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Synthesis of Glycosyl Sulfoximines by a Highly Chemo- and Stereoselective *NH*- and *O*-Transfer to Thioglycosides

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A synthesis of unprecedented and stable glycosyl sulfoximines is reported. The developed strategies represent the first example of highly stereoselective sulfoximine formation directly from thioglycosides. This synthetic protocol has been tested on several β-thioglycosides bearing different aromatics and alkyls as S-substituents, and bearing glucose, mannose and galactose as glycosyl units. The process has been extended to a lactose derived thioglycoside and to a glucose derived sulfonamide. The process resulted chemo- and stereoselective, and X-ray analysis confirmed the structure and provided stereochemical information on the configuration at the sulfur atom. A model for the stereochemical outcome is proposed based on the steric environment of the sulfide.

Introduction

As a consequence of the enhanced hydrolytic stability with respect to *O*-linked analogs, thioglycosides represent a useful class of molecules employed in the preparation of a variety of biologically relevant compounds such as glycoconjugates and glycomimetics.[1,2] Examples of bioactive thioglycosides are the antibiotic pirlimycin and the anti-inflammatory and anti-rheumatic auranofin (Figure 1). An interesting aspect that distinguishes thioglycosides from other glycoconjugates is the possibility to convert the bivalent sulfur atom into other oxidized forms. In fact, glycosyl sulfoxides,[3] sulfilimines[4,5] and sulfones[6] offer the possibility of extending the range of interactions with targets in which the anomeric carbon represents a crucial linking site in natural glycoconjugates. Strategies for the preparation of derivatives of types **1** and **2** (Figure 1) are now available. The sulfoximine group represents an emerging structural motif of interest in medicinal chemistry and agrochemicals.[7] In fact, the particular physicochemical properties brought about by the sulfoximine moiety allowed the recent development of roniciclib, a pan-CDK inhibitor with potential antineoplastic activity (Figure 1),[8] as well as novel insecticides[9] or COX2 inhibitors.[10] In this context, the combination of a glycosyl moiety with the sulfoximine functionality would open new perspectives in the field of glycoconjugates. Interestingly, Kinfe recently reported an example of biologically active compound characterized by the co-presence of a sulfoximine group adjacent to a glycosidic template (**3** in Figure 1), tested as antiplasmodic.[11] Nevertheless, the sulfoximine group in **3** was not directly linked to the anomeric carbon, and to the best of our knowledge, derivatives of the kind of **4** (Figure 1) are still unknown. One possible reason could be ascribed to the lack of methods, for the introduction of the sulfoximine group, compatible with the functional groups on the glycosyl unit.

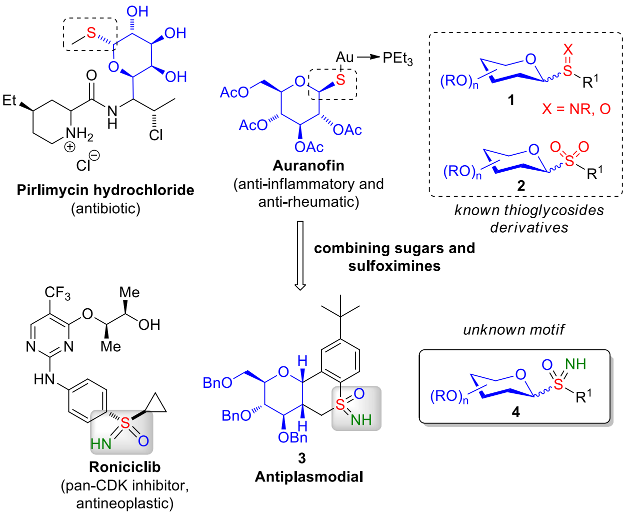

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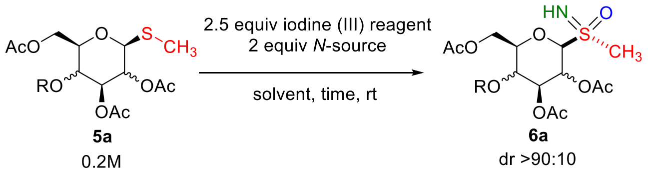
Figure 1 Examples of bioactive thioglycosides and sulfoximines.

