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Uronic Acids in Oligosaccharide Synthesis

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This Microreview covers some general strategies for the preparation of uronic acid residues and their incorporation into anionically charged oligosaccharides. Two distinct strategies can be recognized: (1) glycosylation followed by oxidation, and (2) oxidation of the monosaccharide building blocks followed by glycosylation. Examples of both strategies are discussed, with a focus on the advantages and disadvantages of the respective strategies.

Introduction

Uronic acids are an important class of monosaccharides and are defined as aldohexoses in which the primary alcohol is oxidized to a carboxylic acid.[1,2] Polysaccharides containing uronic acid entities are widespread in nature and display an array of physical properties and biological functions. A well-known class of polysaccharides are the glycosaminoglycans (GAGs), which are composed of uronic acids linked to 2-acetamido-2-deoxyglycosides in an alternating fashion.[3,4] Perhaps the best known member of the GAG family is heparin, containing both D-glucuronic acid and L-iduronic acid moieties, interspaced with *N*-acetyl-D-glucosamine residues.[5] Other GAGs are the hyaluronan[6] (assembled from D-glucuronic acid and *N*-acetyl-D-glucosamine) and the chondroitin[7] (D-glucuronic acid, L-iduronic acid, and *N*-acetyl-D-galactosamine) polysaccharides. A structurally and functionally distinct class of polysaccharides are the homoglycuronans, which contain only uronic acid residues. Examples are alginate[8] (composed of D-mannuronic acid and L-guluronic acid) and pectin[9,10] (D-galacturonic acid), both of which are often used in the food industry.

The structural complexity of polysaccharides that contain uronic acid, combined with their diverse biological properties, has inspired many research groups to study their chemical synthesis. In general, the aim of these studies is the development of methodologies to introduce the required interglycosidic linkages and to apply these to construct oligosaccharides of a defined length and substitution pattern. These are in turn used in structure–function studies to determine the structural features that underlie their biological properties. The potential of this general strategy is best illustrated by the extensive work on heparin leading to the identification of a unique pentasaccharide sequence that provides the basis for the anti-blood coagulation properties that characterize the natural polysaccharide.[3b,11] Ensuing combined efforts at the Organon and Sanofi laboratories led to the development of a closely related pentasaccharide as a drug (Arixtra®) for the treatment of thrombotic disease.

In this Microreview some general strategies for the preparation and incorporation of uronic acid residues in anionically charged oligosaccharides are discussed.[12] Two distinct strategies can be recognized. In most literature examples a target oligosaccharide is assembled from aldose building blocks, after which the appropriate primary hydroxy groups are oxidized to carboxylate groups prior to or after global deprotection (post-glycosidation oxidation). The alternative general strategy entails the use of uronic acid building blocks in the glycosylation scheme (pre-glycosidation oxidation). Examples of both strategies are discussed, with a focus on the advantages and disadvantages of the respective strategies.

Post-Glycosidation Oxidation

The most frequently used method for the construction of acidic oligosaccharides is the initial construction of the oligosaccharide followed by oxidation of (specific) primary hydroxy groups to the desired carboxylic acid functionalities. According to this post-glycosidation approach, Ogawa and co-workers investigated the synthesis of an endogenous phytoalexin elicitor-active α-(1→4)-dodecagalacturonic acid extracted from plant cell wall isolates (Scheme 1).[13–15] Starting from the fluoride donors **1** and **3** and acceptor **2**, dodecasaccharide **4** was assembled in a straightforward manner under Mukaiyama coupling conditions ($SnCl_2$, $AgClO_4$).[16] All glycosylation reactions proceeded predominantly α-stereoselectively, which was due to coordination of

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diethyl ether to the β-face, directing the acceptor to attack from the α-side.[17,18] The secondary alcohol groups were masked as benzyl ethers whereas the primary positions destined for oxidation were capped with acetyl groups. After full construction of dodecasaccharide **4**, selective liberation of the primary hydroxy groups by treatment with base gave dodecaol **5** in good yield. Swern oxidation[19,20] of dodecasaccharide **5** to the intermediate aldehyde and further oxi-

Leendert van den Bos (March 1, 1979) graduated as a synthetic organic chemist at Leiden University in 2002. From 2002 until 2006 he conducted his Ph.D. research in the group of Gijs van der Marel and Herman Overkleeft. He recently developed an independent strategy for the chemoselective oxidation of partially unprotected thioglycosides to provide the corresponding thioglucuronides and their application as donor and acceptor in oligosaccharide synthesis. He defended his thesis on April 18, 2007 and is currently working as a postdoctoral fellow on a collaborative project between Crucell NV and Leiden University.

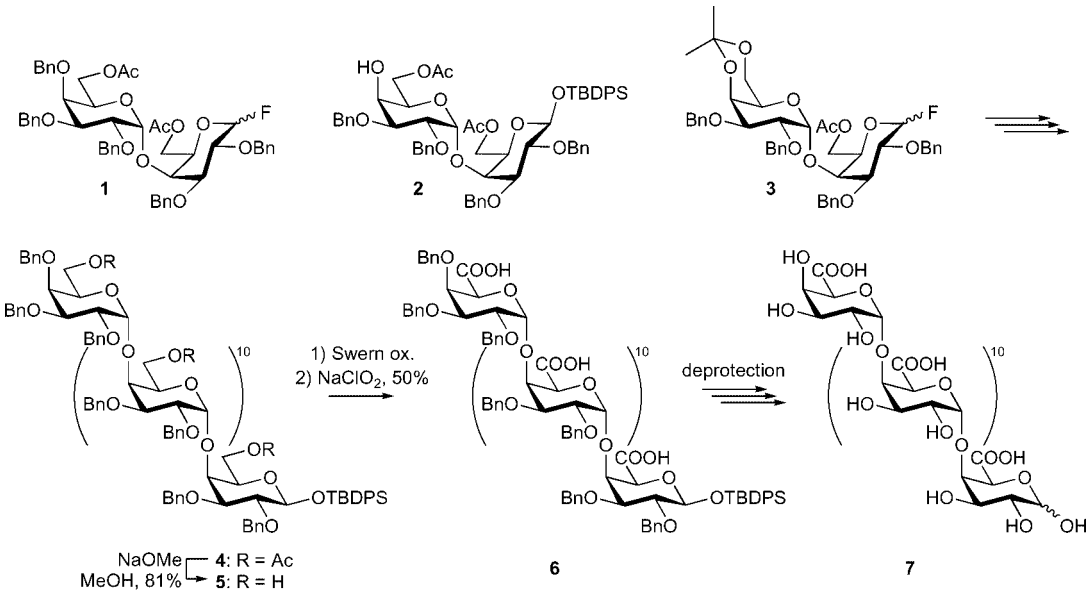
Jeroen Codée (July 30, 1975) studied chemistry at Leiden University, where he received his master's degree in synthetic organic chemistry in 1999. He continued his education as a Ph.D. student at Leiden University, under the guidance of Jacques van Boom and Stan van Boeckel and elaborated the subject of oligosaccharide synthesis with a focus on thioglycosides and glycosaminoglycans. He obtained his Ph.D. degree in 2004 and went for a two-year postdoctoral stay in the laboratory of Peter Seeberger at the ETH in Zürich. In September 2006 he received a VENI-grant, which allows him to investigate the synthesis and biological properties of alginate oligosaccharides. His research interests include glycobiology, carbohydrate chemistry, and automated synthesis.

