Thio-click approach for the synthesis of peptide-oligonucleosides, oligomannoside mimetics and chiral crown ethers

Final reports

1. Introduction

Synthetic oligosaccharides and their mimetics are widely used for elucidating the essential roles that carbohydrates play in living organisms. Thio-linked oligosaccharides and glycoconjugates are valuable glycomimetics, able to resist enzymatic and acidic hydrolysis, which significantly potentiate their application in molecular recognition studies and also in drug development.[1-3] Consequently, thioglycosides are favourable synthetic targets and many methodologies have been developed for their synthesis.[4,5] However, the stereoselective S-glycosylation particularly the selective formation of the 1,2-cis-alpha-S-glycosidic bond still poses a major challenge.

The radical-mediated addition of thiols to non-activated double bonds[6,7] has been used in organic syntheses for a long time and with the advent of click chemistries this transformation has its renaissance in glycochemistry as a robust ligation tool. [8,9] However, it has become evident only in recent years that unsaturated sugars can efficiently be applied as the alkene partners in the thiol-ene coupling reactions. Our group reported for the first time that photoinitiated thiol-ene coupling reactions of 2-substituted glycals can be applied for the stereoselective formation of the challenging 1,2-cis-α-thioglycosidic linkage [10]. We demonstrated on the exemplary case of 2-acetoxy-D-glucal that the UV-light-initiated addition of a range of thiols including amino acid, peptide, and various sugar thiols in the presence of the photoinitiator 2,2-dimethoxy-2-phenylacetophenone (DPAP) occurs with good to high yields and complete stereoselectivity providing an easy access to 1,2-cis-α-linked thiodisaccharides and thioglycoconjugates.

In the frame of the OTKA K109208 project our goal was to exploit this method for the synthesis of carbohydrate based compounds of biological or synthetic relevance starting from various unsaturated sugars.

Our specific aims were:
1. Preparation of oligomannoside mimetics of potential antimicrobial activity by reaction between mannosyl-1-thiol and 2,3-unsaturated glycosides.
2. Synthesis of novel type of peptide-oligonucleosides by addition of cysteine or glutathione onto nucleoside-derived enosides
3. Synthesis of carbohydrate-based crown ethers by intramolecular hydrothiolation of 2,3-unsaturated glycosides.

2. Results

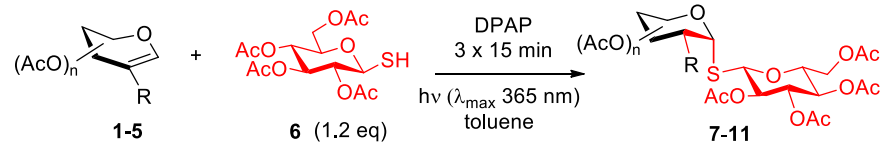
2.1. Photoinduced thiol-ene reactions of 1,2- and 2,3-unsaturated sugars

2.1.1. Photoinduced thiol-ene reactions of 2-substituted hexo- and pentopyranosyl glycals

The α–*O*-glycosides are abundantly found in nature and many 1,2-cis–α–linked sugars including α–L-fucosides, -D-galactosides as well as 2-deoxy-2-aminoglycosides with α–D-*gluco* and α–D-*galacto* configurations play important roles in various biological processes. Synthesis of stable

thio-linked analogues of this biorelevant glycans for biomedical applications is of eminent importance. However, a general synthetic method for the 1,2-cis-S-glycosides has not yet been developed and therefore is required

We studied the photoinitiated thiol-ene coupling reactions of 2-substituted glycals as a generally applicable strategy for the stereoselective 1,2-cis–α–thioconjugation. [11] While all glycals reacted with full α-selectivity, the efficacy of the reactions varied in a broad range depending on their configuration and glycals bearing axial acetoxy substituents reacted with very low efficacy at room temperature. Therefore, we performed a comprehensive optimization and mechanistic study on the photoinduced hydrothiolation of different D- and L- hexoglycals with various thiols at the temperature range of +50 °C to −80 °C (selected examples of this study is shown in Table 1). [11-13] During the optimization experiments, we discovered the very unique temperature effect that heating inhibits, while cooling promotes the thiol-ene coupling reaction. We formulated that the reaction temperature controls the equilibrium of the rapidly reversible thiyl addition (propagation) step of the radical chain process. Conducting the reactions at low temperature proved to be an adequate strategy to prevent the degradation of the intermediate carbon-centered radical, formed in the thiyl addition step, hence allowing it to react with a thiol in the hydrogen abstraction step. We have found that conversion of the starting glycals increased gradually by cooling and good to excellent yields were achieved at -80 °C in most cases (**7**-**11**).[11-13] Although enoses with all-equatorial substitution patterns (**4**, **5**) generally showed good reactivity at room temperature, the cooling was beneficial in those cases too. The heating proved to be detrimental to the reaction as it was demonstrated by running the hydrothiolation of D-galactal **1** and L-fucal **3** at +50 °C.