Results and Discussion

Motivated by this challenge, and taking advantage of our recent interest in the chemoselective O- and NH-transfer to sulfur,[12,13] we have developed a straightforward chemo- and stereoselective preparation of previously unknown glycosyl sulfoximines, via a one-pot transfer reaction of oxygen and NH to thioglycosides. The methodology herein described has proven simple, efficient, tolerant to sugar functional groups, and avoids multistep routes and the use of any metal. Our preliminary investigation was carried out using peracetylated methyl 1-thio-β-D-glucopyranoside **5a** as model substrate (Table 1). The use of a peracetylated substrate was dictated by solubility issues of the thioglycoside. Several factors, such as the nitrogen source, the solvent, the stoichiometry of the oxidant and the reaction time, were considered in the optimization study.

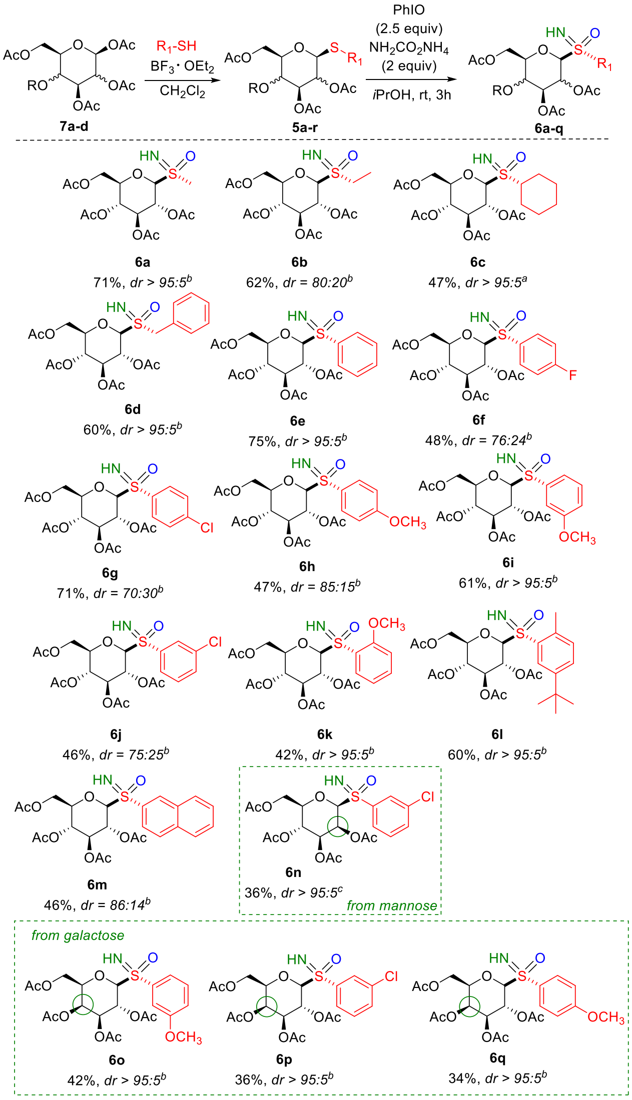
Table 1. *O*- and *N*-transfer to sulfur for glycosyl sulfoximine synthesis.



