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Combining Click Reactions for the One-Pot Synthesis of Modular Biomolecule Mimetics

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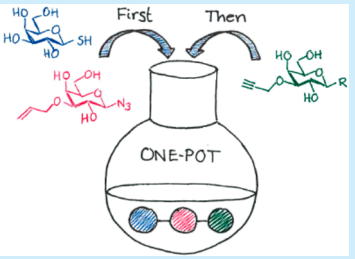
Supporting Information

ABSTRACT: Here, we report on the first combined one-pot use of the two so-called "click reactions": the thiol−ene coupling and the copper-catalyzed alkyne−azide cycloaddition. These reactions were employed in an alternating and one-pot fashion to combine appropriately functionalized monomeric carbohydrate building blocks to create mimics of trisaccharides and tetrasaccharides as single anomers, with only minimal purification necessary. The deprotected oligosaccharide mimics were found to bind both plant lectins and human galectin-3.

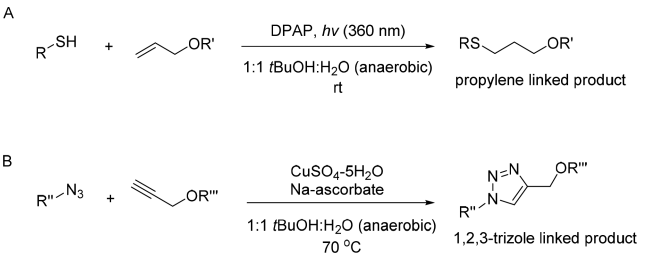


The three biopolymers DNA/RNA, proteins, and saccharides are modular in nature and fundamentally consist of monomeric units linked through phosphate diester, peptide, and glycosidic bonds, respectively. Although the complete synthesis of large representatives from each class has been conducted,[1−8] pitfalls and challenges in the preparation of biopolymers are still present, making the synthesis of simplified structures, or mimics, of the parent compounds desirable. Often, molecules mimicking naturally occurring structures are more easily accessible and have the potential to possess improved characteristics, such as solubility, stability, and affinity.[9−13] To bypass the often cumbersome synthesis of natural oligosaccharides, effort has been directed toward the synthesis of oligosaccharide mimics, achieved by attaching the monosaccharides in a way different from the naturally found *O*-glycosidic linkage,[14−18] which is a subject that has been well reviewed by Werz et al.[19]

Perhaps two of the most prominent click reactions[20]—namely, the thiol−ene coupling (TEC)[21,22] and the copper-catalyzed azide−alkyne cycloaddition (CuAAC)[23,24] (Scheme 1)—have become valuable tools in chemistry and chemical biology for the conjugation of molecular fragments under mild reaction conditions. While the two reactions have been sporadically employed in combination to expand the space of achievable structures, it has so far been necessary to perform purifications between reactions.[25−32]

Therefore, we were keen to investigate whether the TEC[33] and CuAAC[34] reactions could be used to assemble larger biomolecules mimicking naturally occurring motifs in a one-pot sequential reaction to make only minimal purification necessary.

Scheme 1. (A) Thiol−Ene Click Reaction (TEC); (B) Cu-Catalyzed Azide−Alkyne Cycloaddition Click Reaction (CuAAC)[a]



[a]DPAP = 2,2-dimethoxy-2-phenylacetophenone (photoinitiator).

It has been observed that often it is only a small part of the oligosaccharide that interacts with receptor proteins, while the rest of the molecule acts as a scaffold to orient the binding determinants in the desired spatial arrangement.[11,12] Consequently, it should be possible to substitute the natural glycosidic bond with noncarbohydrate motifs while conserving the biological activity of the parent molecule.[34] Our aim was to prepare a series of oligosaccharides possessing non-natural linkages in an iterative fashion, using bespoke building blocks of commonly found monosaccharides. Both the TEC and the CuAAC reactions have a large functional group tolerance, and we hoped it would be possible to omit the use of protecting groups, or at least keep their use to a minimum for easy handling and convenient global deprotection in the final step.

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In addition, we aimed at developing the chemistry to work in an aqueous medium to be later applicable on biomolecules different from saccharides. As a starting point for the desired oligosaccharide mimics it was decided to employ D-*N*-acetyl glucosamine (GlcNAc), D-galactose (Gal), and D-mannose (Man), since, together, these constitute more than 75% of all monosaccharides found in mammals.[35] Furthermore, as established by Werz et al., these monosaccharides are most frequently connected by linkages that are specific in terms of both regiochemistry and anomeric stereochemistry. Accordingly, in the present project, we chose to preserve the naturally preferred linkage pattern found in mammalian glycans,[35] which is β-D-Gal (capping); (3 → 1)-β-D-Gal; α-D-Man (capping); (2 → 1)-α-D-Man; β-D-GlcNAc (capping) and (4 → 1)-β-D-GlcNAc. A series of building blocks possessing the desired functionalities were then synthesized in their *O*-acetyl protected form in order to ease chromatographic purification (Figure 1).

