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Synthesis of *S*-Linked Glycoconjugates and *S*-Disaccharides by Thiol–Ene Coupling Reaction of Enoses†

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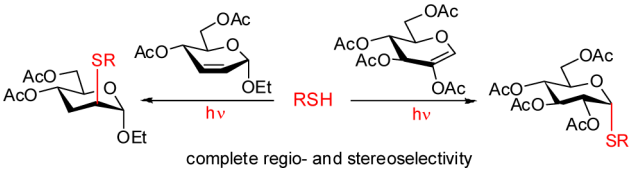
ABSTRACT



Free-radical hydrothiolation of the endocyclic double bond of enoses is reported. Reaction between 2-acetoxy-D-glucal and a range of thiols including amino acid, peptide, glycosyl thiols, and sugars with primary or secondary thiol functions gave *S*-linked α-glucoconjugates and *S*-disaccharides with full regio- and stereoselectivity. Addition of glycosyl thiols to a 2,3-unsaturated glycoside also proceeded with good selectivity and afforded a series of 3-deoxy-*S*-disaccharides.

In the last two decades, carbohydrate mimetics that are resistant toward enzymatic hydrolysis have been synthetic targets in glycochemistry for their potential to be used as probes in biological studies and as leads for new therapeutic agents.[1] Thioglycosides,[2] in which the native *O*-glycosidic linkage is replaced by an *S*-glycosidic bond, are especially valuable glycoside mimetics because of their enhanced chemical stability and resistance to glycosidases.[3]

The thioglycosidic linkages are generally synthesized by glycosylation of thio acceptors with activated glycosyl donors,[4] by S_N2-like displacement of a good leaving group of glycosyl acceptors with 1-thioaldoses,[5] and by Michael addition of 1-thiolates to sugar enones.[6] Ferrier reactions between glycals and sulfur-containing coupling partners[7] and ring-opening of 3,4-anhydro sugars by a 1-thioaldose nucleophile[8] are also included in the list of employed reactions.

Free-radical addition of thiols to alkenes,[9] termed thiol–ene coupling or thiol–ene click reactions,[10] has already been successfully applied to generate thioglycosidic linkages. Syntheses of glycodendrimers,[11] *S*-linked protein

† Dedicated to the memory of András Lipták, deceased June 11, 2012.
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glycoconjugates,[12] and thiodisaccharides[13] have been reported via light-mediated radical addition of glycosyl 1-thiols to terminal double bonds. However, enoses, containing an endocyclic double bond, have not been incorporated within the thiol−ene coupling strategy until very recently. We envisaged the utilization of the easily available enoses such as glycals, 2-acetoxy glycals, and Ferrier glycals (2,3-unsaturated glycosides) as the ene partners in the photoinduced hydrothiolation reaction. During the early stages of this work, Dondoni et al. published their results on the free-radical addition of anomeric sugar thiols to glycals affording stereoisomeric mixtures of 1-deoxy-*S*-disaccharides.[14] Therefore, we focused on the application of 2-acetoxy glycals[15] and 2,3-unsaturated glycosides[16] in the thiol−ene coupling to allow access to *S*-linked glycoconjugates and *S*-disaccharides.

The addition of ethanethiol to 2-acetoxy-3,4,6-tri-*O*-acetyl-D-glucal **1a**[15] in toluene was investigated and optimized initially, irradiating at λ_{max} 365 nm in the presence of 2,2-dimethoxy-2-phenylacetophenone (DPAP) as a cleavage-type photoinitiator[9d] (Table 1). The reaction resulted in the exclusive formation of ethyl 2,3,4,6-tetra-*O*-acetyl-α-thioglucoside **2a**.[17,18]

The conversion rate was higher than 90% after 3 × 15 min irradiation, and the reaction did not go to completion even after prolonged exposure to UV light. It has been found that exclusion of the air slightly improved the yield. Remarkably, the method has been successfully applied on large scale, using 30 g of **1a** to produce efficiently the crystalline **2a** in 80% yield.

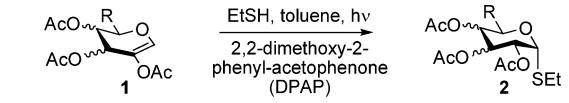
We were pleased to find that hydrothiolation of 2-acetoxy glycals **1b**−**d** with ethanethiol under the optimized conditions took place with full regio- and stereoselectivity and high yield, in all cases affording the corresponding 1,2-*cis* α-thioglycosides **2b**−**d**, respectively. Reactions of the galactal derivative **1b**[15] and the allal **1c**[19] revealed that the orientation of the 3- and 4-*O*-acetyl moieties did not affect the stereochemical outcome of the hydrothiolation (Table 1).

