Synthesis of carbohydrate building blocks via regioselective uniform protection/deprotection strategies

Journal:	*Organic & Biomolecular Chemistry*
Manuscript ID	OB-REV-03-2019-000573.R1
Article Type:	Review Article
Date Submitted by the Author:	21-Apr-2019
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Synthesis of carbohydrate building blocks via regioselective uniform protection/deprotection strategies

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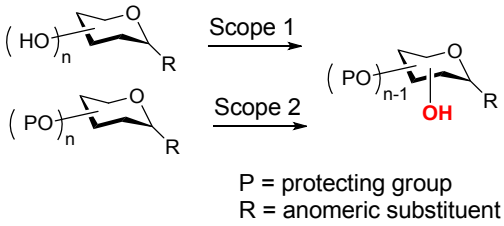


Scope 1: sugar is uniformly protected leaving only one (or two) free hydroxyl;
Scope 2: uniformly protected sugar is deprotected to liberate only one (or two) hydroxyl

ABSTRACT: Discussed herein is the synthesis of partially protected carbohydrates by manipulating only one type of a protecting group for a given substrate. The first focus of this review is the uniform protection of the unprotected starting material in the way that only one (or two) hydroxyl groups remain unprotected. The second focus involves regioselective partial deprotection of uniformly protected compounds in the way that only one (or two) hydroxyl groups become liberated..

Contents

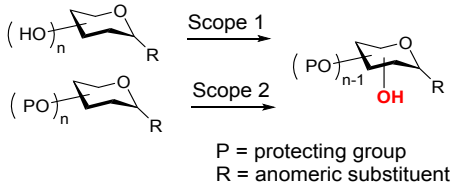
1. Introduction and basic considerations

Carbohydrates are the most abundant molecules among the four essential classes of biomolecules that also include nucleic acids, lipids, and proteins. Unlike proteins and nucleic acids, which follow template-driven synthetic pathways, there is no general route to the synthesis of carbohydrates. Monosaccharides are polyhydroxylated molecules, and regioselective protection and deprotection of specific hydroxyl groups over others represents one of the major challenges in carbohydrate chemistry.[1-3] During sequencing of simple monosaccharides into larger oligomeric networks, most of the functional groups need to be temporarily blocked by protecting groups. On the other hand, functional groups involved in the coupling process need to be left unprotected or regioselectively liberated. Therefore, it is significant to develop regioselective methods to simplify the preparation of partially or differentially substituted synthetic intermediates.[4] As a consequence, regioselective protection and deprotection of carbohydrates has been a vibrant area of research. Orthogonal or selectively removable protecting group manipulations have been extensively employed in oligosaccharide synthesis.[5,6] However, these strategies require a specialized knowledge of various protecting groups, reaction conditions for their installation and removal, and application strategies to different sugar series.

Despite a significant progress in this area, and the availability of streamlining one-pot processes,[7-12] in a majority of the applications a large number of protecting group manipulation steps are required to obtain the desired regioselectively substituted product. While orthogonal, semi-orthogonal, or selectively removable protecting groups represent a very important direction of carbohydrate synthesis, discussed herein in the synthesis of partially protected carbohydrates by manipulating only one type of a protecting group for a given derivative. While some overlap with orthogonal protecting group strategies is inevitable, a more comprehensive coverage

of the topic is available in a number of excellent recent reviews.[5,10,13-16] Two major focuses of this review article are depicted in Scheme 1. The first focus is the protection of the unprotected starting material in the way that only one (or two) hydroxyl groups remain unprotected. The second focus leads to the formation of the same type of derivatives, but it rather involves regioselective partial deprotection of uniformly protected compounds. At times, we chose to discuss these two major focus areas in application to differentially protected carbohydrates. These examples include some new reactions that have only been applied to such molecules, but in our opinion could also be generally relevant to the uniformly protected systems.

Scheme 1. The overview of protecting group strategies described herein

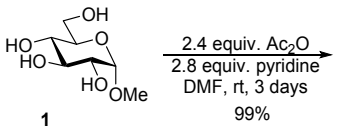


The application of partially protected building blocks is fundamental to oligosaccharide synthesis. Mono-hydroxylated building blocks can be directly utilized as glycosyl acceptors in glycosylation reactions. Di-hydroxylated building blocks can also be utilized as glycosyl acceptors, for example, for the synthesis of branched glycan sequences. Alternatively, the diols are useful synthetic intermediates for further transformations because the differentiation between two hydroxyls is typically much simpler than that of fully unprotected sugars containing four or more hydroxyls.

Inherent difference in reactivity of various hydroxyl groups in carbohydrates have been investigated to achieve selective protection. Primary hydroxyl groups are sterically less hindered than their secondary counterparts, which offers an opportunity for their regioselective protection.[17] The best-known examples is the use of bulky (trityl, silyl) protecting groups to selectively protect primary hydroxyl groups in the presence of secondary ones. Steric hindrance, as well as the electronic effects, can also be utilized to some extent to discriminate between certain secondary hydroxyl groups.[18] In addition, hydrogen bond networks were also proposed as a possible driving force for the regioselective protection.

Early studies by Williams and co-workers revealed general reactivity trends of various hydroxyls.[19] These studies also gave an appreciation that even similarly positioned hydroxyls of different sugar series may have different reactivities towards regioselective protection. Thus, the order of reactivity towards benzoylation was determined to be: 2-OH > 3-OH > 4-OH for D-gluco, 3-OH > 2-OH > 4-OH for D-manno, and 2-OH, 3-OH > 4-OH for the D-galacto series. In 1990, Hanessian attempted partial acetylation of methyl α-D-glucopyranoside **1** with and without the use of zinc chloride additive.[20] Compared with the control experiment, the addition 1 equiv of zinc(II) chloride enhanced the selectivity of the formation of the 3,4-diol product (Scheme 2). However, the regioselectivity and the product distribution was below preparative value for mainstream application in carbohydrate synthesis. This example clearly illustrates the challenge that synthetic chemists dealing with regioselective protection of carbohydrates face.

Scheme 2. Partial acetylation of methyl α-D-glucopyranoside 1 provides a mixture of products



1

Additive	none	$ZnCl_2$
tetra-Ac	7%	4%
4-OH	7%	9%
3-OH	18%	21%
2-OH	8%	trace
3,4-diol	9%	**65%**
2,4-diol	**28%**	trace
2,3-diol	20%	-
mono-Ac	12%	-

2. Synthesis of partially substituted building blocks by uniform regioselective protection

This section is focused on discussing those methods wherein the unprotected (or polyol) starting material is regioselectively protected in the way that only one (or two) hydroxyl groups remain unprotected.

