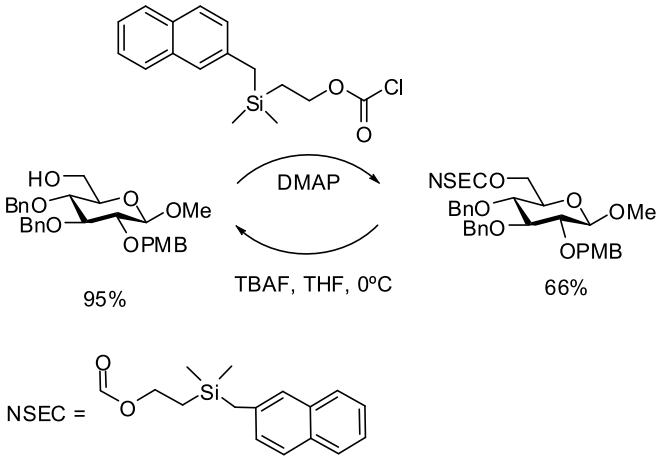
2.4.6 2-[Dimethyl(2-naphthylmethyl)silyl]ethoxycarbonyl (NSEC) Group

The 2-[dimethyl(2-naphthylmethyl)silyl]ethoxycarbonyl group is a novel temporary protecting group to mask hydroxyl groups [285]. In an analogous manner to the Fmoc protection, this group may be particularly useful for the automated assembly of oligosaccharides, as its cleavage can be followed by UV.

The NSEC group can be introduced under standard conditions using NSECCl which is available in three steps from chlorodimethylvinylsilane and 2-(bromomethyl)naphthalene (*Scheme 49*). The NSEC group may be difficult to introduce in sterically demanding positions.



Scheme 48
Fmoc as temporary protecting group in the automated synthesis of oligosaccharides



Scheme 49
NSEC as a protective group in carbohydrates

The NSEC group is stable to glycosylation conditions using glycosyl phosphates, and it is not affected under deprotection conditions that facilitate the removal of Lev, Fmoc, allyl, and PMB groups. For ester-type protecting groups selective deprotection in the presence of NSEC derivatives is not possible.

The removal of NSEC carbonates is carried out by reaction with TBAF in the presence of esters including acetyl, levulinoyl, benzoyl and pivaloyl, but also allyl and PMB ethers are not affected. However, the NSEC group cannot be selectively removed in the presence of Fmoc protecting groups.

2.5 Silylation Reactions: Silyl-Type Protecting Groups

2.5.1 Silyl Ethers. General Aspects

Silyl ethers have become very important alcohol protecting groups, which are used, among other ways, routinely in carbohydrate chemistry [286]. Silyl derivatives are generally stable over a wide variety of reaction conditions and at the same time are selectively removable in the presence of other functional groups including other protecting groups.

Additionally, the ability to vary the organic groups on silicon introduces the potential to alter the R_3Si group in terms of both its steric and electronic characteristics and thereby influence the stability of the silylated species to a wide variety of reaction and deprotection conditions [287].

The synthetic potential of silyl ethers as protecting groups for the hydroxyl groups was appreciated in the early 1970s and now these derivatives are probably used more than any other protecting group in organic synthesis. ❯ *Figure 5* summarizes the structures, names, and abbreviations of the most commonly used silyl ethers.

The usual method for their introduction into sugars is the reaction of one or several hydroxyl functions in the sugar with a trialkylsilyl chloride in the presence of a base, such as pyridine and imidazole. The less sterically hindered the silyl group the easier it is to introduce. The introduction of the sterically unimpeded trimethylsilyl group to a primary, secondary, or tertiary alcohol is a straightforward process taking place with a variety of reagents under mild, high-yield reaction conditions. On the other hand, the introduction of the more steri-

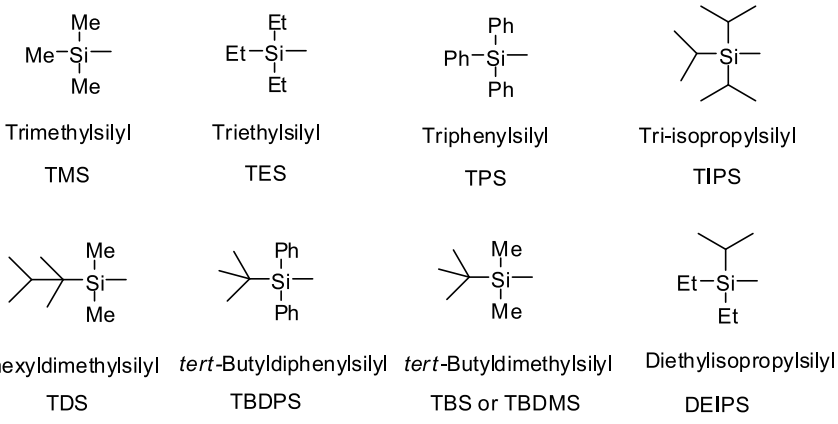


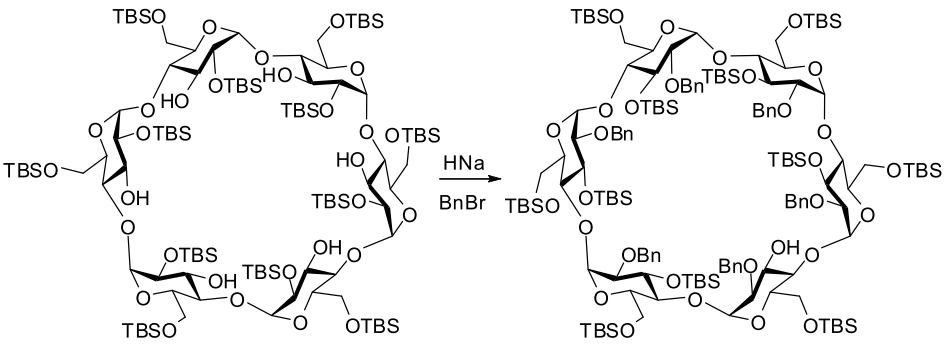
Figure 5
Principal members of the silyl ether family

cally demanding *tert*-butyldimethylsilyl group requires reaction of the alcohol with *tert*-butyldimethylchlorosilane in the presence of imidazole as a catalyst and the formation of the *tert*-butyldimethylsilyl ether of tertiary alcohols is very difficult. Alternatively, a more reactive form such as trialkylsilyl trifluoromethanesulfonates (R_3SiOTf) can be used.

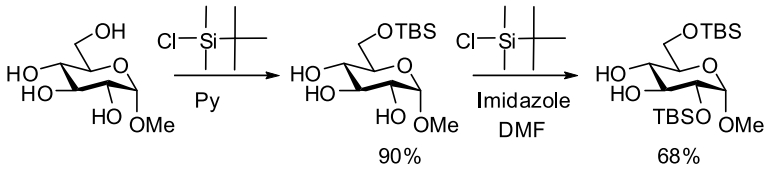
As a rule, the bulkier the substituents, the greater the stability of the resulting silyl derivatives. However, stability is not only a function of steric bulk since electronic effects play a role as well, which can be exploited to differentiate stability under acidic or basic conditions. For example, phenyl-substituted silyl ethers are equal or more reactive than their trimethylsilyl counterparts under alkaline conditions, but less reactive under acidic conditions. In general terms, however, the relative stabilities of the silyl-protected functional groups will follow the order of: $^{i}Pr_3Si$ > $ThMe_2Si$ > $^{t}BuPh_2Si$ > $^{t}BuMe_2Si$ > $^{i}PrMe_2Si$ > Et_3Si > Ph_2MeSi > Me_3Si [288].

On the other hand, silyl groups can migrate between different nucleophilic sites in a molecule under basic conditions. These migrations have to be considered as possible side reactions, and sometimes provide a valuable approach to interesting products that are not directly available [289]. For instance, in the synthesis of chemically modified cyclodextrines, the migration of the TBS groups from the 2-O to the 3-O on all the D-glucopyranose residues was observed during alkylation with sodium hydride in THF (*Scheme 50*) [290].

In general, the size of the substituent on the silicon atom is directly related to the rate of deprotection with smaller silyl substituents being more easily cleaved under acidic conditions. Similarly, if the same protecting group is used to protect two or more hydroxyl groups, the silyl ether derived from the less sterically encumbered alcohol is usually the first to be deprotected [291]. On the other hand, removal of silicon protecting groups occurs under extremely mild and highly specific conditions using a fluorine source. In general, the order of cleavage of silyl ethers with basic fluoride reagents (such as TBAF) parallels the order found for basic hydrolysis; similarly, slightly acidic fluorine-based reagents such as HF-acetonitrile parallel the order found for acid hydrolysis.



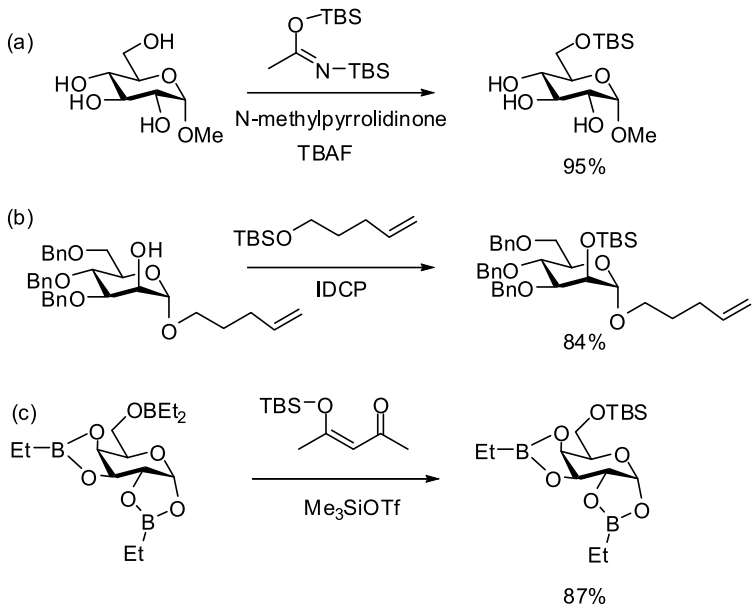
Scheme 50
Migrations of silyl groups in the synthesis of modified cyclodextrines



Scheme 51
Selective silylation of methyl α-D-glucopyranoside

2.5.2 *tert*-Butyldimethylsilyl (TBS or TBDMS) Group

Since its introduction in 1972 [292], the *tert*-butyldimethylsilyl group has become the most popular of the general purpose silicon protecting groups. It can be easily installed in high yields under mild conditions and it is robust to a variety of reaction conditions. The TBS group is commonly introduced via *tert*-butyldimethylchlorosilane, in the presence of basic activators such as DMAP or imidazole in a dipolar aprotic solvent such as DMF (*Scheme 51*). Hindered secondary alcohols can be silylated with TBSOTf using 2,6-lutidine as the base [293]. When the reaction is mediated by equimolecular amounts of dibutyltin oxide, the silylation with TBSCl gives the 6-monosilylated products in excellent yields [294].
N,*O*-Bis(*tert*-butyldimethylsilyl)acetamide silylates tertiary and hindered secondary alcohols in the presence of a catalytic amount of TBAF or another source of fluoride anion. Protection of primary hydroxyl groups in the presence of secondary ones is also possible (*Scheme 52a*) [295].



