ChemPubSoc Europe

DOI: 10.1002/chem.201800668

CHEMISTRY
A European Journal
Communication

Synthetic methodology |*Hot Paper*|

Promotion of a Reaction by Cooling: Stereoselective 1,2-*cis*-α-Thioglycoconjugation by Thiol-Ene Coupling at −80 °C

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Abstract: The photoinitiated thiol-ene coupling reactions of 2-substituted glycals were studied as a generally applicable strategy for stereoselective 1,2-*cis*-α-thioconjugation. Although 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. The study revealed that the reaction progress could be promoted by cooling and inhibited by heating. At −80 °C, the equilibrium of the rapidly reversible addition of the thiyl radical to alkenes is shifted almost completely toward products, leading to efficient addition reactions. By exploiting this unique temperature effect a series of α-thio-L-fucosides, -D-galactosides, and D-GlcNAc derivatives were prepared with high efficacy and complete stereoselectivity.

■■Please provide first names of authors■■The α-*O*-glycosides are abundantly found in nature and many 1,2-*cis*-α-linked sugars including α-L-fucosides, α-D-galactosides■■ok?■■ as well as 2-deoxy-2-aminoglycosides with α-D-*gluco* and α-D-*galacto* configurations play important roles in various biological processes. For example, α-GlcNAc is a key component of lipid II; a precursor molecule used in the biosynthesis of the peptidoglycan cell wall of bacteria,[1] α-galactosylceramide is a glycolipid of an important immunostimulant activity,[2] and the α-*N*Ac-galactosamine linked to serine or threonine represents the conserved region of the mucin *O*-glycoproteins and also known as a tumor-associated carbohydrate antigen (Tn antigen).[3] L-Fucose (6-deoxy-L-galactose), always α-linked at a terminal position, is a common component of many *N*- and *O*-glycoproteins and glycolipids produced by mammalian cells and it is involved in a large number of cellular processes.[4] For example, the blood group antigen sialyl Lewis X is a fucosylated glycan which plays an important role in inflammation, cancer metastasis and fertilization.

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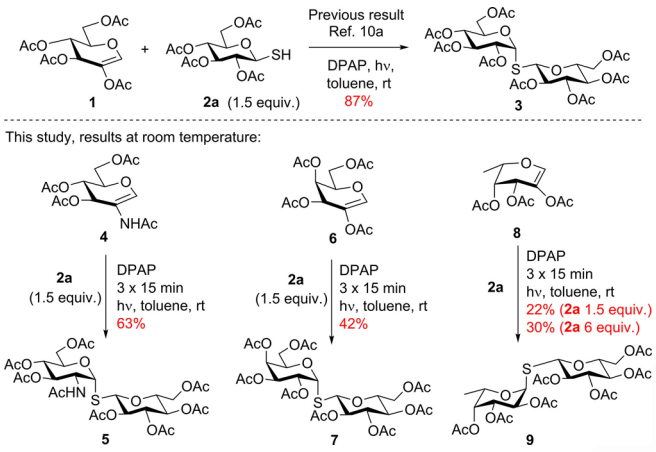
Because of the chemical and enzymatic instability of the *O*-glycosidic bond, recent research has focused on the efficient synthesis of *S*-glycosidic analogues of biorelevant glycosides[5] possessing a higher stability in biological milieu than that of the native *O*-glycosides.[6] However, stereoselective formation of the 1,2-*cis*-α-glycosidic bond is a notoriously difficult task. Although α-glycosyl thiols provide the opportunity to construct α-thio-linked glycoconjugates in a stereoselective manner, their efficient synthesis is not trivial.[7] Therefore, development of complementary strategies for the stereoselective 1,2-*cis*-α-thioconjugation is needed.

The thiol-ene coupling (also called thio-click reaction),[8] where a reactive thiyl radical undergoes an addition reaction onto an alkene to furnish a thioether linkage, has emerged as a mild and efficient method for the preparation of sulfur containing glycoconjugates and thiosugars.[9] Recent studies have revealed that the exocyclic sulfur atom could be efficiently introduced into the sugar backbone through photoinduced thiol-ene reactions employing *endo*-[10] and exoglycals[11] as acceptor substrates. We have demonstrated on the exemplary case of 2-acetoxy-D-glucal derivative **1** that the UV-light-initiated addition of thiol-containing peptides and sugars occurs with high yields and exclusive 1,2-*cis*-α stereoselectivity.[10a] This prompted us to study the thiol-ene coupling of 2-substituted glycals, which are available easily, as a generally applicable method for the preparation of 1,2-*cis*-α-*S*-linked glycans and glycoconjugates.