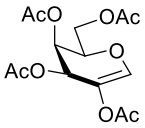
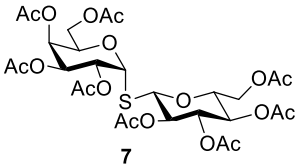
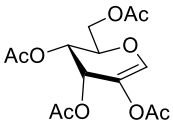
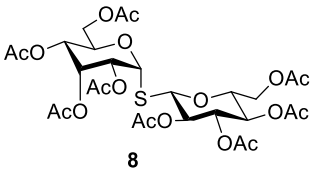
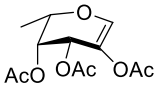
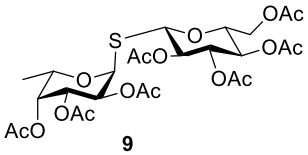
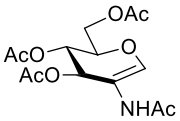
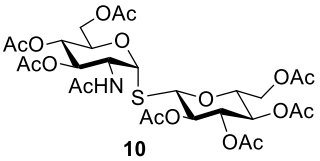
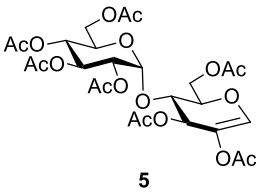
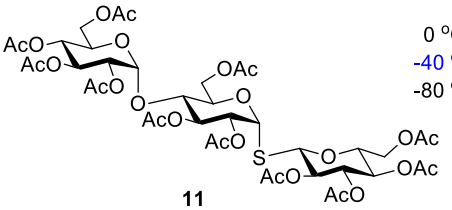
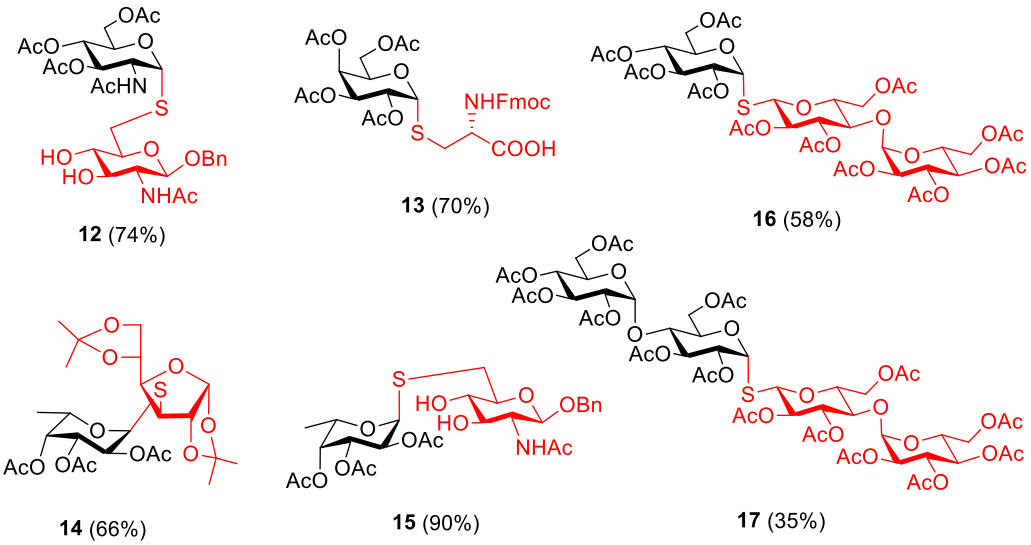
Glycal	Product	Temperature, yield
 1	 7	rt, 42% 0 °C, 48% -40 °C, 65% -80 °C, 85% +50 °C, 16%
 2	 8	0 °C, 38% -40 °C, 76% -80 °C, 92%
 3	 9	rt, 22% rt, 6 eq thiol, 33% 0 °C, 33% -40 °C, 66% -80 °C, 90% +50 °C, 9%
 4	 10	rt, 63% -80 °C, 73%
 5	 11	0 °C, 51% -40 °C, 71% -80 °C, 60%

Table 1. Thiol-ene reactions of selected 2-substituted hexoglycals with 1-thioglucose **6** at different temperatures. DPAP: 2,2-dimethoxy-2-phenylacetophenone

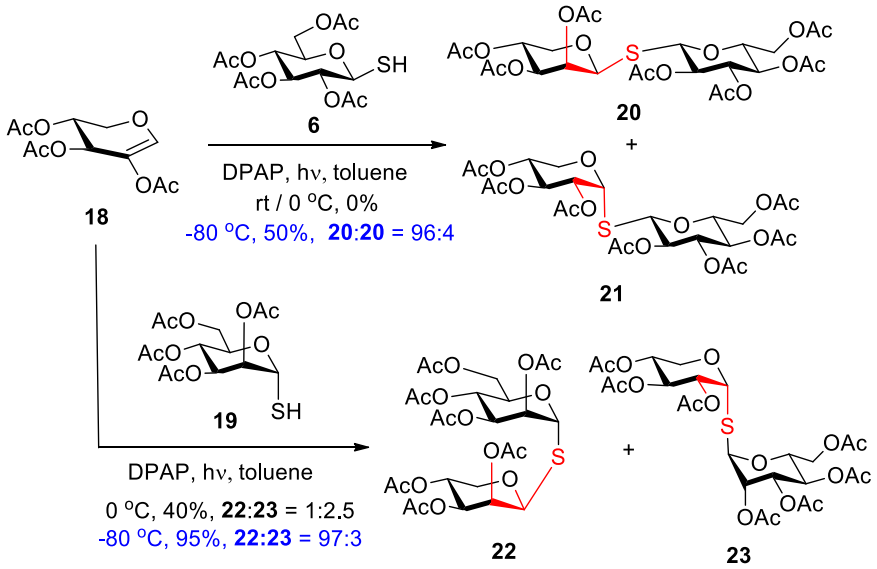
The low-temperature thiol-ene coupling reaction was exploited for the stereoselective synthesis of a series of 1,2-cis-α-thio-linked D-glucoside (**16**), D-galactoside (**13**), L-fucoside (**14**, **15**), D-GlcNAc (**52**-**54**) and maltose derivatives (e.g. **17**) up to pentasaccharide (selected examples are shown in Scheme 1).[11-14]

The thiol-ene coupling reaction of 2-acetoxy-D-glucal allowed multigram-scale synthesis of ethyl 1-thio-α-D-glucopyranoside which was utilized as a starting compound for the preparation of a series of heparinoid pentasaccharide sulfonic acid derivatives of anticoagulant activity. [15,16]



Scheme 1. 1,2-cis-α–Thio-oligosaccharides obtained by thiol-ene reactions of 2-substituted glycals at -80 °C

Extending the hydrothiolation reactions to pentopyranosyl glycals, a lower level of diastereoselectivity was observed (Scheme 2). [13] Addition reactions of 1-thiosugars **6** and **19** to 2-acetoxy D- and L-pentoglycals (e.g. **18**) led to the formation of 1,2-cis-α- (**21**, **23**) and 1,2-cis-β-thioglycosides (**20**, **22**) in varying ratios depending on the temperature and the configuration of both reactants. Cooling had a double positive effect on the reactions, increased the yields and in most cases significantly raised the stereoselectivity. The lack of complete diastereoselectivity in the pentose series can be explained with the higher conformational flexibility of the pentopyranoses.



