Stereoselective Synthesis of Carbon-Sulfur-Bridged Glycomimetics by Photoinitiated Thiol-Ene Coupling Reactions

Magdolna Csávás 1, Dániel Eszenyi 1, Erika Mező 1, László Lázár 2, Nóra Debreczeni 1,3, Marietta Tóth 2, László Somsák 2 and Anikó Borbás 1,*

1 Department of Pharmaceutical Chemistry University of Debrecen, Egyetem tér 1, H-4032 Debrecen, Hungary; csavas.magdolna@science.unideb.hu (M.C.); eszenyid@gmail.com (D.E.); mezo.erika@science.unideb.hu (E.M.); debreczeni.nora@science.unideb.hu (N.D.)
2 Department of Organic Chemistry, University of Debrecen, Egyetem tér 1, H-4032 Debrecen, Hungary; lazlar.laszlo@science.unideb.hu (L.L.); toth.marietta@science.unideb.hu (M.T.); somsak.laszlo@science.unideb.hu (L.S.)
3 Doctoral School of Chemistry, University of Debrecen, Egyetem tér 1, H-4032 Debrecen, Hungary
* Correspondence: borbas.aniko@pharm.unideb.hu; Tel.: +36-52-512900-22472

Received: 20 December 2019; Accepted: 15 January 2020; Published: 16 January 2020

Abstract: Oligosaccharides and glycoconjugates are abundant in all living organisms, taking part in a multitude of biological processes. The application of natural O-glycosides in biological studies and drug development is limited by their sensitivity to enzymatic hydrolysis. This issue made it necessary to design hydrolytically stable carbohydrate mimetics, where sulfur, carbon, or longer interglycosidic connections comprising two or three atoms replace the glycosidic oxygen. However, the formation of the interglycosidic linkages between the sugar residues in high diastereoselectivity poses a major challenge. Here, we report on stereoselective synthesis of carbon-sulfur-bridged disaccharide mimetics by the free radical addition of carbohydrate thiols onto the exo-cyclic double bond of unsaturated sugars. A systematic study on UV-light initiated radical mediated hydrothiolation reactions of enoses bearing an exocyclic double bond at C1, C2, C3, C4, C5, and C6 positions of the pyranosyl ring with various sugar thiols was performed. The effect of temperature and structural variations of the alkenes and thiols on the efficacy and stereoselectivity of the reactions was systematically studied and optimized. The reactions proceeded with high efficacy and, in most cases, with complete diastereoselectivity producing a broad array of disaccharide mimetics coupling through an equatorially oriented methylensulfide bridge.

Keywords: carbohydrate; disaccharide; glycomimetic; thioglycoside; C-glycoside; photochemical addition; thiyl radical; diastereoselective synthesis

1. Introduction

Carbohydrates, in the form of oligosaccharides, polysaccharides, and glycoconjugates, are ubiquitous in nature and play crucial roles in a wide range of intercellular recognition events, including adhesion, signaling, trafficking, immune response, metastasis, inflammation, as well as bacterial and viral infections [1–3]. Due to these important biological functions, the development of sugar-based drugs could be of great pharmaceutical interest [4,5]. However, the sensitivity of the native glycosidic bond to chemical and enzymatic degradation hinders the therapeutic application of carbohydrates [6].

A broad variety of carbohydrate mimetics with various unnatural glycosidic linkages have been prepared to address this issue [6–11]. The replacement of glycosidic oxygen by carbon, sulfur,
selenium, or nitrogen is the most obvious way to produce derivatives with increased stability, while maintaining the biological properties of the natural compounds (Scheme 1(A1)). In recent years, numerous extended linkage modes that consist of two (or even more) bridging atoms in the place of a native O-glycosidic bond have been designed (Scheme 1(A2)) [7,8]. The extended, three-bond interglycosidic connections, including S-S [12–15], Se-S, Se-Se [16], C-S [17,18], C-N [19], N-O [20], and SO2-N [21] bonds, provide specific conformational properties, and, in some cases, advantageous binding capabilities to carbohydrate mimetics.

