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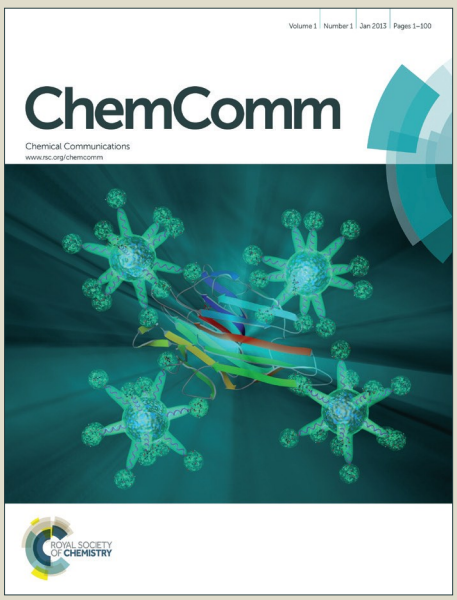

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FEATURE ARTICLE

Regioselective modification of unprotected glycosides

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Selective modification of unprotected carbohydrates is difficult due to the similar reactivity of the hydroxyl groups. In carbohydrate synthesis, therefore, even straightforward transformations often require multiple synthetic steps. The development of selective methods for carbohydrate modification is consequently highly desired. This review describes the methods for the regio- and chemoselective carbohydrate modification, with a focus on novel approaches that mainly apply transition metal catalysis and organocatalysis, and discusses the challenges and opportunities in this field.

Introduction

Carbohydrate chemistry is, because of its importance for biology, a vivid field of research. The chemical synthesis of carbohydrates is, next to glycosidic bond formation, dominated by hydroxyl group protection/deprotection strategies. These strategies are essential for the synthesis of oligosaccharides and carbohydrate-conjugates and as part of this steer the regio- and stereochemical outcome in glycosylation.[1] Although often masterpieces of control on chemical reactivity, carbohydrate synthesis frequently takes a considerable number of steps, also for the straightforward manipulation of commercial available monosaccharides. The requirement for protection hampers in addition the modification of naturally occurring oligosaccharides and conjugation reactions, for example to proteins, in aqueous environment. In order to trim these long synthetic routes, and to allow the application of available (oligo)saccharides, strategies for the selective modification of (partly) *unprotected* carbohydrates have been developed over the recent years. This review gives an overview of these methods and highlights the trends and challenges. The selective protection and non-protective modifications, in particular oxidation, of carbohydrate substrates will be discussed and the main focus lies on, but is not limited to, the protection, modification and oxidation of secondary hydroxyl groups, since their regioselective conversion is particularly challenging. Two reviews on the modification of unprotected carbohydrates have appeared, one from Taylor and Lee[2] focusing on catalyst controlled reactions and a short review from Saloranta *et al.*[3] dealing with potential of unprotected carbohydrates as starting materials in synthesis.

Although glycosylation of unprotected carbohydrates, either chemical or enzymatic, is an important topic in carbohydrate chemistry, it is outside the scope of this review. A review[4] and recent examples can be found elsewhere.[5–13] Furthermore, the modification of aminoglycoside antibiotics is not covered as reviews[14–16] including examples of impressive selectivites[17,18] can be found elsewhere.

Selective protection of glycosides

Here, the concepts used in selective protection, e.g. the inherent reactivity difference of the hydroxyl groups, and the application of metal-catalysis, organocatalysis and enzyme-mediated selective protection of carbohydrates and glycosides are discussed.

Inherent reactivity differences in glycoside hydroxyl groups

Primary hydroxyl groups are sterically less hindered compared to their secondary and tertiary counterparts and this can be used to selectively protect the primary hydroxyl group in glycosides. Bulky protecting groups such as tert-butyldimethylsilyl, tert-butyldiphenylsilyl,[19] triphenylmethyl (trityl)[20] and pivaloyl[21] react with good to high selectivity with primary hydroxyl groups in the presence of secondary ones.

Steric hindrance can also be utilized to some extent to discriminate between secondary hydroxyl groups. Jiang *et al.* have described a selective double acylation of several glycosides using pivaloyl chloride.[22] The isolated yields were generally high and selective protection of the primary hydroxyl group in combination with esterification at either the 2- or 3-position of several glycosides was reported (Scheme 1). The observed higher reactivity of equatorial hydroxyl groups adjacent to axial hydroxyl or alkoxy groups was rationalized with the argument that the bulky pivaloyl chloride approaches the molecule for steric reasons rather sideways than from the bottom or top. Equatorial hydroxyl groups adjacent to axial substituents would therefore be more accessible than equatorial ones flanked by other equatorial hydroxyl groups. Interestingly, when no axial hydroxyl group was present, as in **8**, selective protection of C6 and C3 was observed to give **9**.

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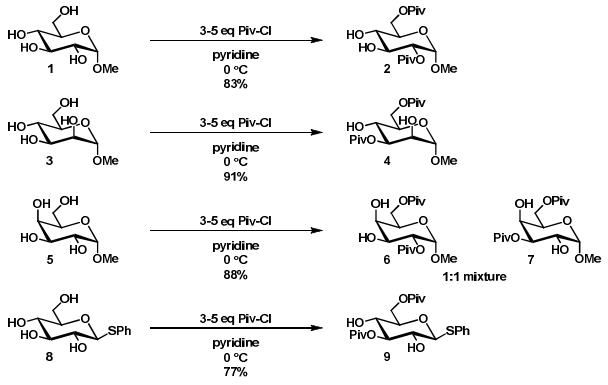
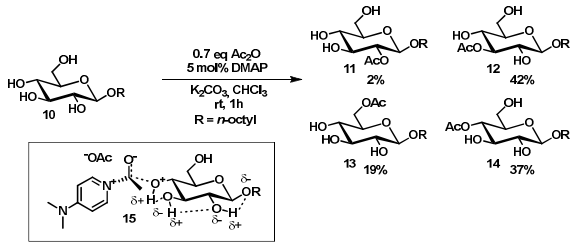


Scheme 1 Selective double protection of glucopyranosides

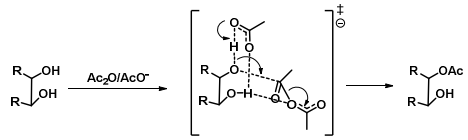
Hydrogen bond networks as a rationale for selective acylation have been proposed by Kurahasi *et al.*.[23] Treatment of octyl α- and β- glucopyranosides with a sub-stoichiometric amount of acetic anhydride and catalytic DMAP in chloroform gave the 3-, 4- and 6-acetyl protected glucosides **11**-**14** in a 2:2:1 ratio (Scheme 2). It was rationalized that the higher reactivity of the C3- and C4-hydroxyl group is due to the ability to spread the developing positive charge over a larger hydrogen bond network (**15**) in contrast to the C2-hydroxyl group.