Scheme 52
Alternative conditions for the *tert*-butyldimethylsilyl ether protection

tert-Butyldimethylsilyl pentenyl ether is also a suitable reagent for efficient silylation of primary and secondary hydroxyl groups (● *Scheme 52b*). Activation is carried out with iodonium di-*sym*-collidine perchlorate (IDCP) and this procedure can be applied even to pentenyl glycosides [296].

An unusual way for the preparation of TBS ethers involves the reaction of diethylboronyl ethers, obtained by the reaction of the corresponding alcohol with BEt_3, with the TBDMS-enolate of pentane-2,4-dione in the presence of a catalytic amount of TMSOTf (● *Scheme 52c*) [297].

The palladium(0) nanoparticle-catalyzed silylation of sugars by silane alcoholysis of *tert*-butyldimethylsilane has been proposed as an attractive alternative to the established silyl chloride method. The methodology gives convenient access to the 3,6-silylated methyl glycopyranosides as the dominant products rather than the 2,6-silylated glycosides typically obtained by the silyl chloride method [298]. Changing to homogeneous cationic catalysts of iridium and rhodium, 2,3,6- and 2,4,6-trisilylated derivatives are obtained in synthetically useful yields [299].

The TBDMS group has also been introduced [300] to alcohols or phenols by the Mitsunobu reaction (DEAD/PPh_3, THF, −78 °C) using *tert*-butyldimethylsilanol.

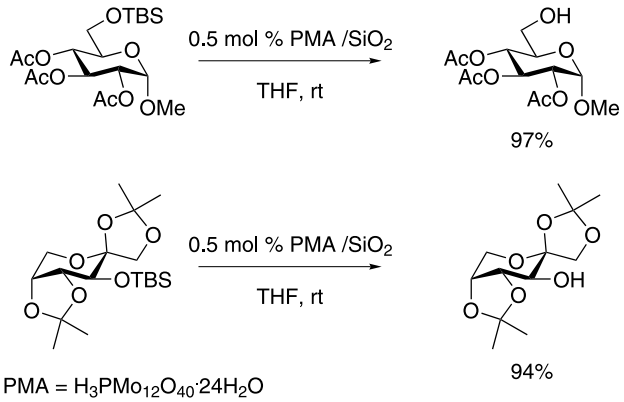
Numerous methods are now available in the literature for the deprotection of TBS ethers under a variety of conditions. One of the most effective ways for the cleavage of silyl ethers is based on the exploitation of the high affinity of silicon towards fluoride ions. Thus, a number of reagents involving one form of fluoride or another, such as tetrabutylammonium fluoride [292], $BF_3{\cdot}Et_2O$ [301], hydrofluoric acid [302], fluorosilicic acid [303], ammonium fluoride [304], silicon fluoride [305], lithium tetrafluoroborate [306], and chlorotrimethylsilane/potassium fluoride dehydrate [307] have been developed for the deprotection of TBDMS ethers. Among these, TBAF is most frequently used but the strong basicity of the fluoride anion makes it inappropriate for base sensitive functionalities.

Similarly, acidic reagents such as HCl [308], H_2SO_4 [309], PPTS [310], TFA [311], TsOH [312] etc., have also been employed for this purpose but cannot be used in the presence of acid-sensitive functionalities. This has led to the development of several Lewis acids and other reagents including $BF_3{\cdot}OEt_2$ [313], BCl_3 [314], $Sc(OTf)_3$ [315], $Ce(OTf)_4$ [316], $InCl_3$ [317], $ZnBr_2$ [318], $Zn(BF_4)_2$ [319], $CeCl_3$–NaI [320], $BiBr_3$ [321], $BiOClO_4$ [322], Cs_2CO_3 [323], CBr_4–MeOH [324], I_2 [325] and CAN [326] for desilylation.

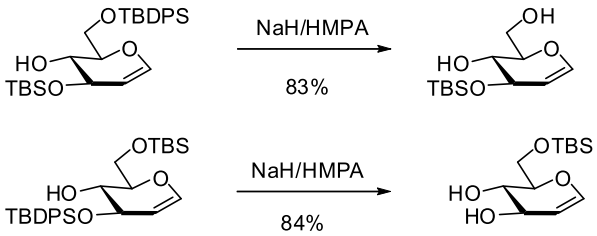
Recently, an environmentally benign phosphomolybdic acid supported on silica gel has been used for the chemoselective deprotection of TBS ethers in carbohydrate derivatives (● *Scheme 53*). The mild conditions are compatible with the presence of other protecting groups such as isopropylidene acetal, OTBDPS, OTHP, OAllyl, OBn, OAc, OBz, *N*-BOc, *N*-CBz, and *N*-Fmoc which are stable under the reaction conditions. Another advantage of this procedure is that the catalyst can be readily recovered and recycled [327].

2.5.3 *tert*-Butyldiphenylsilyl (TBDPS) Group

The TBDPS group was introduced by Hanessian and Lavallee in 1975 [328]. The TBDPS group has greater steric demands than the TBS group and, therefore can result in much more selective protections of hydroxyl groups. The group is also less prone to migrate to proximate hydroxyl groups under neutral or acidic conditions than the TBS group but it may migrate under basic conditions [329].



Scheme 53
The ring oxygen is missing in the fructose derivatives



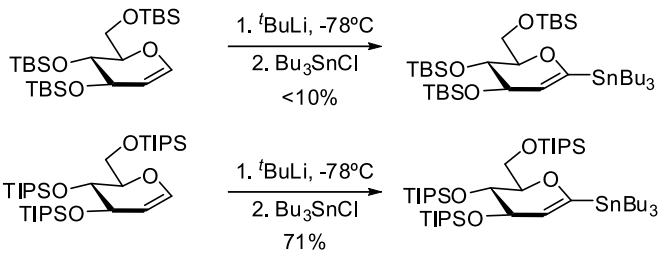
Scheme 54
Selective removal of TBDPS ethers in the presence of TBS ethers

The TBDPS ethers are prepared by treating alcohols with TBDPS-Cl in DMF in the presence of imidazole (the primary hydroxy group reacts faster than the secondary one). Tertiary alcohols do not silylate. The silylation of hindered alcohols is greatly accelerated with the aid of $AgNO_3$, NH_4NO_3, or NH_4ClO_4 [330].

TBDPS ethers are generally cleaved under the same acidic conditions as those used for TBS ethers but longer reaction times are necessary and consequently selective removal of TBS groups in the presence of TBDPS groups is very common [331,332]. The electron-withdrawing effect of the phenyl substituents enhances the electrophilicity of the silicon atom and therefore is more susceptible towards nucleophiles. For this reason it is possible to reverse the tendency of TBS ethers to cleave more easily than TBDPS ethers using ion fluoride or basic hydrolysis [333]. Some examples in glycal derivatives are shown in *Scheme 54*.

2.5.4 Triisopropylsilyl (TIPS) Group

The TIPS group [334] is one of the most sterically hindered silyl protecting groups, being removed only slowly under standard acid- or base-catalyzed hydrolysis conditions. The large steric bulk ensures high selectivity in the protection of primary hydroxyl groups over sec-

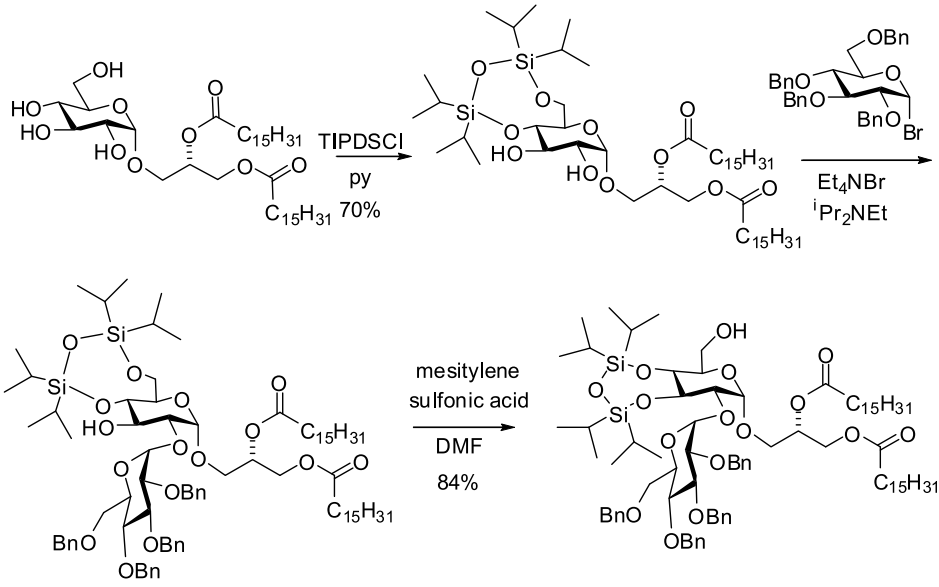


Scheme 55
TBS- vs. TIPS- ethers as protecting groups in the anomeric lithiation of glycals

ondary and valuable stability under a wide range of reaction conditions. It is noteworthy that TIPS groups are inert towards powerful bases such as *tert*-butyllithium, and therefore can be used as protecting groups in the anomeric lithiation of glycals (*Scheme 55*) [335].
The TIPS group is usually introduced from triisopropylchlorosilane [336], but protection of hindered alcohols can be very slow in which case triisopropylsilyl triflate in the presence of 2,6-lutidine is used [293].
TIPS ethers are cleaved under the same conditions as those used for TBS ethers but longer reaction times are frequently necessary; consequently TBS ethers can be removed selectively in many cases.