Entry	Iodine (III) reagent	*N*-source	Time	Solvent	Yield (%) [a]
1	$PhI(OAc)_2$	$AcONH_4$	3h	MeOH	45
2	$PhI(OAc)_2$	NH_3 aq	3h	MeOH	43
3 [b]	$PhI(OAc)_2$	NH_3/MeOH	3h	MeOH	33
4	$PhI(OAc)_2$	$(NH_4)_2CO_3$	3h	MeOH	45
5	$PhI(OAc)_2$	$NH_2CO_2NH_4$	3h	MeOH	50
6	$PhI(OAc)_2$	$NH_2CO_2NH_4$	30 min	MeOH	65
7 [c]	$PhI(OAc)_2$	$NH_2CO_2NH_4$	30 min	MeOH	66
8	PhIO	$NH_2CO_2NH_4$	30 min	MeOH	41
9	$PhI(OAc)_2$	$NH_2CO_2NH_4$	3h	ACN	10
10	$PhI(OAc)_2$	$NH_2CO_2NH_4$	30 min	DMF	40
11	$PhI(OAc)_2$	$NH_2CO_2NH_4$	30 min	Toluene	36
12	$PhI(OAc)_2$	$NH_2CO_2NH_4$	24h	Toluene	65
13	$PhI(OAc)_2$	$NH_2CO_2NH_4$	3h	*i*PrOH	67
14	$PhI(OAc)_2$	$NH_2CO_2NH_4$	30 min	*i*PrOH	60
15 [d]	PhIO	$NH_2CO_2NH_4$	3h	*i*PrOH	32
16	**PhIO**	**$NH_2CO_2NH_4$**	**3h**	***i*PrOH**	**71**

[a] Calculated by ^{1}H NMR using mesitylene as internal standard; [b] Reaction performed in the presence of 10 equiv of *N*-source; [c] Reaction performed at 0 °C; [d] Reaction performed in the presence of acetic acid (0.5 equiv.) according to reported evidence (see ref. 18); **5a** was synthesized according to the procedure reported in the literature.[14]

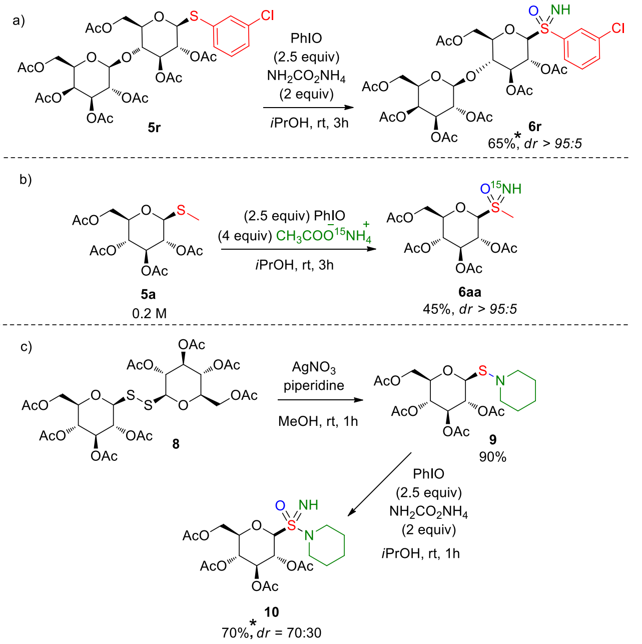
Initially, the role of the nitrogen source was considered (Table 1, entries 1-5), using MeOH as the reaction solvent, and $PhI(OAc)_2$ (2.5 equiv.) as the oxidant. To our delight, all sources of ammonia ($AcONH_4$, NH_3, $(NH_4)_2CO_3$ and $NH_2CO_2NH_4$) were found suitable for this process, and in all cases the expected sulfoximine **6a** was obtained with moderate to reasonable yields (33-50%).



Scheme 1. Scope of the reaction. [a]Stereochemistry at sulfur ascertained by X-Ray analysis. [b]Stereochemistry at sulfur assigned by analogy to **6c**. [c]Stereochemistry at sulfur not assigned. We cannot rule out that the opposite configuration at C2 would affect the stereochemical course of the reaction (*vide infra*).