Scheme 2 The effect of intramolecular hydrogen bonds on the acetylation of glucosides

Hydrogen bond networks play probably only a significant role in nonpolar solvents (and solvents that are no hydrogen bond acceptors or donors); Moitessier *et al.* showed a decrease in selectivity by switching from dichloromethane to tetrahydrofuran.[24] In solvents typically used in carbohydrate synthesis, like DMSO, DMF, MeOH and water, intramolecular hydrogen bonds are probably of minor importance due to hydrogen bonding to the solvent.

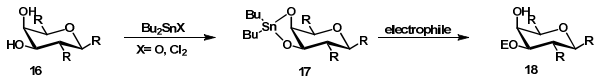
More selective acetylations of glycosides in water have been described by Lu *et al.*.[25] The primary hydroxyl group in a range of unprotected glycosides, triols and diols could be acetylated selectively using acetyl imidazole, with tetramethyl ammonium hydroxide as the catalyst, and isolated in moderate to good yields. Recently, Ren *et al.* described a method for the selective acetylation of glycosides using acetate catalysis.[26] A range of glycosides could be acetylated at either C6 in combination with C3 or at C3 in case of C6 protected glycosides and isolated in good yields. In order to understand the origin of the selectivity, the authors conducted intensive theoretical studies and propose that a bifurcated hydrogen bond together with the geometry in the transition state are responsible for the selectivity. In other words, stereo electronic effects and the inherent structure of the acetate/diol complex determines the selectivity (Scheme 3). In general, care should be taken in the analysis of the formed products as intramolecular acyl-shifts can be fast in particular with acetyl groups. In this case the authors could rule out acyl migration since it would lead to a different product.



Scheme 3 Proposed transition state, representing the bifurcated H-bond, for the acetate catalysed acetylation of diols.

Tin mediated protection of glycosides

Regioselective protection mediated by organotin compounds like tributyltin oxide and dibutyltin oxide is well-known.[27,28] Treatment of glycosides with e.g. dibutyltin oxide gives stannylene acetal **17** and subsequent treatment with an electrophile gives the modified glycoside **18**.

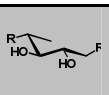
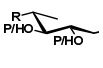


Scheme 4 General tin mediated protection of diols

Using this strategy, regioselective acylation,[29,30] alkylation,[31,32] silylation,[33] sulfonylation[30,34,35] and glycosylation[36,37] is possible.

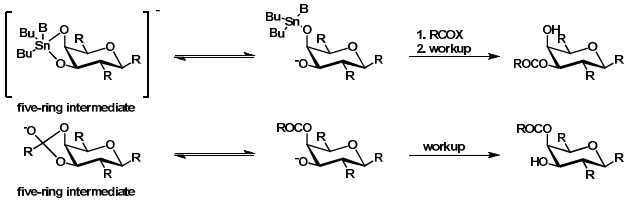
In general, protection via dibutyltin acetals gives 1) for cis-diols a selective protection of the equatorial hydroxyl group[29,38,39] 2) for trans-diols, with adjacent axial or equatorial substituents, a less pronounced selectivity,[40,41] 3) for trans-diols, with one axial and one equatorial adjacent substituent, selective protection of the equatorial hydroxyl group next to the axial substituent[42,43] and 4) a hydroxyl group next to a deoxy center is preferably protected (Table 1).[44]

Table 1 Regioselectivity in the organotin-mediated protection of glycosides

	cis[a]	trans[b]		trans[c]	cis/trans[d]
Diol					
selectivity					
	eq.	less selective		next to adjacent ax.	next to deoxy

[a] cis-diol, [b] trans-diol adjacent to both equatorial or axial substituents, [c] trans-diol adjacent to one axial and one equatorial substituent, [d] cis- or trans-diol adjacent to a deoxy-center, eq.: equatorial, ax.: axial, P: protecting group.

Recent studies by the group of Ramström[45] suggest that the selectivities in the organotin-mediated protection of carbohydrates are not related (as assumed before) to complex stannylene structures such as dimers and oligomers.[27] Ramström and coworkers studied the steric and stereo-electronic effects controlling the geometry of the five-membered ring intermediates (Scheme 5) in acyl migration-, neighboring group participation-, and orthoester transesterification reactions in pyranose rings. It turned out that these effects result in the same product, showing the same selectivity (e.g. acyl migration towards the axial hydroxyl group). Furthermore, the selectivity appeared to be contrary to the above mentioned selectivity in tin-mediated protection. As example, acyl migration as shown in Scheme 5 via the intermediate five-membered ring leads to the axial acylated glycoside, which is contrary to the equatorial acetylated glucoside obtained from the tin-mediated protection. The bond in the intermediate five-membered ring, which is broken in the tin-mediated protection and acyl migration is the same, the equatorial bond. This leads to the experimentally observed opposite selectivities and indicates that the bond breakage is dependent on the stereo-electronic effects of the carbohydrate.[45]



Scheme 5 Comparison of tin-mediated selective protection and acyl migration

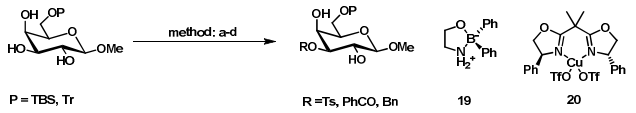
Worthwhile to mention is that the general trend observed for the selective protection mediated by organotin compounds is in accordance with the idea that the electrophile approaches the molecule from the side rather than from the top or bottom. This indicates a dependency on sterics rather than on electronics for the protection,[22] next to the formation of the stannylene acetals of triols or polyols which is probably dependent on the stereo-electronic effects in the carbohydrate.