2.1. Ester groups

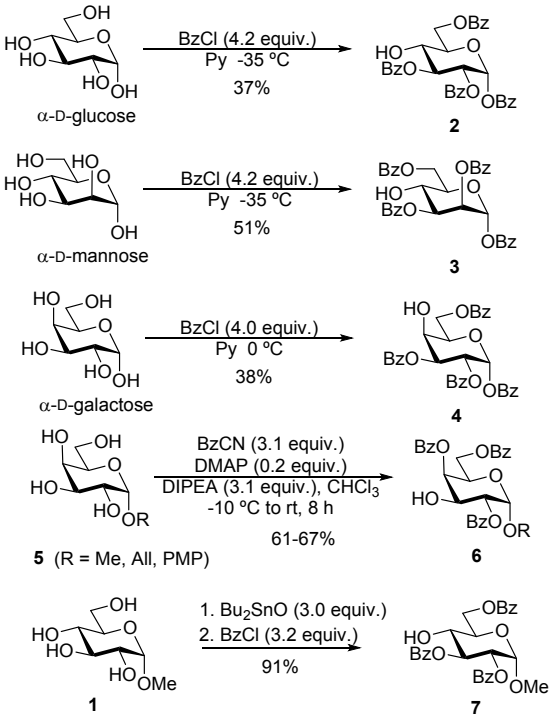
Ester protecting groups are ubiquitous in carbohydrate chemistry because acylation of hydroxyl groups is typically an efficient and high-yielding process. Common methods of esterification utilize an acid chloride or an acid anhydride as the acylating reagent in the presence of pyridine. Sometimes, more reactive nucleophilic catalysts such as DMAP are also employed. In 1975, Williams and co-workers observed that benzoylation of α-D-glucose with benzoyl chloride (4.2 equiv) in anhydrous pyridine at -35 °C provided 1,2,3,6-tetrabenzoate (4-OH derivative) **2** in 37% yield (Scheme 3). When similar conditions were applied to α-D-mannose, the respective 4-OH derivative **3** was obtained in 51% yield.[21] The synthesis of 1,2,3,6-tetrabenzoate **4** from α-D-galactose using benzoyl chloride in pyridine at low temperature was achieved in 38% yield.[22,23] These results clearly demonstrate that 4-OH is typically the least reactive hydroxyl access these sugar series. In contrast, a very recent report describes selective benzoylations of various α-D-galactopyranosides **5** with benzoyl cyanide to produce 3-OH compound **6** in good yields of 61-67%.[24] The regioselectivity achieved was rationalized by the existence of the "cyanide effect" that favors 4-O-benzoylation and "the alkoxy group mediated diol effect" that favors 2-O-benzoylation with BzCN in the presence of DMAP.

An efficient method for regioselective benzoylation of diols and polyols was developed by Dong and co-workers.[25] This regioselective method does not rely on any amine bases or metal-based catalysts. Thus, benzoylation of methyl glycosides of the D-gluco, D-galacto, and D-manno series with benzoic anhydride catalyzed by tetrabutylammonium benzoate led to 2,4-diols in 70-91% yield.

Tin-mediated acylation was initially developed and used for monoacylations of polyhydroxylated compounds.[26,27] The tin-mediated reactions of carbohydrates with acylating reagents has been an effective way to acheive differentiation between 1,2- and 1,3-diol pairs.[28] More recently, Zhang and Wong performed regioselective polyacylation reactions of various sugars using an excess of BzCl and Bu_2SnO at higher temperatures (70-100 °C).[29] The stannylene acetal was proposed as an intermediate of the reaction of methyl α-D-

glucopyranoside **1** with O-2 coordinating with the anomeric methoxy and O-6 coordinating with the ring oxygen. This reaction produced 4-OH glucoside **7** with high regioselectivity in 91% yield (Scheme 3). Interestingly, while a comparable outcome was achieved with the D-manno substrate, the D-galacto counterpart gave much lower regioselectivity.[29] Tosylation and benzylation can also be achieved regioselectively using a similar approach.[30] The principles and applications of tin-mediated reactions have been extensively reviewed.[31-34]

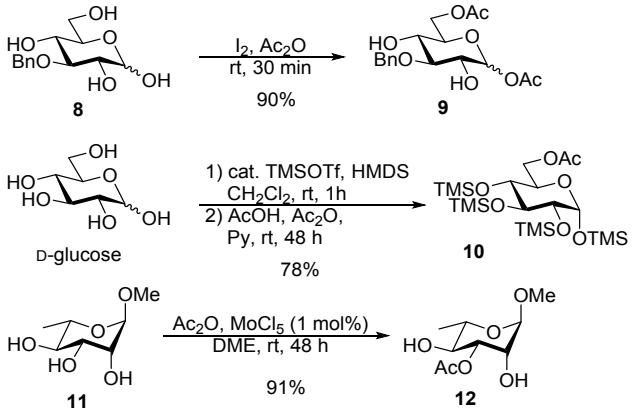
Scheme 3. Regioselective benzoylation



Regioselective acetylation can be achieved by using iodine with ether-protected sugar derivatives.[35] Upon the treatment of 3-*O*-benzyl glucose **8** with acetic anhydride containing iodine at rt, 1,6-di-*O*-acetate **9** was obtained in 90% yield (Scheme 4). The reaction rate was improved at higher temperatures, but the regioselectivity was not affected. Many methods have been known to perform selective acetylation. Joseph *et al.* developed a regioselective one-pot silylation and acetylation method to form a partially acetylated sugar.[36] After TMSOTf-catalyzed silylation of D-glucose with HMDS, followed by acetylation, 6-*O*-acetyl glucopyranose **10** was formed as the major product via per-*O*-trimethylsilylated intermediate (Scheme 4). When per-*O*-TMS protected sugar in a mixture of pyridine and acetic anhydride is treated with acetic acid, regioselective exchange of TMS for acetate protecting groups occurs.[37] This process was termed as Regioselective Silyl Exchange Technology (ReSET). This method has been applied to glucose,[38] galactose, mannose, lactose,[37] and sialic acids.[39] Regiocontrol is achieved by limiting the equivalents of acetic acid, varying thermal conditions and using microwave assistance.

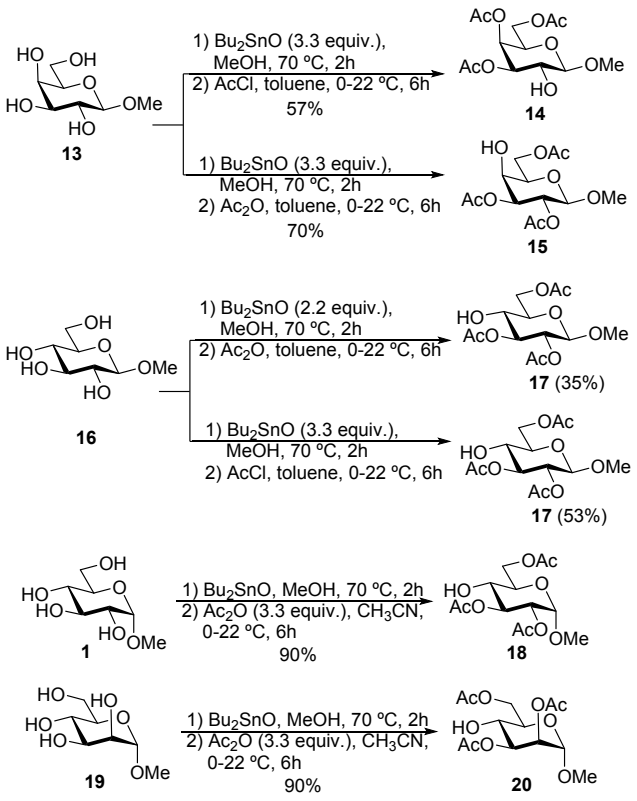
Besides the ReSET approach, many catalysts such as 1-acetylimidazole,[40] C_2-symmetric chiral 4-pyrrolidinopyridine,[41] copper(II),[42] tetrabutylammonium acetate,[43] Mitsunobu conditions,[44] borinic acids,[45,46] and cyanides[47] can help to achieve regioselective acylation. However, very few of them can protect free sugars in one step and leave only one hydroxyl group free. $MoCl_5$ has been used as an effective catalyst for selective 3-acetylation of methyl 6-deoxyhexoses.[48] Acetylation with Ac_2O in the presence of catalytic $MoCl_5$ produced 3-*O*-acetyl derivative **12** regioselectively in 91% yield from methyl α-L-rhamnopyranoside **11** (Scheme 4). Kulkarni and co-worker also studied acylation of rhamnosides.[49] In particular, acetylation of phenylthio β-L-rhamnopyranoside with acetyl or benzoyl chloride (1.1 equiv) in the presence of catalytic Me2SnCl2 at rt afforded the corresponding 3-O-acylated derivatives in 95-98% yield. When the same starting material was benzoylated with 2.1 equiv of BzCl in pyridine at -30 °C, 2,3-di-O-benzoylated rhamnoside was produced in 71% yield.[49]