First, 2-acetamido-3,4,6-tri-*O*-acetyl-D-glucal **4**, 2-acetoxy-3,4,6-tri-*O*-acetyl-D-galactal **6** and 2-acetoxy-3,4-di-*O*-acetyl-L-fucal **8** were reacted with thiosugar **2a** under previously established standard conditions[10a,b] (Scheme 1). We were pleased to find that all reactions proceeded with exclusive stereoselectivity and in the case of 2-acetamido-glucal **4** the expected 1,2-*cis*-α-linked disaccharide **5** was formed in a good yield. However, the D-galactal (**6**) and L-fucal (**8**) derivatives reacted with significantly lower conversions then the gluco congeners **1** and **4**, thereby the corresponding thiodisaccharides were obtained in disappointingly low yields. Prolonged reaction time and further irradiaton cycles did not promote the reactions and applying a very high 6 equiv thiol excess in the reaction of **8** and **2a** only slightly increased the efficacy of the thiol-ene reaction. To evaluate if the conversion can be influenced by the initiation methods, the reaction of **6** with **2a** was repeated upon thermal initiation with azobisisobutyronitrile■■ok?■■ (AIBN), or using Et_3B[12] as the radical initiator. Unfortunately, no addition reaction was observed in either case.



Scheme 1. Synthesis of 1,2-*cis*-α-*S*-linked disaccharides from 2-substituted glycals through photoinduced thiol-ene coupling under previously established standard conditions.[10a,b]

Table 1. Optimization of conditions for UV-initiated hydrothiolation of **8** with **2a**.[a]

Entry	Excess of **2a** [equiv]	Irradiation time [min]	Conc. of **8** [M]	Temperature [°C]	Conversion[b] [%]
1	1.2	3×15	0.15	0–5	33[c]
2	1.2	6×10	0.15	0–5	34[d]
3	1.2	3×15	0.25	0–5	52
4	1.2	2×60	0.25	0–5	40[e]
5	1.5	3×15	0.25	0–5	60[e]
6	1.2	3×15	0.15	−40	66
7	1.2	3×15	0.15	−80	92 (90[e])
8	1.2	3×15	0.25	+50	9[f]

[a] Reactions were carried out on a 0.5–0.7 mmol scale in toluene using 0.1 equiv of DPAP/alkene/irradiation cycle. [b] Determined by ^{1}H NMR spectroscopy of the reaction mixture. [c] Similar conversions (33–36%) were observed in acetone, CH_2Cl_2, or MeOH. [d] 6×0.05 equiv of DPAP was used. [e] Isolated yield.

The thiol-ene reaction is known to begin with a reversible propagation step wherein a thiyl radical adds to an alkene generating a carbon centered radical intermediate. This radical intermediate then undergoes an irreversible chain-transfer step by abstracting a hydrogen from another thiol to form a thioether product along with a new thiyl radical, which can then initiate another propagation step.[8] Recent computational and kinetic analysis of thiol-ene click reactions has revealed the importance of the stability of the carbon-centered radical intermediate, which directly influences both the chain-transfer activation barrier and the reversibility of the propagation step.[13] Our results with 2-substituted glycals **1**, **4**, **6** and **8** suggested that the stability of the carbon-centered radicals is configuration-dependent and the poor yields of **7** and **9** can be explained by the lower stability of the D-galactosyl and L-fucosyl radicals generated from 6 and 8 compared to the corresponding *gluco*-configured radicals. Therefore, a set of reactions were carried out with thiol **2a** and 2-acetoxy fucal **8** in order to study if the stability of the intermediate radical, and thereby the conversion can be increased by changing the conditions (Table 1).