Whereas the classical selective protection uses stoichiometric amounts of the organotin reagent to generate the stannylene acetal, recently several catalytic systems for the selective sulfonylation[34,35] and benzylation[38] have been described. The same selectivity as in the stoichiometric methods was observed, but the amount of toxic organotin reagent was reduced to 2-10 mol%.[34,35,38]

Metal- and metalloid-mediated protection of glycosides other than tin

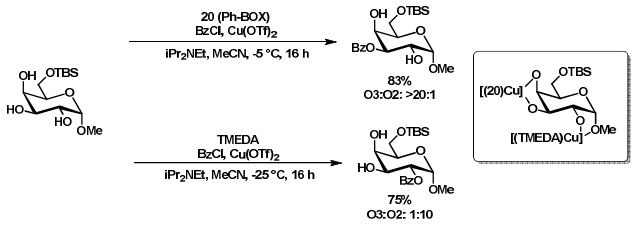
Other systems for the regioselective protection of diols have been reported based on organoboron,[46–48] organosilicon,[49,50] copper(II),[51–55] silver(I),[56] nickel(II)[57] and molybdenum(V) and (II) (Table 2).[58,59] These systems show often a similar selectivity as observed in tin mediated protections. This could indicate that the selectivity also depends on stereo-electronic effects in the carbohydrate[45] or as mentioned before solely depends on steric interactions between carbohydrate and electrophile.[22]

Table 2 Regioselectivity observed for tin-, boron-, copper- and molybdenum-catalyzed protections



	method	electrophile	yield	reference
a	1) 10 mol% Bu_2SnO, toluene, 100 °C, 1 h 2) K_2CO_3, TBAB, MeCN: DMF 10:1, 80 °C 3 h, P = TBDMS	BnBr	90	38
b	5-10 mol% **19**, *i*Pr_2NEt, MeCN, 20 - 40 °C, P = TBS	TsCl BnBr	Ts: 99% Bn: 74%	Ts[47] Bn[48]
c	10 mol% **20**, *i*Pr_2NEt, MeCN, -5 °C, 16 h, P = TBDMS	BzCl	80%	53
d	2 mol% $MoO_2(acac)_2$, sym-collidine, dioxane, rt, 6 h, P = Tr	BzCl	87%	59

Method **c** (Table 2) developed by Dong and coworkers, showed apart from the usual selectivity for a range of C6-TBS-protected methyl- and thioglycopyranosides, also a ligand-controlled protection of glycosides. The selectivity could be inverted by using tetramethylethylenediamine (TMEDA) instead of Ph-box ligand **20** (Scheme 6).[53] The authors reasoned that the complex with the amine-based ligand TMEDA prefers the 1,2-dioxy motif and the complex with the imine-ligand (**20**) the 3,4-diol motif, probably based on the change in electron density of the complex (Scheme 6).

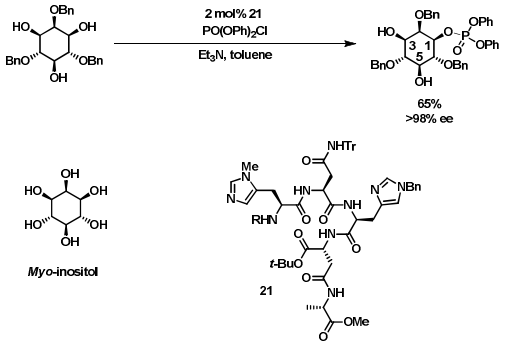


Scheme 6 Ligand controlled inversion of selectivity in the regioselective benzoylation of methyl glucopyranoside

Biomimetic and stereoselective catalysis in glycosides protection

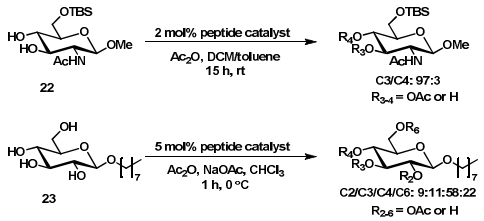
Recently, new biomimetic approaches for selective protection of carbohydrates have been developed. Miller *et al.* developed a "kinase-mimic" for the asymmetric phosphorylation of *myo*-inositol (which is a meso compound).[60,61] Catalyst **21**, a small peptide containing a histidine residue, was found through exhaustive screening of an elaborate peptide library. By

varying the catalyst, either position 1 or 3 of *myo*-inositol was phosphorylated in excellent enantiomeric excess and good isolated yields.[60]



Scheme 7 Peptide-catalyzed phosphorylation of *myo*-inositol

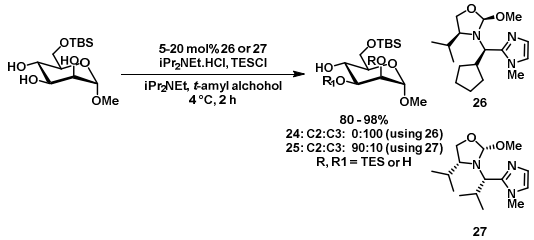
The concept was further expanded to accomplish the selective acylation of carbohydrate-derivatives. For the acylation of **22** one catalyst (from a library of 186) was found which allowed the selective acylation at C3 (97:3 in C3 versus C4) and for **23** the best catalyst gave a mixture of roughly 6:1:1:2 with acylation on C4 as the major product.[62]



Scheme 8 Peptide catalyzed acylation of glucopyranosyl derivatives

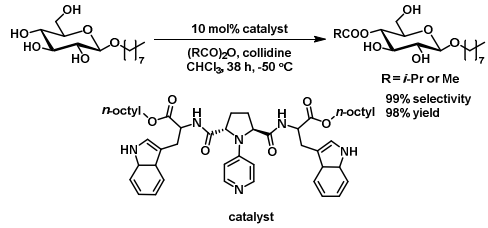
In the future the substrate scope should be extended to identify the success rate of this approach.

Another approach in the selective protection of carbohydrates by mimicking the active site of an enzyme has been reported by Sun *et al.*.[63] Here, selective silylation, acylation and sulfonylation of a range of C6 protected carbohydrate derivatives could be achieved by using catalyst **26** or **27**. Furthermore, catalyst-controlled protection of either the C2 or C3 position of C6-TBS protected methyl α-D-mannopyranoside was demonstrated (**24**/**25**, Scheme 9). Excellent isolated yields and selectivities were achieved.



Scheme 9 Selective silylation as described by Tan *et al.*[63]

Organocatalytic regioselective acylation at C4 of octyl-α glucopyranoside has been achieved by Kawabata *et al.*[64,65] with excellent selectivity and excellent isolated yield. High selectivities could be obtained only with chloroform as solvent, which requires the presence of an octyl or related substituent on the carbohydrate to ensure solubility.



Scheme 10 Organocatalytic acetylation of C4 as described by Kawabata *et al.*[64,65]

Enzyme-catalyzed protection of carbohydrates

Also enzyme-catalyzed methods for selective protection of carbohydrates are well-described and reviewed in the literature,[66–68] some examples will be discussed to illustrate trends and challenges.