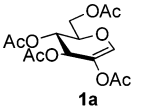
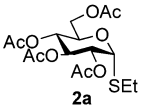
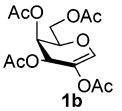
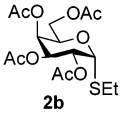
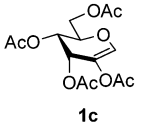
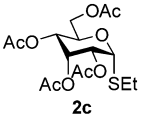
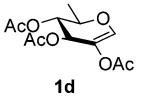
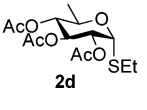
Hydrothiolation of the pentose-derived 2-acetoxy-glycal **3a**,[20] applying the above conditions, gave a stereoisomeric mixture of the 1,2-*cis* and 1,2-*trans* α-thioglycosides **4a**[21] and **5a** in a ratio of 2:1. Analogously, reaction between ethanethiol and **3b**[22] led to the formation of both the 1,2-*cis* and 1,2-*trans* α-thioglycosides **4b** and **5b**. In this case, however, the latter was the main product (Table 2). The above reactions clearly showed that a bulky C-6 group (either acetoxymethyl or methyl) anchored *β*-side to the sugar ring could ensure the stereoselective formation of the 1,2-*cis* C-2-radical intermediates (I) upon addition of the thiyl radical (Figure 1). In the absence of a bulky substituent, the 1,2-*cis* radical (II_{cis}), in which the 2-acetoxy group is equatorial, and the 1,2-*trans* radical (II_{trans}), in which the same group is axial, can both be formed, and the ratio of them depends on the stereochemistry of the adjacent C-3 substituent.

To demonstrate the feasibility of this approach for the synthesis of biorelevant glycoconjugates, compound **1a** was reacted with a range of thiols (**6**−**13**, Table 3). We found that all reactions proceeded with high selectivity in favor of the α-thioglucosides, and the solvent turned to be key to the reaction efficiency. *N*-Acetyl-L-cysteine (**6**) reacted readily with the endocyclic double bond of **1a** in toluene−MeOH and gave **14** in good yield. However, low conversion of the reactants was observed when **1a** was reacted with captopril **7**, an angiotensin-converting enzyme (ACE) inhibitor, under the above conditions. Changing the solvent to MeOH enhanced the conversion significantly and afforded thioglucoside **15** in excellent yield.

Surprisingly, reaction between **1a** and glycerine-1-thiol **8** showed very low conversion of the glycal when either

Table 1. Free-Radical Addition of Ethanethiol to 2-Acetoxy Glycals[a]



Glycal	Product	Yield[b] (%)
 **1a**	 **2a**	81 73[c]
 **1b**	 **2b**	89
 **1c**	 **2c**	86
 **1d**	 **2d**	85

[a] Reaction conditions: abs toluene, under Ar, ~40 mg mL^{-1}, 3 × 5 equiv of EtSH, 3 × 0.1 equiv of DPAP, 3 × 15 min irradiation, room temperature. [b] Yield of isolated compounds. [c] The reaction was performed without deoxygenation.

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(17) Photochemical addition of ethanethiol to **1a** has previously been described by Kushida et al.,[18] who reported that 25 h irradiation of **1a** dissolved in ethanethiol (500 mg/18 mL) afforded the α-thioglucoside derivative **2a** with 77% yield.
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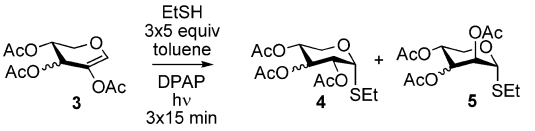
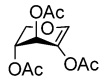
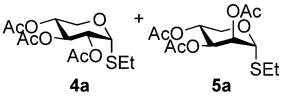
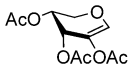
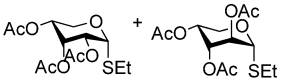
Table 2. Free-Radical Addition of Ethanethiol to Pentose-Derived 2-Acetoxy Glycals



Glycal	Products	Yield[a] (%)
 **3a**	 **4a** **5a**	**4a**: 44 **5a**: 23
 **3b**	 **4b** **5b**	**4b**: 30 **5b**: 58

[a] Yield of isolated compounds.