Scheme 4. Examples of regioselective acetylation



When Kurahashi *et al.* treated octyl α- and β-glucopyranosides with a sub-stoichiometric amount of acetic anhydride in the presence of a catalytic amount of DMAP, 3-, 4- and 6-nonoacetylated glucosides were obtained in a 2/2/1 ratio.[50] Recently, Ren *et al.* described a method for selective acetylation of glycosides using tetrabutylammonium acetate as catalyst.[43] However, all these investigations of inherent reactivity differences and partial protections of glycoside hydroxyl groups did not provide products with exclusive regioselectivity. More recently, mono-hydroxyl building blocks were synthesized by reagent-dependent regioselectively controlled poly-acetylation.[51] For methyl β-D-galactopyranoside **13**, the use of Ac_2O or AcCl as acetylating reagents lead to the formation of 2-OH compound **14** or 4-OH compound **15**, respectively (Scheme 5). For methyl β-D-glucopyranoside **16**, either acetylating reagent gave 4-OH compound **17** as the major product. When treated with 3.3 equiv. of Ac_2O in acetonitrile solvent, both methyl α-D-glucopyranoside **1** and methyl α-D-mannopyranoside **19** gave the corresponding 4-OH products **18** and **20** in 90% yield. To explain the regioselectivity obtained, reagent-dependent thermodynamic and kinetic control and dynamic assistance mechanisms were proposed.[51] Thus, when acetyl chloride was used as the acylating a monodentate chlorostannane complex was generated, whereas acylation with acetic anhydride proceeded via a less reactive bidentate acetoxystannane.

Scheme 5. Reagent-dependent tin-mediated acetylation

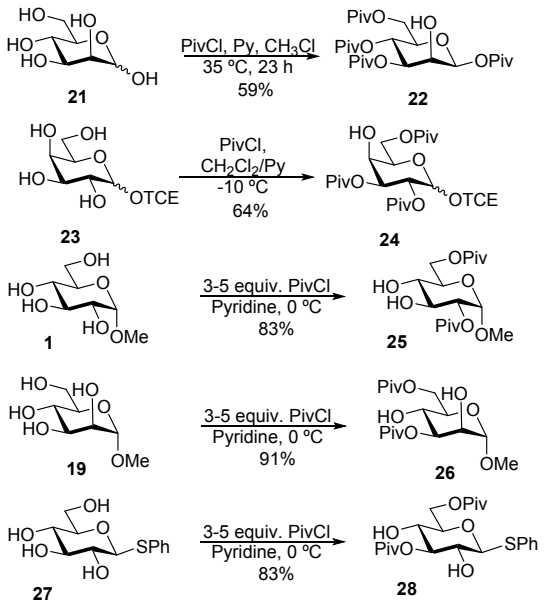


The introduction of bulky ester groups was proven to be a much more promising venue. Becker and Galili prepared partially pivaloylated saccharides by using pivaloyl chloride in the presence of pyridine.[52] 1,3,4,6-Tetra-*O*-pivaloyl derivative **22** was formed in 59% yield as the major product resulting from the reaction of D-mannose **21** with pivaloyl chloride in the presence of pyridine in chloroform at 35 ºC (Scheme 6). Alternatively, a similar reaction performed at -10 ºC produced a tetra-pivaloylated product with the free 4-OH group.[53] Regioselective pivaloylation of trichloroethyl galactoside **23** using pivaloyl chloride in the presence of pyridine in dichloromethane gave 4-OH product **24** in 64% yield (Scheme 6). A selective and high yielding double pivaloylation of different sugar substrates using pivaloyl chloride has also been described. See, for example, the synthesis of diols **25** and **26** depicted in Scheme 6.[54] Equatorial hydroxyl groups adjacent to axial substituents were observed have higher reactivity as they were more accessible than equatorial ones flanked by other equatorial substituents. For compound **27**, which does not have any axial hydroxyl groups, selective protection occurred at the C6 and C3 positions to afford product **28**.

2.2. Alkyl and silyl groups

Alkyl group protection is widely used in carbohydrate chemistry due to its stability. Simple alkyl ethers such as methyl ethers are less preferred in complex carbohydrate synthesis because they are too stable to be removed.[28] Of the numerous alkyl protecting groups known, the most important are the benzyl (Bn) and allyl (All) groups and their derivatives. Direct regioselective benzylation of polyols is fairly rare. One such example was described by Koto *et al* [55]example wherein 3-OH derivative **29** was obtained in 61% from methyl glucoside **1** by controlled heating with excess BnCl in the presence of NaH added potrionwise to 3.3 equiv total (Scheme 7).

Scheme 6. Regioselective protection with pivaloyl groups



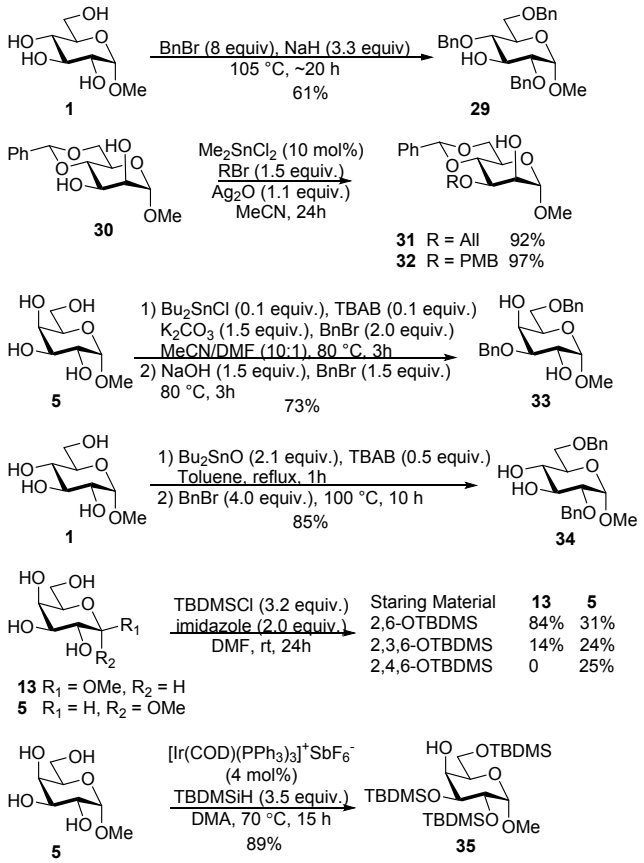
In a majority of applications regioselective alkylations require metal chelating reagents and additives. Alkylations proceeding via tin intermediates is arguably the most common method to achieve regioselective protection.[31,33,56-60] Other metal catalysts such as copper(II),[61] nickel(II),[62] and iron(III)[63] have also been used for regioselective alkylation. These methods are primarily used for selective mono- and di-alkylation, the formation of monohydroxylated products commonly used substrates containing other protecting groups, such as benzylidene acetals.