Enzymatic acylation of carbohydrates is usually carried out by irreversible transesterification in organic solvents (pyridine, THF, dioxane) using enol esters,[69] trihaloethyl esters[70] and oxime esters.[71] Almost exclusive protection of the primary alcohol is obtained using lipases such as porcine pancreas lipase,[70] *Candida antartica* lipase[71] or *Candia cylindracea* lipase[69] for glycosides and reducing carbohydrates. Whereas for primary alcohol protected reducing carbohydrates the selectivity depends on the enzyme (reaction takes place at C2 or C3),[72] in case of primary alcohol protected glycosides the general trend is that α-glycosides are protected at C2 and β-glycosides at C3.[66] Di- and oligosaccharides can in some cases be selectively acetylated, here discrimination between several primary hydroxyl groups is possible also. Klibanov and coworkers described the protection of a range of di- and oligosaccharides using subtilisin (a non-specific protease) in DMF.[73]

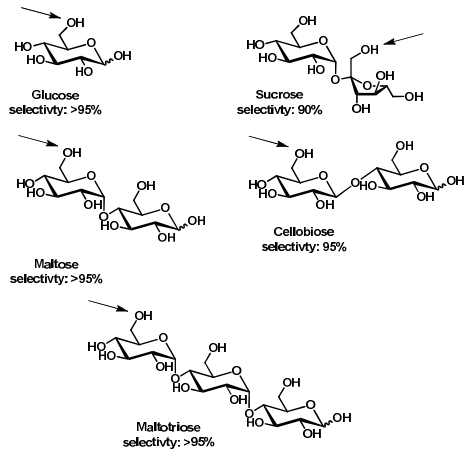


Figure 1 Regioselective acylation catalyzed by subtilisin as described by Klibanov and coworkers.[73] The site of acylation is indicated by an arrow.

The acylation of glucose, maltose, cellobiose and maltotriose is selective for the terminal C6OH, a similar preference is observed using chemical acylation.[74] The acylation of sucrose, however, is selective at the C1' hydroxyl group (Figure 1), contrary to what has been observed using chemical acylation.[75]

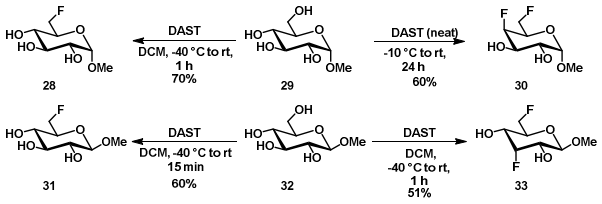
Selective non-protective modification of carbohydrates

The selective modification of single hydroxyl groups of unprotected carbohydrates is particularly difficult. Due to the inherent difference in steric hindrance, most studies concentrate on the modification of the primary hydroxyl group. Introduction of halogens is one of the most popular modifications of unprotected (or partial protected) carbohydrates. Here typical (but often modified) Appel and Mitsunobu conditions show good selectivities.

Halogen introduction

Fluorination

Selective fluorination of glycosides is known in the literature by treatment of the glycoside with diethylaminosulfur trifluoride (DAST). By careful selection of the reaction conditions, either mono- or difluorination has been achieved. The selectivity seems to be dependent on the stereochemistry at the anomeric center. Fluorination of methyl α-D-glucopyranoside (**29**) leads to 4,6-dideoxy-4,6-difluoroglycoside **30** while fluorination of methyl β-D-glucopyranoside **32** leads to 3,6-dideoxy-3,6-difluoroglucopyranoside **33**, selectively and with inversion of configuration (Scheme 11).[21,76,77] Therefore, C6 protected glycosides could be selectively fluorinated at C4 and C3 based on the anomeric configuration.[21]

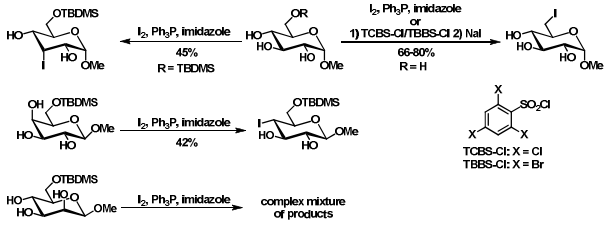


Scheme 11 Selective fluorination of methyl glucopyranoside

Iodination

Regioselective conversion of the primary alcohol group of a range of glycosides into the corresponding iodide has been described by Skaanderup *et al.*. Two methods were reported; treatment with triphenylphosphine and iodine (described earlier by the group of Garegg)[78] and conversion of the alcohol into the 2,4,6-tribromo- or 2,4,6-trichlorobenzenesulfonate prior to sodium iodide treatment (Scheme 12).[79] In both cases the C6-iodo-glycosides were isolated in moderate to good yields after purification by either reversed phase column chromatography or subsequent protection and normal phase column chromatography.

Regioselective iodination of *secondary* hydroxyl groups has been described for 1,2-isopropylidene protected fructopyranoside and psicopyranose and for C6 protected methyl-galacto- and -glucopyranoside.[80] The yields however were moderated at most and the corresponding mannopyranoside showed no selectivity (Scheme 12).



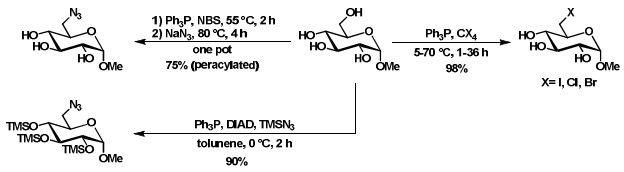
Scheme 12 Regioselective iodination of primary and secondary methyl glucosides

Bromination

Selective bromination of unprotected glycosides and other carbohydrates has been described in several reports in the literature. Usually, selective bromination at C6 is observed,[81,82] but also selective dibromination was shown.[83] Typical bromination conditions involve treatment with triphenyl phosphine and a brominating agent such as tribromoimidazole,[83] N-bromosuccinimide[84] or tetrabromomethane (Appel conditions).[82] Substitution of the latter by tetrachloromethane or tetraiodomethane enables selective chlorination and iodination at C6 (
Scheme 13).[82]