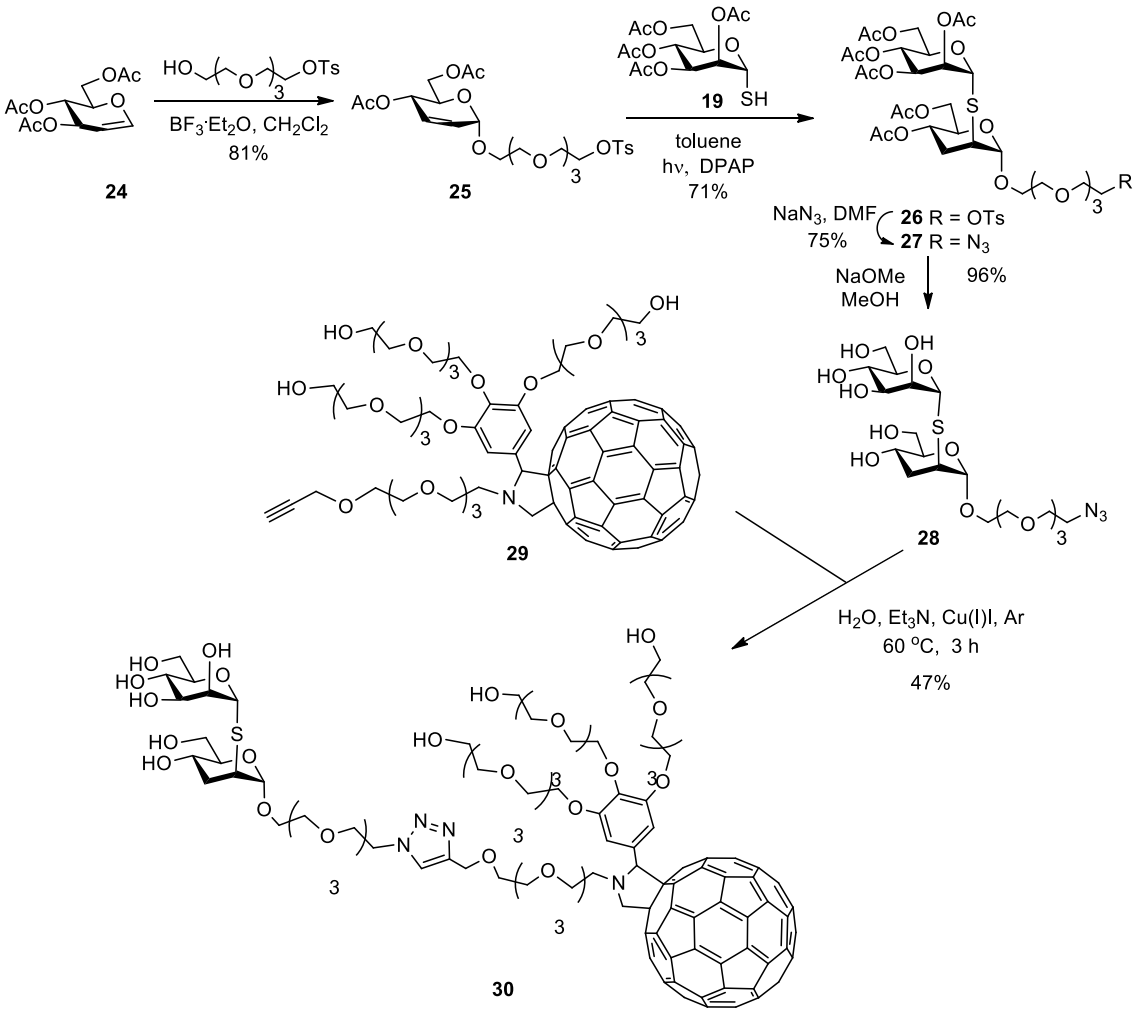
Scheme 2. Hydrothiolation reactions of D-xylose derived **18** with thiols **6** and **19** at different temperature

The effects of solvents, protecting groups and nature of thiols on the efficacy of the thiol-ene reactions were also studied [11, 13,17] Remarkably, the photoinduced radical mediated thiol-ene reactions required mild conditions (irradiation at λmax 365 nm for 3 × 15 min at room temperature), showed tolerance to air, water, and a broad range of functional groups, and provides easy and efficient access to stable glycomimetics for biomedical applications. Therefore, new applications can be predicted.

The relevance of the above results is demonstrated by the fact that two of our articles on this topic [11,13] were accepted and published as Hot Papers in *Chemistry – A European Journal*.