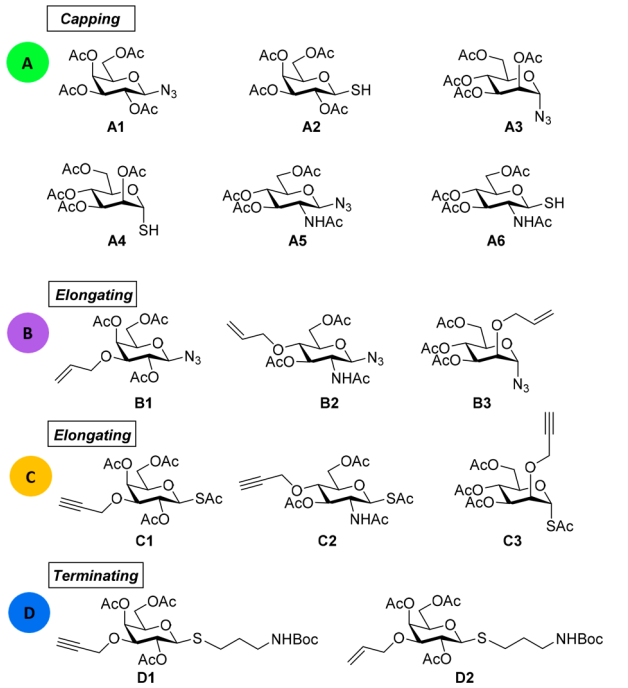
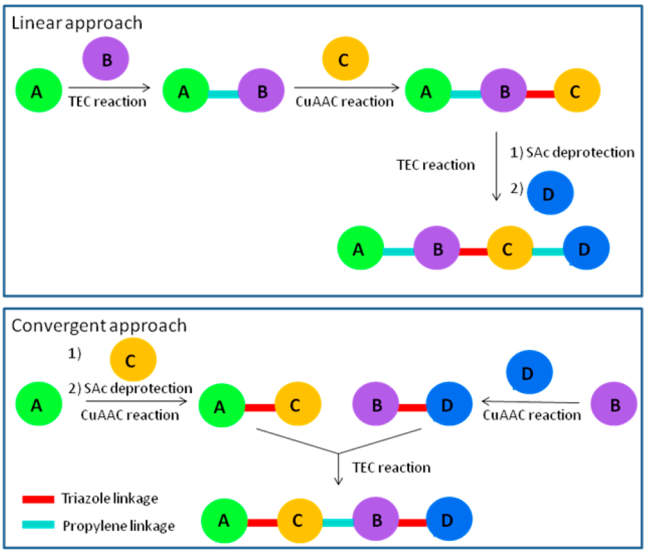


Figure 1. Building blocks for oligosaccharide mimic synthesis.

The building blocks were divided into four groups: A, B, C, and D. Group A compounds only possess one functional handle for extension (thiol or azide) to be used as a capping unit at the nonreducing end. Group B compounds have both an alkene and an azide functionality to enable attachment of a Group A thiol and allow for further attachment to Group C or D alkyne-containing building blocks. Group C compounds possess an alkyne and a thioacetate to be able to undergo reactions with either an azide from Group A, or a larger structure with a Group B azide terminating group. Finally, Group D monomers are reducing end terminating building blocks possessing either an alkyne or alkene with a Boc-protected amine to enable immobilization. These units are suited for reactions with a glycosyl azide or thiol from Group B or with a de-S-acetylated unit from Group C. The overall strategy is outlined in Scheme 2.

Of the listed building blocks (Figure 1), **A1**−**A6** were known compounds, while **B1**−**B3**, **C1**−**C3**, and **D1** and **D2**

Scheme 2. Linear and Block Synthesis Approach the Synthesis of Tetrasaccharide Mimics



were synthesized specifically for this project. A detailed description of their preparation can be found in the Supporting Information.