\[ X-Y = S-S, S-Se, Se-Se, C-S, C-N, N-O, SO_2-N \]

\[ X = S, Se, C, N \]

\[ X = S, Se, C, N \]

**Scheme 1.** (A) Disaccharide mimetics with two-bond and three-bond linkages. Yellow background indicates the three-bond connection, and the C-S bond discussed in this study is highlighted in red. (B) Literature results on the synthesis of C-S-bridged disaccharide mimetics. The newly formed C-S bonds are highlighted in red. (C) This work: systematic study on UV-light induced hydrothiolation reactions of enopyranoses bearing an exocyclic double bond at C1, C2, C3, C4, C5, and C6 positions.
The carbon-sulfur-bridged oligosaccharides may be of particular interest, because they may combine the beneficial properties of the two most common carbohydrate mimetics, thioglycosides [8,9], and C-glycosides [10,11,22].

The radical-mediated addition of thiols to non-activated double bonds is widely used in organic syntheses, material sciences, and glycochemistry as a robust ligation tool [23–26]. Recent results have demonstrated that applying unsaturated sugars as the alkene partners in the thiol-ene coupling reactions offers a rapid route to a broad range of thio-linked glycomimetics, including 1,2-cis α-S-glycosides [27–31], 2-thio-β-mannosides [32] as well as C-S-bonded carbohydrate mimetics, wherein the CH$_2$-S linkage is attached to the C1 or the C5 position of the pyranosyl ring [33–35] (Scheme 1B). Dondoni and co-workers reported that, while photoinduced hydrothiolation of 5-exomethylene pyranoside 1 with 1-thioaldose 2a furnished the corresponding S-linked disaccharide 3 with complete regio- and stereoselectivity, addition reaction to galactopyranosyl 5-exomethylene 4 occurred with only moderate stereoselectivity, yielding a 3:1 mixture of 5a and 5b (Scheme 1(B1)) [33]. Our group and Somsá’s group investigated the synthesis of glycosymethyl-sulfide type disaccharide derivatives by thiol-ene reactions of several hexo- and pentopyranosyl exo-glycals. (Scheme 1(B2)) [34,35]. Addition to the exo-galactal derivative 6 provided the pseudodisaccharide 7 with exclusive β-selectivity [34]. However, upon hydrothiolation of the pentopyranosyl 2-deoxy-exo-glycal, a decreased stereoselectivity was observed, which afforded an anomeric mixture of 9 in favour of the α-configured product [35]. These results demonstrated that the enose structure greatly influences the stereoselectivity and the efficacy of the additions. We decided to perform a systematic study on UV-light initiated radical mediated hydrothiolation reactions of enoses bearing an exocyclic double bond at C1, C2, C3, C4, and C5 positions of the hexopyranosyl ring, as thiol-ene reactions of C2, C3, and C4 exomethylene derivatives of pyranosides have not been reported. Moreover, the hydrothiolation of a galactose-derived hept-6-enopyranose to produce C-S-bridged analogue of the biorelevant N-acetyl-neuraminic-acid-α(2,6)-β-galactose motif is also reported (Scheme 1C).