Azide introduction

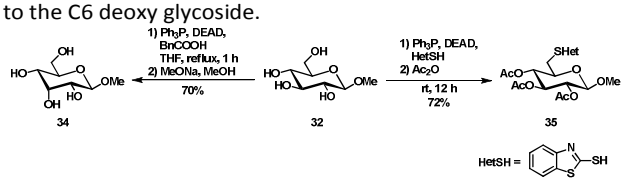
Further development of the method described by Hanessian *et al.* for the selective bromination of glycosides,[84] allowed the selective *in situ* transformation into the C6-azide using N-bromosuccinimide, triphenylphosphine and sodium azide. Extension of this method towards fully unprotected carbohydrates (reducing sugars) was done by Gouin *et al.*. Here, glycosyl azides are obtained also in combination with substitution on C6, however the isolated yields are rather poor (13-49%).[85] Next to typical Appel reaction-type modifications of glycosides and other carbohydrates, Mitsunobu conditions also allowed azidotrimethylsilylation of glycosides with azide introduction selectively on C6 and TMS-protection of the remaining secondary hydroxyl groups.[86]



Scheme 13 Selective Appel- and Mitsunobu-type halogen and azido introduction

Deoxygenation and epimerization of glycosides

A selective thiofunctionalization and subsequent desulfurization towards C6 deoxyglycosides has been published by Thiem *et al.*[87,88] Typical Mitsunobu conditions using diethylazodicarboxylate (DEAD), triphenylphosphine and 2-mercaptobenzothiazole as the nucleophile afforded thioether **35** selectively, which allowed further desulfurization to the C6 deoxy glycoside.



Scheme 14 Epimerisation and thiofunctionalization by Mitsunobu reaction

Epimerisation could be achieved by Mitsunobu reaction using benzoic acid as the nucleophile and subsequent saponification. Selective epimerization at C3 was observed to allose derivative **34** (the parallel Mitsunobu reaction at C6 is inconsequential). The substrate scope is limited to methyl β-glucopyranoside, as the α-anomer gave a mixture of products[89] and the epimerisation of methyl β-xylopyranoside was incomplete and the product could only be isolated in 20% yield.[90]

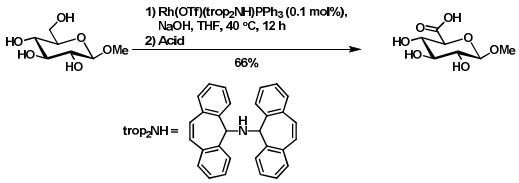
Selective oxidation of carbohydrates

The selective oxidation of carbohydrates is a valuable modification since it is a direct approach and allows in principle a range of further modifications without the need for protection of the remaining hydroxyl groups. Subsequent reactions of the carbonyl group, such as reductive amination, epimerization and deoxygenation, lead to carbohydrate derivatives without a protection / deprotection protocol. Several chemical and enzymatic methods are discussed here.

Chemical oxidation of glycosides

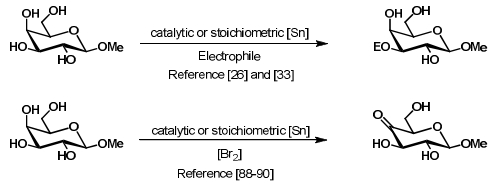
The selective chemical oxidation of the primary hydroxy group in pyranosides to the corresponding acid,[91,92] aldehyde[93] or internal acetal[94] using the 2,2,6,6-tetramethyl-1-piperidinyloxy radical (TEMPO) has been well described. The selectivity is solely based on steric hindrance.

The group of Grützmayer reported a rhodium catalyzed oxidation of primary hydroxyl groups in the presence of secondary hydroxyl groups. In that way also methyl β-D-glucopyranoside could be oxidized selectively to the glucoronic acid.[95]



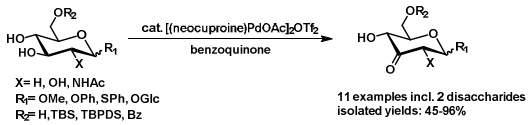
Scheme 15 Rhodium catalyzed oxidation of methyl β-D-glucopyranoside

In contrast, the selective oxidation of the secondary hydroxy groups is extremely difficult and barely known.[2] Tsuda *et al.* have described the selective oxidation of several methyl glycosides with stoichiometric bistributyltin oxide and bromine.[96,97] Although good yields were obtained and the regioselectivity could be steered by choice of the substrate, the use of stoichiometric amounts of organotin reagents limits the use of this approach. Recently a catalytic version of this reaction was published by Muramatsu using 2 mol% of dioctyltin dichloride and trimethylphenylammonium tribromide as the oxidant.[98] The selectivity is the same as described for the stoichiometric oxidation and isolated yields are high for galacto- but only mediocre for gluco-, manno- and rhamno-derivatives. Remarkably, the selectivity for the tin mediated oxidation appears to be in most cases reversed compared to the earlier described tin mediated selective protection. This could be explained by the theory mentioned earlier, where the electrophile or the oxidant enters rather from the side than from the top or bottom of the substrate.[22]



Scheme 16 Reversed selectivity in the protection and oxidation of methyl β-D-galactopyranoside using tin acetals

Recently our lab has developed a method for the palladium catalyzed oxidation of glucosides.[99] A range of glucosides including two disaccharides could be oxidized selectively in good to excellent isolated yields, with oxidation at C3 as sole product (Scheme 17).



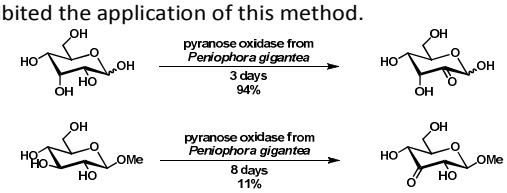
Scheme 17 Palladium catalyzed oxidation of glucosides[99]

Enzymatic oxidation of carbohydrates

Enzymatic oxidation of primary hydroxyl groups of carbohydrates has been described using uridine 5′-diphosphoglucose dehydrogenase[100] and galactose oxidase.[101] The oxidation of uridine 5′-diphosphoglucose by uridine 5′-diphosphoglucose dehydrogenase has been described by Whitesides *et al.*. Unfortunately, the substrate scope has not been investigated and the rather specific substrate limits the general use of this approach. The oxidation by galactose oxidase as described by Kieboom *et al*. allowed selective oxidation to the C6-aldehyde. The scope of the reaction, however is limited to galactose derivatives (including the disaccharides lactose and melibiose).[101]

The enzymatic oxidation of secondary alcohols of several carbohydrates, including glycosides, has been described by

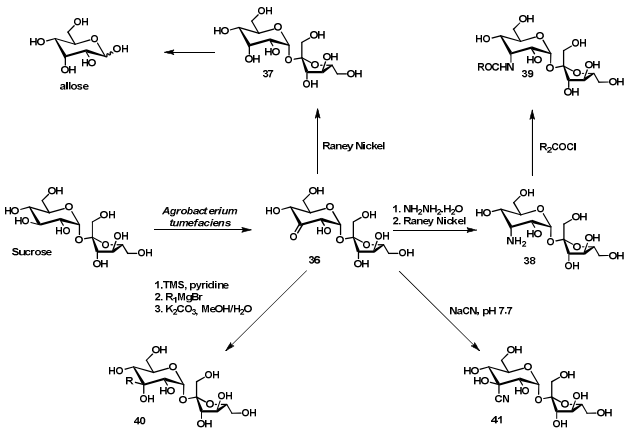
Köpper and co-workers.[102] By using pyranose oxidase, selective oxidation at C2 and C3 was achieved, depending on the substrate. For reducing carbohydrates, the yields were generally high, but for glycosides low yields were observed. The activity of this enzyme is rather low (Scheme 18). This and the substrates being restricted to the β-anomer, have prohibited the application of this method.