Remy Litjens (May 3, 1974) studied chemistry in Leiden and continued to do his Ph.D. research at the same university. Recently, he was granted his Ph.D. degree on his thesis describing the use of sulfonium salt activation in oligosaccharide synthesis. Together with Jeroen Codeé and Leendert van den Bos he developed and applied several new chemoselective and orthogonal glycosylation strategies based on the use of sulfonium activator systems in combination with thioglycosides and hemiacetals. He is currently working as a research associate at the Lead Discovery Unit of Organon Oss, The Netherlands.

Jasper Dinkelaar (November 22, 1979) graduated in 2003 at the University of Amsterdam as a synthetic organic chemist. In the same year he continued his research in the laboratory of Gijs van der Marel and Herman Overkleeft, where he now works on the development of new glycosylation methodologies and the synthesis of glycosaminoglycan and alginate oligosaccharides.

Herman Overkleeft (April 12, 1969) received his Ph.D. education at the University of Amsterdam under the guidance of Upendra Pandit. After receiving his Ph.D. degree on the subject of the synthesis and application of iminosugar glycosidase inhibitors (1997), he moved to Leiden University for a two-year postdoctoral research stay in the group of Gijs van der Marel and Jacques van Boom. From 1999 to 2001 he was a postdoctoral fellow at Harvard Medical School, Department of Pathology, where he worked with Hidde Ploegh in the emerging area of chemical biology. In July 2001 he was appointed to the chair in bioorganic chemistry at Leiden University, where he currently is. His research interests include bioorganic chemistry, glycobiology, and organic synthesis.

Gijs van der Marel (April 3, 1952) received his training at Leiden University, where he graduated in 1977. He did his Ph.D. studies on the subject of DNA oligonucleotide synthesis together with Jacques van Boom and received his Ph.D. degree in 1981. He continued his career at Leiden University, first as Assistant Professor, then as Associate Professor and, since January 2005, as Full Professor in Organic Synthesis. His research is focused on synthetic aspects of biopolymers, primarily nucleic acids, peptides, and carbohydrates, their hybrid structures, and their synthetic analogues.

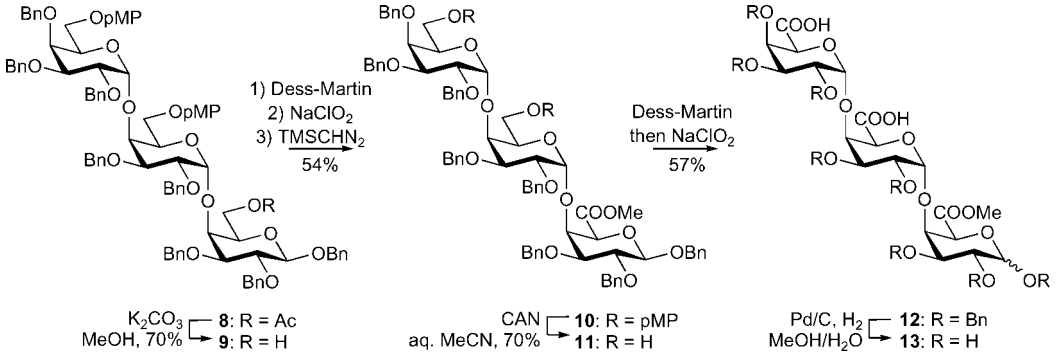


Scheme 1. Ogawa's synthesis of an α-(1→4)-dodecagalacturonic acid **7**.

dation with a freshly prepared solution of $NaClO_2$ in water afforded the expected dodecacarboxylic acid **6** in 50% overall yield. Deprotection and purification afforded the dodecasaccharide **7**.

More recently, Madsen's group published a procedure for the synthesis of defined tri- and hexasaccharide fragments of the homogalacturonans.[21] Here, orthogonality between the primary and secondary alcohol positions was ensured by application of *para*-methoxyphenyl (pMP) and benzyl protective groups. For the oxidation of all primary positions the two-step Dess–Martin periodinane[22]/$NaClO_2$ protocol was employed. Oxidation efficiencies lower than those of the Swern/$NaClO_2$ protocol used by Ogawa's group were found, especially in the case of larger oligosaccharides.

In a related study to elucidate the cleavage pattern of pectic enzymes, Madsen's group embarked on the synthesis of defined, partly methyl-esterified fragments of the homogalacturonan polysaccharide.[23] This pectic polysaccharide basically forms the primary cell wall matrixes of all land plants and contributes both to the physical integrity and to the physiological status of the cell walls.[24] Homogalacturonan is thought to be deposited in cell walls in a highly methyl-esterified form but can subsequently be de-esterified by pectin methyl esterases. Hence, the functionality of the pectin polysaccharide is largely determined by the pattern and degree of methyl esterification of the galacturonic acid backbone. In order to enable the introduction of a partial methyl-esterification pattern in synthetic pectin oligosaccharides, the protective group strategy was slightly expanded. Acetyl protective groups were installed on the hydroxy groups intended for conversion into methyl esters, and *para*-methoxyphenyl protective groups were used for the hydroxy groups intended for conversion into free carboxylic acids. By varying the acetyl and *para*-methoxyphenyl protection along the oligosaccharide backbone, all the different partly methyl-esterified oligosaccharides can in theory be obtained. A typical example is depicted in Scheme 2 and commences with trisaccharide **8**, which was synthesized in a straightforward manner by the *n*-pentenyl glycosylation technique. After deacetylation (**8** → **9**), the two-step Dess–Martin periodinane/$NaClO_2$ oxidation protocol was applied. Treatment of the intermediate carboxylic acid with trimethylsilyldiazomethane afforded methyl ester **10**. Subsequent cleavage of both *para*-methoxyphenyl ethers

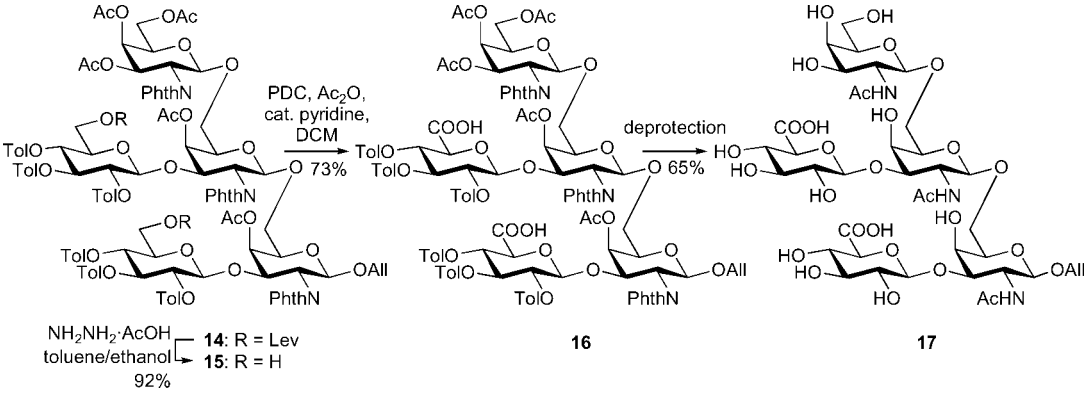


Scheme 2. Madsen's orthogonal approach towards partly methyl-esterified homogalacturonans.