2. Results

The perbenzoylated exo-glucal 10 [36–38] was reacted with thiols 2a, 2c, and 2d while applying the optimized conditions established in our recent work for hydrothiolation reactions of unsaturated sugars [27–29]. Thus, the reactions were carried out in toluene at room temperature with a 1.5:1 thiol:ene ratio by irradiation at $\lambda_{\text{max}} = 365$ nm in the presence of 2,2-dimethoxy-2-phenylacetophenone (DPAP, 0.1 equiv) as the cleavable photoinitiator [24]. The addition of 1-thioglucose tetra-O-acetate 2a onto 2-exomethylene 16 at room temperature readily occurred to result in an inseparable 1:1 mixture of the β-gluco and β-manno configured thiodisaccharides (17a,b) with 91% yield. After the acidic removal of the butane-2,3-diacetal (BDA) group, the partially protected diastereoisomeric glycomimetics 18 and 19 were successfully separated and characterized.
The addition of 1-thioglucose tetra-acetate (OTBDPS, 0.1 equiv) as the cleavable photoinitiator \[24\]. The addition of 1-thiosugar onto the galactose-derived enoside \[21\], \[28\] went to completion within 15 min. to provide \[22\] configured 25 which resulted in a 4:1 mixture of the \[22\] and \[22\] configured products in a 1:1 ratio in 96% yield. The partial deprotection of \[22\] and \[22\] configured \[25\] could be isolated in the pure form.

Next, thiol-ene reactions of enopyranosides bearing an exomethylene moiety at the C2 position were successfully separated and characterized. Recently, we have found that cooling was advantageous to the thiol-ene reactions of enosides to increase the yields of the stereochemical outcome of the hydrothiolation reaction of the glucose-derived enoside \[22\] with TFA gave a mixture of \[25\] and \[26\], from which the D-talo configured \[25\] could be isolated in the pure form.

The methyl group, the partially protected diastereoisomeric glycomimetics 18 and 19 were successfully separated and characterized. In this case a moderate selectivity was observed in favour of the D-configured product.\[40\] (Scheme 3).

Swern-oxidation \[42\] of \[15\] furnished \[16\] with exclusive regio- and stereoselectivity (Figure 1).

Figure 1. Stereoselective synthesis of glycosylmethyl sulfide type glycomimetics by thiol-ene reactions of \(\alpha\)-galactopyranose 21, 3-thio-glucofuranose 22, and, in the case of enofuranosides and pentopyranosyl endoglycals, to raise the stereoselectivity, \[29\], and, \[41\] (Scheme 3).

Figure 1. Stereoselective synthesis of glycosylmethyl sulfide type glycomimetics by thiol-ene reactions of \(\alpha\)-galactopyranose 21, 3-thio-glucofuranose 22, and, in the case of enofuranosides and pentopyranosyl endoglycals, to raise the stereoselectivity.

Scheme 2. Hydrothiolation reaction of the glucose-derived enoside 16 bearing a C2-exomethylene group.
Scheme 3. Addition of thiols onto the C2-exocyclic double bond of the galactose derived 22.

Scheme 4. Hydrothiolation reactions of the β-configured C2-exomethylene enoside 29.
The methyl α-D-galactopyranoside derivative 22 with a C2 exocyclic double bond was also synthesized, starting from compound 20, in order to study the effect of the enose configuration on the stereochemical outcome of the hydrothiolation reaction [41] (Scheme 3). Swern-oxidation [42] of 20, followed by Wittig-olefination of the resulting 2-ulose 21 furnished 22 with good overall yield. Addition of β-1-thiosugar 2a onto the galactose-derived enoside 22 at rt occurred with lower efficacy than in the gluco-case and led again to the formation of an inseparable diastereoisomeric mixture of the corresponding axially and equatorially coupled C-S-bonded disaccharides 23a and 23b. In this case a moderate selectivity was observed in favour of the α-talo-configured product. Recently, we have found that cooling was advantageous to the thiol-ene reactions of enosides to increase the yields [29], and, in the case of enofuranosides and pentopyranosyl endoglycals, to raise the stereoselectivity significantly [18,31]. Indeed, conducting the reaction between 22 and 2a at −80 °C the yield of 23a,b reached 88%. However, surprisingly, a complete lack of stereoselectivity was observed at this temperature.

Reacting 22 with α-1-thiannonose derivative 2e at rt occurred with a higher ν-talo selectivity, which resulted in a 4:1 mixture of the C-S-bonded glycomimetics 24a and 24b. The cooling was again beneficial to the efficacy and detrimental to the diastereoselectivity of the reaction affording the ν-talo and ν-galacto configured products in a 1:1 ratio in 96% yield. The partial deprotection of 24a,b with TFA gave a mixture of 25 and 26, from which the ν-talo configured 25 could be isolated in the pure form.