Recently, Vishwakarma and co-workers improved the tin-mediated alkylation method by using catalytic amount of Me_2SnCl_2 and Ag_2O as additives, which gave excellent selectivity at rt. Thus, 2,3-diol **30** was regioselectively alkylated producing 3-O-allyl and 3-O-p-methoxylbenzyl derivatives **31** and **32** in excellent yields. (Scheme 7).[64] Oshima et al. developed an alkylation method specific for the C-3 position using cyclic phenylboronate in the presence of an amine.[65] Taylor devised C-3 alkylation reaction using a diarylborinic acid derivative.[66] Iadonisi developed another method for selective benzylation that is applicable to primary hydroxyl group using stoichiometric amount of DIPEA and BnBr and catalytic amount of TBAI.[67] Some tin-mediated alkylations allow for multiple protections. Representative examples include the synthesis of 3,6-di-Bn derivative **33** from methyl galactoside **5**,[25] and 2,6-di-Bn derivative **34** from methyl glucoside **1** (Scheme 7).[68] Benzylation of per-TMS-protected sugars via reductive etherification of benzaldehyde[69] has also received notable attention, most prominently as a part of the multi-step one-pot sequences.[9-11]

Halmos *et al.* investigated the regioselective silylation of galactopyranosides using TBDMSCl and imidazole in the presence of DMF.[70] For both the α- and β-anomers **5** and **13**, the corresponding 2,6-di-O-silylated compounds were formed predominantly. Much higher regioselectivity was observed for

β-anomer **13** (Scheme 7). Schlaf and co-worker devised a silane alcoholysis method for selective trisilylation using homogeneous metal catalysts.[71] High selectivity for silylation of galactoside **5** was achieved in the presence of Ir(I) catalyst. As a result, 2,3,6-tri-*O*-*tert*-butyldimethylsilyl galactoside **35** was obtained in 89% yield.

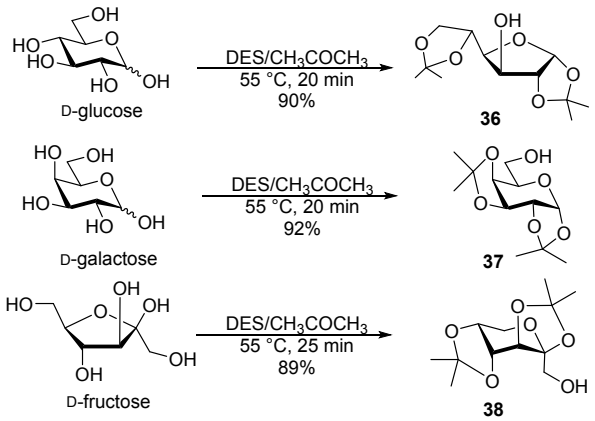
Scheme 7. Regioselective alkylation and silylation



2.3. Cyclic groups

Cyclic acetals and ketals have been widely used for the protection of various diol systems in synthetic carbohydrate chemistry.[72-75] The installation of multiple acetal/ketal groups in a single monosaccharide unit is commonly used for polyols or alditols.[76] Although the double protection using cyclic acetals/ketals would have been a very effective method to obtain building blocks containing only one hydroxyl group in hexoses it remains fairly rare beyond diacetone glucofuranose (3-OH) and galactopyranose (6-OH). Thus, Rokade and Bhate devised a simple and convenient large-scale method for the synthesis of di-*O*-isopropylidene protected sugars by using deep eutectic solvent (DES) prepared from choline chloride and malonic acid.[77] D-Glucose can be directly converted to 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose **36** in 90% yield whereas D-galactose can be converted into 1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranose **37** in 92% yield (Scheme 8). D-Fructose can also be protected as 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose **38** using this method in 89% yield. In case of D-mannose, 2,3:5,6-di-*O*-isopropylidene-α/β-D-mannofuranose with the unprotected anomeric hemiacetal was formed. All these building blocks represent regioselectively protected compounds that have only one hydroxyl group. Hence, these can be used as glycosyl acceptors or intermediates for the further protection directly. In addition, one ketal is typically less stable than another, which offers a convenient opportunity for further diversification.[78] The double protection using benzylidene acetal is much less explored. In one such application, 1,2:3,4-di-*O*-benzylidene-D-galactopyranose could be synthesized from D-galactose using benzaldehyde and $ZnCl_2$.[79] Wood *et al.* improved the preparation of 4,6-O-benzylidene-D-glucopyranose, which lead to the formation of 1,2:4,6-di-*O*-benzylidene-α-D-glucopyranose as an by-product.[80]

Scheme 8. Double ketal protection of hexoses



3. Synthesis of partially substituted building blocks by regioselective deprotection of uniformly protected substrates

In addition to protection strategies, partially substituted derivatives can be obtained by regioselective deprotection of fully substituted precursors. This approach also extends to the uniformly protected precursors.

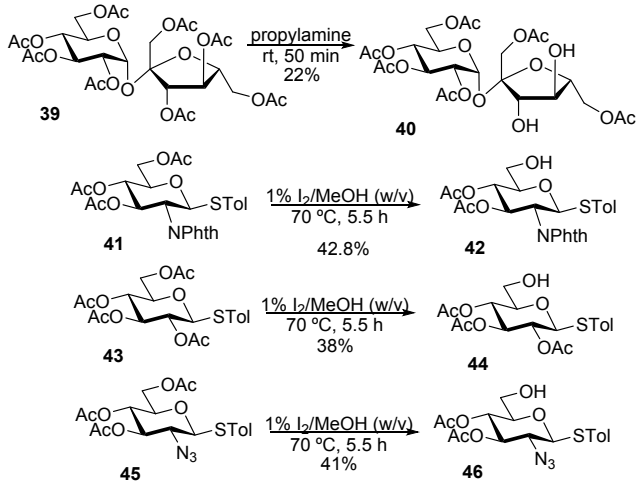
3.1. Ester group removal and migration

In general, esters are moderately stable under acidic conditions in the absence of water and other hydroxylated solvents. However, many esters are labile in the presence of nucleophiles, particularly alkoxides, amines, organometallics, and hydride transfer agents. It has been observed that essentially the same ester groups may have different stability at different positions of the ring. Thus, Haines *et al.* reported that a primary amine can be used for selective deacetylation of sucrose.[81] Fully acetylated sucrose **39** was treated with propylamine at rt for 50 min to give diol **40** in 22% yield (Scheme 9).

Isopropylamine was also investigated but gave even lower yields. Ren and co-workers were able to carry out regioselective deprotections of primary acetyl esters in the presence of iodine.[82] As depicted in Scheme 9, when various S-tolyl (Tol) glycosides **41, 43** and **45** were treated with 1% iodine–methanol solution at 70 °C for 5.5 h, 6-OH products **42, 44** and **46** were obtained in 38-43% yields. It was presumed that the electrophilic attack of iodine on the oxygen atom of the primary acetate is more favorable than that of the more hindered acetates at secondary positions. Very recently, Lecourt and co-workers achieved a similar outcome by using a combination of DIBAL-H and Cp_2ZrCl_2 to promote the

regioselective cleavage of primary acetates on a variety of substrates.[83]