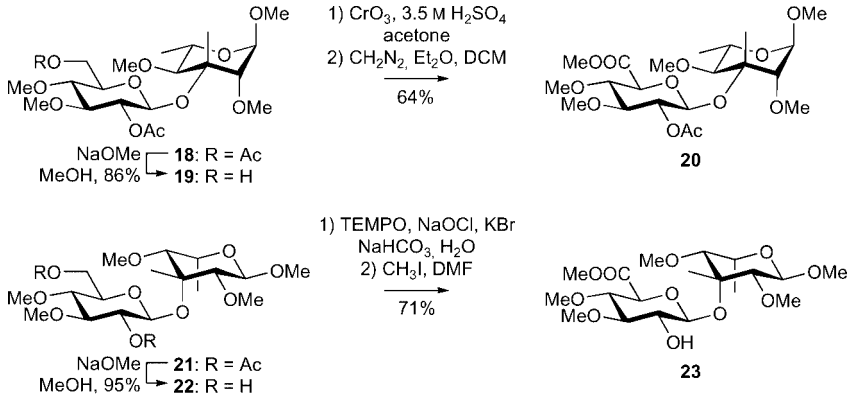
(**11**) and oxidation of the residual primary alcohol positions yielded the trisaccharide **12**, bearing orthogonally functionalized carboxylate groups, while final debenzylation provided the target trisaccharide **13**. By applying the same orthogonal approach, hexasaccharide structures with varying patterns of methyl esters were synthesized.[25]

Chromium-based oxidation methods such as the strongly acidic Jones reagent[26] and the milder pyridinium dichromate[27] (Collins reagent, PDC) and pyridinium chlorochromate[28] (PCC) reagents have also found application in carbohydrate chemistry. Depending on the reaction conditions, either the carboxylic acids or the corresponding carboxylic esters are isolated. Disadvantages of these chromium-based oxidations are purification problems and restricted choice of protective groups.[29] A typical example of the use of PDC is to be found in the group of Vliegenthart and Kamerling in their synthesis of a pentasaccharide fragment (**17**) of the gut-associated circulating anodic antigen (CAA; Scheme 3).[30] After complete assembly of pentasaccharide fragment **14** by trichloroacetimidate chemistry,[31] the C6-OH levulinoyl protective groups on both glucose residues were selectively cleaved, giving compound **15**. Subsequent oxidation with the chromium(VI) oxidant system (PDC, Ac_2O, cat. pyridine) gave uronic acid **16**. Acetic anhydride was added to facilitate cleavage of chromium(VI) from the intermediate ester, thereby accelerating the reaction.[32] Global deprotection yielded pentasaccharide **17** in an overall yield of 65%. In a related study on the synthesis of smaller fragments of pentasaccharide **17**, several other oxidation protocols (including PCC, Jones, and Swern protocols) proved to be less effective.[33]

En route to the preparation of a pentasaccharide hapten of the *Mycobacterium avium* serovar **19**, Lipták's group explored the synthesis of uronates **20** and **23** (Scheme 4).[34] Regioselective deacetylation of the L-*manno*-containing disaccharide **18** proceeded in good yield, giving compound **19**, whereas subjection of the L-*talo*-configured disaccharide **21** to the same conditions gave diol **22**.[35] Jones oxidation of the primary alcohol in disaccharide **19** afforded the intermediate glucuronide, which was transformed into the methyl ester (**20**) by treatment with ethereal diazomethane. In order to achieve oxidation of diol **22**, the authors resorted to a TEMPO-based oxidation method.[36] Sodium hypochlorite was used as co-oxidant, reacting in situ with potassium bromide to generate the more reactive sodium hypobromite.[37] Ensuing addition of methyl iodide and *N*,*N*-dimethylformamide (DMF) to the concentrated reaction mixture afforded the methyl ester disaccharide **23** in good yield. The choice of a different oxidation method was guided by the presence of the unprotected secondary C2′ hydroxy group, which could also be oxidized with chromium(VI)-based oxidants.[38]



Scheme 3. PDC-mediated oxidation to provide the antigenic pentasaccharide **17**.



Scheme 4. Selective oxidations achieved with TEMPO.

The finding that TEMPO is able to oxidize primary hydroxy functions selectively in the presence of secondary hydroxy groups has led to numerous applications of this reagent in oligosaccharide synthesis.[36,39–48] Protective group manipulations to discriminate between primary and secondary hydroxy groups have thus become obsolete and orthogonality between the oxidized and the non-oxidized C6 positions is more easily achieved. Depending on the amount of primary oxidant (co-oxidant) added and the reaction medium (anhydrous or aqueous), the oxidation reaction can be stopped at the aldehyde or carboxylic acid stage (Figure 1). Many primary oxidant systems have been reported, including electrooxidation,[41] *m*-chloroperbenzoic acid,[42] high-valent metal salts,[43] sodium bromite,[44] sodium or calcium hypochlorite,[37,40a,45] hypervalent iodine(III) salts,[46,47] and trichloroisocyanuric acid.[48] The actual oxidizing species in all these reagent combinations is the *N*-oxoammonium intermediate **24**, generated in situ from the reaction between TEMPO and the primary co-oxidant (Figure 1).[36,49] Anhydrous conditions give rise to the aldehyde, whereas in the presence of water, the aldehyde is hydrated, allowing further oxidation to the carboxylic acid. Van Bekkum and co-workers postulated the formation of reaction intermediates **26** and/or **27**, depending on the conditions used.[40b,50]

En route towards synthetic fragments of the heparin[3b] polysaccharide, Boons' group used TEMPO/NaOCl in a regioselective oxidation procedure (Scheme 5).[51] By use of trichloroacetimidate-based glycosylation strategies, trisaccharide **28** was obtained in good yields. In compound **28** the primary hydroxy group in the glucosamine residues is protected as the *tert*-butyldiphenylsilyl (TBDPS) ether. Oxidation of the two C6-OH functions (**29**), followed by desilylation, gave the target trisaccharide **30**. It was reported that best selectivities were achieved when the reaction was performed under basic conditions at pH = 10.

As part of the construction of oligomeric structures corresponding to the capsular polysaccharide *Streptococcus pneumoniae* type 3, Oscarson's group explored the synthesis of dimer **32** (Scheme 6).[52] TEMPO oxidation of the C6′ hydroxy function of the minimally protected disaccharide **31** gave the target uronate **32** in 33% yield. As a side-product, substantial amounts of overoxidized species **33**, resulting from oxidative cleavage of the *trans*-diaxial diol (C2-OH, C3-OH) system in compound **31**, were isolated. Variation of the reaction conditions, such as the use of other solvents and different pH values, met with similar failure. This unwanted oxidative cleavage reaction was prevented by firstly protecting the axially oriented C2 and C3 positions as benzoyl esters, followed by oxidation under biphasic dichloromethane (DCM)/H_2O conditions.[45a]

Field's group studied the oxidation of di- (**34**), tri- (**36**), and tetrasaccharide (**38**) fragments of a rhamnogalacturonan-II polysaccharide with the TEMPO/NaOCl/KBr reagent combination (Scheme 7).[53] The presence solely of oxidized and/or deoxygenated C6 functionalities allows the