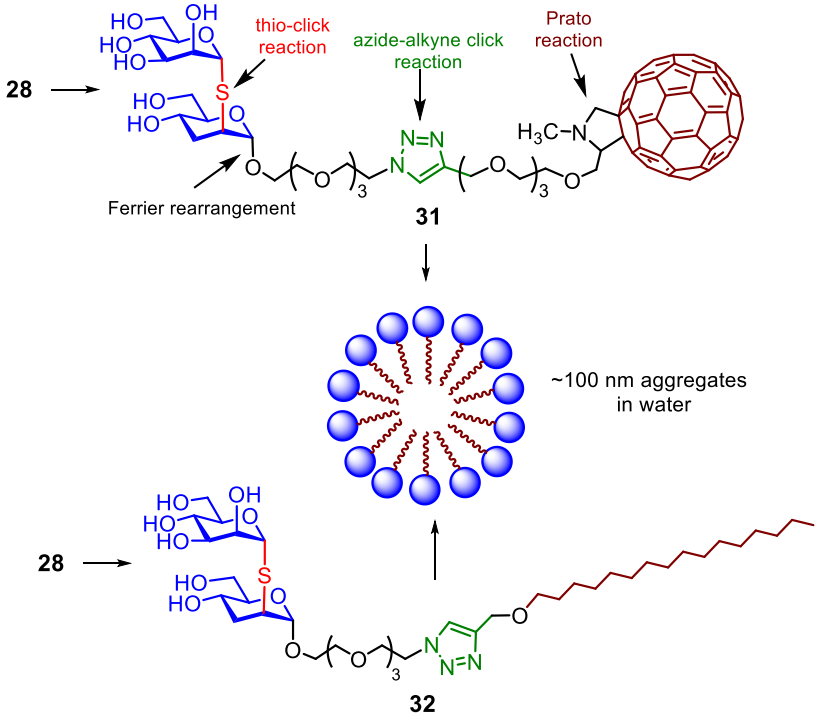
2.1.2. Synthesis of multivalent disaccharide derivatives for lectin binding studies

Photoinduced thiol-ene coupling reaction of 2,3-unsaturated glycosides is a viable strategy for introduction of a thio-linkage to C2-position of glycopyranosides with full stereoselectivity [10]. This method was exploited for the synthesis of α-(1→2)-thio-linked mannobioside derivatives for lectin-binding studies. [18,19]



Scheme 3. Regio- and stereoselective synthesis of spacer-armed α-(1→2)-thio-linked mannobioside **26** and its conjugation, after azidation, to fullerene derivative **29**

Among the pathogen-associated carbohydrate patterns, the Man(α1→2)Manα disaccharide motif is of particular interest because its multivalent derivatives are considered as potential antiviral or antibacterial agents through interaction with mannose-binding lectins. We developed a straightforward synthesis of self-assembling amphiphilic compounds containing a hydrolytically stable S-linked 1,2-mannobioside residue (Scheme 3). The spacer-armed mannobioside mimic **26** was efficiently prepared by Ferrier rearrangement followed by photoinduced radical hydrothiolation. Next, the azide-functionalized disaccharide **28** was conjugated to various, propargyl-containing lipophilic carriers including fullerene derivative **29**. We demonstrated that the obtained amphiphiles (**30**, **31** and **32**) form nanoscale aggregates in water (Scheme 4), therefore they can function as multivalent ligands. [18]

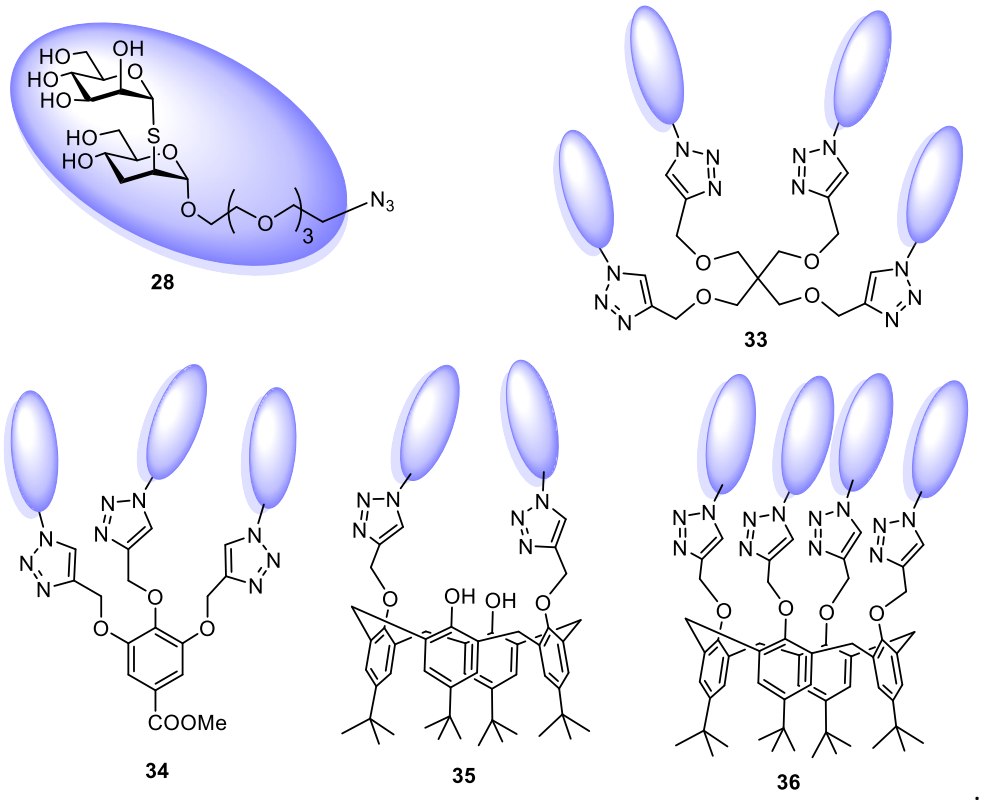


Scheme 4. Structure and self-assembly of Man(α1→2)Manα-containing amphiphiles

The water-soluble fullerene **29** was used for the synthesis of a cluster-forming sialylthio-D-galactose fullerene conjugate as potential inhibitor of the influenza virus hemagglutinin.[20] The aggregating amphiphilic compound did not inhibit the influenza virus hemagglutinin, but it proved to be a modest inhibitor of its neuraminidase with a 50% inhibitory concentration of 81 μM.