Scheme 9. Examples of regioselective deacetylation

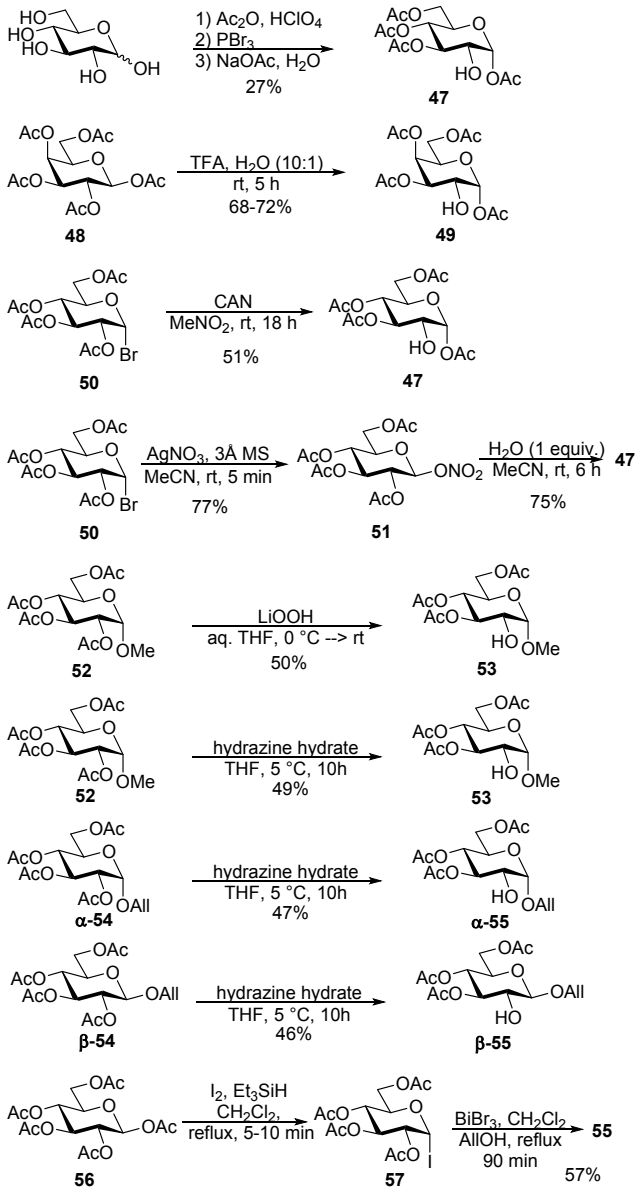


Some acyl groups may undergo migration through a neighboring group effect via the formation of the respective orthoester as an intermediate. Acyl group migration has been proven to be a useful approach to obtain partially substituted building blocks for oligosaccharide synthesis.[84-86] In 1962, Helferich and Zirner[87] synthesized 1,3,4,6-tetra-*O*-acetyl-α-D-glucopyranose **47** from D-glucose via a three-step in-situ procedure. This synthesis requires strict control of the reaction temperature and reactant addition and still gives only 27% yield overall (Scheme 10).

A few years later, Chittenden reported a simplified method for the synthesis of 1,3,4,6-tetra-*O*-acetyl-α-D-galactopyranose using trifluoroacetic acid-water solution.[88] 1,2,3,4,6-penta-*O*-acetyl-β-D-galactopyranose **48** was treated with aqueous trifluoroacetic acid at rt for 5 h to give 1,3,4,6-tetra-*O*-acetyl-α-D-galactopyranose **49** in 72% yield (Scheme 10). The α-anomer of D-galactopyranose/glucopyranose pentaacetate is unreactive under these reaction conditions. When 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose was treated under the same reaction conditions, only 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose was produced as the major product.

Recently, Demchenko *et al*. reinvestigated the synthesis of 2-OH glucose.[89] When acetobromoglucose **50** was treated with cerium(IV) ammonium nitrate (CAN) 2-OH glucose **47** was obtained in 51% yield (Scheme 10). This procedure was recently further improved by using $AgNO_3$ as the additive and glycosyl nitrates were found to be intermediates in this reaction.[90] $AgNO_3$ is able to convert glycosyl bromide **50** to glycosyl nitrate **51** in 77% yield within 5 min. Subsequently, 2-OH glucose **47** formed by re-dissolving compound **51** in wet MeCN (Scheme 10). The isolation of glycosyl nitrate **51** suppressed the formation of by-product 2,3,4,6-tetra-*O*-acetyl-D-glucopyranose. Hanessian and Kagotani found that lithium hydroperoxide could be used to remove the 2-O-acetyl group regioselectively from methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glycoside **52** to afford 2-OH product **53** in 50% yield (Scheme 10).[20] For penta-*O*-acetyl-D-glucose, lithium hydroperoxide removed the acetyl group at C-2 position as well as at the anomeric position.

Scheme 10. The synthesis of 2-OH derivatives



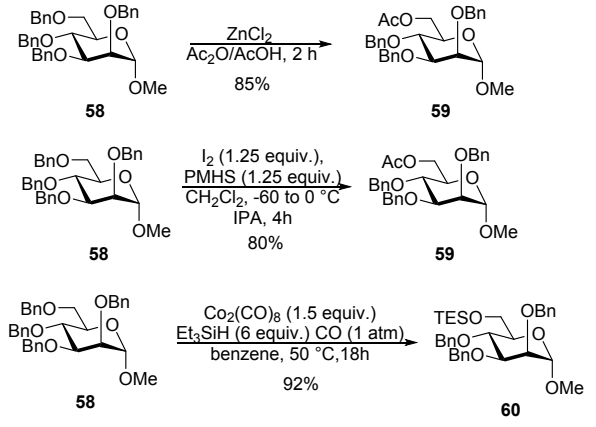
Hydrazine hydrate can also be used for selective deacetylation at C-2 position.[91] On the treatment of various glycosides **52, α-54** and **β-54** the corresponding 2-OH products **53, α-55** and **β-55** was obtained in moderate yields of 46-49% (Scheme 10). When a bismuth(III) salt was used to promote glycosylation of allyl alcohol with glucosyl iodide **57**, obtained from glucose pentaacetate **56**, the corresponding 2-OH allyl glucoside **55** was formed as the major product in 57% yield instead of the anticipated tetra-*O*-acetylated product (Scheme 10).[92] An allyl orthoester intermediate was suggested to form during the bismuth(III) activation step.

3.2. Ether group removal

Benzyl groups are commonly used as protecting groups in carbohydrate chemistry. Due to their general stability, these groups are considered to be "permanent" protecting groups that are only removed at the end of the target synthesis. However, it was observed that some benzyl groups may have different stability at different positions of the ring. In particular, regioselective acetolysis of 6-O-benzyl group in the

presence of secondary benzyl groups is arguably the best known and most commonly applied approach.[93-95] For example, freshly fused $ZnCl_2$ in Ac_2O/AcOH has been used for the acetolysis of 6-O-benzyl groups in mono- and disaccharide derivatives at room temperature.[96] Per-benzylated mannoside **58** was treated with $ZnCl_2$ in Ac_2O/AcOH for 2 h to produce 6-*O*-acetyl product **59** in 85% yield (Scheme 11). The same type of a transformation can be achieved by regioselective acetolysis with toluenesulfonic acid[97] or isopropenyl acetate (IPA) in the presence of iodine or iodine/silane.[67] Thus, when a premixed solution of iodine and polymethylhydrosiloxane (PMHS) in dichloromethane was used followed by the addition of IPA as the acetylating reagent, 6-*O*-acetyl compound **59** was formed from per-*O*-benzylated mannoside **58** in 80% yield. More recently, Li and co-workers developed a highly efficient and mild method for regioselective de-*O*-benzylation by transforming primary benzyl ethers to silyl ethers using $Co_2(CO)_8$-Et_3SiH under 1 atm of CO.[98] Per-*O*-benzylated mannoside **58** was treated with $Co_2(CO)_8$/Et_3SiH/CO conditions to give 6-O-triethylsilyl compound **60** in 92% yield (Scheme 11). This method was also successfully applied to various monosaccharide substrates with different anomeric protecting groups, as well as natural disaccharides and trisaccharides including sucrose, raffinose and others. A similar protocol was applied to the regioselective removal of methyl ether protecting groups.[99] For per-*O*-methylated thioglucoside, primary methyl group was removed selectively and the respective 6-*O*-acetyl product was formed in 52% yield along with 3,6-di-*O*-acetyl compound was also formed as a minor side-product.