2.5.5 1,1,3,3-Tetraisopropyldisiloxane (TIPDS) Group

The tetraisopropyldisiloxane-1,3-diyl group was introduced by Markiewicz et al. for simultaneous protection of the 3′- and 5′-hydroxy groups of ribonucleosides [337]. The group is usually introduced by the reaction of the bifunctional reagent 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane with the substrate in pyridine though imidazole in DMF solution can also be used. When applied to pyranoses, these conditions give the kinetic product, an 8-membered ring, which is formed by rapid reaction first at the least hindered hydroxyl group followed by a second intramolecular silylation with the next proximate hydroxyl at C-4.
Additionally, the eight-membered rings of TIPDS-acetals formed in this way can rearrange under the influence of acidic catalyst to the thermodynamically more stable seven-membered derivatives bridging two vicinal secondary hydroxyl functions [338].
The usefulness of the TIPDS protecting group in carbohydrate chemistry is well illustrated by the synthesis of a glyco(phospho)lipid of *Streptococci* cell membranes (*Scheme 56*). Selective protection of the C-4 and C-6 hydroxyl groups of the pyranose was easily accomplished using the TIPDS group. Then the C-2 hydroxyl participated in a regioselective glycosylation under basic conditions to give the coupling product. At this stage of the synthesis the dynamic properties of the TIPDS group were exploited and the subsequent acid-catalyzed isomerization of the 4,6-O-disilyl-protected product results in the formation of the more stable 3,4-*O*-disiloxane. The freed primary hydroxyl function was then ready to be reacted with stearoyl chloride after which the naturally occurring glycolipid was eventually obtained [339].



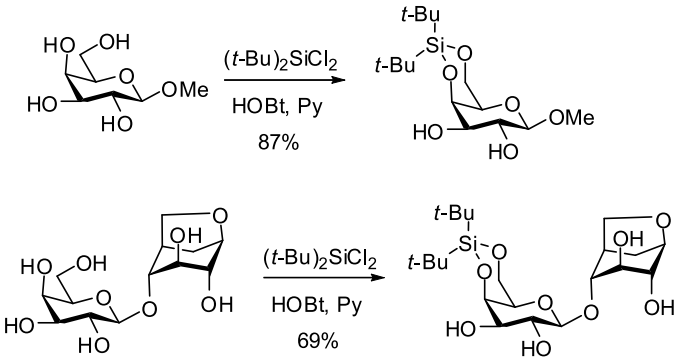
Scheme 56
Application of TIPDS protecting group in the synthesis of a glyco(phospho)lipid

However, despite the attractive properties, which are inherent in the use of the TIPDS protecting group in sugar chemistry, its general applicability is limited, to some extension by the fact that this group can not withstand acidic conditions, which are commonly used in carbohydrate chemistry.

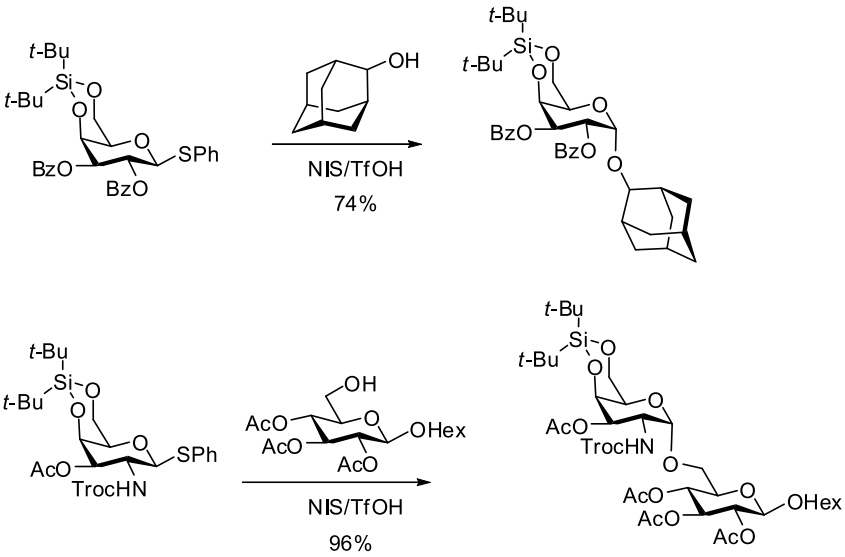
2.5.6 Di-*tert*-butylsilylene (DTBS) Group

The di*tert*butylsilylenediyl is a convenient and versatile protecting group introduced by Trost [340] and often used for the synthesis of anthracyclines [341] and nucleotide [342] derivatives. The DTBS group is not as robust as isopropylidene or benzylidene acetals and therefore its use is appropriate for systems requiring deprotection under very mild conditions. DTBS derivatives survive hydroboration, mild oxidation, Lewis acids, mild protic acids, and strong bases but hydrolysis occurs readily with HF in acetonitrile, HF·pyridine complex, or TBAF.

The formation of the silylene derivatives is effected by treatment of the diol with di*tert*butyldichlorosilane in the presence of 1-hydroxy-benzotriazole (HOBT) (*Scheme 57*) [340]. Di*tert*butylsilyl ditriflate and 2,6-lutidine effects silylene formation faster and under milder conditions than the less-reactive dichloride [343]. When the silylation is carried out in pyranoside derivatives, the reaction proceeds selectively at 1,3-diol groups of C-4 and C-6 positions and the formation of the five-membered DTBS derivatives of 1,2 diols was not observed [344]. It has been shown that a DTBS group at the *O*4-*O*6 position of a galacto-type sugar directs α-predominant selective glycosylation in spite of the presence of a participatory group at C-2 such as benzoyl or Troc groups [345] (*Scheme 58*). This new glycosylation method is a powerful strategy for the synthesis of α-galactosyl and galactosaminyl glycans [346,347].



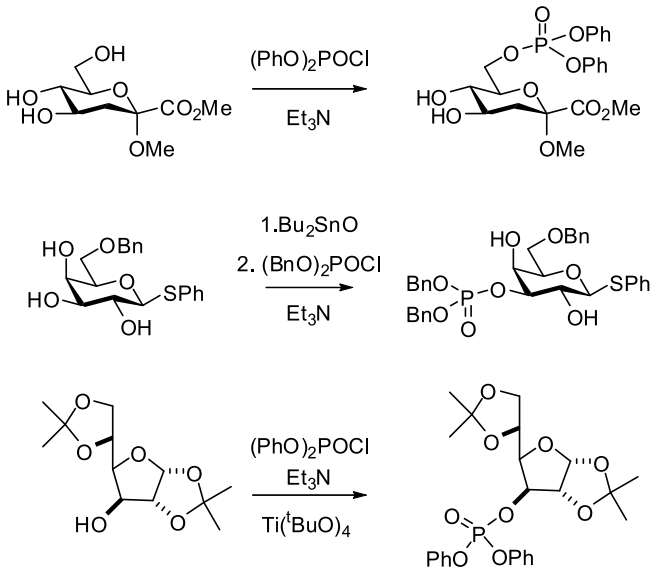
Scheme 57
Cyclic di-t-butysilylene as protecting group



Scheme 58
Examples of di-t-butysilylene-directed α-galactosylation

2.6 Phosphorylation Reactions

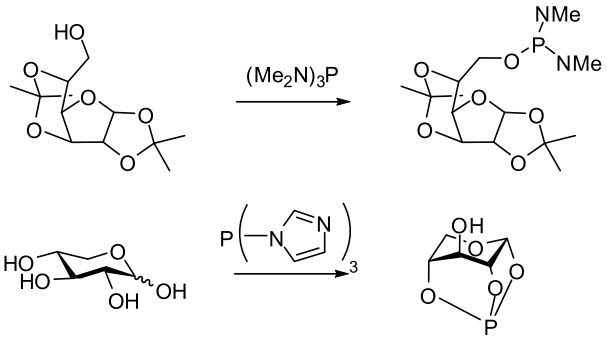
Phosphate esters play an important role in a wide variety of structurally diverse natural and biologically active compounds such as glycolipids, nucleic acids, nucleotides, proteins, coenzymes, steroids, and in particular carbohydrates. Introduction of a phosphate group essentially changes the physical and chemical properties of the parent molecule, resulting in changes to the polarization and intermolecular bonding characteristics of that molecule. Given the importance of this functional group it is not surprising that many methods have been developed for the phosphorylation of alcohol functions [348,349]. Both chemical and enzymic methods are available for the synthesis of specific phosphates.



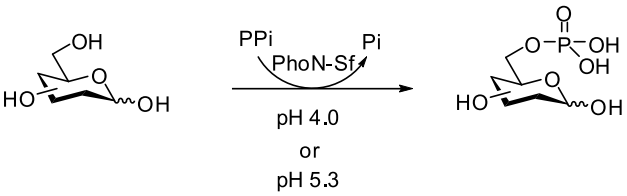
Scheme 59
Examples of chemical phosphorylation with phosphorous (V) reagents

Chemically, the most common phosphorylation reagents used are chlorophosphates [350]. These compounds are generally commercially available and are as stable as their routinely used acyl chloride counterparts to both air and moisture. The problem most commonly encountered with the use of such reagents is the conditions under which they will react. Phosphorylation is usually performed either through formation of the lithium [351] or thalium alkoxide [352], followed by the reaction with the chlorophosphate or simply by use of a proton scavenger such as pyridine [353] or Et_3N [354]. Alternatively, nucleophilic catalysis with DMAP [355] or tin-mediated phosphorylation [356] may be employed. A method for the phosphorylation of hydroxyl groups using a Lewis acid catalyst has been recently reported [357] (*Scheme 59*). Solid-phase phosphorylating reagents have been used for the phosphorylation of unprotected nucleosides and carbohydrates [358,359]. These procedures exhibit high regioselectivity and only one monophosphorylated product is obtained. Carbohydrate and nucleoside diphosphates have also been synthesized by using solid-phase reagents [360].