Scheme 18 Oxidation of allose and methyl- β-D-glucopyranoside by pyranose oxidase

Another enzymatic approach has been described in the group of Haltrich, in which a fungal pyranose dehydrogenase was able to oxidize a series of carbohydrates at C1, C2, C3, C1,3', or C2,3'.[103,104] Yields of isolated products were not reported, however.

The first selective enzymatic oxidation of disaccharides was achieved by De Ley and coworker in 1960.[105] Among others, sucrose could be oxidized selectively at C3 by fermentation with *Agrobacterium tumefaciens*. The group of Buchholz elaborated on this and optimized this fermentation process to yield 3-ketosucrose **36** in 70% on kilogram scale.[106] Furthermore, a series of modifications of 3-ketosucrose including the conversion into allosucrose **37**,[107] allose,[107] 3-amino-3-deoxy-α-D-allopyranosyl β-D-fructofuranoside (**38**),[108,109] corresponding polymer building blocks (**39**),[109] surfactants (**39**),[109] sucrose-amino acid conjugates (**39**),[108] alkylated sucrose via Grignard-reaction (**40**)[109] and the cyanohydrin **41**[110] could be obtained. The derivatives were synthesized usually without the use of protecting groups in 2-4 steps and could be isolated in good yields. This cluster of reports forms a rare example of the power of a selective oxidation method for carbohydrates (Scheme 19).



Scheme 19 Derivatization of 3-ketosucrose

The substrate scope comprises the disaccharides sucrose, isomaltulose,[111] leucrose,[112] maltose and lactose.[113]

Conclusions

Considerable steps have been made in the recent years regarding the selective modification of carbohydrates. However, although different methods and catalysts are used, the results, and in particular the selectivities, are mostly identical. So, the modification of the C6 position is, due to the smaller steric hindrance, a rather straightforward task, but the modification of C4 is hardly observed. This makes some derivatives readily accessible by a variety of methods whereas others only by long and time consuming synthetic routes.

Part of the challenge faced is that apparently the regioselective functionalization of the various secondary hydroxyl groups depends on stereo-electronic effects of the carbohydrate. From a synthetic point of view a rather unfortunate situation since it seems to hamper the possibility for catalyst control. The Holy Grail in carbohydrate functionalization; a general strategy for the discrimination of any specific hydroxyl group in a carbohydrate is therefore still a huge challenge and it has to been shown whether it is at all possible.

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Notes and references

1 J. Guo and X.-S. Ye, *Molecules*, 2010, **15**, 7235–7265.
2 D. Lee and M. Taylor, *Synthesis (Stuttg).*, 2012, **44**, 3421–3431.
3 T. Saloranta and R. Leino, *Synlett*, 2015.
4 S. Hanessian and B. Lou, *Chem. Rev.*, 2000, **100**, 4443–4464.
5 L. J. G. Edgar, S. Dasgupta and M. Nitz, *Org. Lett.*, 2012, **14**, 4226–4229.
6 A. V Gudmundsdottir and M. Nitz, *Org. Lett.*, 2008, **10**, 3461–3463.
7 T. Tanaka, W. C. Huang, M. Noguchi, A. Kobayashi and S. Shoda, *Tetrahedron Lett.*, 2009, **50**, 2154–2157.
8 P. Rawat, M. Kumar, N. Rahuja, D. S. Lal Srivastava, A. K. Srivastava and R. Maurya, *Bioorg. Med. Chem. Lett.*, 2011, **21**, 228–233.
9 Y. Ichikawa, S. Kusaba, T. Minami, Y. Tomita, K. Nakano and H. Kotsuki, *Synlett*, 2011, **2011**, 1462–1466.
10 E. Brachet, J.-D. Brion, M. Alami and S. Messaoudi, *Chemistry*, 2013, **19**, 15276–15280.
11 T. Tanaka, H. Nagai, M. Noguchi, A. Kobayashi and S.-I. Shoda, *Chem. Commun. (Camb).*, 2009, 3378–3379.
12 N. Yoshida, M. Noguchi, T. Tanaka, T. Matsumoto, N. Aida, M. Ishihara, A. Kobayashi and S. Shoda, *Chem. Asian J.*, 2011, **6**, 1876–85.
13 D. Lim, M. A. Brimble, R. Kowalczyk, A. J. A. Watson and A. J. Fairbanks, *Angew. Chem. Int. Ed. Engl.*, 2014, **53**, 11907–11.
14 J. L. Houghton, K. D. Green, W. Chen and S. Garneau-Tsodikova, *Chembiochem*, 2010, **11**, 880–902.
15 D. P. Arya, *Aminoglycoside antibiotics: from chemical biology to drug discovery*, WILEY-VCH Verlag, New Jersey, 2007.