Scheme 11. Examples of regioselective primary debenzylation

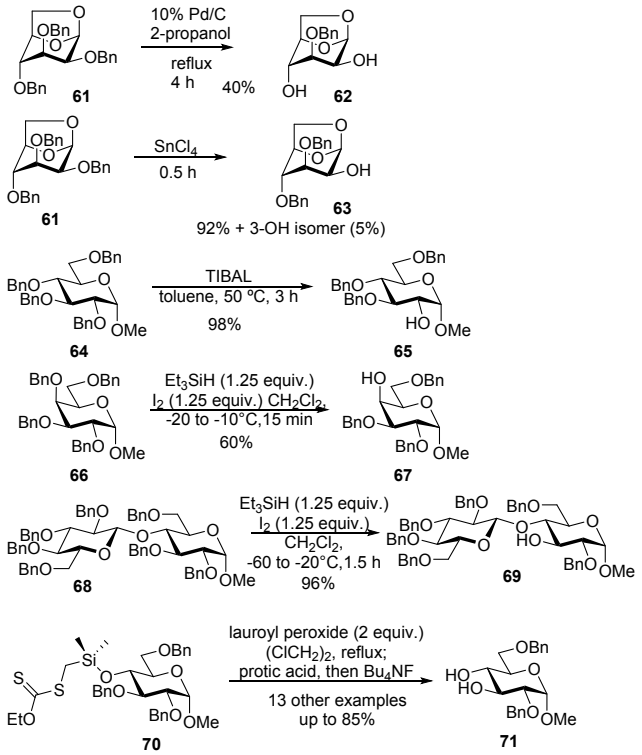


The earlier examples of regioselective de-o-benzylation include that of perbenzylated methyl lyxoside by Grignard reagent,[100] and perbenzylated methyl ribofuranoside with tin tetrachloride.[101] The selective heterogeneous catalytic transfer hydrogenolysis perbenzylated 1,6-anhydrohexoses catalyzed by palladium on charcoal was developed by Martin-Lomas.[102] 1,6-Anhydro-2,3,4-tri-*O*-benzyl-β-D-mannopyranose **61** was treated with 10% Pd/C in refluxing 2-propanol for 4 h, to produce 1,6-anhydro-3-*O*-benzoyl-β-D-mannopyranose **62** in 40% yield (Scheme 12). The regioselective removal of one secondary benzyl substituent in per-benzylated 1,6-anhydrohexoses by Lewis acids $SnCl_4$ and $TiCl_4$ was developed by Meguro and co-workers.[103] 1,6-Anhydro-2,3,4-tri-*O*-benzyl-β-D-mannopyranose **61** was treated with $SnCl_4$ to produce 2-OH derivative **63** in 92% along with its 3-OH regioisomers (5%). A similar result albeit lower yield of **62** due to relaxed regioselectivity were obtained with $TiCl_4$. Spectral studies showed the evidence of the formation of the metal-sugar complexes, thus requiring three appropriately situated alkoxyl groups for the selective de-O-benzylation.

Catalytic transfer hydrogenation (CTH) can be performed using HCO_2NH_4 and Pd/C catalyst to selectively remove 2-O-benzyl groups in derivatives of D-glucose, D-mannose, and D-galactose.[104] Sinay, Sollogoub and their co-workers developed a method for regioselective de-*O*-benzylation of polybenzylated sugars using an excess of triisobutylaluminium (TIBAL) or diisobutylaluminium hydride (DIBAL-H).[105] Treatment of per-benzylated glucoside **64** with 5 equiv. of TIBAL in toluene at 50 °C led to 2-*O*-debenzylated product **65** in 98% yield (Scheme 12). For the reaction to occur, a 1,2-*cis* arrangement of adjacent oxygen atoms is required to form a chelation complex with the first mole of the aluminum reagent. The second mole of the reagent then induces the regioselectivity of the de-alkylation by coordinating preferentially to one of the oxygen atoms of the selected pair. The same transformation, albeit much slower rate, can be performed in the presence of $AlMe_3$.[106]

Iadonisi and co-workers developed another method for regioselective *O*-debenzylation using I_2/Et_3SiH at low temperature.[107] The regioselectivity is dependent on the nature of the precursor and the most sterically hindered position is often deprotected. Methyl galactoside **66** was treated with 1.25 equiv. of I_2 and 1.25 equiv. of Et_3SiH at low temperature for 15 min to afford 4-OH derivative **67**. In case of disaccharide **68**, the 3-*O*-benzyl group was removed with excellent regioselectivity to produce compound **69** in 96% yield (Scheme 12).

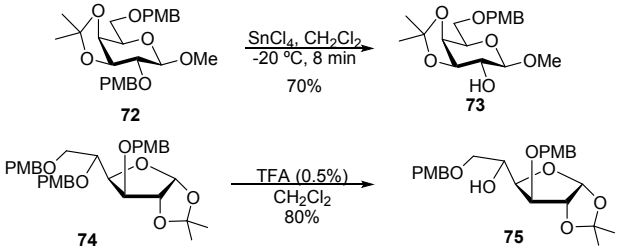
Scheme 12. Examples of regioselective secondary debenzylation



An interesting reaction proceeding via a xanthate-mediated intramolecular 1,7-hydrogen atom transfer of a benzylic hydrogen atom to an *O*-silylmethylene radical was found capable of initiating the regioselective mono-de-*O*-benzylation of benzylated saccharides.[108] This method can be applied to a variety of substrates and gave moderate to good yields (Scheme 12). Xanthate **70** was treated with dilauroyl peroxide, followed by acid and TBAF in refluxing 1,2-dichloroethane to give diol **71** in 75% yield. The reaction terminates by an ionic mechanism and is general for benzylated substrates having a variety of functional groups. Intramolecular activation of per-benzylated *C*-glycosides to affect regioselective deprotection at C-2 can be carried out in the presence of iodine.[109,110] Boron trichloride (BCl_3) has also been investigated as a reagent to achieve regioselective deprotection of 1,2- or 1,3-cis oriented secondary benzyl ethers of poly-benzylated *C*-glycosyl derivatives.[111] Another method for regioselective de-*O*-benzylation of poly-benzylated sugars is to use $CrCl_2$/LiI in moist EtOAc.[112] The regioselectivity is dependent on the three-point coordination between the carbohydrate and Cr.

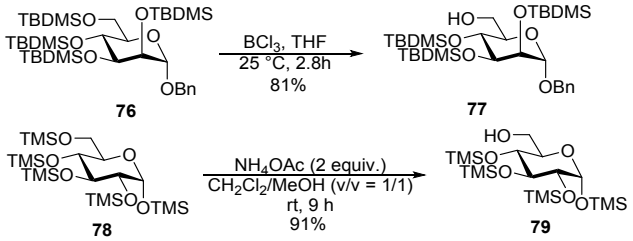
p-Methoxylbenzyl (PMB) ethers are less stable than unsubstituted benzyls. *Kartha* and co-workers explored a possibility for regioselective PMB removal using $SnCl_4$ at low temperature.[113] When di-*O*-PMB derivative **72** was treated with $SnCl_4$ (0.25 mmol) in CH_2Cl_2 at -20 ºC for 8 min, 2-*O*-PMB group was removed and mono-*O*-PMB ether **73** was obtained in 70% yield (Scheme 13). The initial preferential removal of the 2-O-PMB group in **72** was rationalized by the formation of a tin complex as an intermediate. Regioselective removal of *p*-methoxybenzyl (PMB) group at the C-5 position for hexafuranose and pentafuranose derivatives was achieved using a catalytic amount of tin chloride dihydrate ($SnCl_2$-$2H_2O$) or 0.5-10% solution of trifluoroacetic acid (TFA) in dichloromethane in good yields.[114] For tri-*O*-PMB protected glucofuranose **74**, the 5-*O*-PMB group could be removed selectively using a 0.5% solution of TFA in CH_2Cl_2 to form the 5-OH product **75** in 80% yield (Scheme 13).