For studying the impact of the anomeric configuration on the stereochemical outcome of the thiol-ene reaction, compound 29, the β-analogue of 22, was prepared from methyl β-D-galactoside 27 [43] via oxidation and Wittig-olefination (Scheme 4). Surprisingly, the addition of 2a and 2e onto 29 at rt proceeded with lower efficacy resulting in the C-S bridged products 30 and 31 in low yields. On the other hand, an opposite and increased stereoselectivity was observed with both thiols when compared to the α-configured enoside 22. Using 2a as the thiol, a 4:1 mixture was formed at rt in favour of the galacto-configured product with 22% yield, while complete galacto selectivity was observed with thiol 2e, albeit the yield was only moderate at rt. Running the reaction at −80 °C significantly increased the yields and exclusive formation of the ν-galacto configured products was observed with both thiols.

Our investigation was continued with the hydrothiolation of the pyranosyl C3-exomethylene 33 (Scheme 5). The deprotection of glucopuranosyl 3-exomethylene 32 [44] while using TFA, followed by Ac₂O-NaOAc mediated acetylation furnished the pyranose derivative 33 [45] in β-anomeric form. The hydrothiolation of 33 with thiols 2a and 2e occurred with full stereoselectivity and high yields producing the thiodisaccharides 34 and 35 with an equatorial carbon-sulfur linkage at position C3.

![Scheme 5. Thiol-ene reactions of enoside with a C3-exomethylene moiety.](image)

Next, we turned our attention to hydrothiolation of pyranoses containing a C4 exocyclic double bond (Schemes 6 and 7). The oxidation of the methyl α-D-glucopyranoside derivative 36 [39] at
position 4, followed by Wittig-olefination resulted in the unsaturated sugar 37 bearing 6-O-silyl and 2,3-O-butane diacetal protecting groups (Scheme 6). The hydrothiolation of 37 with 1-thioglucose peracetate 2a went to completion within 15 min. to result in an inseparable mixture of two compounds. On the basis of NMR and MS data, the components of the obtained mixture were tentatively identified as the expected disaccharide mimetic 38a and its sulfoxide derivative 38b, although at this stage of the study the configuration of the C4 stereocenter of the methyl glucopyranoside residue was uncertain. The attempted separation of compounds 39a and 39b obtained by TBAF-mediated desilylation failed. Fortunately, after deacetalation while using TFA, the major product was isolated in pure form and, after acetylation, undoubtedly identified as the equatorially 4-C-S-bonded disaccharide mimetic. Interestingly, the acetylation of compound 40 led again to an inseparable mixture of the corresponding fully protected thiodisaccharide 41a and its sulfoxide derivative 41b.

Scheme 6. Addition of 1-thioglucose 2a onto the C4-positioned exocyclic double bond of enopyranoside 37.

Scheme 7. The addition of 1-thioglucose 2a onto the C4-exomethylene derivative 44 using different initiation methods.
We were curious as to whether the susceptibility to oxidation of 38 was due to the C4 position of the C-S bond or the substitution pattern of the enoside reactant. Therefore, C4-exomethylene 44, a 2,3-di-O-methylated analogue of 37, was prepared from 42 [46] via the oxidation-Wittig-olefination reaction sequence (Scheme 7).

UV-light initiated addition of thiol 2a onto 44 occurred with complete diastereoselectivity to provide the corresponding equatorially coupled disaccharide mimetic 45 with 81% yield. The addition between 2a and 44 was also elicited by using triethylborane in combination with catechol, which was recently reported by Renaud and co-workers as an efficient reagent system for radical hydrothiolation of allylic double bonds [47]. The reaction took place with similar efficiency to the one that was observed in the case of photoinitiation and the formation of sulfoxide was not observed in either case.