Performing the reaction at 0 °C with a 1.2:1 thiol/ene ratio, a significant increase of the conversion was observed and the yield of **9** reached 33% (Table 1, Entry 1). In further experiments at this temperature the effects of solvents, concentration, thiol excess and irradiation time were studied. Screening CH_2Cl_2, acetone, and MeOH as the solvent, a notable solvent effect was not observed (Entry 1 and Table S1 in the Supporting Information) and prolonged irradiation was not beneficial (Entries 2 and 4). A significant improvement was observed by increasing the concentration (Entries 3–5) and applying a slightly higher thiol excess. Thus 60% yield of the isolated product was obtained at 0 °C with a 0.25 M alkene concentration and a 1.5:1 thiol-ene ratio (Entry 5).

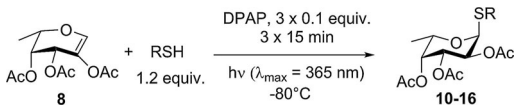
However, satisfactory results were only achieved by further decreases in the reaction temperature (Entries 6 and 7). Running the reaction at −40 °C, by using 1.2 equiv of the thiol and a 0.15 M alkene concentration, the yield of **9** increased to 66%. Finally, repeating this reaction at −80 °C, almost full conversion and an excellent 90% isolated yield of **9** was obtained.[14] We assume that the lifetime/stability of the carbon-centered radical intermediate increases in line with the decreasing reaction temperature that results in the gradually increasing yield. Moreover, disulfide formation from the thiol, which is one of the undesired termination steps of the reaction, was visibly decreased at lower temperatures then at room temperature, which allowed an efficient reaction with a very low thiol excess. Importantly, by running the reaction at +50 °C, low conversion and only a 9% isolated yield was obtained (Entry 8).

After optimizing the conditions, 2-acetoxy-fucal **8** was reacted with a range of thiols including sugars, amino acids as well as sulfonic and carboxylic acid derivatives (Table 2). Depending on the solubility of the thiols various solvents were used, and the low-temperature thiol-ene coupling worked equally well in every solvent to provide the α-thiofucosides with full stereoselectivity in good to excellent yields. Importantly, **11**, a thio-linked analogue of the Fucpα1-6Glc*N*Ac core region of complex *N*-glycoproteins as well as **13** and **14**, stable mimics of the Fucpα1-Ser/Thr residues which occur on essential coagulation glycoproteins were obtained by this procedure with high efficacy.

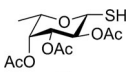
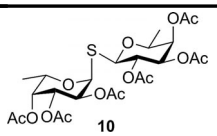
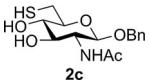
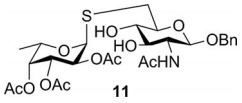
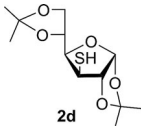
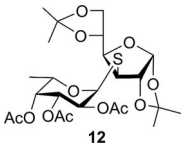
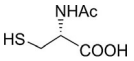
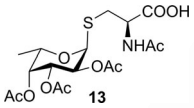
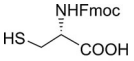
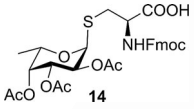
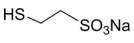
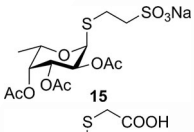
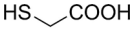
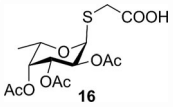
We assumed that the high temperature-dependence of free-radical hydrothiolation of **8** is related to its axially substituted hydroxy group. To test this hypothesis, we studied the temperature effect on the addition of thiol **2a** to 2-acetoxy glycals **6**, **17** and **19** bearing one or two axial OAc substituents (Table 3). Similarly to the case of 6-deoxy-L-hexose derivative **8**, the hydrothiolation of the D-hexose-derived glycals **6**, **17** and **19** proceeded with exclusive α-selectivity, and the low efficacy observed at room temperature could be significantly improved by decreasing the reaction temperature (Entries 1–9).

Starting from glycals **6** and **17** bearing one axial substituent, almost full conversion was observed at −80 °C, and the corresponding galactosyl (**7**) and allosyl (**18**) derivatives were isolated in excellent yields. To further studying the temperature

Table 2. Hydrothiolation of **8** under the optimized conditions.