During test experiments, it was observed that the unprotected version of the Group C alkyne thioacetate building blocks, containing the free thiol, decomposed during the CuAAC reaction. However, this could be circumvented by employing a thiol protecting group, and, for this purpose, acetyl protection of sulfur was found to be optimal, since it was sufficiently stable while also being easy to remove selectively using dimethylamino propylamine (DMAPA).[36]

With all the desired building blocks in hand, synthesis of the oligosaccharide mimics was undertaken using anaerobic conditions with freshly degassed solvents, to prevent the oxidation of Cu(I) to Cu(II) during the CuAAC reaction and thiol to disulfide under the TEC reaction. Furthermore, a standard UV lamp (365 nm) for TLC visualization was employed for the TEC radical chemistry. Otherwise, the reactions were performed on the bench.

The successful preparation of nine trisaccharide mimics listed in Figure 2, using a linear approach, demonstrates the compatibility of the TEC and CuAAC reactions in a one-pot setup. The reported outcomes are after silica gel column chromatography of the final product, since no purification of the intermediate products was performed. An overall yield of 22%−65% was achieved using a ratio of 1:1:1 among the reacting partners. The reactions were optimized utilizing this 1:1:1 stoichiometry as the building blocks were considered to be equally precious. Customarily, for conjugation of smaller decorations to larger scaffolds such as proteins[37,38] and polymers,[25,26] a vast excess of the smaller fragment is used.

A representative synthesis of a trisaccharide mimic is shown in Scheme 3. For the three tetrasaccharide mimics, both a linear approach and a convergent 2 + 2 block synthesis were employed (Scheme 2). Specifically, the linear approach was employed when a Group A thiol was chosen as the capping building block, whereas the convergent approach was utilized when Group A azides were chosen as the capping unit. The convergent approach was not employed with capping thiols from Group A, because this would result in it being necessary

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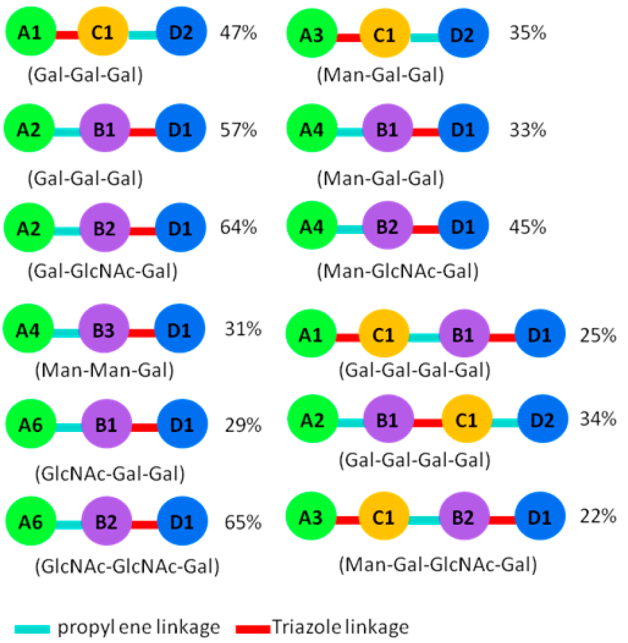
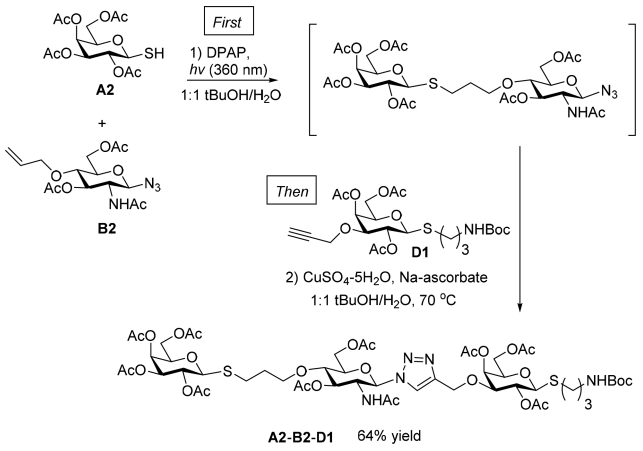


Figure 2. Synthesized protected trisaccharide and tetrasaccharide mimics. [Yields are given as a percentage of the isolated purified targets molecules.]