Scheme 13. Regioselective removal of PMB groups



The regioselective deprotection of a primary *tert*-butyldimethylsilyl (TBDMS) group of fully *O*-TBDMS protected monosaccharides by using boron trichloride (BCl_3) was devised.[115] Fully *O*-TBDMS protected benzyl mannoside **76** was treated with BCl_3 at 25˚C for 2.8 h and gave 81% of the 6-OH product **77** (Scheme 14). The TBDMS group was also observed to migrate from the C-6 to C-4 position of glucosides under typical basic benzylation conditions.[116] Cui *et al.* developed a method to selectively remove a primary trimethylsilyl (TMS) group of per-*O*-TMS protected carbohydrates using ammonium acetate (NH_4OAc).[117] On the treatment of the per-O-TMS protected glucoside **78** with 2 equiv. of NH_4OAc the corresponding 6-OH product **79** was obtained in 91% yield (Scheme 14). Various monosaccharides and disaccharides were investigated under these reaction conditions giving the desired products in excellent yields. When the precursor had no primary TMS group, no reaction occurred under these reaction conditions.

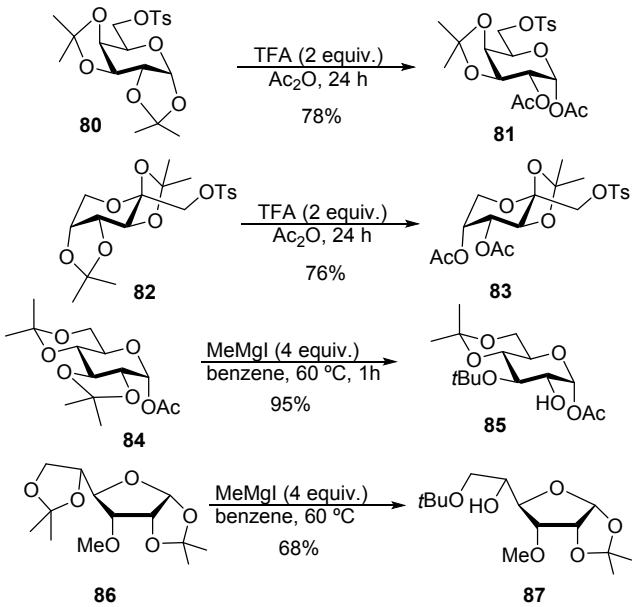
Scheme 14. Regioselective desilylation



3.3. Cyclic group removal and opening

In di-*O*-isopropylidene protected derivative, sometimes one ketal can be removed regioselectively over another. The regioselective removal of the acetal groups of di-O-isopropylidene-protected pyranoses was barely studied. The few known examples include the removal of 3,4-O-isopropyliden in the presence of 1,2-*O*-isopropylidene ketal in diacetone galactose with dilute hydrochloric acid in acetone,[118] and with concentrated nitric acid in ethyl acetate.[34] Recently, Zhang *et al.* developed the removal of 1,2-O-isopropylidene in the presence of 3,4-*O*-isopropylidene ketal in diacetone galactose. Di-*O*-acetate **81** was obtained in 78% yield from the di-*O*-isopropylidene protected pyranose **80** in the presence of TFA and acetic anhydride (Scheme 15).[78] The same conditions were also successfully applied to the regioselective 4,5-*O*-acetolysis of 2,3:4,5-di-*O*-isopropylidene-β-D-fructopyranose **82** to produce compound **83** in 76% yield. The corresponding 1,2-*O*-isopropylidene derivatives were obtained selectively by UV irradiation of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose and 1,2:3,5-di-*O*-isopropylidene-α-D-xylofuranose, respectively.[119]

Scheme 15. Regioselective deprotection of isopropylidene



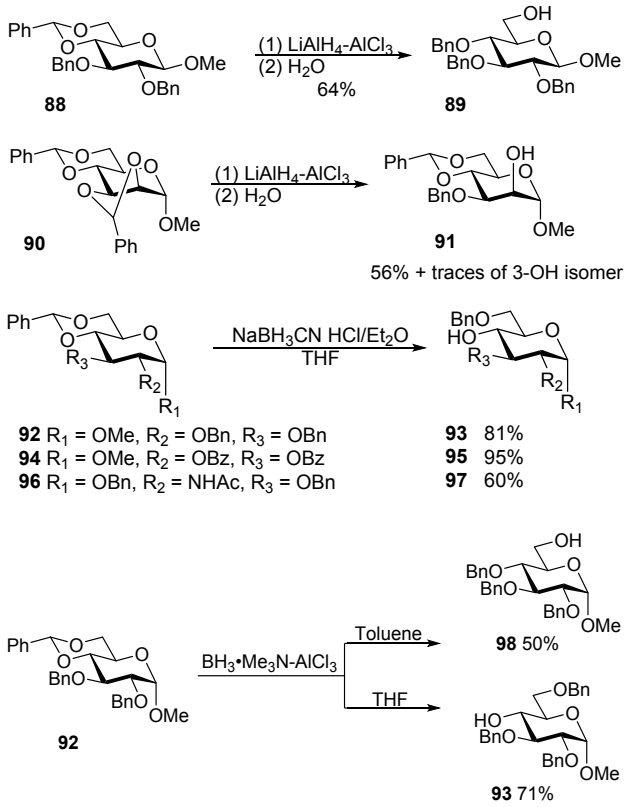
In 1994, Luh and co-workers reported that di-acetonide glucose derivative **84** can be reductively opened to produce mono-hydroxyl derivatives with high regioselectivity using MeMgI.[120] When diacetone glucose **84** was treated with 4 equiv. of MeMgI in benzene at 60 ºC for 1 h, the corresponding 2-OH derivative **85** was formed in 95% yield (Scheme 15). In a similar fashion, treatment of compound **86** with MeMgI afforded **87** exclusively in 68% yield (Scheme 15). Presumably, the chelation of the Grignard reagent with the methoxy group at C-6 controls the regioselectivity.

Cyclic acetals are important protecting groups in carbohydrate chemistry and many can be opened regioselectively to form mono hydroxyl products. Many methods have been developed to dedicated to this topic,[121] and a very recent review by Janssens et al. offers the most up to date coverage of the topic.[122] Discussed herein are only some representative examples relevant to the topic of this review. In 1969, Bhattacharjee and Gorin applied the mixed hydrides in the reduction of carbohydrate series for the first time.[123] One molar equivalent of $LiAlH_4$-$AlCl_3$ (1/1) was used for the reduction of hexafuranose and hexapyranose acetals. After 40 h, a uniformly protected 6-OH derivative **89** was obtained in 64% yield from methyl 2,3-di-*O*-benzyl-4,6-*O*-benzylidene-β-D-glucopyranoside **88** (Scheme 16). The 2-OH derivative **91** was obtained in 56% yield from methyl 2,3:4,6-di-*O*-benzylidene-α-mannopyranoside **90** in 3.5 h when 2 equivalents of $LiAlH_4$-$AlCl_3$ (1/1) mixture was used. The formation of trace amounts of the 3-OH side product was also noted (Scheme 16). The study of the factors that orient the cleavage of a 4,6-*O*-benzylidene group undertaken by Lipták and co-workers showed that the direction of the cleavage of the benzylidene ring is affected by the bulkiness of the protecting group at C-3[124,125] and exo/endo stereochemistry of benzylidene acetal.[126,127] This was investigated on a series of 2,3-*O*-benzylidene protected L-rhamnopyranosides wherein 2-OH products were favored from exo-isomers whereas 3-OH products were obtained from exo-benzylidene precursors.[127-129] It was also demonstrated that the direction of cleavage is independent on the anomeric configuration or the character of the aglycone moiety.[130]