Related to this work, we developed a nucleophilic cyclopropanation-based conjugation method to attach sugar residues to fullerene C60 scaffold by a stable ether-linkage.The presented modification of the malonate-based Bingel reaction, providing biologically stable fullerene conjugates, may find application in the synthesis of fullerene derivatives of potential biomedical activity.[21]

In a next study, multivalent mannoside derivatives were prepared as potential inhibitors of lectin BC2L-A. [19] This lectin is one of the virulence factors deployed by the biofilm-forming Gram-negative bacterium *Burkholderia cenocepacia* in the infection process. The (α1→2)-thio-linked mannobioside mimic **28** was conjugated to different multivalent scaffolds such as propargylated calix[4]arenes, methyl gallate and pentaerythritol by azide-alkyne 1,3-dipolar cycloaddition to produce di- tri and tetravalent mannoclusters **33**-**36** (Scheme 5). The interaction between the glycoclusters and the mannose binding BC2L-A of *Burkholderia cenocepacia* was examined by isothermal microcalorimetry, surface plasmon resonance, inhibition of yeast agglutination and analytical ultracentrifugation. Compounds **33** and **34** were able to inhibit the binding activity of the lectin, although the inhibitory effect was not as high as expected, probably because they are unable to chelate both binding sites of the BC2L-A dimer and achieve increased affinity. [19]



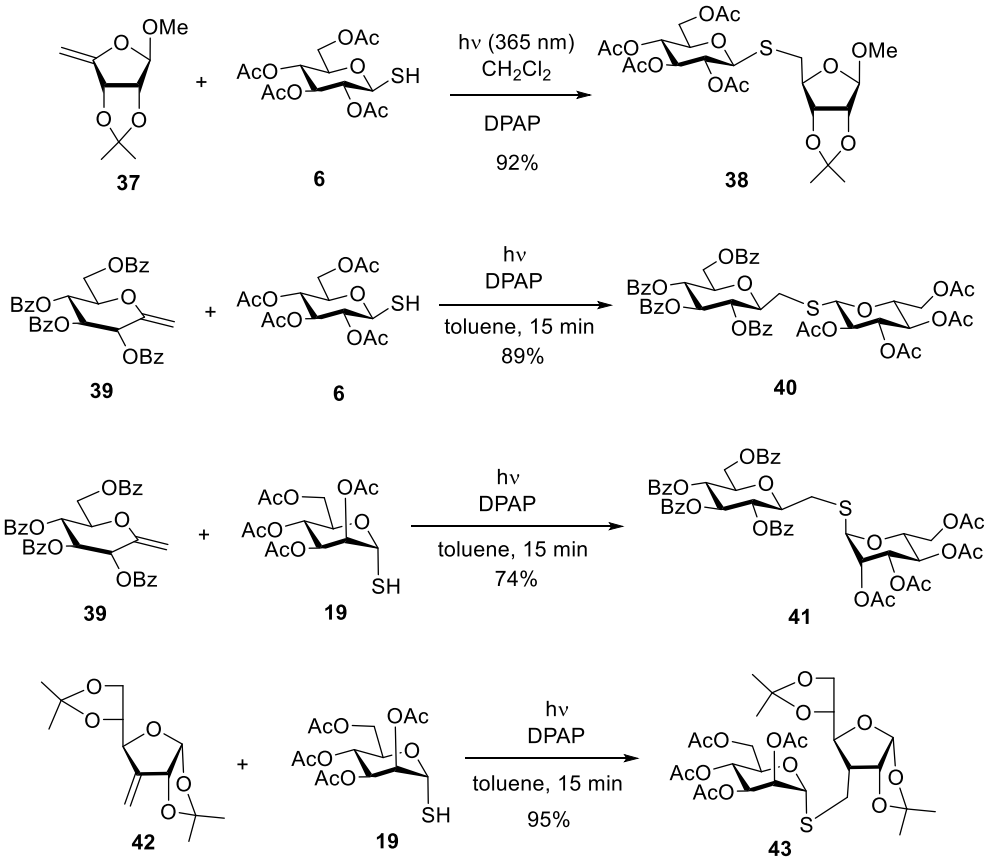
Scheme 5. Multivalent mannoclusters displaying the Man(α1→2)Manα motif

On the basis of the above results, we designed and prepared eight multivalent rhamnobioside derivatives and studied the inhibitory effect of the obtained rhamnoclusters on the interaction of recombinant horseshoe crab plasma lectin (rHPL) with the Gram-positive bacterium *Pseudomonas aeruginosa.* [22] The deeper understanding of the molecular interactions between rHPL and P. aeruginosa may lead to the development of novel rHPL-based strategies for infection diagnosis and even therapy

2.2. Synthesis of C-S-bonded glycomimetics, sugar modified nucleosides and peptide-oligonucleosides

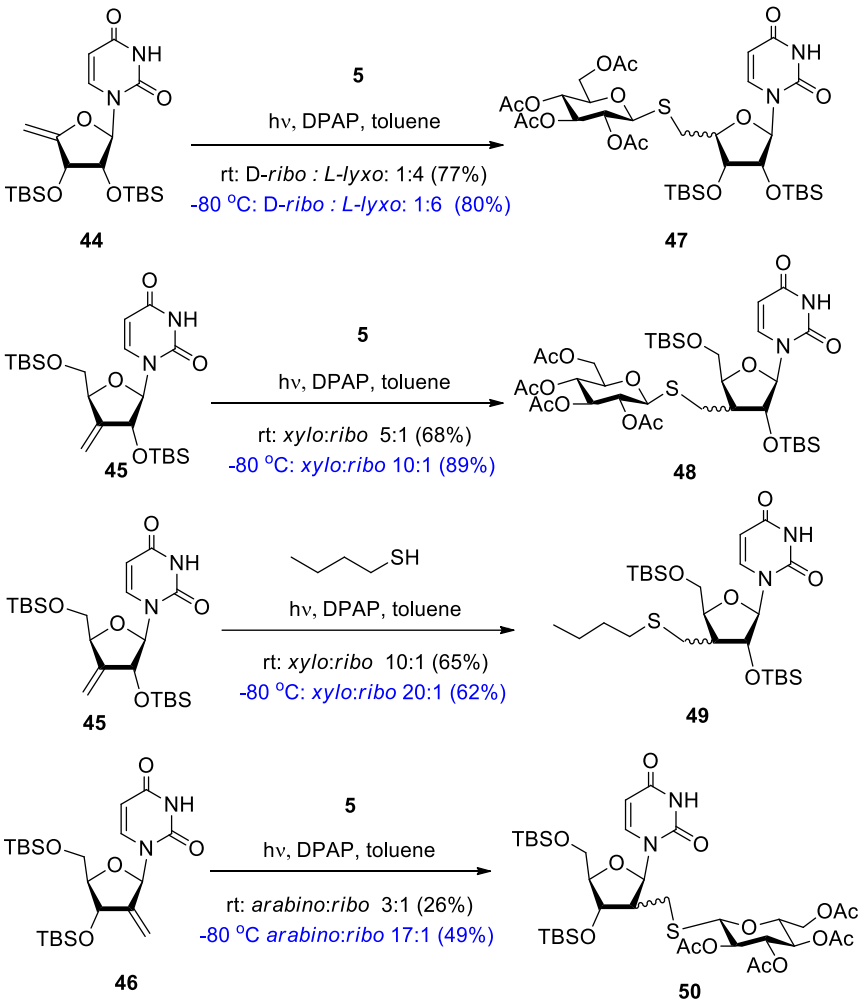
Dondoni and co-workers reported that photoinduced hydrotholation of the furanoside-derived alkene **37** with 1-thiosugar **6** provided the corresponding S-linked disaccharide mimetic **38** with high yield and with excellent diastereoselectivity.[23]