Scheme 3. Representative Linear Synthesis of the Gal-GlcNAc-Gal Trisaccharide Mimic



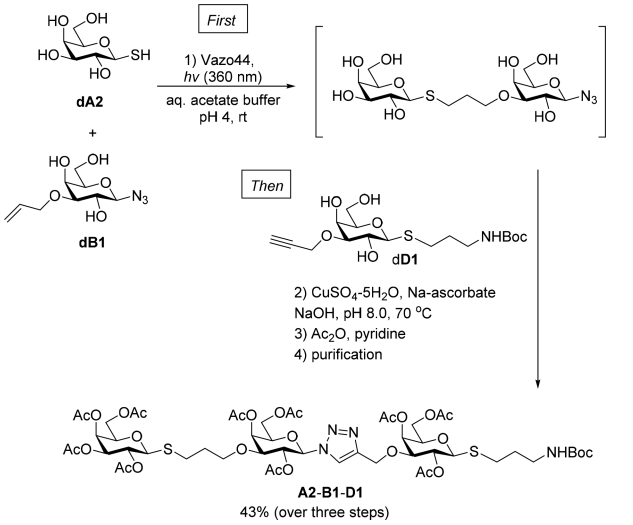
to perform a TEC reaction with a deprotected thiol from Group C and an alkene from Group D. Since the Group C building blocks also contain an alkyne functionality, it would be able to undergo a thiol−yne coupling with a building block from the same group, destroying the desired selectivity of the reaction.

All the mimics could be globally deprotected in excellent yields, using NaOMe in MeOH[39] to obtain the deprotected oligosaccharides.

To explore whether the reactions reported above also were compatible with carbohydrate building blocks in their deprotected form, **dA2** (deprotected **A2**) was reacted with alkene **dB1** (deprotected **B1**) in acetic acid buffer (pH 4.0) containing no organic cosolvent. The previously used radical initiator DPAP was found to be insoluble, while the radical initiator Vazo44[40] developed for radical reactions in an aqueous medium cleanly provided the desired intermediate, as judged by TLC analysis.

For the next synthetic step, it was found to be important to increase the pH via the addition of NaOH to pH 8 for the acid-labile Boc-protecting group to remain stable. After adjusting the pH of the reaction, the addition of **dD1** (deprotected **D1**), together with $CuSO_4 \cdot 5H_2O$ and sodium ascorbate, converted the intermediate to the desired trisaccharide mimic. Since it proved problematic to purify the unprotected trisaccharide mimic,[41] it was acetylated to ease purification and structural verification (see Scheme 4).

Scheme 4. One-Pot Synthesis of Trisaccharide Mimic dA2-dB1-dD1 without Protecting Groups



The ability of the prepared oligosaccharide mimics was next to be investigated as lectin binding ligands. First, a series of plant lectins were explored in a microarray setting. These were Concanavalin A (ConA), wheat germ agglutinin (WGA), *Lycopersicon esculentum* lectin (LEL), and *Vicia villosa* lectin (VVL).

No binding was found to occur to the latter lectin (VVL), which was included as a negative control that typically recognized GalNAc that was not present among the oligosaccharide mimics.

As shown in Figure 3. Con A exhibited binding to the three mimics **dA4-dB1-dD1**, **dA4-dB2-dD1**, and **dA4-dB3-dD1**, all possessing a terminal mannose unit as a thioglycoside. The

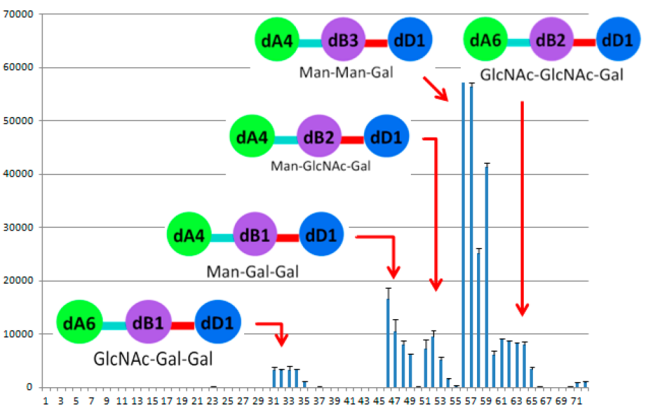


Figure 3. Glycan mimic microarray showing binding to Concanavalin A.

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compound showing the highest binding was **dA4-dB3-dD1**, which had two neighboring mannose residues. GlcNAc has previously been found to have substantial Con A interactions,[42] which could explain the observed cross-reactivity by mannose lacking but GlcNAc-displaying trisaccharides **dA6-dB1-dD1** and **dA6-dB2-dD1**.

WGA was found to bind strongly and exclusively to the oligosaccharide mimics possessing a terminal *N*-acetylglucosamine (GlcNAc) (**dA6-dB1-dD1** and **dA6-dB2-dD1**), as well as the positive control (GlcNAc itself).