To push the scope of the reaction further, we extended our study to disaccharide 47 bearing exocyclic double bonds at positions C5 and C5′ (Scheme 8). The 6,6′-diiodo trehalose derivative 46 [48] was treated with AgF [49] in pyridine to afford the 5,5′-dienoside 47 with 54% yield. The hydrothiolation of 47 with 1-thiomannose derivative 2e at rt while using the usual thiol:alkene ratio (1.5 equiv thiol/double bond) resulted in the thiotrisaccharide as the major product (27%) and the expected dithiotetrasaccharide could not be isolated in pure form. The reaction was carried out in a mixture of DMF and toluene due to the low solubility of 47 in toluene. Conducting the reaction at −80 °C increased the yield and provided 33% of 48 and 18% of 49. Raising the thiol excess to 4.5 equivalents (2.25 equiv. thiol/double bond) and running the addition reaction at −80 °C afforded 49 (60%) as the major product, along with 4% of 48. Changing the solvent to CH2Cl2, a more clean and efficient reaction was observed, providing 49 with 74% yield. As the trisaccharide enoside 48 can be subjected to further hydrothiolation reaction with different thiosugars, the hydrothiolation of a dienoside offers the possibility for homo- and heterodisubstitution, depending on the thiol excess applied.

Scheme 8. Synthesis of higher oligosaccharides by photoinitiated hydrothiolation of disaccharide dienoside 47 with different thiol-ene ratios and different temperatures.
Finally, the thiol-ene reaction was utilized for the synthesis of a C-S-bridged analogue of the biorelevant N-acetyl-neuraminic-acid-α(2,6)-β-galactose disaccharide sequence [50–52]. The galacto-configured 6,7-enopyranose 50 [53–55] was reacted with 2-thio-neuraminic acid derivative 2f to achieve this goal (Scheme 9). The reaction afforded the expected sialyl galactoside mimic 51 with 62% yield at rt and a slightly increased 69% yield at −80 °C.

Scheme 9. Rapid, thio-click route to the biorelevant sialyl galactoside mimic 51.

3. Discussion

We prepared nine enopyranosyl derivatives with an exocyclic double bond at C1, C2, C3, C4, C5, and C6 positions and studied their UV-initiated hydrothiolation reactions while using various sugar thiols. The reactions, except for the C2-exomethylene cases, took place with complete regio- and stereoselectivity providing the corresponding equatorial C-S-bonded di- and oligosaccharide mimetics with high yields.

The thiol-ene reaction proceeds through a reversible thyl addition (propagation) step, followed by an irreversible hydrogen abstraction (chain transfer) step by the carbon centered radical intermediate formed (Scheme 10A) [56–58]. While the addition of thyl radicals to unsymmetrically substituted linear alkenes generally exhibits poor stereoselectivity, in the case of substituted cyclic olefins with an endocyclic double bond, the addition is known to preferentially occur in a trans-diaxial manner as the result of a kinetically favored axial attack of the thyl radical onto the cyclic alkene in its half-chair conformation together with a stereoselective hydrogen abstraction from the thiol into an axial position [27–31,59,60]. We assume that, in the case of exo-glycal 10 and C3-, C4-, and C-5 exomethylene 33, 37, 44, and 47, respectively, the thiol-ene reactions exclusively occur through the stable 4C1 chair conformer of the corresponding carbon-centered radical (Scheme 10B). Axial H-abstraction by these radicals from a thiol leads to the formation of the equatorial C-5 interglycosidic linkages. Other possible carbon-centered radical intermediates of higher energy rather decompose in an intramolecular reaction, instead of forming the final product intermolecularly, due to the rapidly reversible nature of the thyl addition step [58].