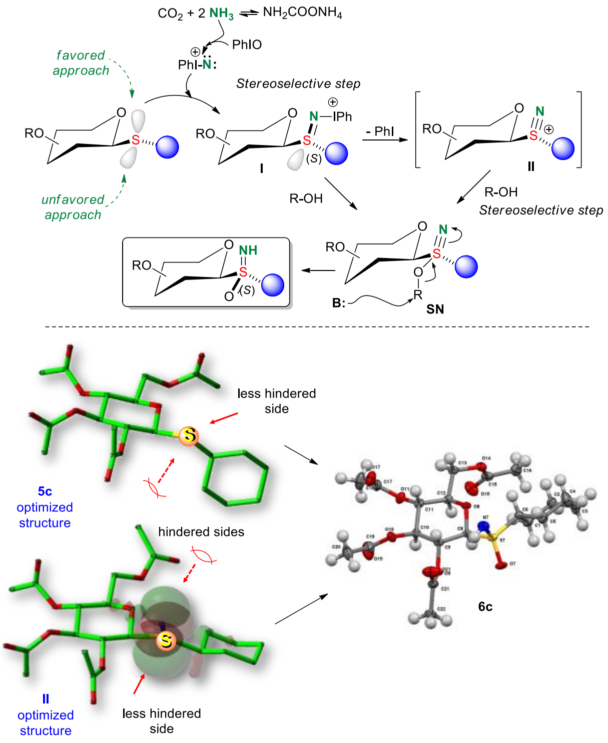
The use of NH_3 (10 equiv.) in MeOH caused a decrease of the yield of **6a** (entry 3) with formation of the corresponding *O*-methyl glucopyranoside, likely resulting from S_N1 displacement of the sulfonimidoyl group with the solvent. In order to minimize this side reaction, the NH transfer was run at shorter reaction time (entry 6), and at lower temperature (entry 7), resulting in yield improvement for **6a** (65% and 66% respectively). The use of PhIO as the oxidant (entry 8) returned a reasonable 41% yield of **6a**, demonstrating the suitability of this alternative oxidizing agent. To further tackle the concurrent O-glycosidation by MeOH, alternative reaction solvents were considered. The use of polar solvents such as acetonitrile and

DMF gave unsatisfactory results (entries 9, 10) while the use of toluene resulted in a satisfactory 65% yield after 24h reaction time (compares entries 11 and 12). The longer reaction time required in toluene is a consequence of the poorer solubility of the N-source in this solvent. The use of *i*-PrOH furnished better results, and no competing *O*-glycosidation was observed. Moreover, using $PhI(OAc)_2$, **6a** could be obtained in 65% yield after 3h (entry 13). Finally, the use of PhIO (2.5 equiv) in *i*-PrOH resulted in optimized conditions with a 71% yield of **6a** (entry 16). Interestingly, in all cases NMR analysis revealed the presence of a major diastereoisomer for the glycosyl sulfoximine **6a** (dr >90:10), whereby the β-configuration at the anomeric carbon was preserved, and the *O*- and *NH*-transfer to the *S*-atom occurred with a high degree of stereoselectivity. For sake of comparison, the reactivity of the corresponding α-thioglycosides was considered. Nevertheless, the preparation of such anomeric derivatives resulted a difficult task, likely because of a β-selectivity in the synthetic sequence.[15] However, the α-thioglycoside bearing the cyclohexyl S-substituent **5c** was fortuitously isolated, and tested under the optimized conditions. Quite unexpectedly, the reaction of the α-anomer provided the corresponding β-O-methylglycoside using MeOH as the solvent and unreacted starting material in *i*-PrOH. With optimal conditions in hand, the scope of the reaction was explored only on β-anomers. β-Thioglycosides **5a-r**, were prepared[15] and tested in the imination/oxidation process (Scheme 1). As reported in Scheme 1, readily available β-thioglycosides **5a-m** were prepared from D-glucose, varying the aglycon with alkyl and aryl groups. The corresponding β-glucosylsulfoximines **6a-m** were obtained in 42-75% yields, and the products were found to be stable and isolable.[16] No epimerization at the anomeric carbon was observed in any of the investigated cases as ascertained evaluating the ^3J vicinal coupling constants for the anomeric proton. [17] The diastereoselectivity of the process was very high (dr >95:5), with a slight lowering (dr >70:30) when electron-withdrawing substituents are installed on the aromatic ring (i.e. **6f,g** and **6j** in Scheme 1). The reaction was tolerant to bulky *S*-substituents such as in the case of **6k**, **6l** and **6m**. The use of different glycosyl units, as in thioglycosides **5n**, and **5o-q** deriving respectively from D-mannose and D-galactose, resulted in modest yields for the corresponding sulfoximines **6n** (36%), **6o** (42%), **6p** (36%) and **6q** (34%). However, ^1H NMR analysis revealed only unreacted starting material as other component of the crude reaction mixture. Nevertheless, such mannosyl- and galactosylsulfoximines were obtained with very high stereoselectivity (dr >95:5). To further benchmark the methodology, the peracetylated thiolactoside **5r** was subjected to the one-pot imination/oxidation protocol, leading to the corresponding sulfoximine **6r** in 65% yield as a single stereoisomeric form (Scheme 2, a).