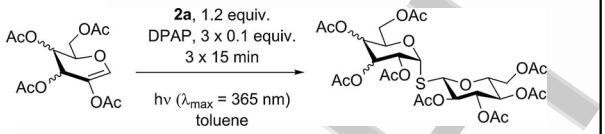


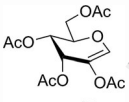
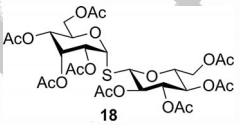
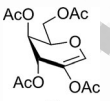
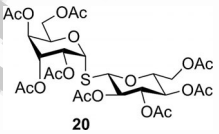
8 → 10-16

Entry	Thiol	Product	Yield[a] [%]
1	 **2b**	 **10**	73[b]
2	 **2c**	 **11**	90[c]
3	 **2d**	 **12**	66[b]
4	 **2e**	 **13**	88[d]
5	 **2f**	 **14**	75[c]
6	 **2g**	 **15**	98[e]
7	 **2h**	 **16**	69[c]

[a] Isolated yield. [b] solvent: toluene. [c] solvent: toluene:MeOH 1:1. [d] solvent: DMF:toluene:MeOH 1:4:6. [e] solvent: DMF:MeOH 1:1.

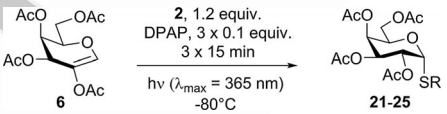
Table 3. Temperature dependence of the thiol-ene couplings of 2-OAc-glycals.



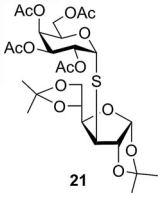
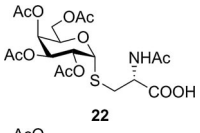
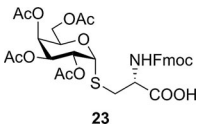
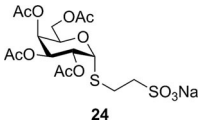
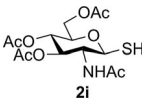
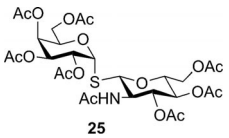
Entry	Glycal	T [°C]	Product	Yield[a] [%]
1	**6**	0	**7**	48
2	**6**	−40	**7**	65
3	**6**	−80	**7**	85
4	**6**	+50	**7**	16
5	 **17**	0	 **18**	38
6		−40		76
7		−80		92
8	 **19**	rt	 **20**	12
9		−80		47

[a] Isolated yield.

Table 4. Addition of thiols to 2-acetoxygalactal



6 → 21-25

Entry	Thiol	Product	Yield[a] [%]
1	**2d**	 **21**	62[b]
2	**2e**	 **22**	93[c]
3	**2f**	 **23**	70[c] 12[d]
4	**2g**	 **24**	98[e] 15[d,e]
5	 **2i**	 **25**	98[b]

[a] Isolated yield. [b] Solvent: toluene. [c] Solvent: toluene/MeOH 3:4. [d] At room temperature with 2 equiv of thiol. [e] Solvent: MeOH.

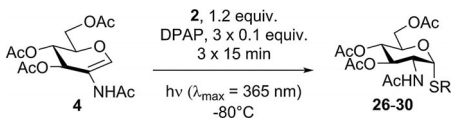
effect, the addition of **2a** to galactal **6** was also carried out at elevated temperature (Entry 4). Running the reaction at +50 °C, low conversion of the glycal was observed that result in a significant decrease in the yield of product **7**. Importantly, the reaction of **1** and **2a** was also performed at +50 °C. In this case, the heating exerted an even greater negative effect on the addition reaction and product **3** was obtained in only 6% isolated yield.

Compound **19** with two axial substituents demonstrated the lowest reactivity upon hydrothiolation and, despite the beneficial effect of cooling, only a 47% isolated yield of the D-gulose-containing thiodisaccharide **20** was obtained at −80 °C (Entries 8 and 9).

