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Stereoselective Synthesis of 1,2-cis-α-Glycosyl Thiols and Trehalose-Type α,α′-Thiodisaccharides by Cryo Thiol-Ene Photocoupling – Thio-Click Reaction in Frozen State

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α-Glycosyl thiols are key building blocks for the formation of stable thioglycoside mimetics of widespread and biologically relevant α-*O*-glycosides, which urges their efficient synthesis. Here, we demonstrate that the photoinitiated radical-mediated addition of thioacetic acid to 2-substituted glycals followed by selective *S*-deacetylation is a generally applicable and fully stereoselective method for the synthesis of 1,2-*cis*-α-glycosyl thiols. The low reactivity of thioacetic acid in the radical reaction was overcome by carrying out the reaction in AcOH at −80 °C, in frozen state, with UVA irradiation, achieving high yields irrespective of the sugar configurations. For effective irradiation and simultaneous effective cooling, a self-made spiral vessel reactor was used, which also enables large-scale synthesis. By subjecting 1,2-*cis*-α-1-thiosugars to a second thiol-ene coupling reaction with 2-substituted glycals, 34 trehalose-type symmetrical and unsymmetrical α,α′-thiodi- and oligosaccharides were obtained with full stereoselectivity. Moreover, the oxidation of α-1-thiosugars provided an easy access to α,α′-diglycosyl disulfides.

Introduction

Carbohydrates play an important role in the regulation of cell adhesion, recognition and signaling, as well as in the development of various pathological conditions.[1–4] Synthetic glycomimetics, in which a sulfur atom or a disulfide bond replaces the interglycosidic oxygen, are stable under biological conditions due to their resistance to glycoside hydrolase enzymes. Therefore, as tools for glycobiological studies and as potential therapeutic agents, these glycomimetics are more attractive than the *in vivo* labile natural glycosides.[5–7]

The synthesis of *S*-linked glycomimetics represents different levels of difficulty depending on the stereochemistry of the thioglycosidic bonds. Though 1,2-*trans*-β-thiols and -β-thioglycosides can be easily synthesized *via* classical nucleophilic substitution reactions by taking advantage of the anchimeric assistance by the C2 acyl group,[4,8] stereocontrolled construction of 1,2-*cis*-α-thio linkages is difficult and has no general solution.[9] To address this problem, our group developed a method based on the photoinitiated thiol-ene coupling reaction, which is a radical-mediated hydrothiolation reaction of alkenes, also known as thio-click reaction.[10] We have shown that if 2-substituted glycals are used as alkenes in the photoinitiated hydrothiolation reaction, 1,2-*cis*-α-thioglycosides, α-thioglycoconjugates and α,β-linked non-reducing thiodisaccharides are formed in a completely stereocontrolled manner. We found that it is crucial for an efficient thiol-ene reaction of glycals to perform the reactions at a temperature as low as −80 °C.[9,11–14] However, the synthesis of trehalose-type α,α′-thiodisaccharides remained unsolved even by this method, which is due to the notorious difficulty of the synthesis of 1,2-*cis*-α-glycosyl thiols.

Importantly, α-glycosyl thiols (α-1-thiosugars) can serve as key building blocks in the synthesis of α-linked thioglycoconjugates with high biological potential, especially α,α′-thiotrehaloses.[15–17] These applications have stimulated the development of some valuable methods for their formation. Literature syntheses include ring opening reactions of *gluco* and *galacto* configured 1,6-anhydrosugars with bis(trimethylsilyl)sulfide upon TMSOTf catalysis,[18,19] direct thionation of reducing sugars,[20] treatment of peracetylated GlcNAc and GalNAc with Lawesson's reagent followed by acid hydrolysis of the formed thiazolidine intermediate,[21,22] or $TiCl_4$-mediated epimerization of 1,2-*trans*-β glycosyl thiols into 1,2-*cis*-α ones.[23,24] These methods, however, are highly dependent on specific carbohydrate configurations and protecting groups,

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or lead to anomeric mixtures. Therefore, we focused our attention on developing a method that is fully stereoselective and can be applied generally.

The α-anomeric thioacetates as thiol precursors can be stereoselectively prepared from 2-substituted pyranosyl glycals using photoinitiated hydrothiolation reaction in a configuration-independent manner, and then *in situ* *S*-deacetylation can afford us the desired α-glycosyl thiols.[13] Thus, radical thiol-ene chemistry has the potential to serve as a general method for the fully stereoselective synthesis of α-glycosyl thiols. However, this potential has remained unexploited until now, due to the very low efficiency of the photochemical addition of HSAc onto 2-hydroxyglycals observed so far.[13]

Here we report the optimization of the thiol-ene coupling reaction between thioacetic acid and a large number of hexose- and 6-deoxyhexose-derived 2-substituted glycals (Figure 1), and the selective *S*-deacetylation of the resulting α-glycosyl thioacetates. After overcoming the low reactivity of thioacetic acid in the radical thiol-ene coupling step by performing the reaction in AcOH in frozen state, this two-step process provided the challenging-to-synthesize 1,2-*cis*-α-glycosyl thiols with full stereoselectivity and very high yields. Furthermore, by subjecting the obtained α-glycosyl thiols to a second thiol-ene coupling reaction, the synthesis of a large number of symmetrical and unsymmetrical α,α′-thiotrehalose analogues became possible, the production of which was hindered until now by the lack of the key α-1-thiosugar building blocks. We also demonstrate here that our method provides facile access to previously unknown 1,2-*cis*-α,α′-diglycosyl disulfides by simple oxidation of the newly formed α-1-thiosugars.