We extended this method to *exo*-glycals and furanoid exomethylene derivatives to produce C-S-bridged glycomimetics (Scheme 6). [17, 24, 25]. Addition of various thiols onto *exo*-glucal **39** furnished the β-C-S-bridged disaccharide products (e.g. **40** and **41**) with complete regio- and stereoselectivity. [24] Hydrothiolation of peracetylated *exo*-galactal and exo-xylal derivatives with thiols also led to exclusive formation of the corresponding β-D-glycopyranosylmethyl-sulfide derivatives.[25] Reactions of 3-*exo*-methylene-glucofuranose derivative **42** with various thiols also proceeded with complete diastereoselectivity to give the corresponding C-S-bonded disaccharide mimetics with D-*allo*-configuration at the furanose unit (e.g. **43**) [17,24].



Scheme 6. Thio-click-based synthesis of C-S-linked disaccharide mimetics (selected examples)

We applied the thiol-ene coupling method, for the first time, on nucleoside enofuranosides to produce sugar-modified nucleoside derivatives. [26,27]. In contrast to analogous reactions of simple sugar exomethylenes, surprisingly, hydrothiolation of nucleoside alkenes under the standard conditions of various initiation methods showed low to moderate yields and low stereoselectivity (Scheme 7). Optimizing the reaction conditions, we have found that cooling the reaction mixture has a significant beneficial effect on both the conversion and the stereoselectivity, and UV-light initiated hydrothiolation of *C*2'- *C*3'- and *C*4'-exomethylene derivatives of nucleosides (e.g. **44**-**46**) at −80 °C proceeded in good to high yields, and, in most cases, with high diastereoselectivity. Beyond the temperature, the solvent, the protecting groups on nucleosides and, in some cases, the configuration of the thiols also affected the stereochemical outcome of the additions.

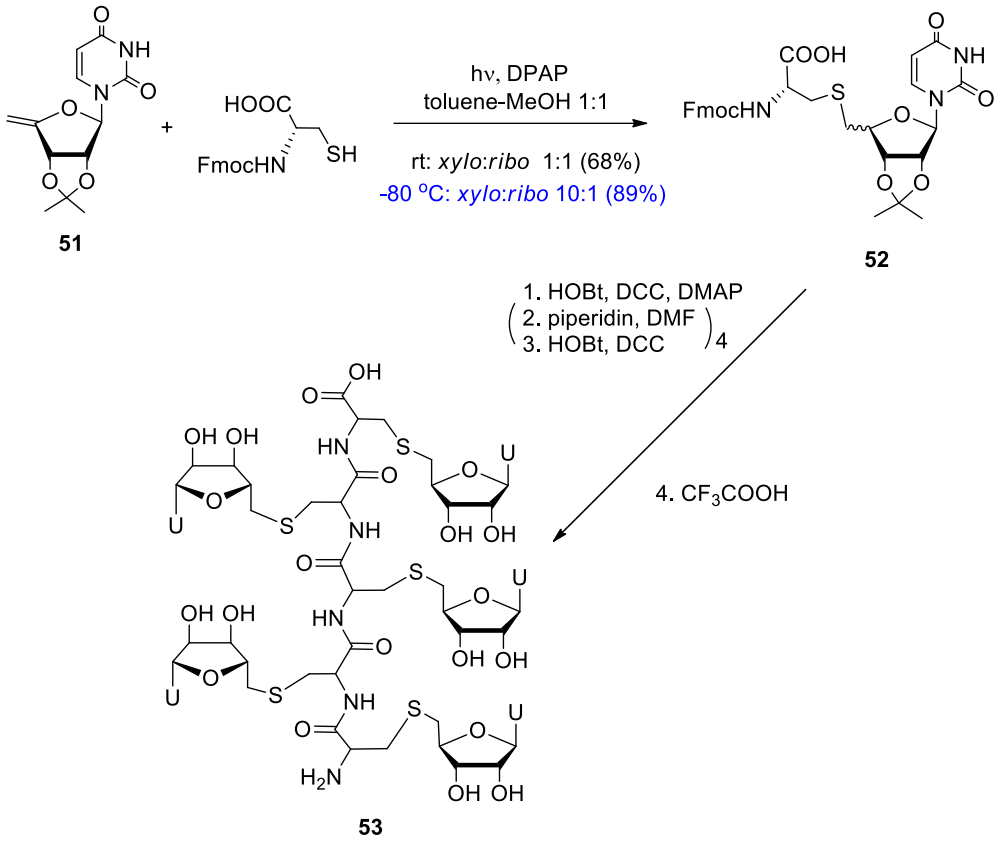


Scheme 7. Application of the thio-click approach for the synthesis of sugar modified nucleoside analogues (Selected examples)

The bioactivity of 3'-deoxy-C3'-substituted xylofuranosyl-pyrimidine nucleoside analogues was studied on tumorous SCC (mouse squamous carcinoma cell) and immortalized control HaCaT (human

keratinocyte) cell lines. Several alkyl-substituted analogues (e.g. *n*-butyl derivative **49**) elicited promising cytostatic activity in low micromolar concentrations with a slight selectivity toward tumor cells. [27].