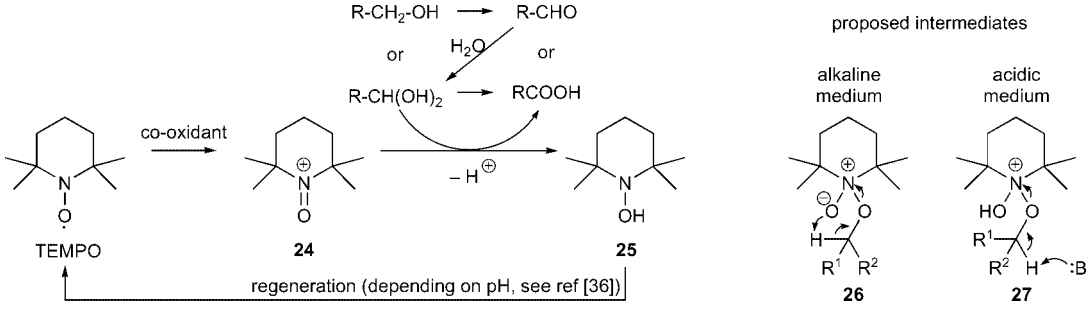
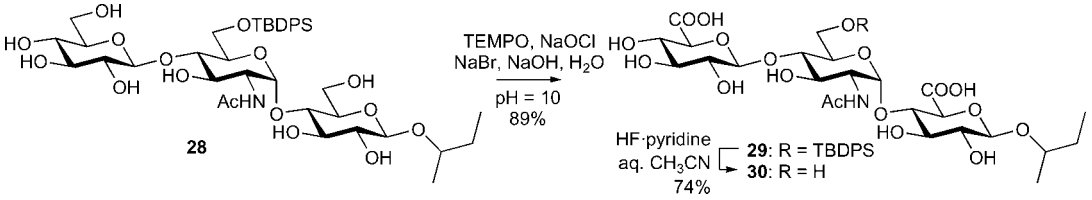
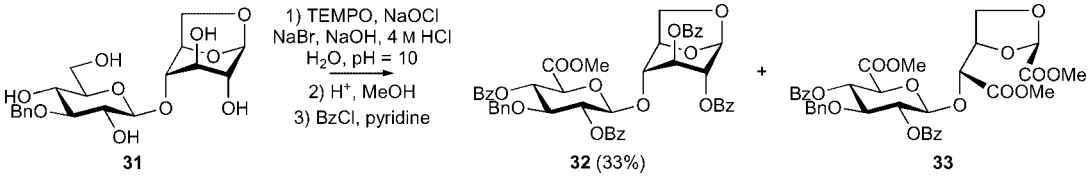


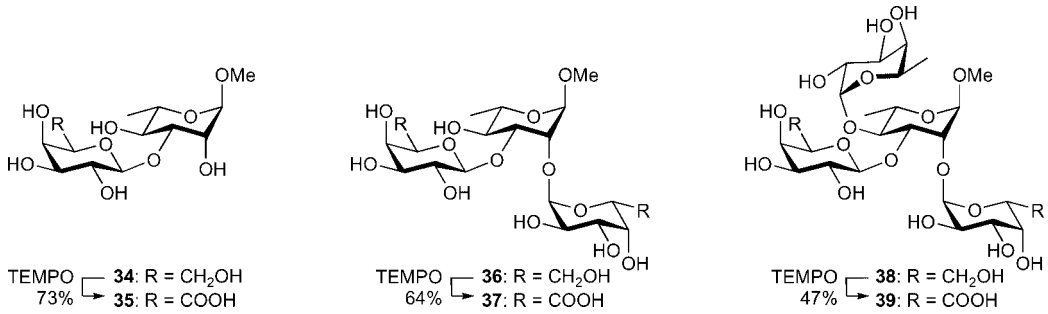
Figure 1. Catalytic cycle and postulated intermediates in TEMPO-catalyzed reactions.



Scheme 5. Boons' approach towards a trisaccharide portion of the heparin polysaccharide.



Scheme 6. Side-reaction observed with use of TEMPO.



Scheme 7. Decreasing reaction efficiencies with increasing oligosaccharide complexity.

oxidation of the completely unprotected precursors **34**, **36**, and **38**. The yields of the reactions decreased with the increasing complexity of the oxidation targets; this trend can be explained by the increased steric bulk, which has been found to be an important factor in oxidation reactions under alkaline conditions (cf. **26**, Figure 1).[36,40]

Anelli and co-workers reported biphasic DCM/H_2O as a highly suitable medium for TEMPO/NaOCl-mediated oxidations of partially protected oligosaccharides.[45a] It was revealed that under standard conditions, initial oxidation to the aldehyde is rather slow. Addition of the quaternary ammonium salt tetra-*n*-butylammonium bromide (TBABr) as a phase-transfer catalyst considerably accelerates the oxidation rate. Furthermore, use of alkaline conditions, such as aqueous $NaHCO_3$, increases both reactivity and selectivity for primary alcohols (see Figure 1).[50a] Flitsch and co-workers applied this method for the first time on protected monosaccharide residues.[45b] Petillo and co-workers reported on the NaOBr-mediated oxidation of the partly protected trisaccharide **40** en route to the hyaluronan oligosaccharide **41** using the biphasic DCM/H_2O system (Scheme 8).[54] We used this biphasic TEMPO oxidation protocol in the synthesis of the repeating unit trisaccharide of the lysoamidase bacteriolytic complex.[55]

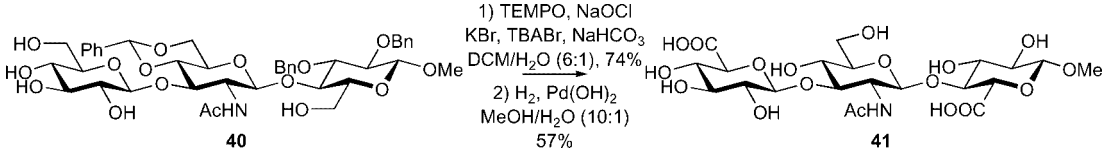
Recently, Huang and co-workers reported a two-step oxidation procedure for a partially protected hexasaccharadic hyaluronan fragment.[56] Initial conversion of the substrate into the aldehyde with the TEMPO/NaOCl reagent combination was followed by further oxidation to the corresponding uronic acid derivative with sodium chlorite ($NaClO_2$). The increased lipophilicity of the substrate reduces the hydration rate of the intermediate aldehyde and thereby decreases the efficiency of the overall oxidation. This procedure, and in particular the use of $NaClO_2$ in combination with *t*BuOH, is claimed to be less sensitive to changes in the hydrophobicity of the substrate molecule.

Pre-Glycosidation Oxidation

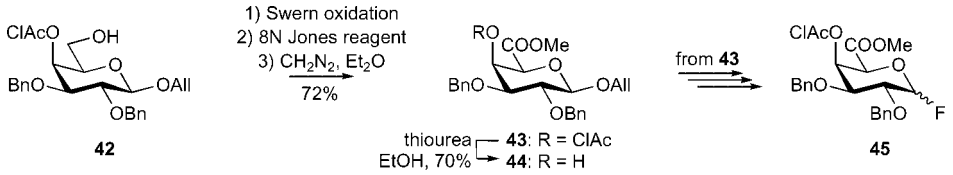
In pre-glycosidation oxidation strategies, suitably protected donor and/or acceptor glycuronates are employed in the construction of acidic oligosaccharides. The presence of the electron-withdrawing ester function make these uronic acids less reactive than their unoxidized counterparts. Donor uronic acid derivatives that have found application in oligosaccharide synthesis over the years include anomeric bromides,[57] fluorides,[58] orthoesters,[59] trichloroacetimidates,[60] *n*-pentenyl glycosides,[61] and 1-thioglycosides.[56]