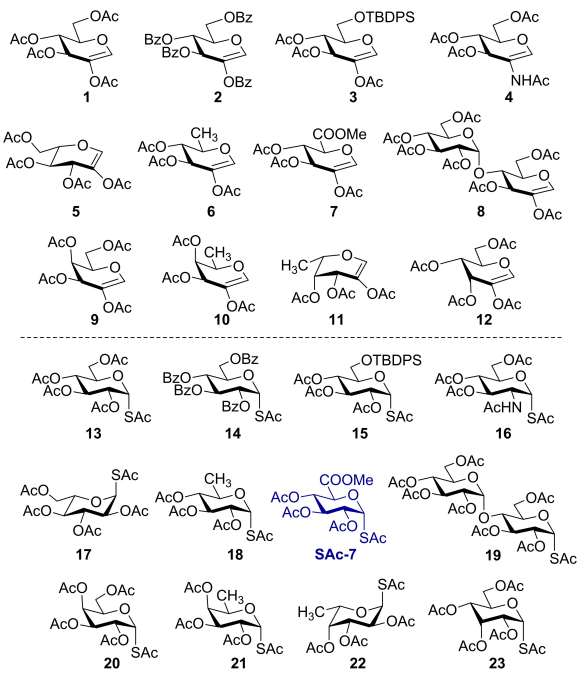


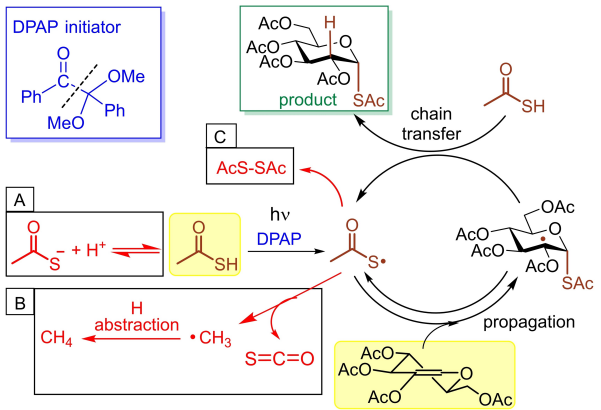
Figure 1. Structures of 2-substituted glycals **1**–**12** used for hydrothiolation reactions, and the glycosyl α-SAc products **13**–**23**. Glycals **1**,[31] **2**,[32] **4**,[33] **6**,[34] **7**,[35] **8**,[36] **9**,[31] **11**[37] and **12**[38] were prepared according to the literature procedures.

Results and Discussion

Since we aimed to develop a synthetically useful and scalable method, we mostly included acetyl-protected glycals in the study, which can be produced from free sugars in three steps, *via* acetylation, bromosugar formation and base-catalyzed HBr elimination, with high yields. Furthermore, 6-*O*-silylated glycal (**3**), 6-deoxyglycals (**6**, **10**, and **11**) and glucuronic acid-derived glycal (**7**) were chosen as alkene partners to explore how the electron-donating and electron-withdrawing groups adjacent to the ring oxygen affect the reaction.

In the initial experiments, the previously optimized conditions were used, which resulted in good to complete conversions during the hydrothiolation of 2-substituted glycals.[12,13] The reactions were carried out in toluene, at high concentration (1 mmol glycal/1-2 mL), with 3 x 15-minute UV light irradiation, adding 0.1 equivalent of 2,2-dimethoxy-2-phenylacetophenone (DPAP) as a cleavable photoinitiator[25] before each irradiation cycle. The radical thiol-ene addition takes place in a chain reaction (Scheme 1), which is characterized by fast kinetics in both the reversible propagation step and the chain transfer step (10^5-0^7 $M^{-1}s^{-1}$ for alkyl thiols).[26] In the case of thioacids, the efficiency of the addition can be impaired by ionic dissociation into thiolate, decomposition of thiyl radicals into carbonyl sulfide[27,28] and recombination into thioacyl disulfide (Scheme 1, A–C). According to *ab initio* calculations, the acetyl thiyl radical has low stability,[29] which may also be unfavorable by reducing the rate of the hydrogen abstraction step.[30] We assumed that the low reaction temperature effectively inhibits the chain-terminating disulfide formation reaction, and, on the other hand, favorably increases the lifetime of both the acyl thiyl radical and the carbon-centered radical, shifting the reaction towards the H-abstraction step, thus inhibiting the reverse propagation step. Furthermore, side reactions A and B were planned to be compensated with a large excess of HSAc. Therefore, the reactions were conducted in the temperature range of −20 and −80 °C while using 6 to 18 equivalents of thiol.

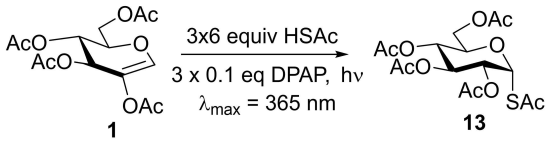
With the exception of glucuronic acid glycal **7**, which did not react with HSAc at all, completely stereoselective formation



Scheme 1. Mechanism of photoinitiated addtion of HSAc onto 2-OAc-D-glucal **1** and the side reactions (A–C) that impair efficiency

of the desired α-SAc derivatives was observed. Although both the low temperature and the high thiol excess had a beneficial effect on the reaction efficacy, the conversion of glycals remained insufficient, and the yields were in most cases very modest, 10–30% (Table 1 for **1** and Tables S3-S13 for **2–12**).

Table 1. Optimization of the radical mediated addition of thioacetic acid to 2-acetoxy-D-glucal.



Entry	Additive	Temp.	Solvent	Time (min)	Isolated yield
1	–	−40 °C	toluene	3x15	6%[a]
2	–	−80 °C	toluene	3x15	18%
3	MAP	−80 °C	toluene	3x15	30%
4	MAP	−80 °C	toluene	1x60 2x15	55%
5	MAP	−80 °C	toluene	2x60	49%[b]
6	MAP	−80 °C	toluene	3x60	62%
7	MAP	−80 °C	toluene	4x60	63%
8	–	−80 °C	toluene: acetone 1:2	1x60 2x30	60%
9	benzophenone	−80 °C	toluene	1x60 2x15	55%
10	–	−80 °C	acetone	1x60 2x30	67%
11	MAP	−80 °C	neat HSAc	4x60	57%
12	MAP	−80 °C	ethyl acetate	3x60	40%
13	MAP	−80 °C	DCM	3x60	48%
14	MAP	−80 °C	toluene-MeOH	3x60	32%
15	β-naphthol	−80 °C	toluene	3x60	64%[c]
16	20 equiv. HFIP	−80 °C	toluene	1x60 2x15	53%
17	MAP	−80 °C	HFIP	3x60	48%
18	2 equiv. TFA	−80 °C	toluene	1x60 2x15	50%
19	MAP + AcOH	−80 °C	toluene	3x60	51%[d]
20	MAP	−80 °C	formic acid	3x60	40%
21	MAP	−80 °C	AcOH	3x60	82%, 85%[e]
22	MAP	−80 °C	glacial AcOH	1x60 2x30	73%
23	–	−80 °C	AcOH	3x60	80%
24	MAP, TEMPO	−80 °C	AcOH	3x60	no reaction