Next, the efficacy of the thiol-ene coupling under the optimized conditions was further demonstrated by reacting the galactal derivative **6** with various thiols (Table 4). The additions proceeded with good to excellent yields providing valuable thio-analogues of galactans of major clinical significance such as, e.g., **21** showing the terminal (1–3)α-Galp motif of the α-Gal epitope of the anti-Gal antibody.[15]

To test if the cooling has a beneficial effect on the thiol-ene reaction of glycals without an axial substituent, the reaction of 2-acetamido-glucal **4** with thiol **2a** was carried out at −80 °C. To our great delight, the yield of **5** increased from the 63% observed at room temperature (Scheme 1) to 73% by cooling (Table 5, Entry 1). Next, compound **4** was reacted with a range

Table 5. Addition of thiols to 2-acetamido-glucal



4 → 26-30

Entry	Thiol	Product	Yield[a] [%]
1	**2a**	**5**	73
2	**2c**	**26**	74[b]
3	**2e**	**27**	70[c] / 24[c,d]
4	**2f**	**28**	66[e]
5	**2g**	**29**	72[f]
6	**2i**	**30**	73[e] / 46[d,e]

[a] Isolated yield. [b] Solvent: DMF. [c] Solvent: toluene:MeOH 1:3. [d] At room temperature with 2 equiv of thiol. [e] Solvent: toluene:MeOH 1:1. [f] Solvent: MeOH.

of thiols at low temperature (Table 5). All of the couplings proceeded in good-to-excellent yields by using only 1.2 equiv thiol. In some instances, we demonstrated that the hydrothiolation of **4** proceeded with a significantly lower efficacy at room temperature than at −80 °C (Entries 3 and 6). It is worth mentioning that thiol-ene couplings of 2-deoxy-2-aminoglycals were hitherto unknown.■■ok?■■

The observed configuration-dependent reactivity of glycals at rt can be explained on the basis of the energy-profile of the rapidly reversible propagation step (Figure 1). Owing to the steric congestion between the equatorial C2 and C3 substituents in the $^4H_5$ half-chair conformation, the transition complex of 2-acetoxy-D-glucal (red) is at a higher energy level than the corresponding 2-acetoxy-D-galactal (blue). In contrast, among the formed carbon centered radical intermediates existing in a $^4C_1$ chair conformation, the *gluco* configured radical has lower energy, owing to the all-equatorial substitution pattern. Thus,

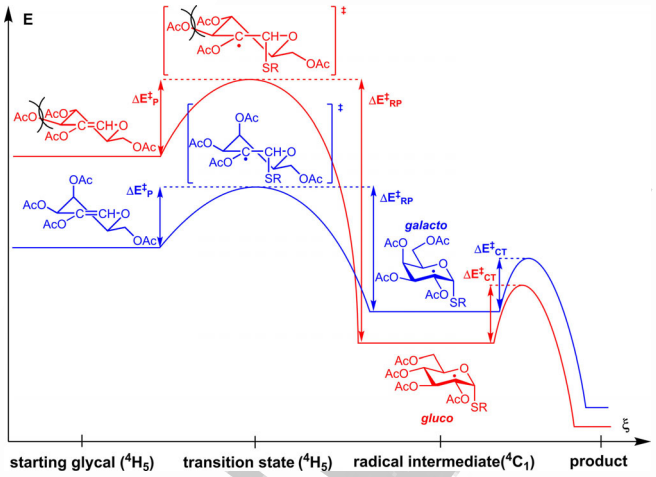


Figure 1. Energy profile of the thiol-ene couplings of 2-acetoxy-D-glycals with all-equatorial (red) and axial/equatorial (blue) substitution patterns. $\Delta E^{\ddagger}_{R}$: activation energy barrier of the propagation step; $\Delta E^{\ddagger}_{RP}$: activation energy barrier of the reverse propagation (fragmentation) step; $\Delta E^{\ddagger}_{CT}$: activation energy barrier of the chain transfer step.

the difference between the activation energy barriers of the forward and reverse reactions is higher for glucal than galactal. At rt, the high energy barrier efficiently prevents the fragmentation of the *gluco*-intermediate ensuring the efficiency of the thio-click process.[10a] However, in the case of the *galacto*-intermediate the small difference in energy barriers allows the reverse reaction at rt which decreases the efficiency of the product formation. According to our experimental results, the energy profile of all glycals having axial substituents is similar to that of 2-acetoxy-D-galactal, which explains their low reactivity observed at rt.