16 J. Zhou, G. Wang, L.-H. Zhang and X.-S. Ye, *Med. Res. Rev.*, 2007, **27**, 279–316.
17 A. A. Bastian, A. Marcozzi and A. Herrmann, *Nat. Chem.*, 2012, **4**, 789–793.
18 A. A. Bastian, E. M. Warszawik, P. Panduru, C. Arenz and A. Herrmann, *Chemistry*, 2013, **19**, 9151–9154.
19 I. Fokt, S. Skora, C. Conrad, T. Madden, M. Emmett and W. Priebe, *Carbohydr. Res.*, 2013, **368**, 111–119.
20 L. Zou, R. B. Zheng and T. L. Lowary, *Beilstein J. Org. Chem.*, 2012, **8**, 1219–1226.
21 P. J. Card and G. S. Reddy, *J. Org. Chem.*, 1983, **48**, 4734–4743.
22 L. Jiang and T.-H. Chan, *J. Org. Chem.*, 1998, **63**, 6035–6038.
23 T. Kurahashi, T. Mizutani and J. Yoshida, *J. Chem. Soc. Perkin Trans. 1*, 1999, 465–474.
24 N. Moitessier, P. Englebienne and Y. Chapleur, *Tetrahedron*, 2005, **61**, 6839–6853.
25 Y. Lu, P. Wei, Y. Pei, H. Xu, X. Xin and Z. Pei, *Green Chem.*, 2014.
26 Y. Zhou, M. Rahm, B. Wu, X. Zhang, B. Ren and H. Dong, *J. Org. Chem.*, 2013, **78**, 11618–22.
27 S. David and S. Hanessian, *Tetrahedron*, 1985, **41**, 643–663.
28 T. B. Grindley, *Advances in Carbohydrate Chemistry and Biochemistry Volume 53*, Elsevier, 1998, vol. 53.
29 F. Peri, L. Cipolla and F. Nicotra, *Tetrahedron Lett.*, 2000, **41**, 8587–8590.
30 K. Takeo and K. Shibata, *Carbohydr. Res.*, 1984, **133**, 147–151.
31 V. K. Srivastava and C. Schuerch, *Tetrahedron Lett.*, 1979, **20**, 3269–3272.
32 L. Ballell, J. A. F. Joosten, F. A. el Maate, R. M. J. Liskamp and R. J. Pieters, *Tetrahedron Lett.*, 2004, **45**, 6685–6687.
33 A. Glen, D. A. Leigh, R. P. Martin, J. P. Smart and A. M. Truscello, *Carbohydr. Res.*, 1993, **248**, 365–369.
34 M. J. Martinelli, R. Vaidyanathan, J. M. Pawlak, N. K. Nayyar, U. P. Dhokte, C. W. Doecke, L. M. H. Zollars, E. D. Moher, V. Van Khau and B. Košmrlj, *J. Am. Chem. Soc.*, 2002, **124**, 3578–3585.
35 M. J. Martinelli, R. Vaidyanathan and V. Van Khau, *Tetrahedron Lett.*, 2000, **41**, 3773–3776.
36 G. Hodosi and P. Kováč, *J. Am. Chem. Soc.*, 1997, **119**, 2335–2336.
37 G. Hodosi and P. Kováč, *Carbohydr. Res.*, 1997, **303**, 239–243.
38 H. Xu, Y. Lu, Y. Zhou, B. Ren, Y. Pei, H. Dong and Z. Pei, *Adv. Synth. Catal.*, 2014, **356**, 1735–1740.
39 F.-Y. Dupradeau, J. Prandi and J.-M. Beau, *Tetrahedron*, 1995, **51**, 3205–3220.
40 F. Dasgupta and P. J. Garegg, *Synthesis (Stuttg).*, 1994, **1994**, 1121–1123.
41 H. Qin and T. B. Grindley, *J. Carbohydr. Chem.*, 1996, **15**, 95–108.
42 D. D. Manning, X. Hu, P. Beck and L. L. Kiessling, *J. Am. Chem. Soc.*, 1997, **119**, 3161–3162.
43 S. David and A. Malleron, *Carbohydr. Res.*, 2000, **329**, 215–218.
44 R. S. Coleman and J. R. Fraser, *J. Org. Chem.*, 1993, **58**, 385–392.
45 H. Dong, Y. Zhou, X. Pan, F. Cui, W. Liu, J. Liu and O. Ramström, *J. Org. Chem.*, 2012, **77**, 1457–1467.
46 D. Lee and M. S. Taylor, *J. Am. Chem. Soc.*, 2011, **133**, 3724–3727.
47 D. Lee, C. L. Williamson, L. Chan and M. S. Taylor, *J. Am. Chem. Soc.*, 2012, **134**, 8260–8267.
48 L. Chan and M. S. Taylor, *Org. Lett.*, 2011, **13**, 3090–3093.
49 Y. Zhou, O. Ramström and H. Dong, *Chem. Commun. (Camb).*, 2012, **48**, 5370–5372.
50 C.-C. Wang, J.-C. Lee, S.-Y. Luo, S. S. Kulkarni, Y.-W. Huang, C.-C. Lee, K.-L. Chang and S.-C. Hung, *Nature*, 2007, **446**, 896–899.
51 H. M. . Osborn, V. A. Brome, L. M. Harwood and W. G. Suthers, *Carbohydr. Res.*, 2001, **332**, 157–166.
52 C. L. Allen and S. J. Miller, *Org. Lett.*, 2013, **15**, 6178–6181.
53 I.-H. Chen, K. G. M. Kou, D. N. Le, C. M. Rathbun and V. M. Dong, *Chemistry*, 2014, **20**, 5013–5018.
54 E. V Evtushenko, *Carbohydr. Res.*, 2012, **359**, 111–119.
55 E. V. Evtushenko, *J. Carbohydr. Chem.*, 2015, **34**, 41–54.
56 S. Malik, V. A. Dixit, P. V Bharatam and K. P. R. Kartha, *Carbohydr. Res.*, 2010, **345**, 559–564.
57 U. B. Gangadharmath and A. V Demchenko, *Synlett*, 2004, 2191–2193.
58 E. V. Evtushenko, *Synth. Commun.*, 2006, **36**, 1593–1599.
59 E. V. Evtushenko, *J. Carbohydr. Chem.*, 2010, **29**, 369–378.
60 B. R. Sculimbrene, A. J. Morgan and S. J. Miller, *J. Am. Chem. Soc.*, 2002, **124**, 11653–11656.
61 B. R. Sculimbrene and S. J. Miller, *J. Am. Chem. Soc.*, 2001, **123**, 10125–10126.
62 K. S. Griswold and S. J. Miller, *Tetrahedron*, 2003, **59**, 8869–8875.
63 X. Sun, H. Lee, S. Lee and K. L. Tan, *Nat. Chem.*, 2013, **5**, 790–795.
64 T. Kawabata, W. Muramatsu, T. Nishio, T. Shibata and H. Schedel, *J. Am. Chem. Soc.*, 2007, **129**, 12890–12895.
65 H. Takeuchi, K. Mishiro, Y. Ueda, Y. Fujimori, T. Furuta and T. Kawabata, *Angew. Chemie*, 2015, **127**, 6275–6278.
66 D. Kadereit and H. Waldmann, *Chem. Rev.*, 2001, **101**, 3367–3396.
67 B. La Ferla, *Monatshefte für Chemie / Chem. Mon.*, 2002, **133**, 351–368.
68 H. G. Park, J. H. Do and H. N. Chang, *Biotechnol. Bioprocess Eng.*, 2003, **8**, 1–8.
69 E. W. Holla, *Angew. Chemie Int. Ed. English*, 1989, **28**, 220–221.
70 W. J. Hennen, H. M. Sweers, Y. F. Wang and C. H. Wong, *J. Org. Chem.*, 1988, **53**, 4939–4945.
71 R. Pulido and V. Gotor, *Carbohydr. Res.*, 1994, **252**, 55–68.
72 M. Therisod and A. M. Klibanov, *J. Am. Chem. Soc.*, 1987, **109**, 3977–3981.
73 S. Riva, J. Chopineau, A. P. G. Kieboom and A. M. Klibanov, *J. Am. Chem. Soc.*, 1988, **110**, 584–589.
74 74R. Khan, *The Chemistry of Maltose*, Elsevier, 1981, vol. 39.
75 R. Khan, *Pure Appl. Chem.*, 1984, **56**, 833–844.
76 C. W. Somawardhana and E. G. Brunngraber, *Carbohydr. Res.*, 1983, **121**, 51–60.
77 P. J. Card, *J. Org. Chem.*, 1983, **48**, 393–395.
78 P. J. Garegg, *Pure Appl. Chem.*, 1984, **56**, 845–858.
79 P. R. Skaanderup, C. S. Poulsen, L. Hyldtoft, M. R. Jørgensen and R. Madsen, *Synthesis (Stuttg).*, 2002, 1721–1727.
80 A.-C. Simao, S. Silva, A. P. Rauter, P. Rollin and A. Tatibouët, *European J. Org. Chem.*, 2011, **2011**, 2286–2292.
81 W. Xue and L. Zhang, *Chinese J. Chem.*, 2012, **30**, 1429–1432.
82 A. Kashem, M. Anisuzzaman and R. L. Whistler, *Carbohydr. Res.*, 1978, **61**, 511–518.
83 B. Classon, P. J. Garegg and B. Samuelsson, *Can. J. Chem.*, 1981, **59**, 339–343.
84 S. Hanessian, M. M. Ponpipom and P. Lavallee, *Carbohydr. Res.*, 1972, **24**, 45–56.
85 S. G. Gouin and J. Kovensky, *Tetrahedron Lett.*, 2007, **48**, 2875–2879.
86 M. R. L, S. K. Yousuf, D. Mukherjee and S. C. Taneja, *Org. Biomol. Chem.*, 2012, **10**, 9090–9098.
87 I. Dancy, L. Laupichler, P. Rollin and J. Thiem, *Liebigs Ann. der Chemie*, 1993, **1993**, 343–350.
88 I. Dancy, L. Laupichler, P. Rollin and J. Thiem, *Synlett*, 1992, 283–284.