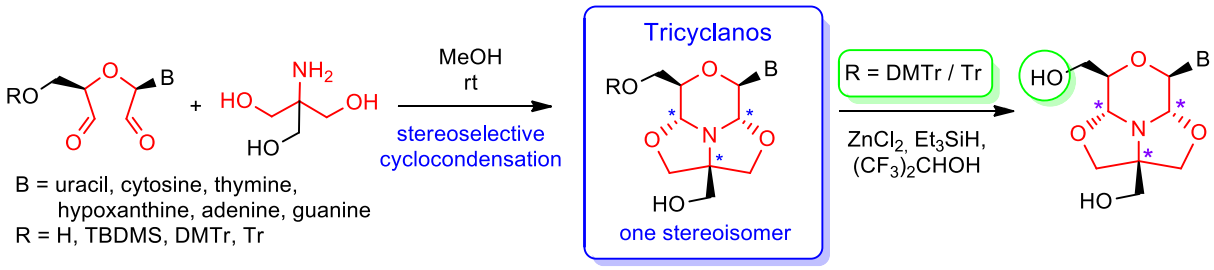
Upon hydrothiolation of the *C*4'-exomethylene-uridine **51**, the corresponding D-*ribo* configured cysteinyl conjugate **52** [26] was obtained in high yield (Scheme 8). This derivative was coupled to Wang resin and oligomerized by solid phase peptide synthesis to produce cysteinyl uridine pentapeptide **53**, the first member of a novel type of peptide nucleic acids. [28] Optimization experiments of the synthesis and purification of **53** is under way in our laboratory.



Scheme 8. Synthesis of cysteinyl uridine conjugate **52** by thio-click approach and its oligomerization on Wang resin by solid phase peptide synthesis

Synthesis of a novel type of nucleoside analogues, called tricyclanos, in which the sugar part is replaced by a new, morpholine-containing heterotricycle was also developed. [29] 1,5-Dialdehydes obtained from properly protected uridine, ribothymidine, cytidine, inosine, adenosine and guanosine by metaperiodate oxidation reacted readily with tris(hydroxymethyl)aminomethane to provide the corresponding tricyclic derivatives with three new stereogenic centers (Scheme 9). Through a double

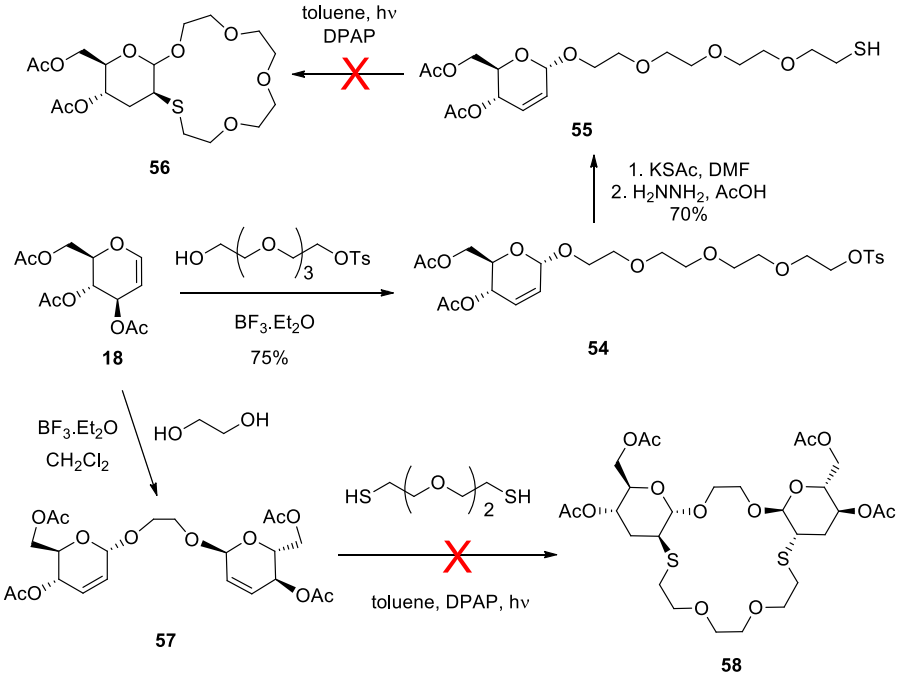
cyclisation cascade process the tricyclic compounds were obtained in good to high yields, with very high diastereoselectivity. Formation of one stereoisomer, out of the eight possible, was observed in all cases. Using a mixture of $ZnCl_2$, Et_3SiH and hexafluoroisopropanol for deprotection of the acid-sensitive tricyclano nucleosides mild and efficient detritylation was achieved. [29,30]



Scheme 9. Synthesis of tricyclano derivatives from nucleoside dialdehydes by substrate-controlled asymmetric synthesis