Garegg *et al*. discovered that reductive opening of 4,6-O-benzylidene acetals of hexapyranosides using $NaBH_3CN$-HCl gave different regioselectivity than $LiAlH_4$-$AlCl_3$, yielding 6-*O*-benzyl product 4,6-*O*-benzylidene acetals.[131,132] 6-*O*-Benzyl derivatives **93, 95** and **97** were obtained from the reductive cleavage of the starting materials **92, 94** and **96** in 60-95% yield (Scheme 16). This may be explained by steric factors. When a reducing agent with a greater steric demand like $LiAlH_4$-$AlCl_3$ is used, the reductive opening reaction tends to for 6OH products. When $NaBH_3CN$-HCl is used, the steric requirement of the electrophile is much smaller and the direction of the equilibrium is governed mainly by the relative basicities of O-4 and O-6, and the formation of the secondary 4-OH product typically prevails. The direction of regioselective opening of 4,6-*O*-benzylidene acetals of hexapyranosides using BH_3•Me_3N-$AlCl_3$ in different solvents were investigated by Ek et al.[133] For the reaction of 4,6-*O*-benzylidene derivative **92** in toluene 6OH product **98** was obtained. When THF was used as the reaction solvent, 4OH product **93** was obtained (Scheme 16). A pronounced solvent effect was also reported by Oikawa *et al.* who used BH_3•Me_2NH/BF_3•OEt_2 to perform a regioselective reductive opening of the 4,6-*O*-benzylidene acetals.[134] When the reaction was carried out in CH_2Cl_2, the 6-OH product was regioselectively obtained. Conversely, when the reaction was performed in CH_3CN, 4-OH product was predominantly formed.

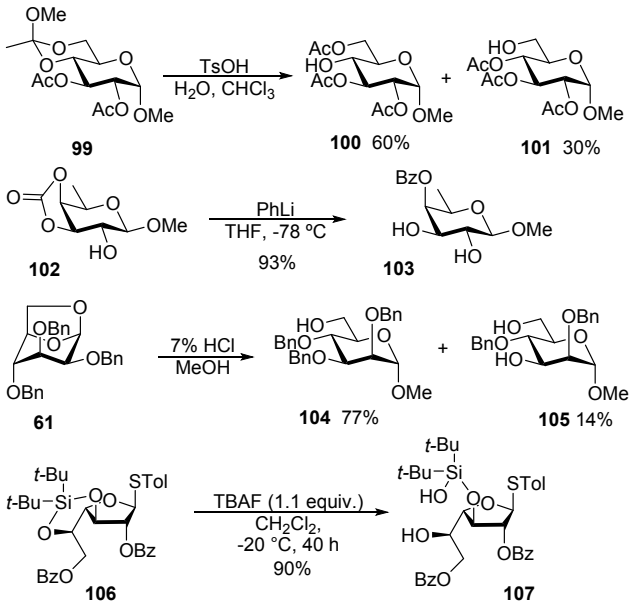
Other useful methods to affect the regioselective opening of benzylidene include DIBAL,[135-138] Et_3SiH-TFA,[139] Et_3SiH-BF_3·Et_2O,[140] BH_3•THF-Bu_2BOTf,[141] BH_3•NMe_3-Me_2BBr at -78 °C,[142] BH_3 in combination with metal triflates at rt,[143] BH_3 or Me_2EtSiH with $Cu(OTf)_2$,[144] BH_3•THF and $CoCl_2$,[145] Et_3SiH and I_2,[146] among others.[122] The development of new methods has been complemented by a variety of mechanistic investigations.[147-152] 4-Methoxybenzylidene acetals can also be selectively opened in a similar fashion and using similar reagents to as benzylidene acetals.[153,154] Regioselective opening of other acetals including 4,6-*O*-prop-2-enylidene,[132] fluorous benzylidene[155] phenylsulfonylethylidene[156] has also been explored. Oxidative and photooxidative methods for opening of benzylidene acetal have also been developed. *N*-Bromosuccinimide (NBS) was found to be an effective reagent to regioselectively open 4,6-*O*-benzylidene acetals to afford 6-bromo 4-benzoates.[157] Regioselective partial deprotection of carbohydrates protected as benzylidene acetals can be achieved by irradiation of the protected sugar with NBS in the presence of water.[158] Photolysis is an alternative mild and regioselective method to open an acetal protecting group. Early studies by Tănăsescu and co-workers on light-induced cleavage of *o*-nitrobenzylidene acetals.[159,160] have been complemented by more recent studies dedicated to photochemical conversion of cyclic acetals to the corresponding esters.[161-164]

Scheme 16. Reductive opening of benzylidene acetals



Orthoesters are other common type of protecting groups in carbohydrate chemistry. Orthoesters can be regioselectively opened to the corresponding hydroxyacetate derivatives under mild acidic conditions.[165] The substrate α-D-glucoside **99** was treated with a mixture of water and chloroform in the presence of TsOH, giving the corresponding 4-OH derivative **100** as the major compound in 60% yield as well as the minor product 6-OH isomer **101** in 30% yield (Scheme 17). Among other applications, orthoesters can be reduced into the corresponding acetals.[166,167] Nicolaou and co-workers showed that cyclic 1,2-carbonates can be regioselectively cleaved with organolithium reagents at low temperature to afford regioselective esters.[168] Thus, derivative **102** was treated with PhLi to afford 4-*O*-benzoyl derivative **103** in high yield (Scheme 17). A number of useful ring-opening reactions can be achieved with anhydrosugars.[103,169-174] Thus, Hori and co-workers performed acid-catalyzed methanolysis of 1,6-anhydro-2,3,4-tri-*O*-benzyl-β-D-mannopyranose **61** using 7% HCl MeOH solution (Scheme 17).[103] This reaction produced methyl 2,3,4-tri-*O*-benzyl-α-D-mannopyranoside **104** in 77% yield together with methyl 2,4-di-*O*-benzyl-α-D-mannopyranoside **105** that was isolated in 14% yield. An efficient method was developed for selective 5-*O*-opening of 3,5-*O*-di-*tert*-butylsilylene-D-galactofuranosides to give the corresponding 5-OH derivative.[173] Thiogalactofuranoside **106** was treated with 1.1 equiv. of TBAF at -20 °C for 40 h and gave 5-OH derivative **107** in 90% yield (Scheme 17).

Scheme 17. Regioselective ring opening of other cyclic groups.



4. Conclusions and outlook

The application of partially protected building blocks is fundamental to carbohydrate chemistry. The Glycoscience community has been working for many years on developing methods for the synthesis of building blocks. Some efforts to commercialize advanced synthetic intermediates have been made. Nevertheless, this remains an underdeveloped area of research. As Seeberger notes *"differentially protected monosaccharide building blocks is currently the bottleneck for chemical synthesis"*.[175] Indeed, most bench time in carbohydrate chemistry lab is dedicated to making building blocks. It is very common that researchers experience significant setbacks because they have to continue to remake building blocks. The synthesis of even simple compounds may require six, eight, ten or even more steps. As a result, poor accessibility to regioselectively protected building blocks hampers development of all methods, both traditional manual syntheses of glycans in solution and modern automation platforms.[176-178]

This review article summarizes advances in the area made towards the regioselective protection/partial deprotection with the major focus on the synthesis of mono- or di-hydroxyl derivatives in one step form the completely unprotected or uniformly protected precursors in one step. *"Unlike the synthesis of peptides and oligonucleotides, there are no universal building blocks or methods for the synthesis of all glycans"*.[179] It is also true for methods used for the synthesis of building blocks. Some excellent methods can only be applied to the synthesis of sugars of a particular series, whereas attempts to apply certain conventions to a broader range of substrates may fail even with one different stereocenter.

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ACKNOWLEDGMENT

This work was supported by the National Institute of General Medical Sciences (GM120673) and the National Science Foundation (CHE-1800350).

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