In addition, weak LEL binding was observed to the same two compounds with a slightly higher specificity for **dA6-dB2-dD1** that contains two GlcNAc building blocks. Contrary to WGA, LEL did not bind significantly to the GlcNAc positive control. For figures showing binding to WGA and LEL, see the Supporting Information.

Given the positive results from the plant lectin studies, we next turned our attention to a human lectin (galectin) involved in health and disease. Galectins are a structurally related family of proteins that binds to β-galactoside motifs through a highly conserved carbohydrate recognition domain (CRD). They are involved in a pleiotropic number of fundamental biological processes, and they are key contributors to the homeostasis but also take part in many pathologies such as cancer progression, diabetes, and inflammatory and immune diseases.[43] They are classified in three groups: (i) dimeric galectins, which contain two CRDs; (ii) monomeric galectins, which contain a single CRD but form homodimers in vivo; and, finally, (iii) the so-called chimeric galectin, galectin 3, which is the only one that also contains a non-CRD region. This new region mediates the polymerization of galectin-3. Thus, in summary, all galectins are functionally multivalent in vivo. Since human galectin-3, which is known to be sensitive to a multivalent ligand presentation, is one of the prominent members of this lectin family and has been identified as a potential therapeutic target, it was evaluated as a possible target of the herein-synthesized (oligo)-galactosides as lactosamine mimics. Evaluation of their binding affinities toward the galectin-3 was performed by competitive fluorescence polarization assay, using known 2-[(fluoresceinyl)thioureido]ethyl 4-*O*-[3-*O*-(3-methoxybenzyl)-β-D-galactopyranosyl]-β-D-glucopyranoside probe[44] and 1,2-diacetamido-4-*O*-(β-galactopyranosyl)-1,2-dideoxy-β-D-glucopyranose[45] as a positive control.

In our assay, K_d of monogalactoside β-GalS$(CH_2)_3$NHBoc was found to be above 5 mM, which is a value in accordance with that usually reported for methyl β-D-galactopyranoside (4.4 mM)[46] (see Table 1). On the other hand, affinities consistently increased when switching from the monosaccharides to the disaccharides, up to the tetrasaccharides, and were, at least, higher by 1 order of magnitude. Disaccharide **dA1-dD1** was the least potent inhibitor, compared to other oligomers. The two galactosides are connected to a triazole scaffold which might confer too much rigidity or less than optimal orientation to accommodate the CRD binding site. Otherwise, characteristics of the spacers (nature or position) do not seem to significantly influence the recognition for higher oligomers. Noticeably, these linear oligo-galactosides proved more potent than classical cluster galactosides that were linked by their reducing end to a scaffold whose affinity for the galectin-3 was found in the upper mM range.[47,48]

Table 1. Dissociation Constants for Ligands of Galactin-3 at Room Temperature, Performed as Duplicates

ligand[a]	K_d (mM)	valency[b]
β-GalS$(CH_2)_3$NHBoc	>5	1
dA1-dD1	1.32	2
dA2-dD2	0.62	2
dA1-dC1-dD2	0.34	3
dA2-dB1-dD1	0.36	3
dA1-dC1-dB1-dD1	0.20	4
dA2-dB1-dC1-dD2	0.18	4

[a]Ligands are ranked according to their number of galactose moieties. [b]Valency is determined based on the number of galactose moieties.

In summary we have reported the first combined one-pot application of the CuAAC and TEC reactions and demonstrated their use in the preparation of mimics of natural oligosaccharides incorporating the most common oligosaccharide building blocks and conserving the naturally preferred linkage pattern. A collection of nine trisaccharide mimics and three tetrasaccharide mimics possessing acetyl groups were prepared in a mixture of ^{t}BuOH/H_2O, before being deacetylayed to provide the deprotected oligosaccharide mimics. The synthesis of a trisaccharide mimic from the deprotected building blocks was also demonstrated in aqueous buffer under anaerobic conditions.

It was possible to show that the prepared compounds were both recognized by plant lectin and human galectin-3. Regarding the latter, a cluster effect was observed, suggesting that these linear oligomers could be an alternative to the dendronized or branched multivalent structures usually proposed. The stable intermonomeric linkages should confer higher survival to these oligomers in biological media, designing them as valuable surrogates to natural oligosaccharides.

The developed strategy combines the convenience of the CuAAC and TEC reactions with a one-pot strategy and a desirable stoichiometry of reactants and can be employed to prepare an array of biomolecule mimics or for bioconjugation.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02811.

Experimental synthetic procedure and characterization with detailed description of lectin binding evaluation and data (PDF)

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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