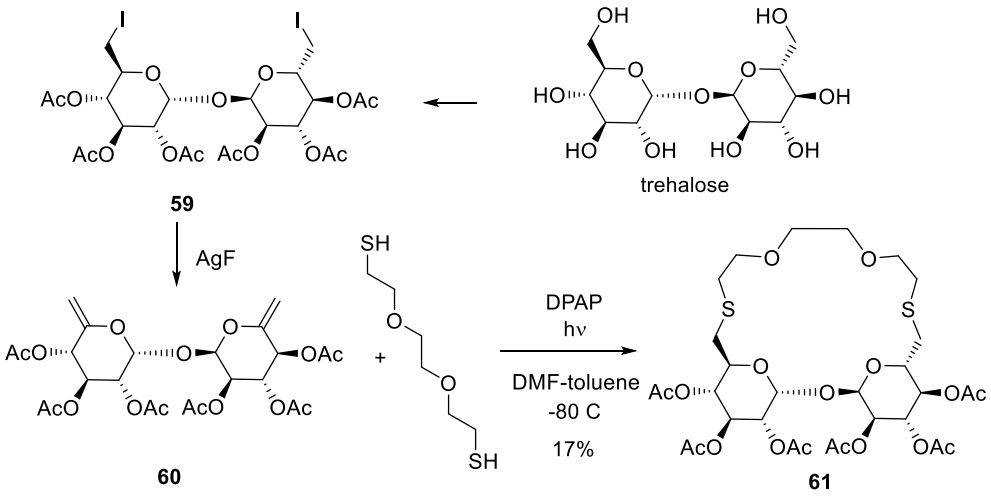
2.3. Towards synthesis of oxathia-crown ethers

We planned to exploit the UV-light induced thiol-ene reactions for the synthesis of carbohydrate-based oxathia-crown ethers. However, our efforts to elicit addition of oligoethylene glycol-type thiol to 2,3-unsaturated sugar by either an intra- (**55**) or an intermolecular way (**57**) were unsuccessful, probably due to the decreased reactivity of the oligoether-type thiol in the radical-mediated addition reaction (Scheme 10). [31]



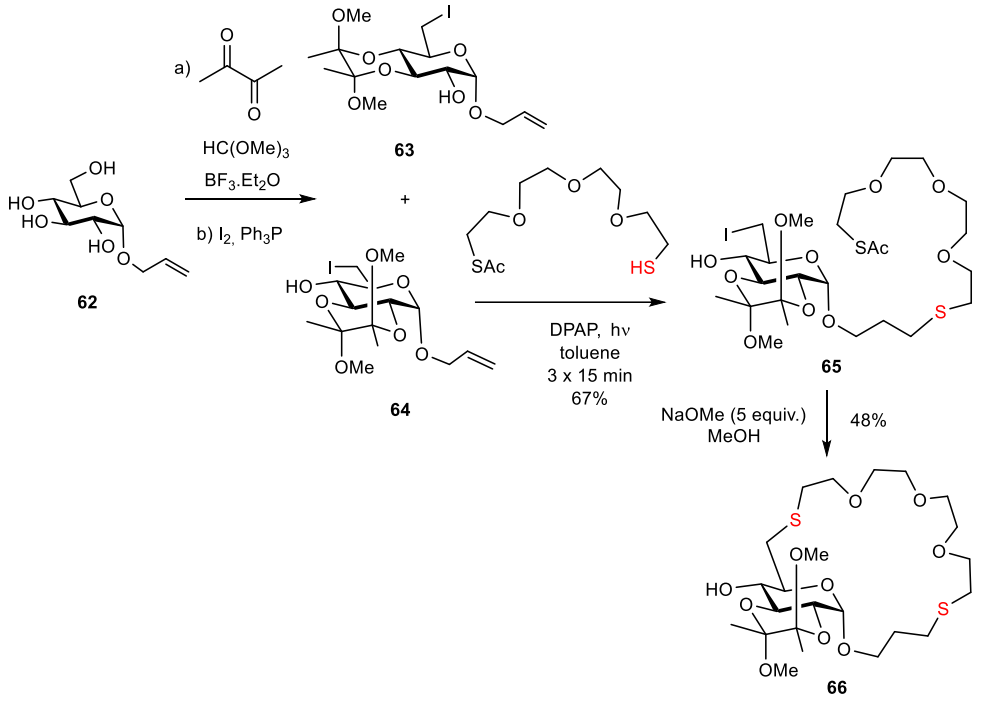
Scheme 10. Attempeted intra- or intermolecular hydrothiolation reaction of 2,3-unsaturated glycosides **55** and **57**

Applying the trehalose-derived disaccharide diolefin **60** possessing exocyclic double bonds in the thiol-ene reaction with triethyelene glycol dithiol led to the formation of the desired oxathia-crown ether **61**, albeit with very low yield (Scheme 11). [32]



Scheme 11. Intermolecular thioladdition onto exocyclic double bonds of trehalose-derived diolefin **60**

As a new approach, the thiol-ene method was combined with a nucleophilc substitution reaction in the cyclization step (Scheme 12). Starting from allyl glycoside **62**, through the corresponding butane diacetal derivatives [33], the sugar- triethyelene glycol dithiol conjugate **65** was efficiently prepared by the thiol-ene coupling reaction. Finally, it was thio-cyclized by a NaOMe mediated nucleophilc substitution reaction to produce crown ether **66** with acceptable yield. The optimization of this reaction route is under way.



Scheme 12. Synthesis of sugar-based oxathia-crown ether **66** by thiol-ene reaction followed nucleophilic substitution reaction

2.4. Miscellaneous results

Two versions of the free-radical thiol–ene addition, a photoinduced reaction, and a UV-light-free hydrothiolation using triethylborane as the initiator, were studied for the conjugation of fluorescent dithiomaleimide to biologically active compounds. The compounds all showed almost identical absorption and emission spectra, proving that the structure of the thiols has no influence on the fluorescence properties of the maleimide part of the molecules [34]

In the frame of this project various conjugation methods were developed for lipophilic modification of the glycopeptide antibiotic teiicoplanin. The obtained derivatives showed good to excellent antibacterial and/or antiviral activities. [35-38]

Refrences (articles with the OTKA identification number are highlighted in red)

[1] B. Ernst, J. L Magnani, *Nat. Rev. Drug Discov.* **2009**, *8*, 661-667.

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