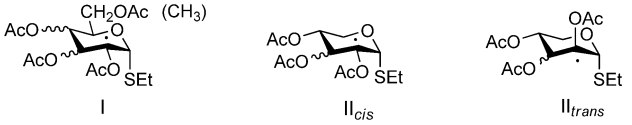


Figure 1. Radical intermediates formed by addition of ethanethiyl to hexose- (I) and pentose-derived (II) 2-acetoxy glycals.

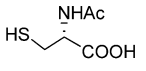
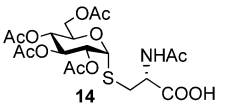
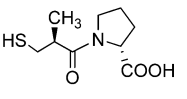
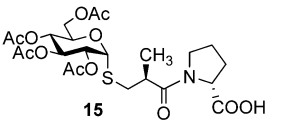
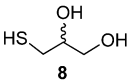
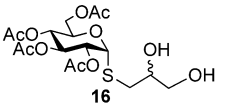
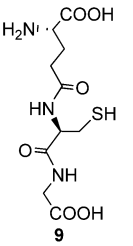
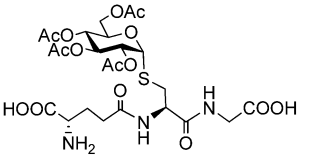
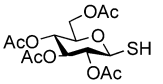
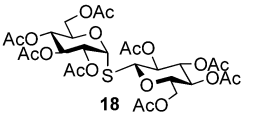
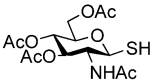
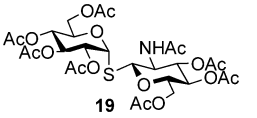
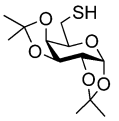
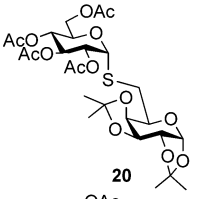
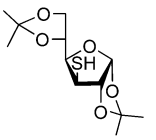
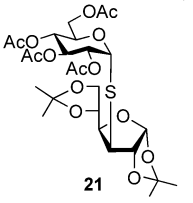
toluene–MeOH or MeOH were used as the solvent. Our attempts to improve the yield of product **16** by applying an excess of thiol, increasing the amount of DPAP, and prolongation of the irradiation time were unsuccessful.

Dondoni et al. published that DMF–water was a suitable medium for thiol–ene-based synthesis of *S*-linked glycopeptides when the thiol reactant was unprotected.[23] Hence, coupling of **8** with the olefin was carried out in 1:1 mixture of water and DMF, and this turned out to be successful. Considerably higher conversion of the glycal occurred, and the glucoside **16** was isolated in 51% yield.

The water–DMF mixture was also suitable for reacting the commercially available tripeptide glutathione **9** with compound **1a** to give **17** in good yield. This approach offers a third variant for protein glycosylation that is based on the photoinduced thiol–ene coupling. Previously, Dondoni and co-workers have applied allyl-*C*-galactoside as the ene partner to couple to native protein,[23] while Davis et al. have advocated the reaction between glycosyl thiyls and homoallylglycine-containing modified proteins.[12]

To achieve *S*-disaccharides, sugar thiols including acetyl-protected glycosyl thiols (**10**[24] and **11**[25]) and

Table 3. Stereoselective Synthesis of α-Linked Thioglucosides from **1a**

Thiol	Product	Yield[a] (%)
 **6**	 **14**	61[b]
 **7**	 **15**	39[b,c] 88[d]
 **8**	 **16**	15[b] 17[d,e] 51[f]
 **9**	 **17**	60[f]
 **10**	 **18**	86[g] 87[g,h]
 **11**	 **19**	55[i] 53[i,j]
 **12**	 **20**	69[g]
 **13**	 **21**	59[g]

[a] Yield of isolated compounds after 3 × 15 min irradiation, using 2 equiv of thiol and 3 × 0.1 equiv of DPAP. [b] Toluene/MeOH 1:1. [c] 40% of **1a** was recovered. [d] MeOH. [e] 4 × 15 min irradiation, 4 equiv of thiol, 0.8 equiv of DPAP. [f] DMF/H_2O 1:1. [g] Toluene. [h] 1.2 equiv of thiol. [i] Toluene/MeOH 3:1. [j] 6 equiv of thiol.