89 M. Kim, B. Grzeszczyk and A. Zamojski, *Carbohydr. Res.*, 1999, **320**, 244–249.
90 90K. Weinges, S. Haremsa and W. Maurer, *Carbohydr. Res.*, 1987, **164**, 453–458.
91 N. J. Davis and S. L. Flitsch, *Tetrahedron Lett.*, 1993, **34**, 1181– 1184.
92 A. De Nooy, A. Besemer and H. Van Bekkum, *Tetrahedron*, 1995, **51**, 8023–8032.
93 T. Breton, G. Bashiardes, J.-M. Léger and K. B. Kokoh, *European J. Org. Chem.*, 2007, **2007**, 1567–1570.
94 94A. Gassama and N. Hoffmann, *Adv. Synth. Catal.*, 2008, **350**, 35–39.
95 M. Trincado, K. Kühlein and H. Grützmacher, *Chemistry*, 2011, **17**, 11905–11913.
96 Y. Tsuda, M. Hanajima, N. Matsuhira, Y. Okuno and K. Kanemitsu, *Chem. Pharm. Bull.*, 1989, **37**, 2344–2350.
97 H.-M. Lui, Y. Sato and Y. Tsuda, *Chem. Pharm. Bull.*, 1996, **41**, 491–501.
98 W. Muramatsu, *Org. Lett.*, 2014, **16**, 4846–4849.
99 M. Jäger, M. Hartmann, J. G. de Vries and A. J. Minnaard, *Angew. Chem. Int. Ed. Engl.*, 2013, **52**, 7809–7812.
100E. J. Toone, E. S. Simon and G. M. Whitesides, *J. Org. Chem.*, 1991, **56**, 5603–5606.
101A. Siebum, A. van Wijk, R. Schoevaart and T. Kieboom, *J. Mol. Catal. B Enzym.*, 2006, **41**, 141–145.
102S. Freimund, A. Huwig, F. Giffhorn and S. Köpper, *Chem. - A Eur. J.*, 1998, **4**, 2442–2455.
103J. Volc, P. Sedmera, P. Halada, G. Daniel, V. Přikrylová and D. Haltrich, *J. Mol. Catal. B Enzym.*, 2002, **17**, 91–100.
104P. Sedmera, P. Halada, E. Kubátová, D. Haltrich, V. Přikrylová and J. Volc, *J. Mol. Catal. B Enzym.*, 2006, **41**, 32–42.
105M. J. Bernaerts and J. De Ley, *J. Gen. Microbiol.*, 1960, **22**, 129–136.
106E. Stoppok and K. Buchholz, *Carbohydrate Biotechnology Protocols (Methods in Biotechnology)*, Humana Press, Totowa, NY, USA, 1999th edn., 1999.
107V. Timme, R. Buczys, K. Buchholz and B. Germany, *Starch - Stärke*, 1998, **50**, 29–32.
108J. Anders, R. Buczys, E. Lampe, M. Walter, E. Yaacoub and K. Buchholz, *Carbohydr. Res.*, 2006, **341**, 322–331.
109M. Pietsch, M. Walter and K. Buchholz, *Carbohydr. Res.*, 1994, **254**, 183–194.
110V. Timme, R. Buczys and K. Buchholz, *Chemie Ing. Tech.*, 2001, **73**, 1357–1361.
111M. Noll-Borchers and K. Buchholz, *Biotechnol. Lett.*, 1993, **15**, 139–144.
112J. Walter, E. Stoppok and K. Buchholz, *Chemie Ing. Tech.*, 1991, **63**, 631–633.
113E. Stoppok, J. Walter and K. Buchholz, *Appl. Microbiol. Biotechnol.*, 1995, **43**, 706–712.