Aside from P^V reagents, the most widely used and most successful of all chemical phosphorylation techniques is the use of reagents containing trivalent phosphorous which ensure the highest phosphorylation rates and permits one to avoid many side processes [361]. This methodology has been well developed and is used extensively in the construction of oligonucleotides. Phosphorous triamides phosphorylate efficiently monosaccharides whose molecules contain one free alcoholic hydroxyl [362] (*Scheme 60*). Phosphorylation by dialkyl [363] or alkanediyl phosphoramidites [364], phosphonamidites [365] and phosphinamidites [366] follows a similar pathway. Treatment of monosaccharide derivatives whose molecules contain two closely located hydroxy groups with phosphamides results in cyclophosphorylation [367].



Scheme 60
Examples of chemical phosphorylation with phosphorous (III) reagents



Scheme 61
Example of enzymatic phosphorylation

A non-specific bacterial acid phosphatase from *Shigella flexneri* (PhoN-Sf) has been screened for regioselective phosphorylation of primary alcohol(s) of more than 20 different cyclic and acyclic monosaccharides using pyrophosphate as the phosphate donor (*Scheme 61*) [368]. These studies have shown that PhoN-Sf is capable of phosphorylating a range of hexoses (D-glucose epimers, glycosides, and C-2 derivatives), pentoses, heptoses, ketoses, and acyclic carbohydrates.

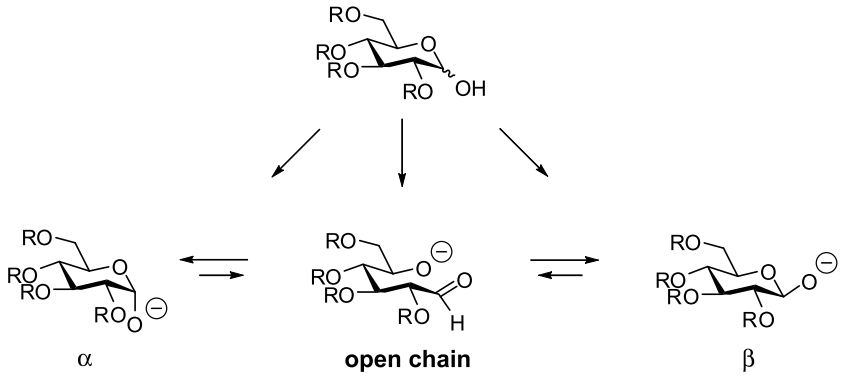
3 Reactions at the Anomeric Hydroxyl

3.1 Alkylation Reactions

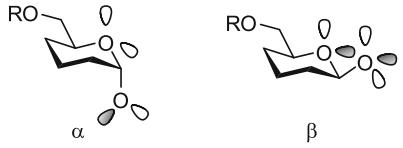
In general, reactions and conditions for the introduction of protecting groups in the anomeric hemiacetal group are the same as those mentioned previously for non-anomeric hydroxyl groups. Probably, the only exception relates to the alkylation reaction since alkyl ethers of the anomeric hydroxyl group, which are acetals rather than ethers, are normally formed under Fischer glycosylation conditions using the alcohol as the aglycon [369]. This process involves cleavage of the C-1–O-1 bond at the anomeric center and, therefore will not be treated here, but it is the method of choice for the preparation of alkyl glycosides.

3.1.1 Anomeric *O*-Alkylation and *O*-Arylation

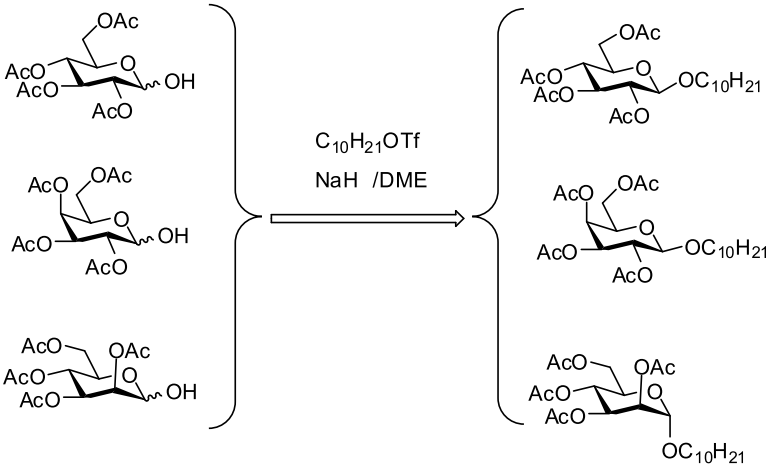
The 1-*O*-alkylation of carbohydrates with simple alkylating agents, particularly methyl iodide and dimethyl sulfate, has long been known [370,371,372]. The reactivity of pyranoses and furanoses deprotonated at *O*-1 is, thus, analogous to that of alkoxides. Alkylation of fully protected pyranoses, due to the ring chain tautomerism between the two anomeric forms α and β and the open chain form (● *Scheme 62*), can take place at three different sites [373].
However, when the alkylation of 2,3,4,6-tetra-*O*-benzyl D-glucose is carried out in dioxane with sodium hydride and methyl triflate, the β-glucoside was obtained practically exclusively [374]. This selectivity has been explained on the basis of an enhanced nucleophilicity of the β-oxide atom which can be attributed to a steric effect in combination with a stereoelectronic effect resulting from repulsion of the lone electron pairs (kinetic anomeric effect) in the β-oxide [375] (● *Fig. 6*). Conversely, if the reaction is carried out at lower temperatures (−40 °C) the formation of α-anomer is preferred. Despite of the use of NaH, neither acyl migration nor orthoester formation occurred during the 1*O*-alkylation of acetyl-protected derivatives (● *Scheme 63*) [376,377]. The stereoelectronic effects in α- and β-furanosyl oxides should differ less for conformational reasons and the stereocontrol results primarily from steric and chelation effects.
The higher acidity of the 1-OH group of the hemiacetal (resulting from the indirect stabilization by the ring oxygen atom) allows for regioselective *O*-alkylation at this position regardless of the presence of other sugar hydroxy groups. Thus, as shown in ● *Scheme 64*, the alkyla-



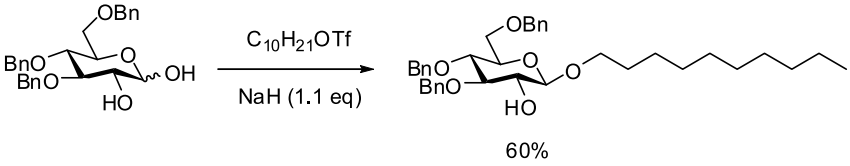
● Scheme 62
Ring chain tautomerism of fully protected pyranoses



● Figure 6
Kinetic anomeric effect in the β-oxide



Scheme 63
Stereoselective anomeric *O*-alkylation of acyl-protected sugars



Scheme 64
Anomeric *O*-alkylation of partially protected pyranoses

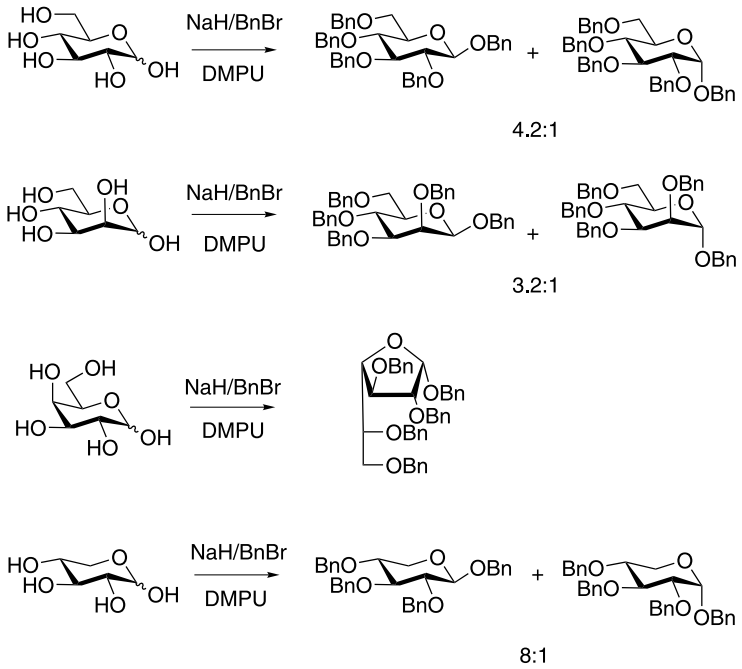
tion of 2-*O*-unprotected tribenzylglucopyranose afforded exclusively the 1-*O*-alkylated product when the reaction was done with one equivalent of NaH, whereas the undesired 1,2-disubstituted isomer was also obtained when two equivalents of NaH were used [378].

Although ring-chain equilibration permits the formation of many products in fully unprotected monosaccharides, the regiocontrol in the per-*O*-benzylation towards uniform glycoside bond formation is generally very high [379,380] (› *Scheme 65*).

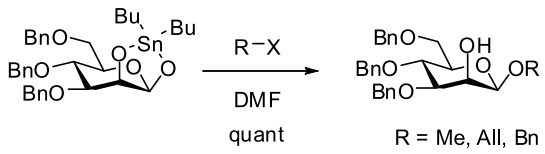
The 1-*O*-alkylation of pyranoses has also been used for glycosidic bond formation [381].

An alternative activation of the anomeric hydroxyl makes use of 1,2-*O*-dibutylstannylene acetals [382]. Thus, for instance condensation of the stannylene acetal of 3,4,6-tribenzylmannose with methyl iodide, allyl or benzyl bromide afforded the corresponding β-mannosides in almost quantitative yields (› *Scheme 66*).