It is important to note, that although 2-acetoxy-glycals exist in a rapid interconversion equilibrium between $^4H_5$ and $^5H_4$ half chair conformations,[16] we surmise that the free-radical hydrothiolation of 2-substituted D-glycals occurs exclusively via the $^4C_1$ conformer of the carbon-centered radical that is formed from the $^4H_5$ half-chair conformer of the glycal upon bottom-face attack of the thiyl radical. Attacks of thiyl radicals on the $^5H_4$ conformer produce high-energy C2-centered radical intermediates that fragment to starting compounds very rapidly (for detailed explanation see Scheme S1). We assume that the exclusivity of this reaction path and the kinetically preferred axial attack of thiols to cyclic alkenes[17] together ensure the exclusive α-stereoselectivity of the reaction. Analogously, owing to the exquisite stability of the $^1C_4$ conformer of L-hexoses, in the case of the L-fucal derivative the reactions proceed through the corresponding $^5H_4$ half chair and $^1C_4$ chair conformers.

To understand the very unusual promoting effect of cooling on the thio-click reaction, the relative energy barriers of both the propagation step and the chain-transfer step should be taken into account. By cooling, the equilibrium of the exothermic propagation step can be shifted toward the carbon-centered radical intermediate. However, this intermediate can only be transformed into the product if the chain-transfer barrier is sufficiently low. Our experimental results demonstrate that this

is the case for all the glycals studied. The calculated, low chain-transfer energy barrier for hydrothiolation of vinyl and allyl ethers (ca. 8 kcal mol^{-1}) published by Northrop and Coffey are in line with our results.[13b] Importantly, the insufficient reactivity of the 2-acetamido derivative **4** at room temperature, which is probably caused by electronic effects, could also be increased by cooling.

In conclusion, we have developed an efficient strategy for stereoselective 1,2-*cis*-α-thioconjugation by UV-light-initiated thiol-ene coupling reaction of 2-substituted hexoglycals at −80 °C. Our study revealed that the reaction temperature profoundly influences the efficacy of the reactions by controlling the equilibrium of the reversible propagation step of the radical chain process. Although heating is detrimental to the thiol-ene coupling reactions of glycals, cooling has a very efficient promoting effect. This unique temperature effect can be applied to further optimize the thiol-ene reactions in synthetic chemistry.

Acknowledgements

The authors gratefully acknowledge the National Research, Development and Innovation Office of Hungary (OTKA K 109208 and TÉT_15_IN-1-2016-0071) and the Gedeon Richter's Talentum Foundation (1103 Budapest, Gyömrői út 19-21) for financial support. The research was also supported by the EU and co-financed by the European Regional Development Fund under the project GINOP-2.3.2-15-2016-00008.

Conflict of interest

The authors declare no conflict of interest.

Keywords: glycals · photoinitiation · radical reactions · stereoselective · temperature-controlled · thioglycosides