di-*O*-isopropylidenated sugars with primary (**12**[26]) or secondary thiol functions (**13**[27]) were applied as the thiol partners. The reactions were accomplished in toluene or toluene–MeOH with a thiol/ene ratio of 2:1 resulting in stereoselective formation of the α-linked *S*-disaccharides

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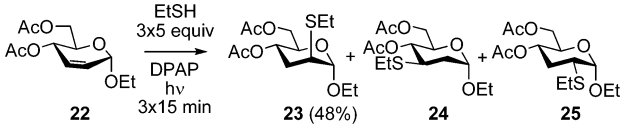
18–**21** in good to excellent yield, respectively (Table 3). The conversion of the glycal remained unchanged when the excess of the thiol was either decreased (**10**/**1a** 1.2:1) or increased (**11**/**1a** 6:1).[28]

To extend the thiol–ene coupling reaction to 2,3-unsaturated glycosides[16] the glycoside **22**[29] was chosen as the glycal reagent, and its hydrothiolation with ethanethiol was studied initially (Scheme 1). The radical addition, carried out in toluene in the presence of DPAP, proceeded with high regio- and stereoselectivity affording compound **23** as the main product, together with small amounts of the regio- and stereoisomers **24** and **25**.[30]

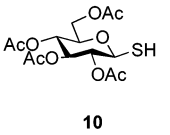
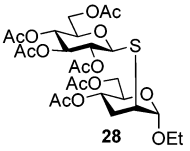
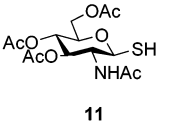
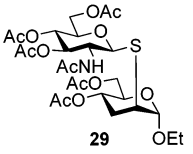
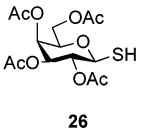
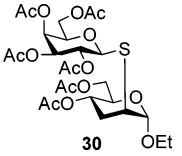
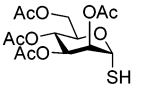
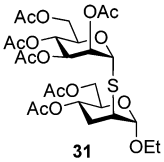
Scheme 1. Free-Radical Addition of Ethanethiol to Enose **22**



Next, compound **22** was subjected to coupling with a range of glycosyl thiols (**10**, **11**, **26**,[31] and **27**[32]) in toluene or toluene–MeOH. Pleasingly, selective addition occurred in all cases with the thiyl radical adding axially to C-2 of the enose, thus resulting in the 3-deoxythiodisaccharides **28**–**31**, respectively (Table 4). Noteworthy, complete conversion of **22** was observed in each case after 15 min irradiation. The synthetic utility of the thiol–ene coupling of Ferrier glycals is demonstrated by the simple and efficient entry into **31**, a 1,2-mannobioside mimic of the biologically important oligomannosides.[33]

In summary, we have described a high-yielding regio- and stereoselective synthesis of *S*-linked glycoconjugates and two families of *S*-disaccharides by photoinduced free-radical hydrothiolation of the double bond in endocyclic enoses. It has been shown that addition of thiols to hexose-derived 2-acetoxy glycals and a 2,3-unsaturated glycoside proceeded with total selectivity offering an easy access to 1,2-*cis* α-thioglucosides and 3-deoxy-*S*-disaccharides, whose synthesis would be very difficult by other methods. The pentose-derived 2-acetoxy glycals turned out to be less useful ene partners within the thiol–ene coupling because of the modest stereoselectivity observed in the hydrothiolation reactions. Extension of the approach to other enoses is in progress in our laboratory.

Table 4. Stereoselective Synthesis of *S*-Disaccharides from **22**

Thiol[a]	Product	Yield[b] (%)
 **10**	 **28**	71
 **11**	 **29**	63[c]
 **26**	 **30**	72
 **27**	 **31**	78

[a] 2 equiv of thiol, 0.1 equiv of DPAP, 15 min irradiation, rt. [b] Yield of isolated compounds. [c] toluene/MeOH 1:1, 3 × 0.1 equiv DPAP, 3 × 15 min irradiation.

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Supporting Information Available. Experimental procedures and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(30) The reaction gave a mixture of **23**, **24** and **25** in ~15:3:1 ratio. Because of the very similar chromatographic behavior of the isomers, the isolated yield of **23** was moderate and **24** and **25** could not be obtained in pure form.

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