We have found that the hydrothiolation of the C2-exomethylene derivatives 16, 22, and 29 led to diastereoisomeric mixtures of disaccharide mimetics linked through axial and equatorial methylenesulfide bonds. We assume that, in these cases, the reaction can proceed through both the 4C1 chair and 4H5 half-chair conformers of the C2-centered radical bearing an equatorial or a quasi equatorial C2 substituent (Scheme 11). The equatorially C-S-linked products can be formed either through the 4C1 or the 4H5 conformation of the C2 radicals via axial H-abstraction from the upper face. At the same time, axial H-abstraction by the 4H5 conformer from the bottom face might lead to the formation of the epimeric disaccharides with an axial interglycosidic connection at position C2. The ratio of products showed great variation, depending on the configuration of enosides and thiols, as well as the temperature. The different stereoselectivity that was observed with the different thiosugars can be explained by the different fitting of the C2 radicals to thiols of different configurations. This phenomenon, which is known as double stereodifferentiation, is well-documented in the field of chemical glycosylation [61,62]. In the case of the β-configured 29, the addition reactions occurred with remarkable or complete α-galacto-selectivity, which was probably due to the 1,3-diaxial repulsion...
between the aglycon and the C4-substituent in the $^{4}H_{5}$ conformation, which increases the energy, thereby decreasing the lifetime of this conformer.

![Diagram](https://example.com/diagram.png)

**Scheme 10.** (A) Reversible thiyl addition (propagation) step and irreversible hydrogen abstraction (chain transfer) step upon addition of thiols onto exocyclic double bonds. (B) Carbon-centered radical intermediates with an equatorial methylenesulfide moiety formed by addition of a thiyl radical to C1-, C3-, C4-, or C5-positioned exomethylene group.

![Diagram](https://example.com/diagram.png)

**Scheme 11.** Assumed conformations of the C2-centered radicals and the configuration of the possible products formed from these radicals upon axial H-abstraction.

According to our previous results [27–31], cooling was beneficial to the efficacy of the additions, which can be explained by the rapid reversibility of the thiyl addition step. At higher temperatures, the dissociation of the carbon-centered radical is entropically favored, which shifts the equilibrium toward reactants before the carbon-centered radical can be trapped through hydrogen abstraction from a thiol, thus reducing the overall conversion. Conducting the reaction at −80 °C increases the life-time of the intermediate radical, allowing it to react with a thiol in the irreversible hydrogen abstraction step and, thus, increasing the overall conversion.

Conducting the reactions at low temperature also modified the stereoselectivity of the reactions by shifting the product ratio toward the stereoisomer, the formation of which required lower transition state energy.
We demonstrated that the thiol-ene coupling reaction can successfully be extended to disaccharide dienoside 47, which opens the way for a rapid synthesis of higher thio-oligosaccharides under mild conditions. The practical utility of the presented method was also demonstrated by the efficient synthesis of 51, a novel thio-linked analogue of the sialyl-α(2,6)-galactoside structure that is of high biological importance.