On the other hand, carbohydrates carrying an aromatic aglycon are important natural products and therefore methods for the arylation of anomeric hemiacetals have also been developed. Both Mukaiyama [383] and Smith [384] have synthesized aryl glycosides by nucleophilic aromatic substitution for use as glycosyl donors. The method is quite efficient but requires activation by electron-withdrawing groups in the aromatic counterpart. Thus, direct reaction of 1-fluoro-2,4-dinitrobenzene with the 1-OH group of the hemiacetal gave 2,4-dinitroglycosides in excellent yields (› *Scheme 67a*). In the case of dinitrosalicylic (DISAL) acid



Scheme 65
Two bonds are missing in the first compound



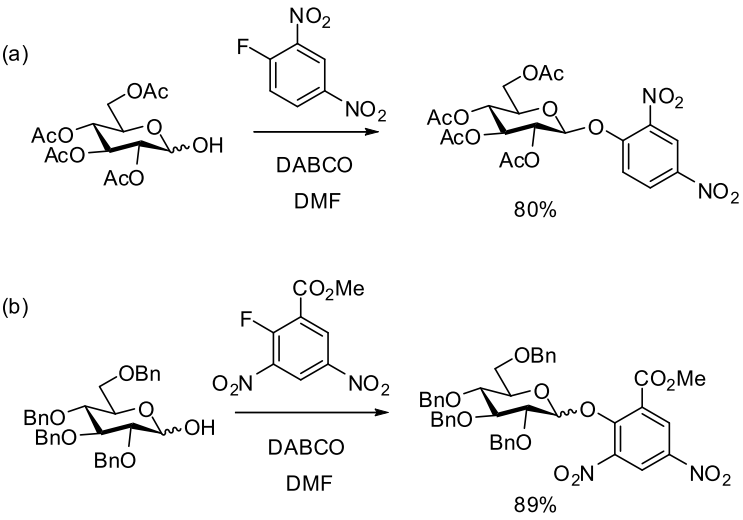
Scheme 66
Anomeric *O*-alkylation via 1,2-*O*-stannylene acetals

derivatives, the use of DMAP as the base gave an α/β ratio similar to the starting 1-OH derivative. In contrast, formation of the β-anomer was favored using 1,4-dimethyl piperazine (*Scheme 67b*) [385,386,387].

The reverse situation, in which the phenol acts as the nucleophile attacking activated carbohydrate hemiacetals, has also found several practical applications preparing *O*-aryl glycosides [388]. However, this situation implies an attack at the anomeric carbon and not at the anomeric oxygen.

3.1.2 Anomeric *O*-Dealkylation

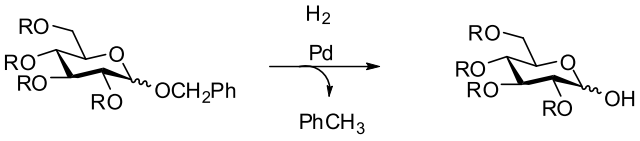
On treatment with aqueous acid, glycosides are hydrolyzed to give the corresponding alcohol and the reducing sugar. Solvolysis of glycosidic bonds is one of the most general and important reactions in carbohydrate chemistry and so the literature on the acid hydrolysis of *O*-glycosidic



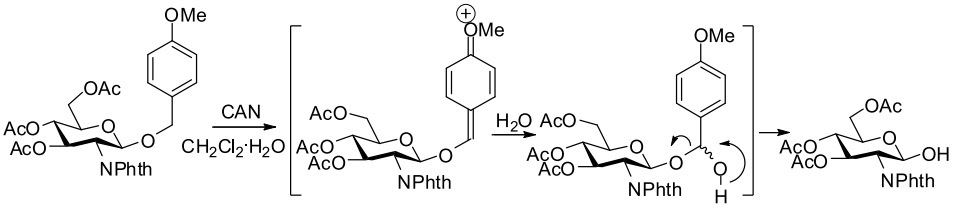
Scheme 67
Anomeric *O*-arylation via nucleophilic aromatic substitution

bonds covers thousands of titles. The data on more detailed studies of this reaction are covered by several reviews [389,390,391,392]. Although this process is formally the reverse direction of the alkylation reaction, the key step involves reaction at the anomeric carbon rather than at the anomeric oxygen and thus is beyond the scope of this chapter.
Nevertheless, a variety of protecting groups have been applied to the anomeric center, which are synthetically useful and provide alternative ways for the selective liberation of the anomeric oxygen. These include the following:

Benzyl Glycosides In 1928, Freudenberg found that benzyl ethers of sugars were cleaved by hydrogenolysis with sodium amalgam and by catalytic hydrogenolysis that could be effected in acetic acid in the presence of platinum metals [393]. On palladium catalysis, hydrogen splits off the benzyl β-D-glycosides, at room temperature and atmospheric pressure to afford toluene and the reducing sugar (*Scheme 68*) [394]. Hydrogenolysis is commonly carried out using hydrogen gas with a palladium catalyst absorbed on charcoal although modifications involving hydrogen transfer have been used.



Scheme 68
Hydrogenolysis of benzyl glycosides



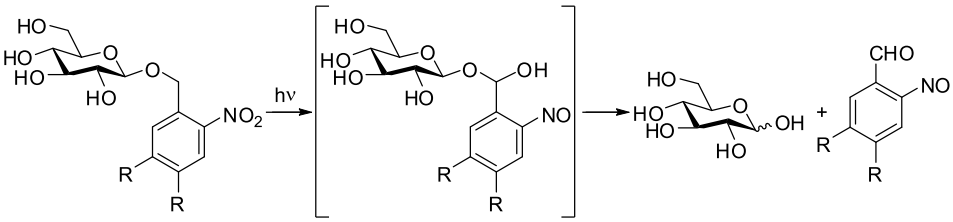
Scheme 69
Oxidative deprotection of p-methoxybenzylglycoside

A remarkable rate difference in the hydrogenolysis of α- and β-benzyl D-gluco-and D-galactopyranosides has been reported, with the β-anomers being more readily cleavable [395]. Ferric chloride has been employed for anomeric debenzylation in oligosaccharides [18].

Methoxy-substituted benzyl glycosides have been used as precursors for reducing sugars [396]. As mentioned in *Sect. 2.1.3* under *"p-Methoxy Benzyl (PMB) Ethers"*, their utility lies in the fact that they are more readily cleaved oxidatively than the unsubstituted benzyl ethers (*Scheme 69*). All these transformations have great synthetic value although the process is not regioselective since it is operational for all the benzyloxy groups present in the sugar.

Particularly useful in protecting the anomeric hydroxyl are those substituted benzyl groups that are light-sensitive. Such groups are stable to a wide variety of chemical treatments and at the same time are sensitive to irradiation under conditions that leave other functional groups in the molecule unaffected. Thus, 2-nitro benzyl and 3,4-dimethoxy-6-nitrobenzyl (6-nitroveratryl) glycosides are more stable to acid hydrolysis than are the corresponding benzyl glycosides but are readily photolyzed at 320 nm to the reducing sugars in high yields (*Scheme 70*) [397]. In this context photocleavable linkers for solid-phase synthesis, based on the lability of 2-nitro benzyl moieties under irradiation, have been applied to the liberation of the anomeric center in oligosaccharides [398].

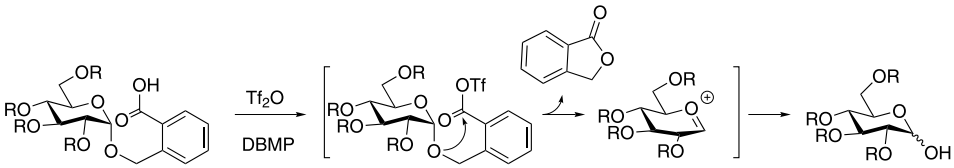
Other substituted-benzyl glycosides that can be selectively removed in the presence of unsubstituted benzyl ethers have been developed. For example, 2-(hydroxycarbonyl)benzyl glycosides are easily sovolyzed by treatment with Tf_2O in the presence of di-*tert*-butylmethylpyridine (DBMP). The reaction implies anomeric C–O bond cleavage since it takes place by lactonization via the mixed anhydride to generate phthalide and the oxocarbenium ion (*Scheme 71*) [399].



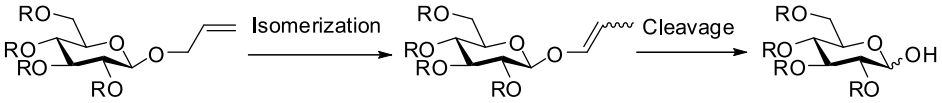
R= H, OMe

R= H, OMe

Scheme 70
Example of light-sensitive glycosides: 2-nitrobenzyl and 6-nitroveratryl glycosides