The reactions were performed on a 1.0 - 3.0 mmol scale in 2.0 - 6.0 mL of solvent; 0.3 equiv. of MAP was used. [a]1 x 6 equiv. of HSAc was used; [b]2 x 6 equiv. of HSAc was used; [c]0.3 equiv. of β-naphthol was used; [d]5.0 equiv. of 96% AcOH was used; [e]in 20 mmol scale with 3x4 equiv. of HSAc. MAP: 4-methoxyacetophenone, HFIP: hexafluoroisopropanol

Better yield of 50% for the desired product (**16**) was observed only in the case of GlcNAc-derived glycal **4**. The results clearly showed that the standard photoinitiation conditions were not fully efficient for the reaction between 2-acetoxy glycals and thioacetic acid.

In a previous work, Defaye and co-workers found that in the thiol-ene reaction between HSAc and D-glucal **1**, initiation by peroxide was superior to the one *via* photoinitiation, and in the presence of *tert*-butyl hydroperoxide or cumene hydroperoxide catalyst in acetone the desired α-SAc product is formed in 60–70% yield.[39] This prompted us to study whether the peroxide-catalyzed HSAc addition could be extended to 2-substituted glycals of other configurations. However, when **1**, **8**, **9**, **11** and **12** were reacted with thioacetic acid (8 equiv.) in acetone in the presence of cumene hydroperoxide at room temperature for 48 hours, efficient hydrothiolation was only observed with glycal **1** (51% yield). Maltal **8** still reacted with a modest conversion and galactal **9** with a low conversion (12% and 6%, respectively), however, in the other cases no reaction occurred at all (Table S1, Supporting Information). The little or no conversion observed for axially substituted glycals (**9**, **11**, **12**) can be explained by the low stability of the carbon-centered radical intermediates formed upon thiyl addition, and supports our previous finding that cooling plays a key role in the efficient thiol-ene reaction of endoglycals by increasing the stability of the radical intermediate.[12,13] Thus, we returned to the optimization of low-temperature photoinitiated reactions.

According to Scanlan's pioneering work in exploiting the radical-mediated addition between thioacids and open-chain terminal alkenes, the acyl thiyl radicals can be generated very efficiently using the synergistic photosensitizer-photoinitiator pair 4-methoxyacetophenone (MAP) and DPAP.[40–44] Considering these results, DPAP was combined with various photosensitizers in the reaction of HSAc and glycal **1**. The efficiency of the reaction indeed increased in the presence of MAP, but in the case of 15-minute irradiation cycles, the yield did not exceed 30% (entry 3, Table 1). By using the MAP-DPAP combination and increasing at least one irradiation cycle to 1 hour, the yield reached 55%. We found that reinitiation significantly increases efficiency, 1 hour plus 2 x 15 minute irradiation was more effective than 1 x 2-hour irradiation (entries 4 and 5). The efficiency increased further when all three irradiation cycles lasted for 1 hour, but additional irradiation cycles no longer resulted in notable improvement (entries 6 and 7). Further experiments showed that acetone was significantly better a photosensitizer than MAP, while benzophenone proved to be similar to MAP (entries 8–10). Next, the solvent effect was studied. In neat HSAc, the reaction was no better than in toluene (entry 11). In ethyl acetate, contrary to literature results,[45] we observed a modest conversion (entry 12). Both dichloromethane (DCM) and methanol were inferior to toluene as reaction media (entries 13–14).

We studied the replacement of DPAP with alternative initiators, such as phosphines[46] and other organocatalysts,[47] but only 4% yield was achieved with triphenylphosphine and no reaction could be induced with acridine (See Supporting Information).

We attempted to increase the efficiency of the addition between HSAc and *gluco*-configured glycals by applying different acids such as β-naphthol,[48] CF_3COOH, AcOH, and HFIP (hexafluoroisopropanol) (entries 15–19). As expected, the acids somewhat promoted the addition by suppressing the dissociation of HSAc.[49] However, this effect generally fell short of the beneficial effect of MAP, and unfortunately no synergism was observed when MAP and these acids were used together.

Recently, Upadhyay et al. reported that anti-Markovnikov hydrothiolation of styrenes takes place very efficiently in formic acid.[50] Encouraged by this, we studied the hydrothiolation of glycal **1** using formic acid and acetic acid as reaction medium (entries 20–23). To our great delight, we achieved almost complete conversion in 96% acetic acid with an isolated yield of 82%, while the yield was slightly lower in glacial acetic acid. Interestingly, replacing the acetic acid with either the stronger acid HCOOH (entry 20) or the weaker acid HFIP, (entry 17) significantly worsened the conversion. In contrast to the reaction in toluene, MAP in acetic acid medium did not play a key role in the efficiency of HSAc addition, only having a minor yield-enhancing effect (entries 2, 3 *vs* entries 21, 23).

To study the mechanism of the reaction in an acidic medium, the addition was performed in the presence of the radical scavenger TEMPO. No reaction occurred, which clearly proved the radical mechanism of the reaction (Table 1, entry 24).

To shed light on the role of AcOH, we performed the reaction in deuterated acetic acid. The ^{1}H NMR spectrum of the product showed a H-2:D-2 ratio of ~5:2 (Figure S4). The incorporation of deuterium into the product is presumably the result of a proton-deuterium exchange between thioacetic acid and deuteroacetic acid. This result, on the one hand, confirms that HSAc remains largely protonated, allowing hydrogen abstraction, and on the other hand, excludes the participation of acetic acid in H atom transfer reactions.[29,51] Acetic acid probably forms a hydrogen bond with the thiol function, thereby reducing the bond dissociation energy and accelerating the hydrogen abstraction step.

