Total synthesis of alginate and zwitterionic SP1 oligosaccharides

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General Introduction

Introduction

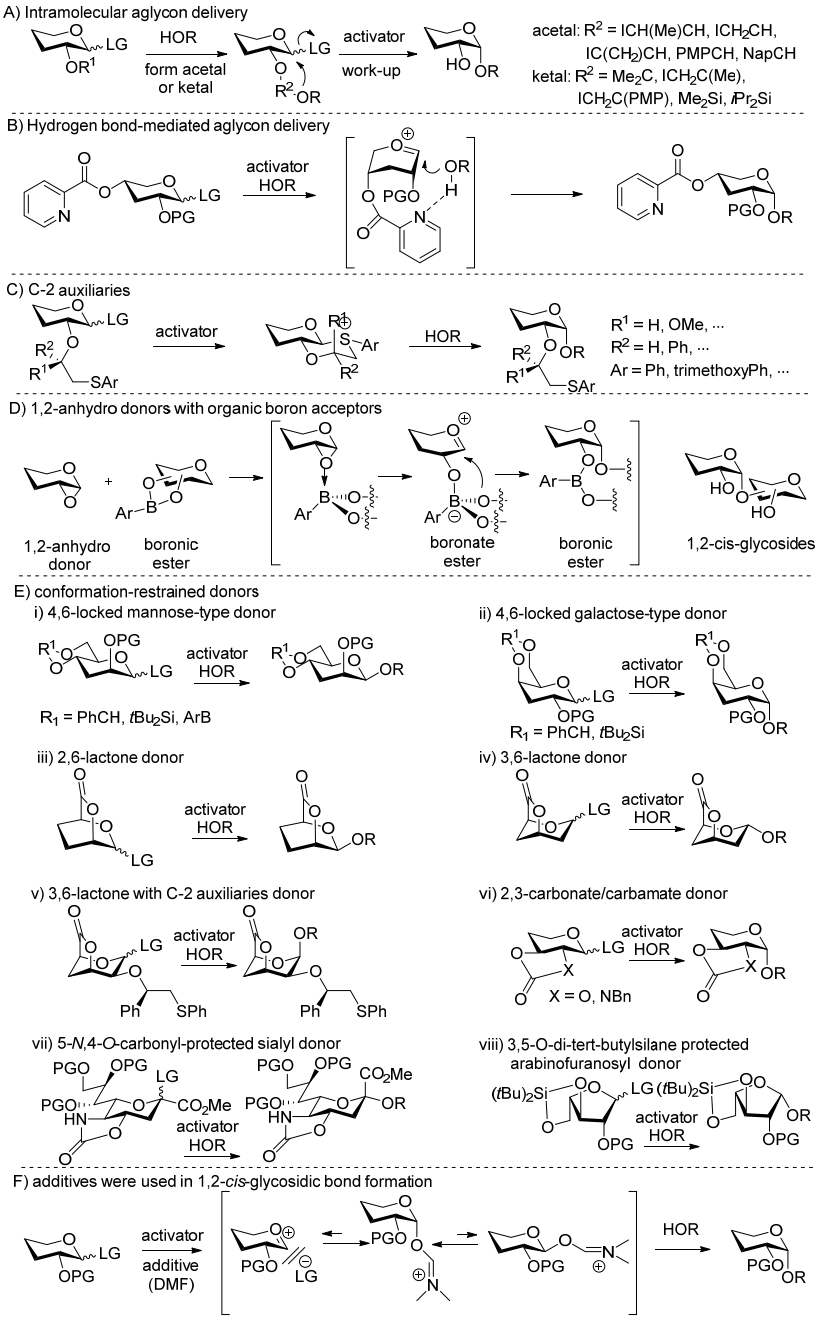
Carbohydrates are one of the major classes of biopolymers, alongside nucleic acids and proteins, and they fulfill a plethora of biological functions.[1] Carbohydrates not only serve as intermediates in cellular energy production but also as important structural components (cellulose is the most abundant biomolecule on earth) and as signaling molecules. They also play an important role in normal cell functions as well as in major pathologies, including cancer, cardiovascular disease and inflammatory diseases.[2] To investigate their biological functions,[3] enable medical applications such as the development of carbohydrate-based vaccines,[4] generate functional materials,[5] sufficient amounts of structurally well-defined and pure oligo- and polysaccharides and glycoconjugates are needed. Often it is difficult to get enough pure carbohydrates from natural resources and therefore synthesis, either through organic chemical or enzymatic means, has become one of the main suppliers delivering these molecules.

Synthetic carbohydrate chemistry has made considerable progress over the last half century. Effective protecting group strategies have been developed to address the multitude of different hydroxyls functions in the carbohydrate building blocks.[6] Many powerful glycosylation methods have been developed,[7] employing various donor glycosides, such as anomeric halides (in the classical Koenigs-Knorr method for example),[7e] thioglycosides,[7m] trichloroacetimidates[7c] and the closely related N-phenyl trifluoroacetimidates[7l] and O-alkynylbenzoates.[7o] To streamline oligosaccharide assembly, various effective strategies have been developed, including reactivity-based,[8]

orthogonal activation[9] or pre-activation[10] enabled one-pot syntheses. Automated solid phase oligosaccharide synthesis is growing into a mature synthesis technique,[11] with a commercial instrument now available. Long (up to a 50-mer) and complex oligosaccharides have already been assembled using a fully automated set-up. Over the years many enzymes have become available for the regio- and stereoselective construction of glycosidic linkages and many of the mammalian glycosides can now in principle be generated using enzymatic or chemoenzymatic synthesis.[12] Especially for the construction of sialic acid containing oligosaccharides enzymatic synthesis has become the method of choice.