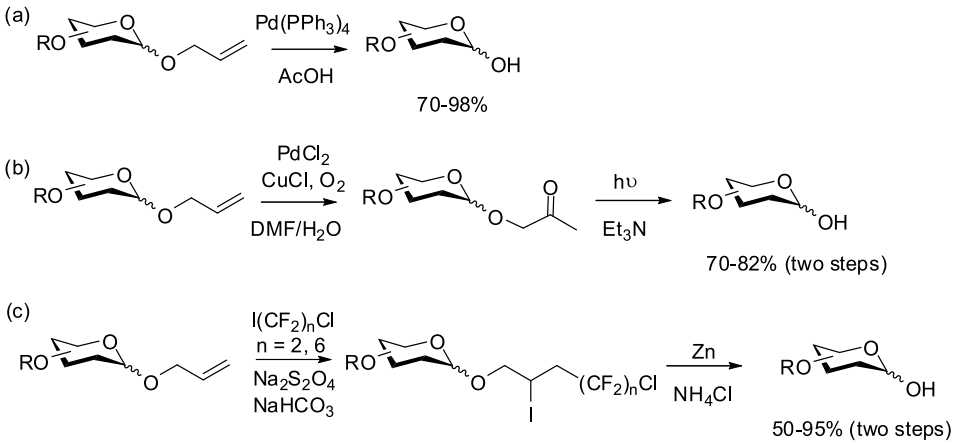


Scheme 71
Solvolysis of 2-(hydroxycarbonyl)benzyl glycosides

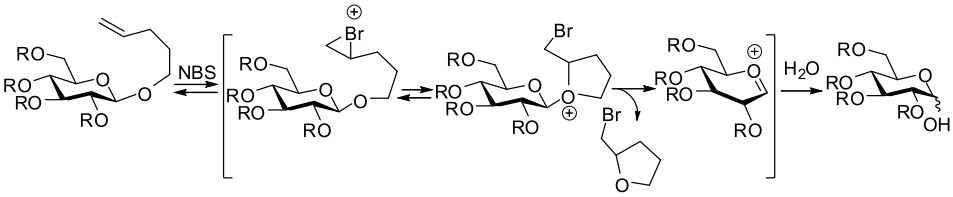


Scheme 72
Usual method for the deprotection of allyl glycosides

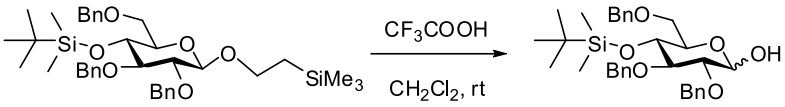
Allyl Glycosides Another commonly used protecting group for the anomeric oxygen is the allyl group [400,401]. The most usual method for deblocking allyl glycosides involves the two-step reaction in which the allyl group is first converted into the more labile propenyl group and then is cleaved under mildly acidic conditions (see ❯ *Sect. 2.1.4*, ❯ *Scheme 72*).
Alternative methods for the deprotection of the allyl group at the anomeric position include $Pd(PPh_3)_4$/AcOH [402], in which the reaction proceeds by the formation of a π-allyl complex, or $PdCl_2/CuCl/O_2$ followed by photolysis in the presence of triethylamine [403]. Perfluoroalkylation with perfluoroalkyl iodide under sodium dithionite and sodium bicarbonate followed by elimination in the presence of zinc powder and ammonium chloride has also been disclosed as an efficient procedure for deprotection of the anomeric allyl group of carbohydrates (❯ *Scheme 73*) [404]. The reaction goes through the intermediacy of a radical addition of a perfluoroalkyl iodide to the double bond followed by Zn-mediated reductive β-elimination.



Scheme 73
Alternative methods for the deprotection of the allyl group at the anomeric position



Scheme 74
Deprotection of n-pentenyl glycosides



Scheme 75
Deprotection of 2-(trimethylsilyl) ethyl glycosides

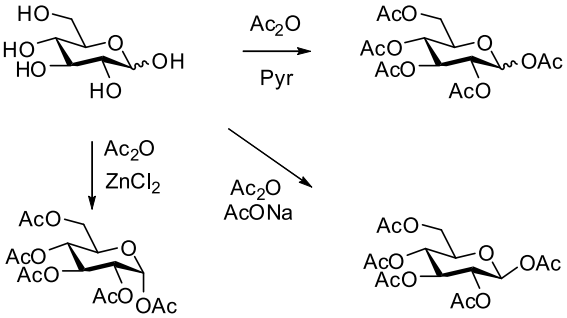
n-Pentenyl Glycosides In 1988 Fraser-Reid and Mootoo reported the NBS-mediated reaction of *n*-pentenyl glycosides, in the presence of water to yield reducing monosaccharides (*Scheme 74*) [405]. This transformation proved to be highly chemoselective leaving a wide variety of other functional groups unaffected.
The reaction takes place with cleavage of the anomeric C–O bond by electrophilic addition to the olefin followed by intramolecular displacement by the ring oxygen and eventual expulsion of the pentenyl chain, in the form of a halomethyltetrahydrofuran, to form an oxonium species (*Scheme 74*). Trapping with water then leads to the reducing sugar. This transformation has also been extended to the use of *n*-pentenoyl esters [406,407].

2-(Trimethylsilyl) Ethyl Glycosides An alternative procedure for protecting the anomeric center is based on the use of 2-(trimethylsilyl) ethyl glycosides [408,409]. Lipshutz et al. first found that $LiBF_4$ in CH_3CN caused the deblocking of the anomeric center [408], although extensive experimentation led Magnusson and coworkers to report on the use of trifluoroacetic acid in dichloromethane as the most effective reagent to carry out the same transformation (*Scheme 75*) [409]. The reaction conditions are fully compatible with most of the normally used protecting groups, including silyl ethers and therefore this protecting group has found wide application in the synthesis of complex oligosaccharides.

3.2 Acylation Reaction

3.2.1 Anomeric *O*-Acylation

Free sugars, since they are polyhydroxy aldehydes or ketones, can be acylated through their hydroxyl groups (including the anomeric hydroxyl group) to give esters. However, the unusual property of the anomeric center to be a mixed function (ester and acetal) confers the glycosyl esters a special reactivity. Acetylation of unprotected sugars is complicated by the fact that they exist in solution as equilibrium mixtures of tautomers. The isomer obtained depends on



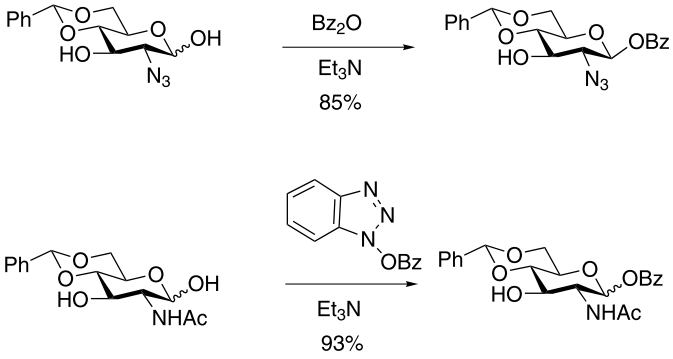
Scheme 76
Acetylation of D-glucopyranose

the catalyst used and on the temperature. For example, acetylation of pure α- and β-D-glucopyranoses with Ac_2O and pyridine at 0 °C occurs with retention of the configuration at the anomeric carbon [410], whereas acetylation of a mixture of α- and β-D-glucopyranoses in the presence of an acid catalyst (Ac_2O, $ZnCl_2$) takes place with predominant formation of the thermodynamically preferred (anomeric effect) α-D-glucopyranose pentaacetate, due to acid-induced anomerization. Conversely, β-D-glucopyranose pentaacetate, is formed preferentially when the acetylation is carried out in the presence of sodium acetate at higher temperatures (Ac_2O, NaOAc, Δ), a fact which has been explained on the basis of a lower rate for acetylation when compared with mutarotation together with a preferential reactivity for the equatorial anomeric hydroxyl groups (*Scheme 76*). For acetylation of ketoses low temperature acidic catalysts are preferred.

The ring size of the cyclic acetates formed under common acetylation procedures is normally pyranoid although sugars that form relatively stable furanose rings give more complex mixtures. D-Galactose, for instance, in the presence of sodium acetate or pyridine at elevated temperatures gives appreciable amounts of furanose acetates [411].

Sugar benzoates have also been widely used since they are easy to prepare and more stable than the corresponding acetates. Benzoyl chloride in pyridine is the reagent of choice to carry out this transformation [412], and benzoylation in hot pyridine may lead to the isolation of glycofuranose benzoates [413]. More recently, a new method for the benzoylation of alcohols has been described using TMEDA as a base, which gave the expected benzoates in excellent yields [414]. In 2-*N*-protected 4,6-*O*-ketal derivatives of D-glucosamine a highly regio- and stereoselective acylation of the anomeric hydroxyl groups is possible using 1*N*-benzyloxy-1,2,3-benzotriazol (BzOBT) or benzoic anhydride and triethylamine as a base [415,416]. Because of the kinetic stereoelectronic effect or 1,3-diaxial repulsion, the *O*- is oriented in the equatorial position and only the β-anomer is formed (*Scheme 77*).

When positions other than 1-OH are fully protected, anomeric acylation can be carried out by the usual methods for the esterification of alcohols (*Scheme 78*). For example, carbodiimide-mediated coupling [417,418] was the method used for the preparation of glycosyl benzyl phthalates [419] or *n*-pentenoyl esters [406,407] from the corresponding 1-OH sugars (*Scheme 78a*). Combination of carbodiimides, active ester-forming reagents, and base catalysts have been studied for the selective acylation of monoprotected glucuronate esters and the uranium reagent HATU [420] has been found to be the reagent of choice [421].