Importantly, in acetic acid at −80 °C the reaction mixtures are in frozen state (the melting point of acetic acid is ~16 °C), and it is very likely that the frozen state also promotes the reaction, although the details of this intriguing mechanism have not yet been revealed. It is known from the literature that freezing to frozen state accelerates some chemical reactions through the "freezing concentration" phenomenon, and it can also be an effective way to prevent side reactions.[52–54] Furthermore, cryopolymerization is an emerging field in polymer chemistry,[55] and in this field we found one literature example of the use of a frozen state thiol-ene reaction.[56]

After establishing the optimal conditions for the addition of thioacetic acid to glycal **1**, frozen state hydrothiolation was performed on all glycals with HSAc, and good to excellent yields were achieved in all cases except for glucuronate derivative **7** (Table 2). The highest conversion was observed for *galacto*-configured glycals, with yields approaching or exceeding 90% (entries 7–9). Most of the glucosyl products (**14**-**18**) were formed in excellent (77-83%) yields. The lowest yields of 62–65% were found for maltose and allose derivatives. Among the 6-acetoxy and 6-deoxy pairs, the former ones reacted with higher conversions. It is important to note that in all cases we observed a significant yield increase of 10–15% compared to reactions carried out in toluene (see Supporting Information Tables S3-S13 for optimization reactions of glycals **2**–**12**).

It should be noted here that the optimization reactions were initially carried out in round flasks, which were placed as close as possible to the light source (~4 cm), and an efficient reaction was observed up to a maximum reaction mixture volume of 5 mL (Figure S1). In the case of a larger reaction volume and a higher distance from the light source, the yield of thiol-ene reactions decreased significantly. In order to increase the efficiency of irradiation and simultaneous cooling, and make the reaction scalable, we designed a spiral vessel reactor (Figure 2 and Figures S2-S3). In this reactor, the reactions were well reproducible (the reaction mixture was a constant ~3 cm away from the light source), and it was possible to carry out reactions on a scale of 20–30 mmol.

The exclusive 1,2-cis-α selectivity of the addition is due to the following factors: i) the kinetically preferred trans diaxial addition of thiols to cyclic alkenes, ii) the significantly different stability of the possible carbon-centered radical intermediates formed upon addition of the thiyl radical, and iii) the rapidly reversible nature of the thiyl addition step.[9,12,13] We assume that the reaction proceeds exclusively through the most stable chair conformational form of the intermediate C2-centered radicals ($^4C_1$ in the D-series and $^1C_4$ in the L-series), while the other carbon-centered radical intermediates are of high-energy, therefore rapidly dissociate to the starting compounds in the reversible propagation step before reacting with a thiol in the chain-transfer (H-abstraction) step (Scheme 2 and Schemes S4-S6 in the SI).

Having efficiently obtained the glycosyl α-SAc products, the S-acetyl group was removed by selective deacetylation[57–60] using equimolar NaOMe in deoxygenated methanol at 0 °C and 1,2-*cis*-α glycosyl thiols were produced in excellent yields (Figure 3).

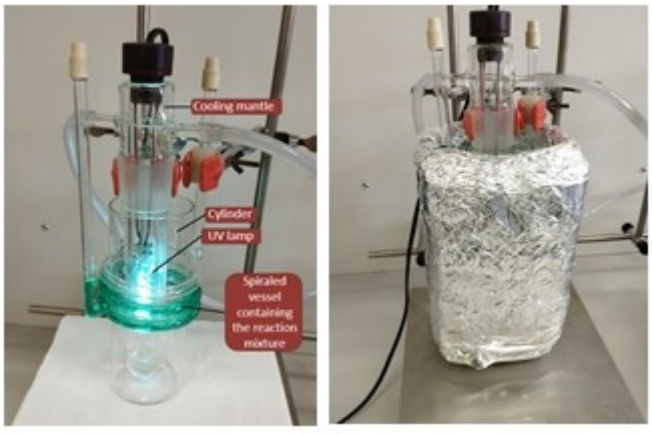
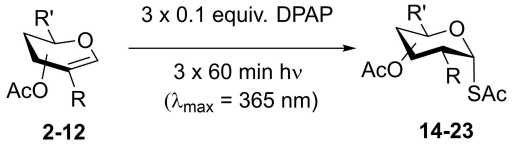
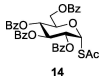
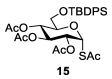
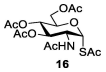
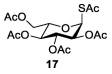
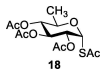
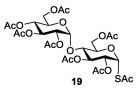


Figure 2. Self-made spiral-vessel UV reactor designed for the low-temperature (−80 °C) thiol-ene reactions.

Table 2. Optimized conditions for the syntheses of the α-*S*-acetyl hexoses.[a]



2-12 **14-23**

Entry	Glycal	Product	Solvent	Yield
5	**2**	 **14**	AcOH:DCM 3:1	77%[b]
2	**3**	 **15**	AcOH	78%
3	**4**	 **16**	AcOH	83%
4	**5**	 **17**	AcOH	79%
5	**6**	 **18**	AcOH	70%[b]
6	**8**	 **19**	AcOH	65%[b]
7	**9**	 **20**	AcOH	95%[c]
8	**10**	 **21**	AcOH:DCM 3:1	83%
9	**11**	 **22**	AcOH:DCM 3:1	88%[c]
10	**12**	 **23**	AcOH	62%[b]

[a] The reactions were performed on a 0.5-1.0 mmol scale in 0.6-2 mL of solvent, using 0.3 equiv. of MAP. [b] Four irradiation cycles were used. [c] Performed in 15–20 mmol scale with 3x4 equiv. of HSAc.