[1] A. Welsh, A. Taguchi, K. Schaefer, D. Van Tyne, F. Lebreton, M. S. Gilmore, D. Kahne, S. Walker, *J. Am. Chem. Soc.* **2017**, *139*, 17727 – 17730.
[2] Y. Kinjo, D. Wu, G. Kim, G. Xing, M. A. Poles, D. D. Ho, M. Tsuji, K Kawahara, C. H. Wong, M. Kronenberg, *Nature* **2005**, *434*, 520 – 525.
[3] M. A. Hollingsworth, B. J. Swanson, *Nat. Rev. Cancer* **2004**, *4*, 45 – 60.
[4] D. J. Becker, J. B. Lowe, *Glycobiology* **2003**, *13*, 41R – 53R.
[5] Selected publications for thio analogues of α-*O*-glycosides: a) S. Knapp, D. S. Myers, *J. Org. Chem.* **2001**, *66*, 3636 – 3638; b) R. T. Dere, X. Zhu, *Org. Lett.* **2008**, *10*, 4641 – 4644; c) N. Floyd, B. Vijayakrishnan, J. R. Koeppe, B. G. Davis, *Angew. Chem. Int. Ed.* **2009**, *48*, 7798 – 7802; *Angew. Chem.* **2009**, *121*, 7938 – 7942; d) A. Borbás, P. Herczegh, *Carbohydr. Res.* **2011**, *346*, 1628 – 1632; e) A. Noel, B. Delpech, D. Crich, *Org. Lett.* **2012**, *14*, 4138 – 4141; f) X. Zeng, R. Smith, X. Zhu, *J. Org. Chem.* **2013**, *78*, 4165 – 4170; g) C. Aydillo, I. Compañón, A. Avenoza, J. H. Busto, F. Corzana, J. M. Peregrina, M. M. Zurbano, *J. Am. Chem. Soc.* **2014**, *136*, 789 – 800; h) S. André, S. O'Sullivan, C. Koller, P. V. Murphy, H.-J. Gabius, *Org. Biomol. Chem.* **2015**, *13*, 4190 – 4203; i) S. André, S. O'Sullivan, H.-J. Gabius, P. V. Murphy, *Tetrahedron* **2015**, *71*, 6867 – 6880; j) L. Zhang, C. McCarthy, X. Zhu, *Carbohydr. Res.* **2017**, *448*, 43 – 47; k) C. C. Lin, T.-C. Kuan, H.-R. Wu, A. K. Adak, B.-Y. Li, C.-F. Liang, S.-P. Chiou, J.-T. Hung, A. L. Yu, J. R. Hwu, *Chem. Eur. J.* **2017**, *23*, 6876 – 6887.■■ok?■■
[6] Z. J. Witczak, J. M. Culhane, *Appl. Microbiol. Biotechnol.* **2005**, *69*, 237 – 244.
[7] a) K. Pachamuthu, R. R. Schmidt, *Chem. Rev.* **2006**, *106*, 160 – 187; b) G. J. L. Bernardes, D. P. Gamblin, B. G. Davis, *Angew. Chem. Int. Ed.* **2006**, *45*, 4007 – 4011; *Angew. Chem.* **2006**, *118*, 4111 – 4115; c) R. T. Dere, Y. Wang, X. Zhu, *Org. Biomol. Chem.* **2008**, *6*, 2061 – 2063; d) R. T. Dere, A. Kumar, ; V. Kumar, X. Zhu, R. R. Schmidt, *J. Org. Chem.* **2011**, *76*, 7539 – 7545; V. Kumar, X. Zhu, R. R. Schmidt, *J. Org. Chem.* **2011**, *76*, 7539 – 7545; e) L. M. Doyle, S. O'Sullivan, C. Di Salvo, M. McKinney, P. McArdle, P. V. Murphy, *Org. Lett.* **2017**, *19*, 5802 – 5805.
[8] a) T. Posner, *Ber. Dtsch. Chem. Ges.* **1905**, *38*, 646 – 657; b) F. R. Mayo, C. Walling, *Chem. Rev.* **1940**, *27*, 351 – 412; c) K. Griesbaum, *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 273 – 287; *Angew. Chem.* **1970**, *82*, 276 – 290; d) N. B. Cramer, S. K. Reddy, M. Cole, C. Hoyle, C. N. Bowman, *J. Polym. Sci. Part A* **2004**, *42*, 5817 – 5825; e) C. E. Hoyle, C. N. Bowman, *Angew. Chem. Int. Ed.* **2010**, *49*, 1540 – 1573; *Angew. Chem.* **2010**, *122*, 1584 – 1617; f) C. E. Hoyle, A. B. Lowe, C. N. Bowman, *Chem. Soc. Rev.* **2010**, *39*, 1355 – 1387; g) F. Dénès, M. Pichowicz, G. Povie, P. Renaud, *Chem. Rev.* **2014**, *114*, 2587 – 2693.
[9] a) A. Dondoni, *Angew. Chem. Int. Ed.* **2008**, *47*, 8995 – 8997; *Angew. Chem.* **2008**, *120*, 9133 – 9135; b) A. Dondoni, A. Marra, *Chem. Soc. Rev.* **2012**, *41*, 573 – 586; c) L. McSweeney, F. Dénès, E. M. Scanlan, *Eur. J. Org. Chem.* **2016**, 2080 – 2095.
[10] a) L. Lázár, M. Csávás, M. Herczeg, P. Herczegh, A. Borbás, *Org. Lett.* **2012**, *14*, 4650 – 4653; b) L. Lázár, M. Csávás, Á. Hadházi, M. Herczeg, M. Tóth, L. Somsák, T. Barna, P. Herczegh, A. Borbás, *Org. Biomol. Chem.* **2013**, *11*, 5339 – 5350; c) S. Staderini, A. Chambery, A. Marra, A. Dondoni, *Tetrahedron Lett.* **2012**, *53*, 702 – 704; d) L. Lázár, L. Juhász, G. Batta, A. Borbás, L. Somsák, *New J. Chem.* **2017**, *41*, 1284 – 1292.
[11] a) M. Fiore, A. Marra, A. Dondoni, *J. Org. Chem.* **2009**, *74*, 4422 – 4425; b) L. Lázár, M. Csávás, M. Tóth, L. Somsák, A. Borbás, *Chem. Pap.* **2015**, *69*, 889 – 895■■not found in Crossref, please check and update if needed.■■; c) M. Richard, C. Didierjean, Y. Chapleur, N. Pellegrini-Moïse, *Eur. J. Org. Chem.* **2015**, 2632 – 2645; d) J. József, L. Juhász, T. Z. Illyés, M. Csávás, A. Borbás, L. Somsák, *Carbohydr. Res.* **2015**, *413*, 63 – 69; e) M. Bege, I. Bereczki, M. Herczeg, M. Kicsák, D. Eszenyi, P. Herczegh, A. Borbás, *Org. Biomol. Chem.* **2017**, *15*, 9226 – 9233.
[12] a) G. Povie, A.-T. Tran, D. Bonnaffé, J. Habegger, Z. Hu, C. Le Narvor, P. Renaud, *Angew. Chem. Int. Ed.* **2014**, *53*, 3894 – 3898; *Angew. Chem.* **2014**, *126*, 3975 – 3979; b) J. Gorges, U. Kazmaier, *Eur. J. Org. Chem.* **2015**, 8011 – 8017; c) L. Lázár, M. Nagy, A. Borbás, P. Herczegh, M. Zsuga, S. Kéki, *Eur. J. Org. Chem.* **2015**, 7675 – 7681.
[13] a) N. B. Cramer, S. K. Reddy, A. K. O'Brien, C. N. Bowman, *Macromolecules* **2003**, *36*, 7964 – 7969; b) B. H. Northrop, R. N. Coffey, *J. Am. Chem. Soc.* **2012**, *134*, 13804 – 13817.
[14] Similar temperature-dependence was observed when **8** was reacted with 1-thio- and 6-thio-galactose derivatives. See: D. Eszenyi, L. Lázár, A. Borbás, R. McCourt in *Carbohydrate Chemistry: Proven Synthetic Methods, Vol. 4* (Eds.: P. Kováč, C. Vogel, P. Murphy), CRC Press, Boca Raton, **2017**, pp. 33 – 44.
[15] U. Galili, *Immunol. Cell Biol.* **2005**, *83*, 674 – 686.
[16] M. Rico, J. Santoro, *Org. Magn. Res.* **1976**, *8*, 49 – 55.
[17] A. LeBel, R. F. Czaja, A. DeBoer, *J. Org. Chem.* **1969**, *34*, 3112 – 3126.