Scheme 77
The 1-OH shall be 1-OBz in the lower right structure

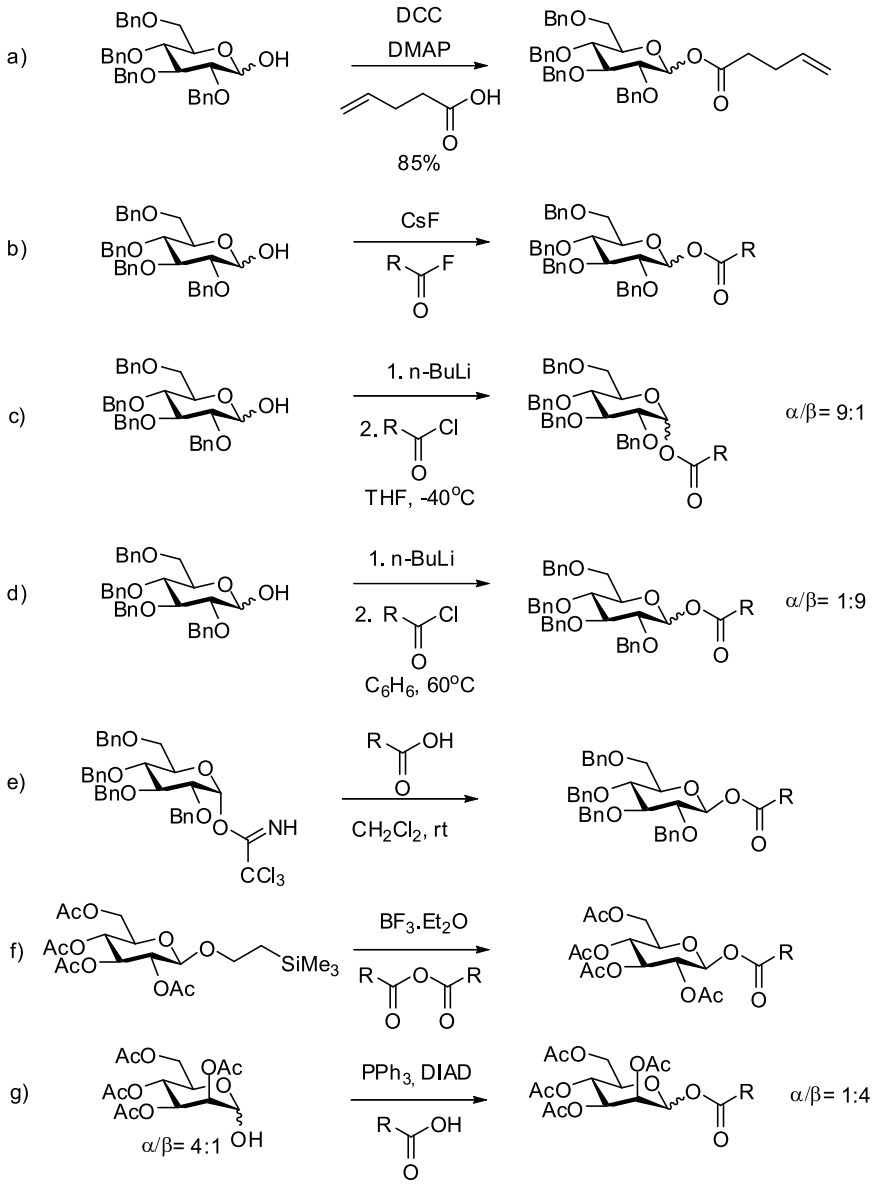
1-OH sugars react with acyl fluorides in the presence of cesium fluoride to furnish the corresponding glycosyl esters under essentially neutral conditions, with the α/β ratio being affected by changes in the order of addition of the reagents (*Scheme 78b*) [422].

Acylation of the lithium salt of 1-OH sugars allows complete stereocontrol in the formation of glycosyl esters [423,424]. Metalation of 2,3,4,6-tetra-*O*-benzyl-α-D-glucopyranose, in tetrahydrofuran at $-40\,°C$ with 1.1 equiv. of *n*-BuLi, followed by acylation with acid chlorides produce mainly or exclusively α-glucosyl esters (*Scheme 78c*). Increasing the reaction temperature and changing the solvent to benzene led to the preferred formation of β-glucosyl esters (*Scheme 78d*). Analogously, tributylstannyl alkoxides can be used in place of the corresponding lithium salts [425].

2-Acylthio-3-nitropyridines, prepared from the corresponding carboxylic acids, have been used as acylating agents when the corresponding acid chlorides are unstable [426].

As an alternative to the direct esterification of the anomeric hydroxyl group, glycosyl esters have been prepared by displacement of a good leaving group at the anomeric position, although in that case the key step involves reaction at the anomeric carbon rather than at the anomeric oxygen. In this context, the direct glycosylation of trichloroacetimidates [427] with carboxylic acids is a particularly advantageous method (*Scheme 78e*) [428]. This reaction, which involves inversion of the configuration at the anomeric center, is the method of choice for the stereoselective preparation of β-acyl-glycosides. The requisite trichloroacetimidates can be selectively produced from the corresponding hemiacetals under thermodynamically controlled conditions [429]. Analogously, 2-(trimethylsilyl) ethyl glycosides have also been transformed into the corresponding 1-*O*-acyl sugars by reaction with the appropriate anhydride in the presence of $BF_3{\cdot}Et_2O$ (*Scheme 78f*) [430].

The Mitsunobu protocol has also been investigated in the stereocontrolled synthesis of glycosyl esters (*Scheme 78g*) [431]. Complete stereochemical inversion at C-1 of the starting sugar is observed when the esterification is conducted with anomerically pure glycosyl hemiacetals. By corollary, complementary ratios of inverted products are formed when an anomeric mixture of sugars is esterified. The stereochemical outcome of the esterification is not affected



Scheme 78
Acylation reactions of fully protected pyranoses

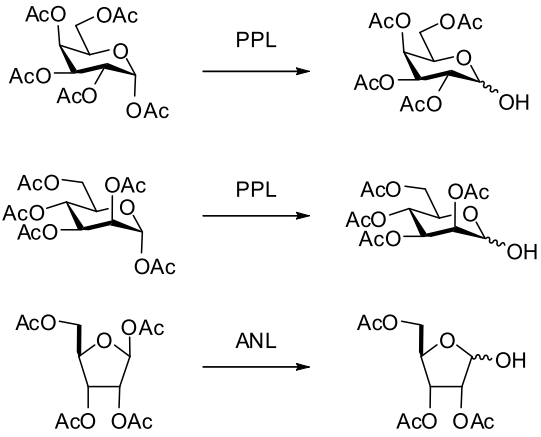
by anchimeric assistance from acyl groups at C-2. Accordingly, 2,3,4,6-tetra-*O*-acetyl-D-mannose furnishes a mixture of 1-*O*-benzoates in which the β-anomer predominates, a result that is especially significant in view of the difficulties generally encountered in obtaining β-glycosides of D-mannose.

3.2.2 Anomeric *O*-Deacylation

Deprotection of the anomeric acyl group in acylated sugars can be effected in a number of manners including chemical and enzymatic methods.

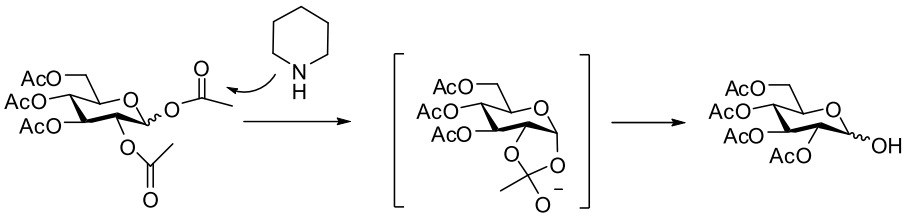
Enzymic Deacylation Both furanose and pyranose sugars can be efficiently deacetylated by suitable lipases under proper reaction conditions. The removal of the 1-*O*-acetyl group of glucose pentaacetate by *Aspergillus niger* lipase was reported after 20% conversion [432]. More recently it was found that the regioselectivity could be enhanced in the pyranose case by the presence of DMF [433]. Porcine pancreatic lipase in 10% DMF exclusively cleaved glucose pentaacetate ester at C-1 (70% isolated yield), and similar selectivities (and yields) were obtained for several peracetylated hexopyranoses. Peracetylated furanoses were deacylated at C-1 by the use of the lipase from *Aspergillus niger*. Finally, peracetylated reducing disaccharides have been specifically hydrolyzed at the anomeric center with a lipase from *Aspergillus niger* (Lipase A Amano 6) in a mixture of organic solvents and phosphate buffer (*Scheme 79*) [434].

Chemical Deacylation Several methods for the regioselective 1-*O*-deacylation of carbohydrates have been reported. Most of them involve regioselective nucleophilic attack upon the carbonyl group at *O*-1 thus liberating the anomeric oxygen. Nitrogen-containing nucleophiles have been widely used in this transformation: piperidine [435], hydrazine acetate [436], and hydrazine hydrate [437], have been reported to selectively hydrolyze anomeric acetates in peracetylated disaccharides (*Scheme 80*). Hydrazine acetate in DMF [436], benzylamine in chloroform [438], hydrazine hydrate in pyridine [439], ammonia in an aprotic solvent [440], and 2-aminoethanol [441], have been used to regioselectively 1-*O*-deacylate per-*O*-



PPL = Porcine pancreas lipase
ANL = *Aspergillus Niger* lipase

Scheme 79
Enzymic deacylation of acyl-glycosides



Scheme 80
Chemical deacylation of acyl-glycosides

acylaldoses. Other reagents used include potassium hydroxide [442], potassium cyanide [442], sodium methoxide [443], bis(tributyltin)oxide [442,444], tributyltin methoxide [444], ammonium carbonate [445], ammonium acetate [446], and mercuric chloride/mercuric oxide [447]. Heterogeneous anomeric deacetylation has also been reported by the use of magnesium oxide in methanol [448], or silica gel in methanol [449].

Finally, acid-catalyzed solvolysis of per-*O*-acyl hexopyranoses ($SnCl_4$, CH_3CN, H_2O) is an efficient method for removal of the anomeric acetyl group [450]. In this case the reaction takes place by cleavage of the C-1–OAc bond [451]. This reaction proceeds in 1 h at room temperature for sugars containing 1,2-trans-acetoxy groups and at 40 °C for 1,2-*cis* acylated pyranoses, and confirms the anchimeric assistance provided by the ester group at C-2.