Scheme 2. *Stereochemistry at sulfur not assigned. a) *NH*- and *O*-transfer reaction to thiolactoside; b) ^{15}N-labeled glycosyl sulfoximine case; c) synthesis of an unprecedented glycosyl sulfonimidamide.

Interestingly, the use of ^{15}N-labeled ammonium acetate as the N-source, gave access to glucosyl sulfoximine **6aa** in reasonable yield and again as a single diastereoisomer (Scheme 2, b). Given the recent renaissance of sulfonimidamides[18] as isosteres of sulfonamides, the synthesis of an unprecedented glycosyl sulfonimidamide was attempted. Starting from disulfide **8**, the corresponding sulfenamide **9** was first prepared, then subjected to the *O*- and *NH*-transfer reaction in the presence of ammonium carbamate and PhIO.[19] Under these conditions, we were pleased to isolate the first glucosyl sulfonimidamide **10** in 70% yield (Scheme 2, c). After assessing the scope of the methodology, we turned out our attention to the somewhat unexpectedly high stereoselectivity of the process. While the stereochemistry at the anomeric carbon could easily be ascertained based on ^1H NMR analysis, and $^3J_{HH}$ coupling constant values, the assignment of the stereochemistry at the *S*-centre was more difficult to establish. However, after several attempts, we were able to crystalize the *S*-cyclohexyl glucosylsulfoximine **6c**, confirming the structure and the sulfur stereochemistry by X-ray analysis (Scheme 3). Establishing the absolute (S_S) stereochemistry in **6c** prompted us to build a model to justify the stereoselective *O*- and *N*-transfer to the sulfur atom. Based on previous findings on the mechanism of this chemoselective imination/oxidation process,[18,19] we propose the mechanism reported in Scheme 3. The iodonitrene ($[PhI-N]^+$) intermediate attacks preferentially the sulfur atom of the thioglycoside to afford the intermediate **I** (Scheme 3). Elimination of PhI and attack of the alcoholic solvent will generate the alkoxysulfanenitrile **SN**, which acts as an electrophilic agent to form the sulfoximine. Importantly, the nature of the stereo-determining step remains unstudied. The mechanism may proceed through intermediate **II**, where elimination precedes ROH attack, in which case the bonding with the alcohol would fix the stereochemistry. Alternatively, in a concerted process for attack of ROH and elimination of PhI (**I** →**SN**), the sulfur configuration would be expected to be set in the initial nitrene attack. Therefore, considering the observed (S_s)-stereochemistry of **6c**, it is reasonable to consider two possible stereo-determining steps – the attack of N or the attack of O.



Scheme 3. Proposed mechanism and stereoselectivity.