Despite all the progress made, the stereoselective introduction of 1,2-*cis*-glycosidic bonds still remains a major challenge in many oligosaccharide synthesis campaigns. Scheme 1 summarizes some of the methods that are currently available for the stereoselective construction of glycosidic linkages. In an intramolecular aglycon delivery (IAD) strategy (Scheme 1A), as developed by Stork,[13] Bols,[14] and Ogawa and Ito[15] for example, the donor and acceptor are tethered together and this way the activated donor glycoside can only be attacked from one face of the ring. Recently, hydrogen bond-mediated aglycon delivery (HAD) was introduced by Demchenko to direct the acceptor to the desired face of the donor glycoside.[16] Boons and co-workers developed C2-chiral auxiliaries, to selectively shield one face of the donor glycoside as depicted in Scheme 1C.[17] Takahashi and Toshima[18] reported on the use of borinic esters to glycosylate minimally protected carbohydrates in an S_Ni-type reaction with glycosyl epoxides.[19] Several conformationally restricted donor systems have been introduced over the years to allow the stereoselective construction of glycosidic linkages (See Scheme 1E). A major

breakthrough was accomplished by Crich and co-workers,[20] who introduced 4,6-benzylidene mannosyl donors for the stereoselective formation of β-mannosides. Silylidene protected galactosides reliably provide 1,2-*cis*-galactosides in glycosylation reactions by effective steric shielding of the β-face of the donor.[21] Lactone donors have been used by the groups of van der Marel and Codée,[22] Ito,[23] and Boltje.[24] Cyclic 2*N*,3*O*-carbamates, introduced by Kerns and co-workers, have successfully been employed for the stereoselective introduction of α-glucosamine linkages.[25] Later this principle was translated to cyclic carbonates and applied for the construction of α-sialic acids.[26] Also, furanosyl donors have been equipped with cyclic protecting groups to control the conformation of the glycosylating species in order to attain stereoselective glycosylation reactions.[27] 3,5-silylidene protected arabinofuranoses can be used for the construction of 1,2-*cis*-arabinosides.[28] Much recent effort is directed at the *in situ* generation of reactive species that allow for stereoselective glycosylation reactions through the use of nucleophilic additives, or reactivity modulators. Notable achievements include the use of DMF in the construction of 1,2-*cis*-glucosides as initiated by Mong and co-workers.[29] An important asset of the use of nucleophilic additives is the fact that they can tune the reactivity of the glycosylating species to match the reactivity of the acceptor at hand as shown by Wang *et al.*[30]



Scheme 1. Examples of 1,2-*cis*-stereoselective glycosylation. A) intramolecular aglycon delivery; B) hydrogen bond-mediated aglycon delivery; C) C-2 auxiliaries; D) 1,2-anhydro donors with stannylated acceptors; E) conformation-restrained donors; F) using additives.

The methods depicted in Scheme 1 show that many clever solutions have been conceived for the stereoselective synthesis of 1,2-cis-glycosidic linkages. The diversity of the methods however, also makes it clear that there is not a unified solution to the problem and the assembly of complex oligosaccharides, featuring rare (deoxy) building blocks, labile functional groups or complex substitution patterns requires the development of ever more sophisticated synthesis strategies. This thesis addresses the synthesis of two classes of complex polysaccharides: the alginates and zwitterionic polysaccharides.

Aim and outline of this thesis

This Thesis reports the synthesis of fragments of alginates and zwitterionic Streptococcus pneumonia SP1 polysaccharides. Alginate is an important constituent of the biofilm produced by Pseudomonas aeruginosa and Chapter 1 provides a concise overview of the synthesis of alginate oligosaccharides, featuring β-d-mannuronic acid or α-l-guluronic acid linkages. Chapter 2 describes all syntheses of zwitterionic polysaccharides fragments, reported to date. Chapter 3 and Chapter 4 describe the synthesis of alginate fragments containing both β-d-mannuronic and α-l-guluronic acids. Chapter 5 shows the synthesis of guanosine diphosphate mannuronic acid (GDP-ManA) and its C-4-O-methyl and C-4-deoxy congeners to be used for alginate biosynthesis studies. Chapter 6 introduces a new oxidation protocol for the selective oxidation of primary alcohols to carboxylic acids by use of a two-step one-pot TEMPO/BAIB-Pinnick oxidation sequence, which can be used for the generation of complex uronic acid containing oligosaccharides. Chapter 7 describes the total synthesis and structural analysis of long zwitterionic SP 1 oligosaccharides. Chapter 8 finally summarizes the results obtained in this Thesis and outlines some future prospects.

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