4. Materials and Methods

4.1. General Methods

The carbohydrate thiols 2a [63], 2b [64], 2c [65], 2d [66], 2e [67], and 2f [68] were prepared according to the literature procedures; 2,2-dimethoxy-2-phenylacetophenone (DPAP) was purchased from Sigma–Aldrich Chemical Co. (St. Louis, MO, USA) Optical rotations were measured at room temperature with a Perkin–Elmer 241 automatic polarimeter. Thin-layer chromatography (TLC) was performed on Kieselgel 60 F254 (Merck) with detection by immersing into 5% ethanolic sulfuric acid solution, followed by heating. Column chromatography was performed on Silica gel 60 (Merck 0.063–0.200 mm). Organic solutions were dried over MgSO4 and concentrated in vacuum. The 1H NMR (360 and 400 MHz) and 13C NMR (90.54 and 100.28 MHz) spectra were recorded with Bruker DRX-360 and DRX-400 spectrometers at 25 °C. Chemical shifts are referenced to Me4Si or DSS (0.00 ppm for 1H) and to the solvent signals (CDCl3: 77.00 ppm for 13C). ESI-QTOF MS measurements were carried out on a maXis II UHR ESI-QTOF MS instrument (Bruker), in positive ionization mode. The following parameters were applied for the electrospray ion source: capillary voltage: 3.6 kV; end plate offset: 500 V; nebulizer pressure: 0.5 bar; dry gas temperature: 200 °C and dry gas flow rate: 4.0 L/min. The MS method was tuned according to the examined mass range, which was 200–1000 m/z. Constant background correction was applied for each spectrum, and the background was recorded before each sample by injecting the blank sample matrix (solvent). Na-formate calibrant was injected after each sample, which enabled internal calibration during data evaluation. Mass spectra were recorded by otofControl version 4.1 (build: 3.5, Bruker) and processed by Compass DataAnalysis version 4.4 (build: 200.55.2969). MALDI-TOF MS analyses of the compounds were carried out in the positive reflectron mode using a BIFLEX III mass spectrometer (Bruker, Germany) equipped with delayed ion extraction. The matrix solution was a saturated 2,4,6-trihydroxy-acetophenone (THAP) solution in MeCN. Elemental analyses (C, H, S) were performed while using an Elementar Vario MicroCube instrument.

4.2. Synthesis

4.2.1. General Method for Photoinduced Addition of Thiols to Exoglycals or Sugar Exomethylene Derivatives

Sugar thiol (1.2–1.5 equiv.) and 2,2-dimethoxy-2-phenylacetophenone (DPAP, 0.10 equiv/alkene) were added to a solution of the starting unsaturated monosaccharide in dry toluene (it is indicated when some other solvent was used) (7–8 mL/1 mmol alkene). The solution was irradiated at room temperature (it is indicated when the reaction was performed at lower temperature) for 15 min. The progress of the reaction was monitored by TLC after this reaction period and irradiation and addition of DPAP were repeated if necessary, once or twice more. In these cases, no additional thiol was added to the reaction mixture. Subsequently, the solution was concentrated and the residue was purified by column chromatography or flash column chromatography.

4.2.2. 2,6-Anhydro-3,4,5,7-tetra-O-benzoyl-1-deoxy-1-S-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucopyranosyl)-1-thio-D-glycero-D-gulo-heptitol (11)

Exo-glucal 10 (50 mg, 0.084 mmol) and thiol 2a (44 mg, 0.12 mmol) were reacted according to the general method. The crude product was purified by silica gel chromatography in hexane/ethyl acetate 6/4 to give compound 11 (72 mg).
Yield: 89%, white foam. [α]D²⁰ = -14.6 (c 0.2, CHCl₃). Rf 0.45 (CH₂Cl₂/acetone 95/5). ¹H NMR (360 MHz, CDCl₃): δ = 8.10–7.79 (m, 8H, arom.), 7.59–7.24 (m, 12H, arom.), 5.89 (t, J = 9.6 Hz, 1H), 5.70 (t, J = 9.8 Hz, 1H), 5.54 (t, J = 9.7 Hz, 1H), 5.25 (t, J = 9.6 Hz, 1H), 5.09 (t, J = 9.7 Hz, 1H), 4.48 (t, J = 9.8 Hz, 1H), 4.73 (d, J = 10 Hz, 1H, H-1'), 4.72 (dd, J = 9.6, 2.1 Hz, 2H), 4.50 (dd, J = 12.2, 5.2 Hz, 1H), 4.24–4.02 (m, 4H), 3.70–3.65 (m, 1H), 3.13 (dd, J = 14.6, 9.0 Hz, 1H, SCH₂), 2.81 (dd, J = 14.6, 2.5 Hz, 1H, SCH₂), 2.11 (s, 3H, COCH₃), 2.05 (s, 3H, COCH₃), 2.01 (s, 3H, COCH₃), 1.98 (s, 3H, COCH₃). ¹³C NMR (91 MHz, CDCl₃): δ = 170.6, 170.0, 169.3, 169.3, 166.0, 165.8, 165.1, 165.1 (8C, 8xCO), 133.4–128.2 (24 C, arom.), 133.4–128.4 (24C, arom.), 109.3 and 108.6 (2C, 2xCH), 73.9, 73.8, 73.7, 71.4, 70.2, 69.4, 68.1 (10C, skeleton carbons), 62.8, 61.7 (C-7, C-6'), 30.5 (SCH₂), 20.7, 20.5, 20.5, 20.5 (4C, 4xCOCH₃). MS (ESI-TOF) m/z: [M + Na]+ Calcd for C₄₉H₄₈O₁₈NaS 891.2439; Found 891.2459; [M + Na]+.