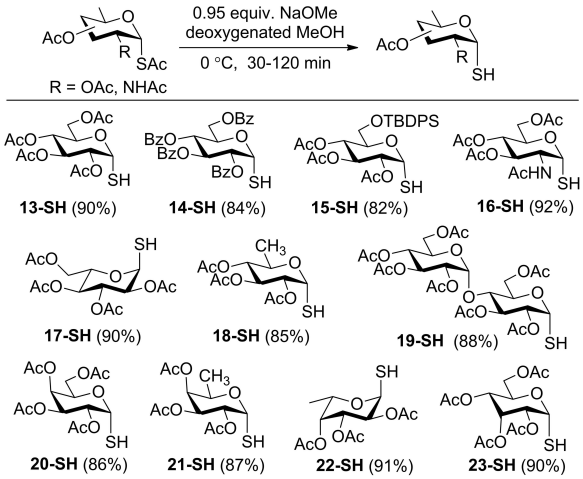
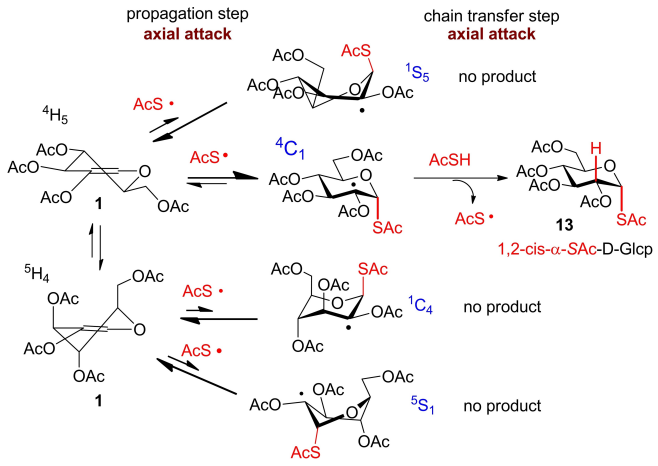


Figure 3. Structure and yield of 1,2- *cis*-α-glycosyl thiols obtained by selective S-deacetylation

Next, the 1-thiosugars were subjected to photoinitiated thiol-ene reaction with glycals **1–12** to produce trehalose-type α,α′-thiodi- and oligosaccharides (Scheme 3). High conversions have been observed after 3 x 15 minutes of irradiation cycles, in toluene, at −80 °C. The synthesis of thiotrehalose **24a** was also performed in acetic acid on a 20 mmol scale. The reaction went slightly better than in toluene, yielding 85% of the product, which is probably due to the higher concentration of the reaction in acetic acid.

It is important to note that the formation of the glycosidic bond with α-1-thiosugars gave a similarly good yield as what was previously observed with β-1-thiosugars.[9,12,13] This highlights the advantage of radical mediated glycosylation over nucleophilic substitution based glycosylation, since in the latter case the α-glycosyl donors (having axial anomeric group) show much lower reactivity than their β-counterparts (having equato-



Scheme 2. Reversible thiyl addition (propagation) step and irreversible hydrogen abstraction (chain transfer) step upon addition of HSAc onto 2-substituted glycals, as exemplified by D-glucal **1** existing in interconversion equilibrium between the $^4H_5$ and $^5H_4$ half-chair conformations. The reaction proceeds exclusively via the most stable of the possible C2 radical intermediates, the $^4C_1$ chair conformational form.

rial anomeric group). Also, it is noteworthy that glucuronic acid glycal **7** also reacted with 1-thiosugars with acceptable conversions, although the yields of uronic acid-containing thiodisaccharides **35–37** were significantly lower than that of the other disaccharides. On the one hand, this points to the very high reactivity of glycosyl thiols in thiol-ene reactions, and on the other hand, it proves, for the first time, that uronate glycals, despite the electron-withdrawing effect of the carboxyl group in the C5 position, can be suitable alkene partners in the thiol-ene reaction with thiols of appropriate reactivity.

Among the thioglycosides produced, non-symmetrically substituted disaccharides **25**, **26** and **35** can be valuable building blocks for the synthesis of desymmetrized trehalose analogues, which are of great interest, as they can be used to develop potential therapeutics for tuberculosis and other diseases associated with mycobacteria.[61–66] Furthermore, digalactoside **46** can be used for the synthesis of α-congeners of β-thiodigalactoside (TDG) derivatives,[67–69] which are promising antitumor compounds due to their Galectin-3 inhibitory properties, and thiodisaccharides containing fucose and galactose can be utilised as inhibitors of *Pseudomonas aeruginosa* lectins.[70]

In the NMR spectroscopic characterisation of the compounds we observed that of the symmetric D,D/L,L- and D,L-thiodisaccharide pairs (glucosides **24**, **27** and **28**; fucosides **48–50**), the anomeric carbon of the latter always appears with 4–5 ppm higher shift values in the ^{13}C NMR spectra (Table S13). The phenomenon may be due to the fact that the glycosidic bonds connecting identical monomers and those connecting enantiomeric pairs have different φ torsional angles.[71]

Finally, some sugar thiols were also used in oxidation reactions to furnish protected α,α′-diglycosyl disulfides (Scheme 4). Method A, when deacetylation preceded oxidation, gave the free diglycoside in good yield from the GlcNAc thiol. In the other cases, the desired free diglycosides could be prepared in good yields if oxidation preceded deacetylation.

Conclusions

A new and highly efficient synthesis route has been developed for the synthesis of 1,2-cis-α-glycosyl thiols with complete stereoselectivity and high yields by coupling thioacetic acid to 2-substituted glycals. The key to the efficient reaction proved to be the use of acetic acid as a solvent in the frozen state. The optimal conditions include 3x 60 min UV irradiation (λ_{max} = 365 nm) in the presence of DPAP in AcOH at −80 °C. The obtained thiols were utilized for the synthesis of α,α′ thiotrehalose and its analogues, by means of a second cryo thiol-ene coupling reaction in toluene.

The generality of the method is demonstrated by the synthesis of 1,2-*cis*-α-glycosyl thiols (7 new out of 11) and 1,2-*cis*-α,α′ thiodi- and oligosaccharides with complete stereoselectivity, in 34 examples of which 29 were new compounds. The newly formed 1,2-*cis*-α-1-thiosugars were also used in oxidation reactions to furnish 8 new symmetrical diglycosyl disulfides.