Manuscript received: February 9, 2018
Accepted manuscript online: February 19, 2018
Version of record online: ■■ ■■, 0000

COMMUNICATION

Synthetic methodology

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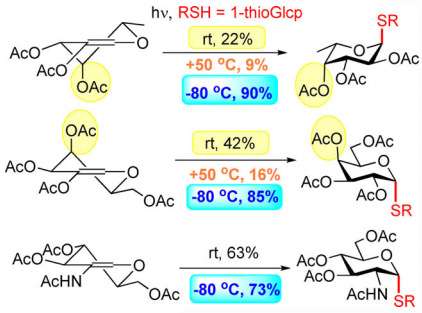
Promotion of a Reaction by Cooling: Stereoselective 1,2-*cis*-α-Thioglycoconjugation by Thiol-Ene Coupling at −80 °C



Sulfur sugars: Reaction temperature influences the thiol-ene reactions of cyclic alkenes in a very unique fashion: cooling promotes whereas heating inhibits the reaction. Unfavorable steric and electronic effects resulting in low conversions at room temperature were overcome by conducting the reactions at −80 °C. The thiol-ene coupling reaction of 2-substituted hexoglycals at −80 °C is an efficient strategy for stereoselective 1,2-*cis*-α-thioconjugation.

Borbás and coworkers from University of Debrecen couple thiol containing glycals: temperature makes the difference! SPACE RESERVED FOR IMAGE AND LINK

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D.E. Writing – original draft: Supporting
P.H. Conceptualization: Supporting; Supervision: Supporting; Writing – original draft: Supporting.