Ogawa's group investigated the glycosylation properties of protected galacturonic acid fluorides in the synthesis of truncated pectic polysaccharides (see below).[58] Fluoride donor **45** and acceptor allyl uronate **44** were synthesized from substrate **42** (Scheme 9). Jones oxidation led not only to a sluggish and incomplete reaction but also to migration of the chloroacetyl group to the thermodynamically favored C6 position. Catalytic oxidation with Pt/$NaHCO_3$/H_2O resulted in incomplete reactions. Swern oxidation of compound **42** followed by Jones oxidation of the intermediate aldehyde and subsequent treatment with ethereal diazomethane afforded uronic acid derivative **43** in a yield of 72%. Exchange of the anomeric allyl group (**43**) for a fluorine atom afforded uronate donor **45**. Galacturonate acceptor **44** was obtained by treatment of fully protected compound **43** with thiourea. Takeda and co-workers also encountered problems during the synthesis of C4-OH-unprotected galacturonates and therefore opted for the post-glycosidation oxidation strategy in their synthesis of a pectic polysaccharide repeating unit.[62]

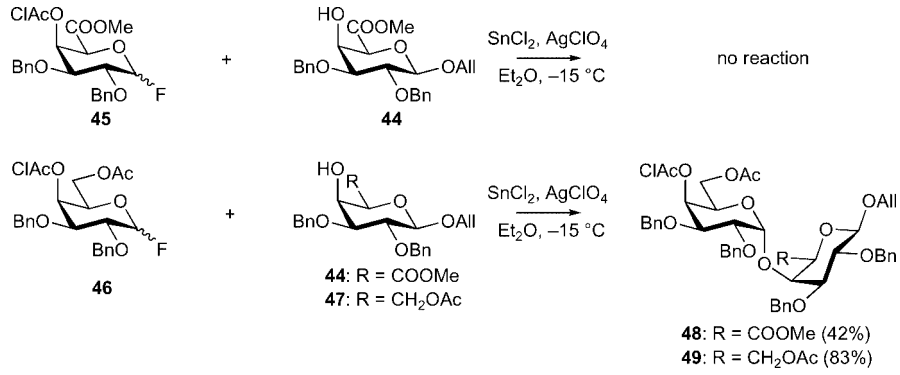
Subjection of uronic acids **45** and **44** to Mukaiyama conditions ($SnCl_2$, $AgClO_4$)[16] did not result in a productive glycosylation reaction, most probably due to the deactivating influence of the remotely attached uronic acid esters (Scheme 10). Indeed, application of galactosyl fluoride **46**



Scheme 8. TEMPO oxidations using NaOBr generated in situ.



Scheme 9. Synthesis of galacturonic acid building blocks.

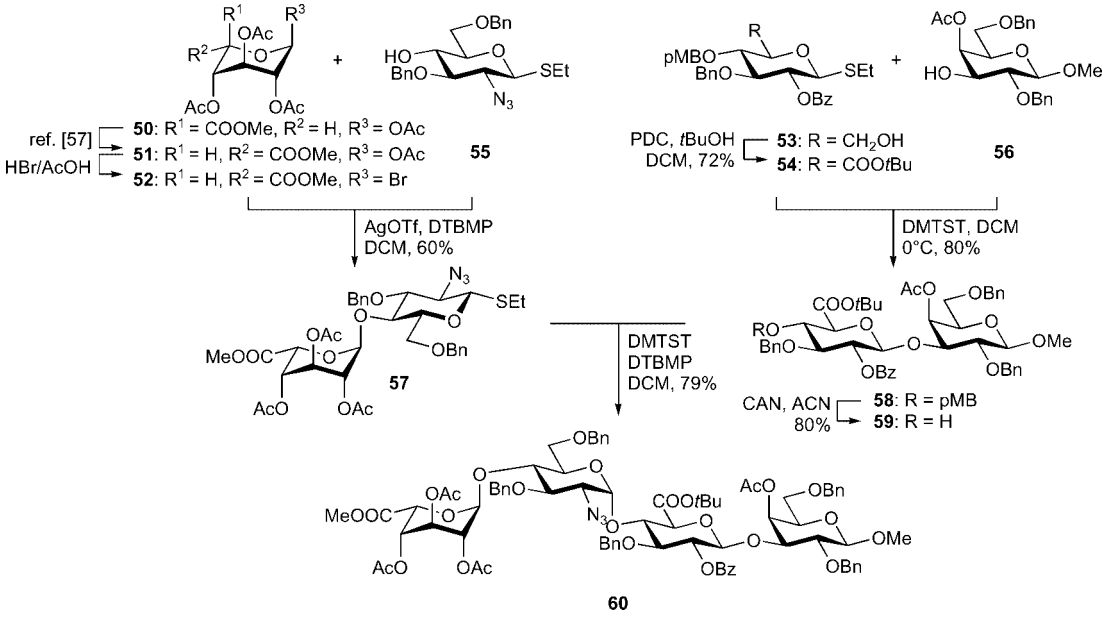


Scheme 10. Pre-glycosidation oxidation approach towards specific pectic polysaccharides.

as a more reactive donor gave α-linked disaccharide **48** in a yield of 42%. The yield was further improved by using the unoxidized, acetyl-protected acceptor **47** instead, giving the α-linked disaccharide **49** in 83% yield. From these results it can be concluded that the use of anomeric fluorides in combination with Mukaiyama activation conditions is less suitable in the pre-glycosidation oxidation approach.

Vogel and co-workers investigated the trityl-cyanoethylidene glycosidation method[63,64] for the construction of acidic oligosaccharides.[65] This method proved to be successful in the synthesis of β-(1→2)- and β-(1→3)-linked digalacturonic acid residues. The attempted construction of the demanding β-(1→4)-linked dimers, however, resulted in complex reaction mixtures with minor product formation.[66]

Westman and co-workers reported on the use of anomeric bromides and 1-thioglycuronides in the synthesis of defined fragments of a known glycosaminoglycan tetrasaccharide.[67] In order to minimize protective group manipulations a block-type synthesis strategy was chosen in combination with an orthogonal glycosylation strategy.[12e] Starting from peracetylated methyl glucuronate **50**, the corresponding iduronic acid donor **51** was obtained by a radical-initiated epimerization of C5 (Scheme 11).[57a,57b] The iduronic acid **51** was then converted into the bromide donor **52** by treatment with a hydrogen bromide (HBr) solution in

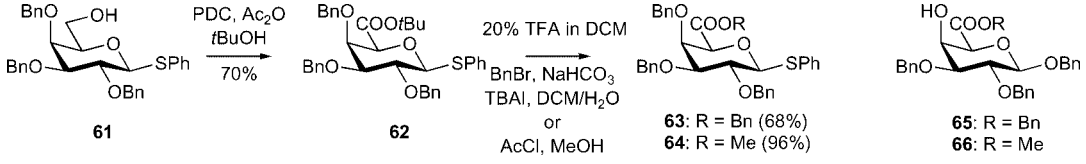


Scheme 11. Westman's approach to the defined glycosaminoglycan fragment **60**.