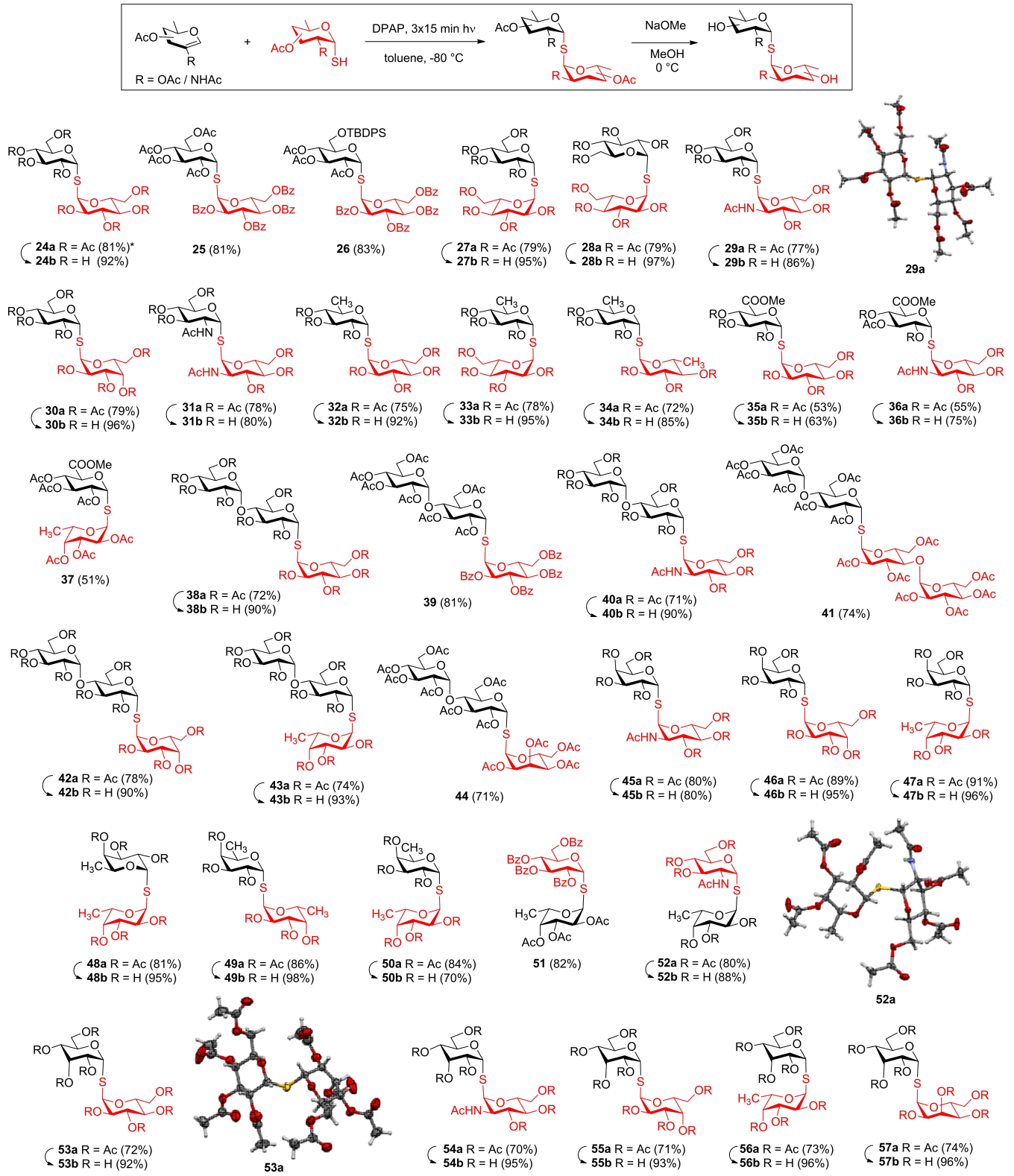
The cryo thiol-ene reaction is compatible with ester and silyl ether groups and independent of sugar configurations. The only limitation that prevented HSAc addition to the uronic acid glycal was the presence of a strongly electron-withdrawing group on the pyranose ring. However, the uronic acid glycal also readily reacted in thiol-ene reactions with highly reactive thiols such as 1-thiosugars.

Experimental

Included here are synthetic and characterizing data for compounds **13**, **17**, **13-SH**, **24 a** and **27 a**. Complete data, NMR spectra of all compounds, and details of crystallographic study[72] are included in the supporting information.

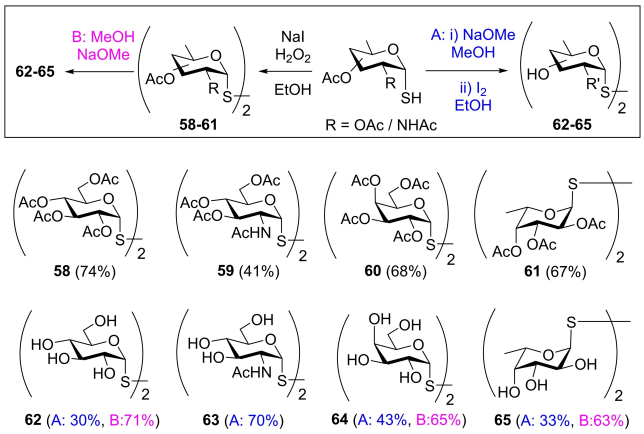
Compound 13: 2-Acetoxy-D-glucal **1** (6.60 g, 20.0 mmol), thioacetic acid (4.0 equiv, 80.0 mmol, 5.6 mL), DPAP (0.1 equiv, 2.0 mmol, 512 mg) and MAP (0.3 equiv, 6.0 mmol, 900 mg), were dissolved in 96% acetic acid (12.0 mL), and the solution was transferred to the spiral vessel. The reaction mixture was cooled to −80 °C and was irradiated with UV light for 60 minutes. After irradiation, another 4.0 equiv. of thioacetic acid and 0.1 equiv. of DPAP were added and the irradiation was continued for 60 min. The addition of 4.0 equiv. of thioacetic acid and 0.1 equiv. of DPAP, and the 60 min irradiation was repeated one more time. The solvent was evaporated in vacuo and the crude product was purified by crystallization (ethyl acetate - hexane) to give compound **13** (6.90 g, 85%) as white crystals. R_f = 0.20 (*n*-hexane:acetone = 8:2) $[\alpha]_D^{20}$ = +132.8 (*c* = 0.28 in $CHCl_3$) lit.[39] $[\alpha]_D^{20}$ = +143.5; m. p.: 128–129 °C, lit.[39] m. p.: 123–125 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 6.22 (d, *J* = 5.2 Hz, 1H, H-1), 5.24 (dd, *J* = 10.1, 5.1 Hz, 1H, H-2), 5.18 (t, *J* = 9.5 Hz, 1H, H-3), 5.10 (t, *J* = 9.5 Hz, 1H, H-4), 4.28 (dd, *J* = 12.5, 4.1 Hz, 1H, H-6a), 4.05 (dd, *J* = 12.5, 2.2 Hz, 1H, H-6b), 3.96 (ddd, *J* = 9.9, 4.0, 2.3 Hz, 1H, H-5), 2.43 (s, 3H, AcCH_3), 2.08 (s, 3H, AcCH_3), 2.03 (s, 3H, AcCH_3), 2.02 (s, 3H, AcCH_3), 2.02 (s, 3H, AcCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 170.1, 169.5, 169.4 (4 C, 4xAc*C*O), 80.5 (1 C, C-1), 71.6, 71.3, 69.2, 68.0 (4 C, skeletal carbons), 61.7 (1 C, C-6), 31.6 (1 C, SAcCH_3), 20.8, 20.7, 20.7 (4 C, 4xOAcCH_3) ppm.; ESI-HRMS: *m/z* calcd for $C_{16}H_{22}NaO_{10}S$ $[M+Na]^+$ 429.0826, found 429.0835.