To shed some light on this stereoselective reaction, we ran DFT calculations at (SMD(MeOH)/B3LYP/6-311++g** level, Gaussian 09), on the thioglycoside **5c**, and on the corresponding S≡N intermediate **II** (Scheme 3). In both cases, it is possible to identify in the optimized structures a less hindered side with lower steric demand around the S atom (Scheme 3). Interestingly, the approach from the less hindered side of the iodonitrene on **5c**, or the solvent ROH on intermediates **II,** would both lead to the observed $(S)_S$ stereochemistry in the final product **6c**. The geometry of **II** was optimized by minimizing the energy with respect to all the geometrical parameters, without imposing any molecular symmetry constraints. Vibrational analysis, HOMO-LUMO orbitals calculations and NPA analysis were also carried out. In the optimized structure, the geometry around the sulfur atom is almost planar, with two similar C-S bonds lengths (1.93 and 1.94 Å) while the C-N is a multiple bond (1.48 Å). Moreover, according to the NPA analysis the S atom bears the maximum positive charge (see Supplementary material). The small HOMO-LUMO energy gap reflects the high reactivity of the intermediate with tree HOMO orbitals almost degenerates, and the LUMO well separated from the other virtual orbitals. The corresponding 3-D plots showed that the HOMO orbitals are all delocalized over the molecule while the LUMO orbital is a localized S-N π* antibonding orbital. To rationalize the stereochemistry of the reaction, the two faces of the LUMO orbital have been considered (Figure 3). Since one of the faces is easily accessible while the other is affected by the steric hindrance and, perhaps, also by electronic repulsion of the CH_2OAc group, it is reasonable to assume that the nucleophile could discriminate between the two faces. However, this result cannot alone distinguish between the two proposed pathways (Scheme 3), which remains an unanswered question.[20, 21]

Conclusions

In conclusion, a method for the synthesis of new glycosyl NH-sulfoximines has been developed by using a highly chemo and stereoselective one-pot O and NH transfer to the sulfur atom of β-thioglycosides. This method allows for a straightforward preparation of carbohydrate structures bearing a sulfoximine group bound to the anomeric carbon. This protocol was applied to diverse thioglycosides, and proved to be feasible to disaccharides such as lactose, and to glycosylsulfenamides. X-Ray analysis confirmed the structure and established the stereochemistry of one glycosyl sulfoximine, while DFT calculations helped to rationalise the stereoselectivity of the transformation. Further investigations are ongoing on the use of these new and interesting glycosyl sulfoximines.

Acknowledgements

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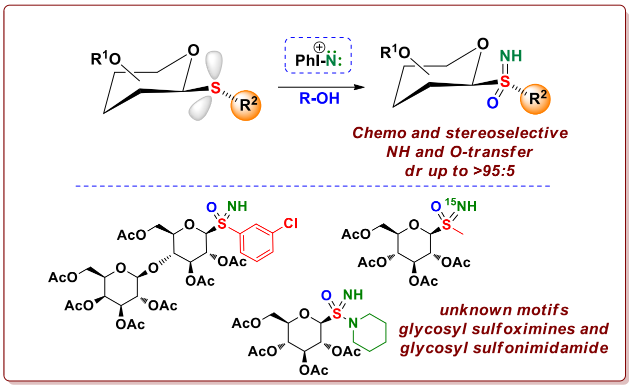
21 As support to the involvement of intermediate **II**, the lower stereoselectivity with electron-poor aryl substituents (as in **6f,g** and **6j**) could be justified with an higher energy content of the corresponding cationic intermediate.

TOC

Synthesis of Glycosyl Sulfoximines by a Highly Chemo- and Stereoselective NH- and O-Transfer to Thioglycosides



Abstract: *The synthesis of unprecedented glycosyl sulfoximines is reported. The developed strategies represent the first examples of highly stereoselective sulfoximine formation directly from sulfides. X-ray analysis and a computational model were used to establish the configuration at the sulfur atom.*