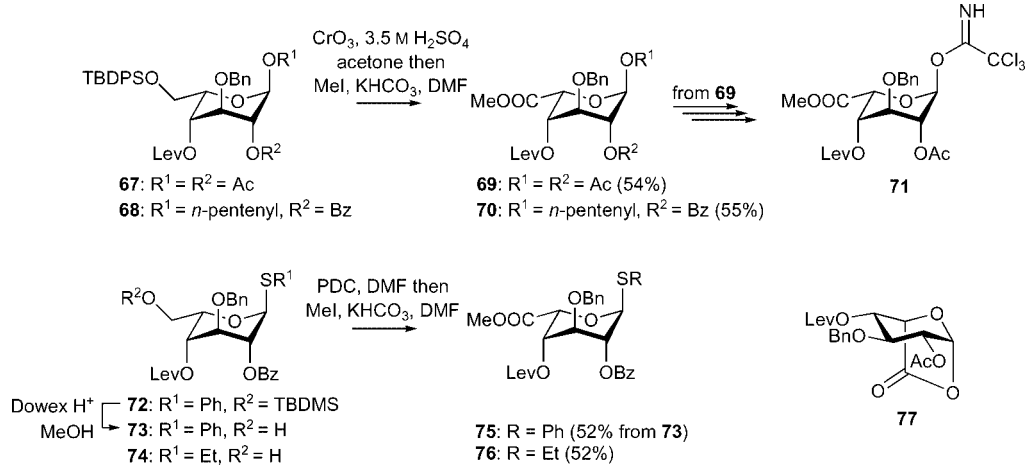
acetic acid. The thio donor **54** was obtained by oxidation of compound **53** with PDC and acetic anhydride in a mixture of *tert*-butyl alcohol and DCM.[68] In this process, the intermediate aldehyde is trapped by *tert*-butyl alcohol to give the *tert*-butyl hemiacetal, which is further oxidized to give the *tert*-butyl uronate **54**. No oxidation of the thiophenyl function to the corresponding sulfoxide or sulfone is reported. In an orthogonal glycosylation strategy, the iduronic acid bromide **52** was condensed with the ethylthio glucosazide **55** to give the 1-thiodisaccharide **57** in a yield of 60%. The 1-thioglucuronide **54** was glycosylated with acceptor **56** under the agency of dimethyl(methylthio)sulfonium triflate (DMTST) to give compound **58**.[69] The synthesis of tetrasaccharide **60** was completed by oxidative cleavage of the *para*-methoxybenzyl (pMB) group (**58** → **59**) and DMTST-mediated coupling between thiodisaccharide **57** and glucuronide acceptor **59**. This approach highlights the usefulness of the stable 1-thioglucuronides as both donor and acceptor in acidic oligosaccharide synthesis.

Another successful application of 1-thioglycuronic acid esters in acidic oligosaccharide synthesis was published by Robert-Baudouy's group in their synthesis of defined fragments of the pectic polysaccharide.[70,71] Chemoselective oxidation of the partially protected 1-thioglycoside **61** was accomplished with the PDC/Ac_2O/*t*BuOH oxidation system (Scheme 12). Exchange of the acid-labile *tert*-butyl ester in compound **62** for either a benzyl or a methyl ester yielded galacturonates **63** and **64**. The benzyl and methyl esters were introduced under acidic conditions in order to prevent putative β-elimination or epimerization reactions, previously observed by the groups of Sinaÿ[72] and Vogel.[72–74] Direct application of the *tert*-butyl ester functionalized glycosides sometimes resulted in compromised coupling efficiencies due to the increased steric bulk.[75] It was found that application of the *N*-iodosuccinimide (NIS)/trifluoromethanesulfonic acid (TfOH) activator system[76] was successful (high yields and fully α-stereoselective) in the glycosidation of these deactivated galacturonate building blocks **63** and **64** with the acceptor building blocks **65** and **66**.

Sinaÿ and co-workers published a study in which the glycosylation properties of *n*-pentenyl- (**70**), trichloroacetimidate- (**71**), and 1-thio-functionalized (**75** + **76**) iduronic acid donors are compared (Scheme 13).[61] By starting from the 6-*O*-*tert*-butyldimethylsilyl-protected compounds **67** and **68**, uronic acid esters **69** and **70** were obtained by treatment with Jones reagent (CrO_3, 3.5 M H_2SO_4) and subsequent methylation. Disaccharides could also be oxidized by this one-pot silyl cleavage/oxidation protocol, although the yields dropped slightly.[70] After oxidation, the 1-*O*-acetyl derivative **69** was transformed into the corresponding trichloroacetimidate donor **71** by a known sequence of reactions [α-Ac → α-Br → α/β-OH → α/β-OC(NH)CCl_3].[77] Jones oxidation of the corresponding 6-*O*-TBDMS-functionalized phenylthio residue **72** proceeded less straightforwardly and, along with the desired 1-thio-α-L-iduronic acid ester **75** (26%), considerable amounts of sulfoxide and sulfone were isolated (together ca. 50%).[78] Acidic cleavage of the silyl group (**72** → **73**) and oxidation with the milder pyridinium dichromate (PDC) gave a substantially improved yield of 1-thioiduronic acids **75** and **76** (both 52%). Table 1 summarizes the glycosidations performed with the donors **70** and **71**. It can be concluded that trichloroacetimidate **71** and *n*-pentenyl glycoside **70** are equally efficient in glycosylating acceptors **78** and **79**. On the other hand, the corresponding 1-thioiduronates **75** and **76** did not yield the expected disaccharides with DMTST[69] as the activator

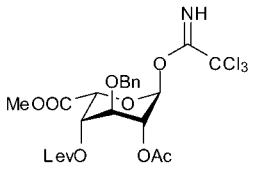
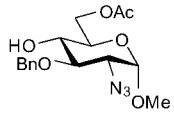
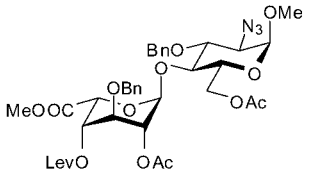
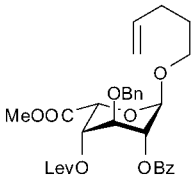
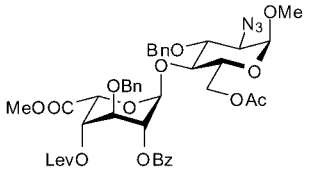
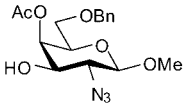
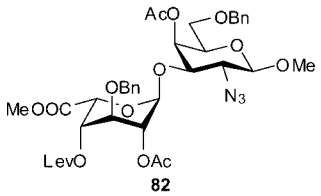
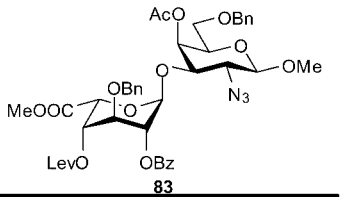


Scheme 12. PDC-mediated chemoselective oxidation of 1-thioglycosides.



Scheme 13. Synthesis of *n*-pentenyl-, trichloroacetamide-, and 1-thio-functionalized iduronic acid donors.