Compound 17: 2-Acetoxy-L-glucal **5** (330 mg, 1.0 mmol), thioacetic acid (6.0 equiv, 6.0 mmol, 0.42 mL), and MAP (0.3 equiv, 0.3 mmol, 45 mg), were dissolved in 96% acetic acid (2.0 mL) in a 5 ml



Scheme 3. Synthesis of trehalose analogues, with the thiol components highlighted in red. The molecular structures of **29a**, **52a** and **53a** were unambigously proven by single crystal X-ray diffraction study[72] (See Supporting Information). (*__24a__ was obtained with 85% yield in AcOH in 20 mmol scale.).

borosilicate flask. The flask was placed ~4 cm from the UV light source. The reaction mixture was cooled to −80 °C and was irradiated with UV light for 60 minutes. After irradiation, another 6.0 equiv. of thioacetic acid and 0.1 equiv. of DPAP were added and the irradiation was continued for 60 min. The addition of 6.0 equiv. of thioacetic acid and 0.1 equiv. of DPAP, and the 60 min irradiation was repeated one more time. The solvent was evaporated in vacuo and the crude product was purified by flash column chromatog-



Scheme 4. Synthesis of protected and deprotected disulfides.

raphy (*n*-hexane:acetone 8:2) to give compound **17** (321 mg, 79%) as white powder. R_f = 0.22 (*n*-hexane:acetone = 8:2), $[\alpha]_D^{20}$ = −124.3 (*c* = 0.14 in $CHCl_3$) m. p.: 125–128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.22 (d, *J* = 5.2 Hz, 1H, H-1), 5.24 (dd, *J* = 10.0. 5.2 Hz, 1H, H-2), 5.18 (d, *J* = 6.5 Hz, 1H), 5.10 (t, *J* = 9.5 Hz, 1H), 4.28 (dd, *J* = 12.5, 4.1 Hz, 1H, H-6a), 4.05 (dd, *J* = 12.5, 2.2 Hz, 1H, H-6b), 3.97 (ddd, *J* = 9.9, 4.0. 2.3 Hz, 1H), 2.43 (s, 3H, SAcC*H*$_3$), 2.08 (s, 3H, OAcC*H*$_3$, H-5), 2.03 (s, 3H, OAcC*H*$_3$), 2.03 (s, 3H, OAcC*H*$_3$), 2.02 (s, 3H, OAcC*H*$_3$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.4 (1 C, SAcCO), 170.6, 170.0. 169.4 (4 C, 4xOAcCO), 80.4 (1 C, C-1), 71.5, 71.2, 69.1, 67.9 (4 C, skeletal carbons), 61.6 (1 C, C-6), 31.5 (1 C, SAcCH_3), 20.7, 20.6, 20.6 (4 C, 4xOAcCH_3) ppm. MALDI-ToF-HRMS: *m/z* calcd for $C_{16}H_{22}NaO_{10}S$ [M + Na]$^+$ 429.0826, found 429.0816.

Compound 13-SH: The SAc-derivative **13** (406 mg, 1.0 mmol) was dissolved in methanol (10 mL), then the solution was deoxygenated by thoroughly bubbling with argon. The reaction mixture was cooled to 0 °C, stirred vigorously, and 0.95 equiv. of sodium methylate stock solution (1 M, 950 µL) was added in two portions. The reaction mixture was stirred at 0 °C until no starting material was observed on TLC (60 min). The solution was neutralised with Amberlite IR-120 H^+ ion exchange resin. The resin was filtered off, the solvent was evaporated *in vacuo* and the crude product was purified by flash column chromatography (*n*-hexane:acetone 8:2) to give compound **13-SH** (323 mg, 90%) as colourless foam. R_f = 0.26 (*n*-hexane:acetone 8:2) ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.94 (t, *J* = 5.4 Hz, 1H, H-1), 5.38 (t, *J* = 9.8 Hz, 1H, H-3), 5.14 – 4.98 (m, 2H, H-2, H-4), 4.50 – 4.40 (m, 1H, H-5), 4.30 (dd, *J* = 12.4, 4.2 Hz, 1H, H-6a), 4.11 (dd, *J* = 12.4, 2.3 Hz, 1H, H-6b), 2.09 (2 s, 6H, 2x AcCH_3), 2.04 (2 s, 6H, 2x AcCH_3), 1.92 (d, *J* = 5.6 Hz, 1H, S*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 169.9, 169.7, 169.6 (4 C, 4xAcCO), 77.1 (1 C, C-1), 70.3 (1 C, C-2), 69.9 (1 C, C-3), 68.3 (2 C, C-4, C-5), 61.7 (1 C, C-6), 20.7, 20.7, 20.7, 20.6 (4 C, 4xAcCH_3) ppm. MALDI-ToF-HRMS: *m/z* calcd for $C_{14}H_{20}NaO_9S$ [M + Na]$^+$ 387.0720, found 387.0710.