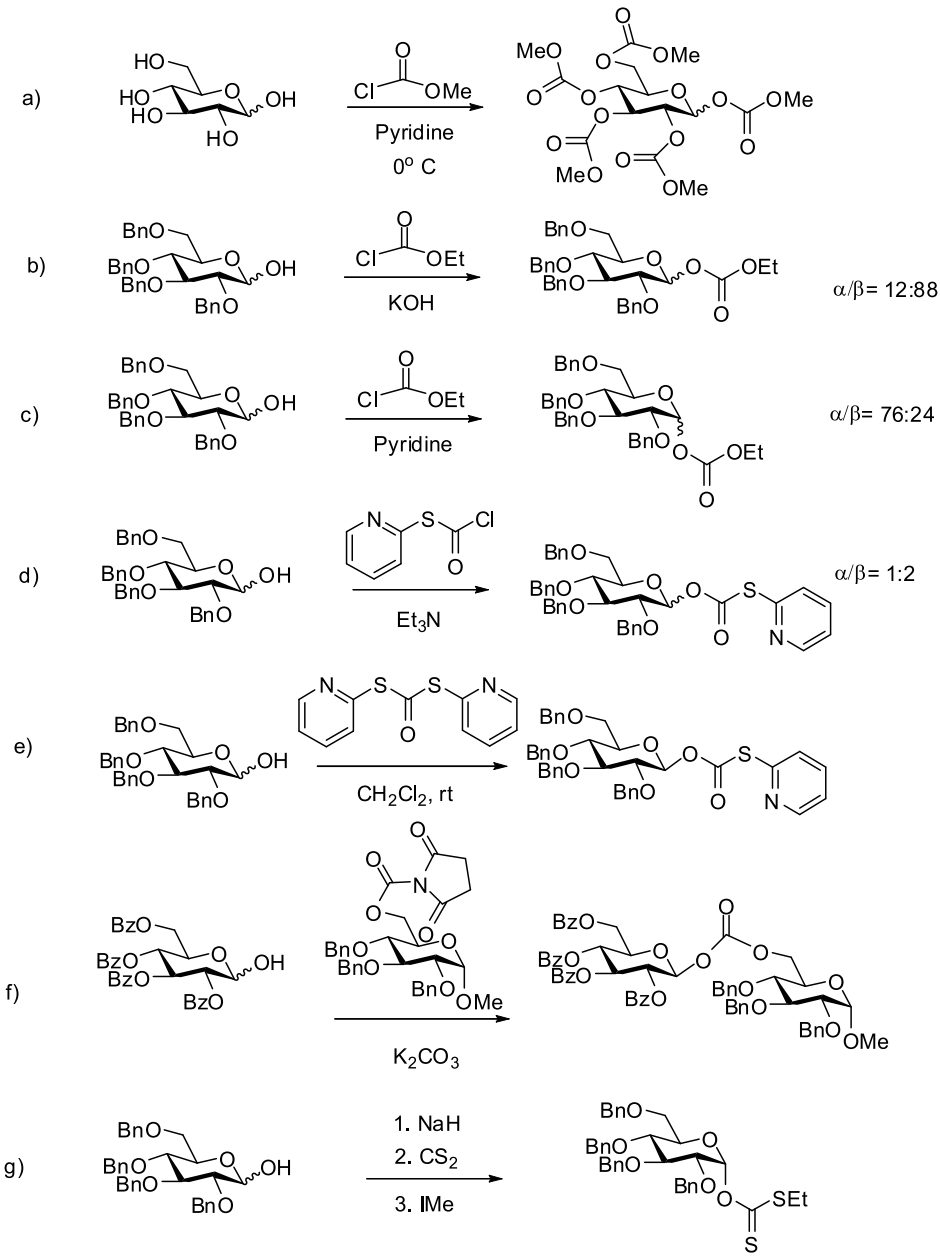
3.3 Carbonylation and Thiocarbonylation of the Anomeric Hydroxyl

The reagents most commonly used for the preparation of sugar carbonates are phosgene, alkyl chloroformates, and diaryl carbonates. Phosgene reacts with free sugars giving rise to cyclic carbonates preferentially having five-membered rings. Depending on the sugar the anomeric position may be involved, for instance when D-glucose is treated with phosgene and pyridine a 1,2:5,6-diester derivative is obtained. Unprotected sugars also react with chloroformic esters in the presence of pyridine, although to yield alkoxycarbonyl compounds (*Scheme 81a*) [452].

In the case of protected sugars, the anomeric hydroxy group reacts with chloroformic esters to give mixed esters (*Scheme 81b*). Usually the coupling reaction is not stereoselective giving rise to an anomeric mixture of carbonates, although the α/β ratio can be influenced by the choice of the proper base (*Scheme 81c*) [453]. Reaction of 2-thiopyridyl chloroformate with a glucose derivative results in an anomeric mixture (α:β, 1:2) (*Scheme 81d*) whereas the use of bis(2-thiopyridyl)carbonate yields exclusively the β-anomer (*Scheme 81e*) [454]. Very recently, a highly regio- and stereoselective reaction of D-glucopyranose 1,2-diols with allyl chloroformate or ethyl chloroformate has been reported [455].

Diaryl carbonates (e. g. carbonyl diimidazol, 4-nitrophenyl carbonate) can react sequentially with carbohydrate derivatives to furnish mixed sugar carbonates (*Scheme 81f*) [456]. Although normally anomeric mixtures are generated the use of a succinimidyl group, in the presence of K_2CO_3, was effective for the synthesis of pure β-carbonates.

Anomeric alkyl xanthates are prepared by treatment of 1-OH sugars with sodium hydride in the presence of a catalytic amount of imidazole, carbon disulfide, and an alkyl halide (*Scheme 81g*) [457].



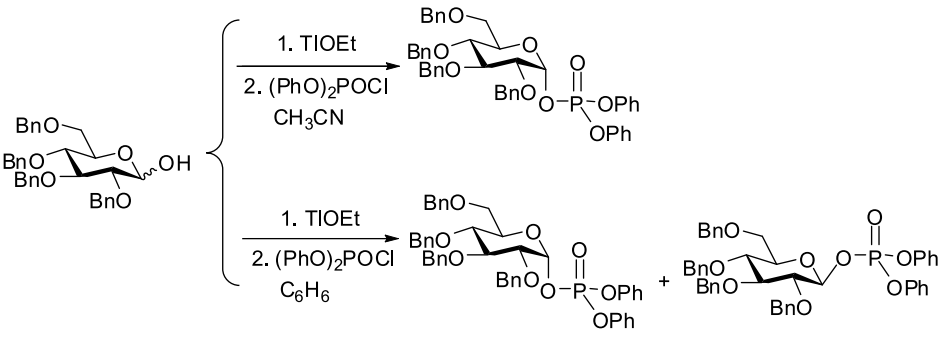
Scheme 81
Preparation of sugar carbonates

3.4 Silylation

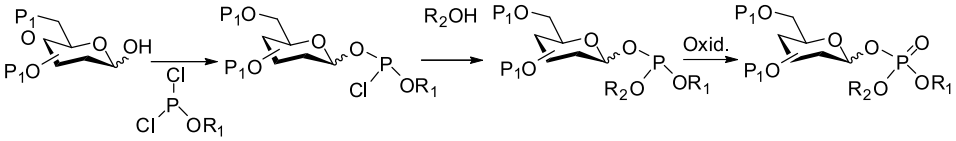
Anomeric silyl ethers have been prepared from 1-OH sugars and the corresponding silyl chloride in the presence of a base. When the hydroxyl group at C-2 is unprotected silyl group migrations away from the anomeric center have been observed [458].

3.5 Phosphorylation and Phosphitylation

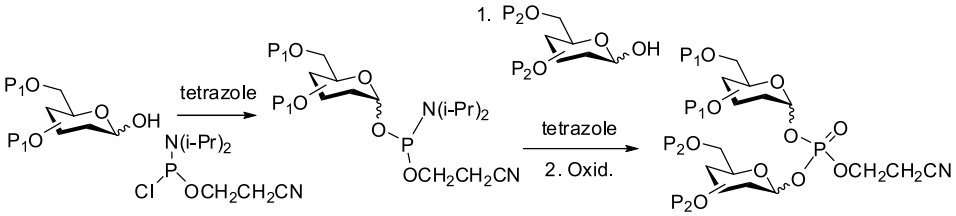
Glycosyl phosphates are intermediates in biological glycosyl transfer and are constituents of cell membranes [459]. Both chemical and enzymic methods are available for the synthesis of specific phosphates. In the preparation of certain glycosyl phosphates, enzymic synthesis with the appropriate phosphorylase provides the simplest preparation. In this fashion, α-D-glucopyranosyl phosphate is readily prepared by the phosphorolysis of starch or glycogen [460].
Chemically, synthesis of glucosyl phosphates also may involve two different approaches based either on activation of the glycosyl oxygen or activation at the anomeric carbon. In the latter, glycosyl acetates [461], orthoesters [462], glycosyl halides [463], trichloroacetimidates [464], vinyl glycosides [465], glycals [466], or 1,2-orthoesters [467] are used as glycosyl donors and they are not the aim of this chapter. The above two-step procedures ensure in most cases the anomeric purity of the final glycosyl phosphates.
On the other hand, several alternative procedures for the synthesis of glycosyl phosphates involving 1-OH activation have been developed. The thallium salt of the anomeric hydroxyl readily undergoes substitution with a phosphochloridate in benzene or acetonitrile (*Scheme 82*) [468]. The configuration of an organo-phosphate moiety introduced at the anomeric position is strongly influenced by the choice of solvent, so that a preponderance of either the α- or β-phosphate may be attained. These differences are reminiscent of solvent effects observed in syntheses of *O*-acyl esters and reflect differences in the anomeric composition in the reducing sugars as well as in the relative reactivities of the two anomers. Similarly, α-phosphates of *N*-acylglucosamine are prepared in high yields via the reaction of the corresponding 1-*O*-lithium salts with phosphorochloridate at low temperatures [469].



Scheme 82
Preparation of aldosyl phosphates



Scheme 83
Preparation of aldosyl phosphates



Scheme 84
Preparation of glycosyl phosphodiesters

A different approach to the synthesis of aldosyl phosphates involves the intermediacy of aldosyl phosphites [470]. The reaction of the anomeric hydroxyl group, with a trivalent phophitylating reagent, furnished an anomeric phosphorochloridite, which is able to react with a hydroxyl-containing compound, to generate a phosphorous triester which, upon oxidation gives the corresponding aldosyl phosphoric triester (*Scheme 83*).

More recently phophitylating reagents which, after oxidative transformation to the corresponding phosphates, allow removal of the protecting group at phosphorous (V) by mild base treatment, have been reported [471,472].

Recent studies have shown that stabilization in *O*-glycosyl phosphites can be achieved with the help of an electron-withdrawing *O*-alkyl group at the phosphite moiety (e. g. trichloroethyl vs. ethyl group) [473].

The phosphytilation approach has also been applied for the preparation of compounds in which two anomeric centers are part of a phosphodiester bond (*Scheme 84*) [471].

Acknowledgement

A.M.G. is grateful to the Ministerio de Educación y Ciencia of Spain [CTQ2006–15279-CO3–02/BQU] for financial support.

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