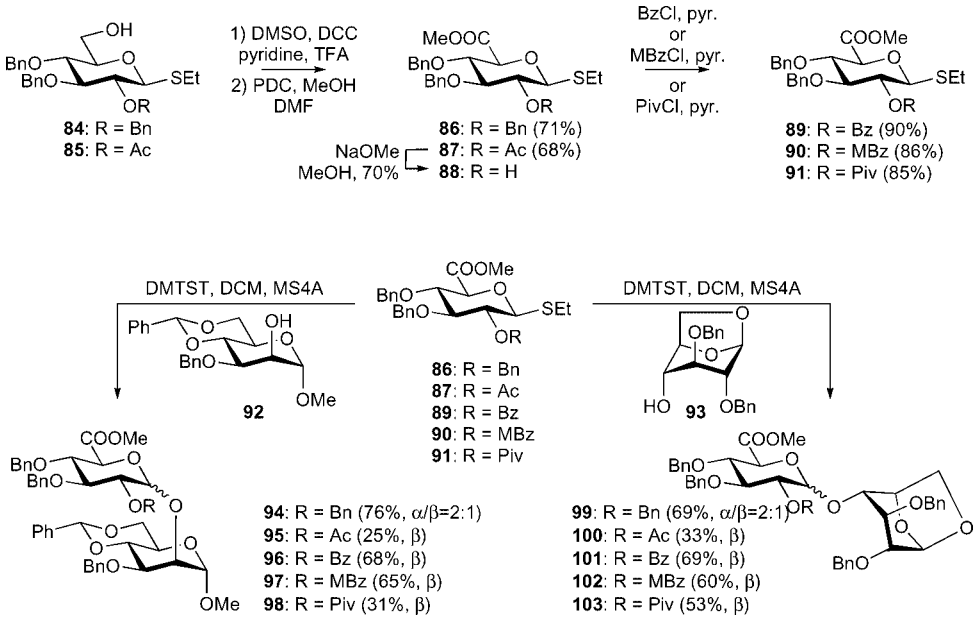
Table 1. Study of the glycosylating properties of donors **70** and **71**.

Entry	Donor	Acceptor	Activator Yield (a/ß)	Disaccharide
1	 **71**	 **78**	TMSOTf 91% (1:0)	 **80**
2	 **70**	**78**	NIS/TfOH 80% (1:0)	 **81**
3	**71**	 **79**	TMSOTf 86% (1:0)	 **82**
4	**70**	**79**	NIS/TfOH 85% (1:0)	 **83**

system.[79] Closer inspection revealed that thiophenyl donor **75** was completely inert towards DMTST activation, whereas thioethyl donor **76** showed minor formation of lactone **77**.

Garegg's and Oscarson's group investigated the use of 1-thioglycuronides in their study geared towards the synthesis of naturally occurring acidic polysaccharides isolated from *Streptococcus pneumoniae* and *Cryptococcus neoformans*.[80] In agreement with the observations of Ogawa and coworkers,[81] Lewis acid mediated reaction between ethanethiol and peracetyl methyl (β-D-glucopyranoside) uronate resulted in a moderate yield and low stereoselectivity. It was therefore decided to examine direct oxidation of the suitably protected ethyl 1-thioglycoside **84** (Scheme 14). Oxidation was accomplished by a two-step oxidation protocol comprising initial Pfitzner–Moffat oxidation[82] of alcohol **84** to the intermediate aldehyde and subsequent treatment with excess PDC, giving donor **86** in a yield of 71%. In the same way, the 2-*O*-acyl donor **87** was prepared from compound **85**. Furthermore, basic hydrolysis of the 2-*O*-acetate (**87** → **88**) and reprotection yielded donor species **89**, **90**, and **91**. The glycosylation properties of donor **86**, with a C2 benzyl group, and of donors **87**, **89**, **90** and **91**, each with a C2 acyl group, were investigated with acceptors **92** and **93** and DMTST as promoter system. DMTST-mediated coupling of tri-*O*-benzyl-substituted 1-thioglucuronide **86** with acceptors **92** and **93** afforded the corresponding disaccharides **94** and **99** as anomeric mixtures. In a later study by the same group it was found that 2-*O*-benzylated 1-thioglucuronide donors are sensitive to changes in reaction conditions, such as the use of different promoter systems, different protective groups, and application of a participating solvent.[83] This was independently verified in a study by Misra and Roy, who reported complete α-selectivity when using the tribenzylated donor **86** in methyl triflate mediated glycosylations.[84] Glycosylations using 2-*O*-acylated donors **87** and **91** proved problematic, whereas 2-*O*-benzoylated derivatives **89** and **90** showed good coupling efficiencies.

We recently reported on the use of the TEMPO/[bis(acetoxy)iodo]benzene (BAIB) reagent combination for the efficient oxidation of variously functionalized 1-thioglycosides (Figure 2).[85,86] Both the starting glycoside (glucose, glucosamine, galactose, and idose) and the nature of the protective groups (benzyl, benzoyl, isopropylidene, *tert*-butyldimethylsilyl, azide, and phthalimide) can be varied without major implications for the outcome of the oxidation step. Furthermore, the mild oxidation conditions allow the presence of unprotected secondary hydroxy functions and various substituted 1-thio functions. Subjection of 4,6-unprotected thioglycosides **104** to the TEMPO/BAIB oxidation conditions afforded the corresponding uronic acids **105**,[85] whereas use of the 3,6-unprotected thioglycosides **107** resulted in a tandem oxidation/lactonization process giving the corresponding 6,3-lactones **108**.[86] Methyl ester



Scheme 14. Influence of the C2 protective group on the glycosylation properties of 1-thioglucuronates.

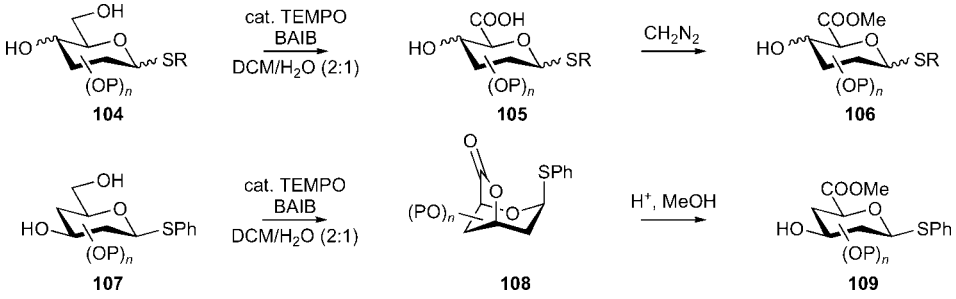


Figure 2. Broad application of the TEMPO/BAIB reagent system.

106 was obtained upon treatment of uronic acid **105** with ethereal diazomethane, and acidic cleavage of lactone **108** in MeOH gave methyl ester **109**. In a related study using the TEMPO/$NaClO_2$ oxidation system, Huang and co-workers also reported on the chemo- and regioselective oxidation of variously protected 1-thiotolylglycosides.[56]

The donor and acceptor properties of uronates **106** and **108** with the BSP (**110a**)/Tf_2O[87] or Ph_2SO (**110b**)/Tf_2O[88] activator systems were investigated (Figure 3). It was assumed that the electrophilic natures of these activator systems would be sufficient to overcome the reduced nucleophilicity of the anomeric sulfur atom due to the remotely attached carboxyl function. Indeed, both activator systems proved successful in the glycosidation of oxidized gluco- and galactopyranosides, although activation had to be performed at a temperature slightly higher (–40 °C to –50 °C) than that used in the standard procedure.