Compound 24 a: 2-Acetoxy-D-glucal **1** (6.60 g, 20.0 mmol), thiol **13-SH** (1.1 equiv, 8.0 g, 22.0 mmol) and DPAP (0.1 equiv, 2.0 mmol, 512 mg) were dissolved in 96% AcOH (24 mL), and the solution was transferred to the spiral vessel. The reaction mixture was cooled to −80 °C and was irradiated with UV light for 15 min. After irradiation, another 0.1 equiv. of DPAP was added and the irradiation was continued for another 15 min. The addition of 0.1 equiv. of DPAP and the 15 min of irradiation was repeated one more time. The solvent was evaporated in vacuo and the crude product was recrystallized from ethanol to give **24 a** (8.44 g from the first crystallization, 3.39 g from recrystallizing the mother liquor, in a total of 11.83 g, 85%) as white crystals. R_f = 0.21 (*n*-hexane:acetone 7:3), $[\alpha]_D^{20}$ = +285.0 (*c* = 0.2 in $CHCl_3$), lit.[73] +259.2; m. p.: 197–198 °C, lit.[73] 191–192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (d, *J* = 5.9 Hz, 1H, H-1), 5.41 – 5.31 (m, 1H), 5.10 – 4.97 (m, 2H), 4.28 – 4.18 (m, 2H), 4.10 – 4.02 (m, 1H), 2.11 (s, 3H, AcCH_3), 2.10 (s, 3H, AcCH_3), 2.05 (s, 3H, AcCH_3), 2.04 (s, 3H, AcCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 169.9, 169.6, 169.5 (4 C, 4xAcCO), 78.5 (1 C, C-1), 70.4, 70.2, 68.5, 68.4 (4 C, skeletal carbons), 61.8 (1 C, C-6), 20.7, 20.6, 20.6 (4 C, 4xAcCH_3) ppm. MALDI-ToF-HRMS: *m/z* calcd for $C_{28}H_{38}NaO_{18}S$ [M + Na]$^+$ 717.1672, found 717.1682.

Compound 27 a: 2-Acetoxy-D-glucal **1** (110 mg, 0.3 mmol), thiol **17-SH** (1.2 equiv, 131 mg, 0.36 mmol) and DPAP (0.1 equiv, 8 mg, 0.03 mmol) were dissolved in toluene (1.0 mL) in a 5 ml borosilicate flask. The flask was placed ~4 cm from the UV light source. The reaction mixture was cooled to −80 °C and was irradiated with UV light for 15 minutes. After irradiation, another 0.1 equiv. of DPAP were added and the irradiation was continued for 15 min. The addition of 0.1 equiv. of DPAP, and the 15 min irradiation was repeated one more time. The solvent was evaporated in vacuo and the crude product was purified by flash column chromatography (*n*-hexane:acetone 7:3) to give compound **27 a** (159 mg, 77%) as white foam. R_f = 0.23 (*n*-hexane:acetone 7:3); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.71 (d, *J* = 5.6 Hz, 1H, H-1), 5.38 – 5.29 (m, 1H), 5.07 (t, *J* = 9.9 Hz, 1H), 5.05 – 4.96 (m, 1H), 4.29 (dd, *J* = 12.3, 4.4 Hz, 1H, H-6a), 4.22 (ddd, *J* = 10.3, 4.3, 2.0 Hz, 1H, H-5), 4.07 (dd, *J* = 12.3, 2.1 Hz, 1H, H-6b), 2.08 (s, 3H, OAcCH_3), 2.06 (s, 3H, OAcCH_3), 2.04 (s, 3H, OAcCH_3), 2.03 (s, 3H, OAcCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 170.0. 169.8, 169.6 (4 C, 4xOAcCO), 83.0 (1 C, C-1), 70.8, 70.5, 69.7, 68.1 (4 C, skeletal carbons), 61.7 (1 C, C-6), 20.7, 20.6 (4 C, 4xOAcCH_3) ppm. MALDI-ToF-HRMS: *m/z* calcd for $C_{28}H_{38}NaO_{18}S$ [M + Na]$^+$ 717.1671, found 717.1688.

Supporting Information

The authors have cited additional references within the Supporting Information.[74–84]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords: carbohydrate · thiol-ene reaction · stereoselective · radical chain reaction · frozen state reaction •

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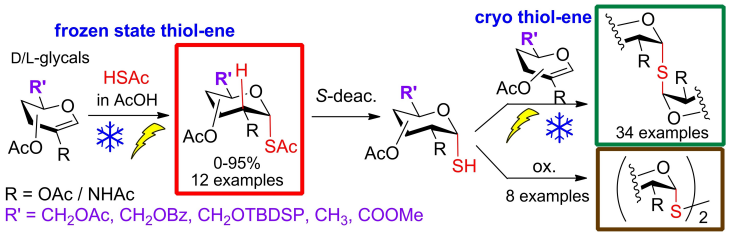

A double photochemical cryo thiol-ene coupling process was developed as a general method for the synthesis of 1,2-cis-α,α′-thio-linked di- and oligosaccharides. The procedure includes i) UV-initiated coupling reaction of 2-substituted glycals with HSAc in AcOH at −80 °C in frozen state, ii) selective *S*-deacetylation of the resulting glycosyl-α-SAc derivatives, iii) cryo thiol-ene reaction of the obtaining α-1-thiosugars with 2-substituted-glycals.

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Stereoselective Synthesis of 1,2-cis-α-Glycosyl Thiols and Trehalose-Type α,α′-Thiodisaccharides by Cryo Thiol-Ene Photocoupling – Thio-Click Reaction in Frozen State