Comparison of the "open-form" uronate **112** and lactone **115** shows the latter to be more α-selective in glycosidation reactions with the same acceptor molecule **113** (Table 2, Entries 1 and 2). Even fully acylated donor **117** was efficiently glycosidated with acceptor **113** under the agency of the BSP/Tf_2O reagent combination (Entry 3). Illustrative in this respect are the examples published by Garegg and Oscarson's group, who had to install at least two activating benzyl functions or a 3,4-tetraisopropyldisiloxy group at the thioglucuronate donors (**89**, for instance) to obtain sufficient activation with DMTST (see Scheme 14).[80] *N*-Benzyloxycarbonyl-protected glucosamine **119** was efficiently employed as acceptor nucleophile, giving disaccharide **120** with full α-selectivity (Entry 4). This reaction proceeded more slowly than the other glycosidations, possibly due to reduced reactivity of the acceptor alcohol as a result of intramolecular hydrogen bonding.[89] We recently described a modular synthesis approach towards a defined heparin pentasaccharide using 1-thioglucuronic and -iduronic acid building blocks.[90]

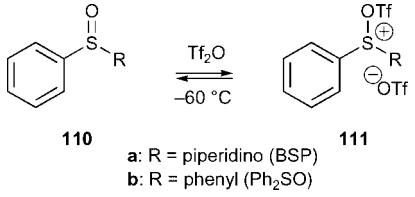
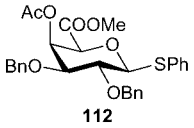
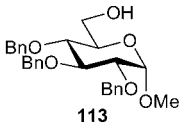
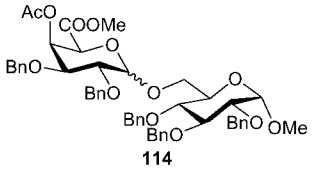
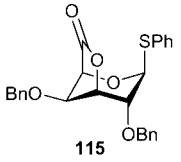
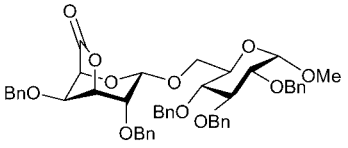
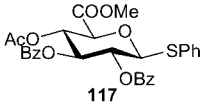
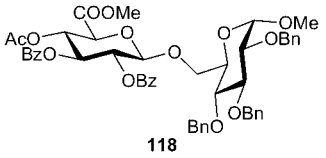
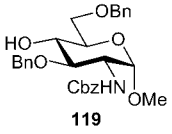
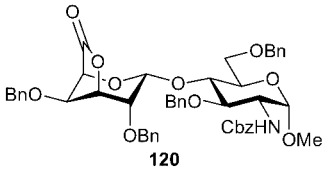
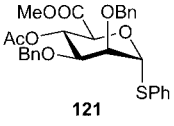
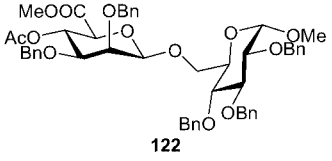


Figure 3. Sulfonium-based activator systems.

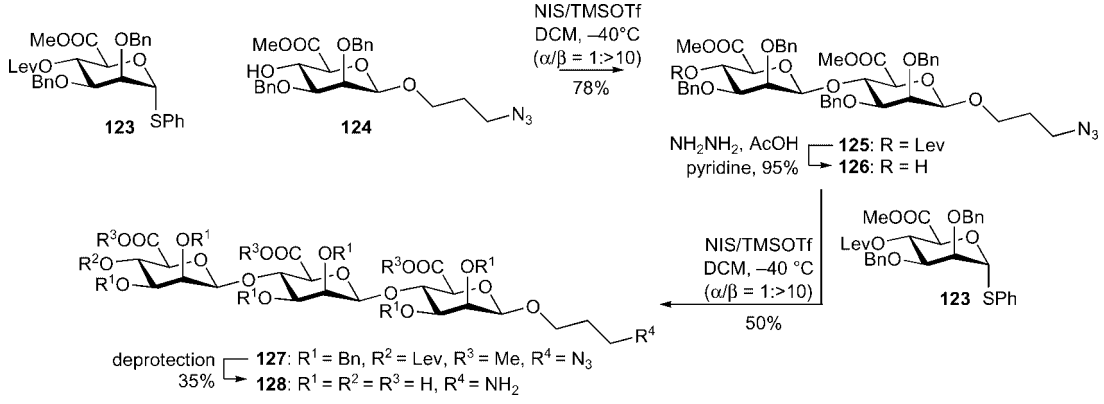
Glycosidations using the 1-thiomannuronic acid ester donors (e.g., **121**) have outcomes different from those of their

Table 2. Glycosylating properties of various oxidized glycuronides.

Entry	Donor	Acceptor	Activator Yield (a/ß)[a,d]	Disaccharide
1	 **112**	 **113**	Ph_2SO/Tf_2O[b] 80% (1:2)	 **114**
2	 **115**	**113**	Ph_2SO/Tf_2O[b] 69% (1:0)	 **116**
3	 **117**	**113**	BSP/Tf_2O[b] 68% (0:1)	 **118**
4	**115**	 **119**	Ph_2SO/Tf_2O[c] 69% (1:0)	 **120**
5	 **121**	**113**	Ph_2SO/Tf_2O[b] 81% (0:1)	 **122**

[a] Isolated yields. [b] 2.5 equiv. TTBP. [c] 1 equiv. TTBP. [d] Anomeric ratios were determined by ^1H NMR spectroscopy.

1-thioglucuronic and galacturonic acid ester congeners (Entry 5). The *gluco*- and *galacto*-configured uronate donors show preferences for α-product formation, while almost all the mannuronic acid derivatives exclusively afford the β-oriented product.[91] In analogy with the findings of Crich[92] and Bols,[93] it is assumed that the strongly electron-withdrawing nature of the remotely attached carboxy group combined with the anomeric effect in the *manno* series dictates the reaction towards the β-product. In Scheme 15 the strategy for the first synthesis of alginate trisaccharide **128** is depicted.[91] The synthesis starts from the nonreducing end monosaccharide **124** and makes use of levulinoyl groups for temporary C4 protection. NIS/TMSOTf-mediated glycosylation[94] of donor **123** and the azidopropyl-functionalized acceptor **124** afforded disaccharide **125** with excellent stereoselectivity. Removal of the Lev group in disaccharide **125** afforded the new acceptor **126**, which was again stereoselectively condensed with donor **123** to give



Scheme 15. Synthesis of an alginate trisaccharide.

trisaccharide **127** in 50% yield. Global deprotection afforded alginate trisaccharide **128**. In the same way, 1-thio-functionalized mannosaziduronic acid showed promise as a donor and acceptor glycoside in carbohydrate chemistry.[95]

Conclusions

This review summarizes the developments in the synthesis of acidic oligosaccharides. Both approaches for the introduction of uronic acid residues (that is, oxidation prior to or post glycosylation) in acidic oligosaccharides are discussed and typical examples are presented. It can be concluded that the post-glycosylation strategy requires additional protective-group manipulation and risks of losing valuable oligosaccharide during oxidation. The pre-glycosylation protocol avoids these difficulties, although the reactivity at the anomeric center of the glycuronic acid is impaired relative to the nonoxidized counterparts.

In general, the advent of TEMPO as an oxidizing reagent has greatly stimulated the development of new and efficient ways for the synthesis of acidic oligosaccharides. In comparison to the other, more robust oxidation methods, the applied protective group pattern is only minimally restricted, allowing the oxidation of partially or completely deprotected carbohydrate structures. Furthermore, it has inspired the development of procedures employing oxidized monosaccharide residues as building blocks in acidic oligosaccharide synthesis. In particular, application of the versatile thiogluronic acid esters holds promise in the synthesis of complex acidic oligosaccharides.

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