4.2.3. 2,6-Anhydro-3,4,5,7-tetra-O-benzoyl-1-deoxy-1-S-(1’2’3’4’-di-O-isopropylidene-α-D-galactopyranose-6’-yl)-1-thio-α-D-glycero-D-gulo-heptitol (12)

**Exo-glucal 10** (59 mg, 0.10 mmol) and thiol 2c (42 mg, 0.15 mmol) were reacted according to the general method. The crude product was purified by silica gel chromatography in CH₂Cl₂/acetone 95/5 to give compound 12 (70 mg).

Yield: 83%, colorless syrup. [α]D²⁰ = -11.4 (c 0.9, CHCl₃). Rf 0.45, (CH₂Cl₂/acetone 9/1). ¹H NMR (360 MHz, CDCl₃): δ = 8.19–7.73 (m, 8H, arom.), 7.64–7.15 (m, 12H, arom.), 5.89 (t, J = 9.6 Hz, 1H), 5.63 (t, J = 9.6 Hz, 1H), 5.50 (t, J = 9.6 Hz, 1H), 5.45 (d, J = 5.1 Hz, 1H, H-1'), 4.64 (dd, J = 12.2, 2.8 Hz, 1H), 4.52 (dd, J = 7.9, 2.3 Hz, 1H), 4.44 (dd, J = 12.2, 5.2 Hz, 1H), 4.25 (dd, J = 5.1, 2.4 Hz, 1H), 4.21 (dd, J = 7.9, 1.8 Hz, 1H), 4.18–4.09 (m, 1H), 4.10–3.98 (m, 1H), 3.85 (t, J = 6.2 Hz, 1H), 3.00–2.73 (m, 4H, 2xSCH₂), 1.50 (s, 3H, CH₃), 1.48 (s, 3H, CH₃), 1.27 (s, 3H, CH₃), 1.26 (s, 3H, CH₃), 13C NMR (91 MHz, CDCl₃): δ = 166.3, 166.0, 165.5 and 165.4 (4C, 4xCOPh), 133.5, 133.3, 133.2, 130.0, 129.8, 129.0, 128.5 and 128.4 (24C, arom.), 109.3 and 108.6 (2C, 2xCq, i-propylidene), 96.7 (C-1), 79.8, 76.4, 74.4, 72.2, 71.9, 71.1, 70.6, 69.9 and 67.3 (9C, skeleton carbons), 63.5 (C-7), 33.3 (C-6'), 32.7 (SCH₂), 26.2, 26.0, 25.0 and 24.5 (4C, 4xCH₃). MS (ESI-TOF) m/z: [M + Na]+ Calcd for C₄₇H₄₆O₁₄NaS 891.2662; Found 891.2657 [M + Na]+.

4.2.4. 2,6-Anhydro-3,4,5,7-tetra-O-benzoyl-1-deoxy-1-S-(1’2’5’6’-di-O-isopropylidene-α-D-glucopyranose-3’-yl)-1-thio-D-glycero-D-gulo-heptitol (13)

**Exo-glucal 10** (59 mg, 0.10 mmol) and thiol 2d (42 mg, 1.5 mmol) were reacted, according to the general method. The crude product was purified by silica gel chromatography in hexane/acetone 8/2, and then in CH₂Cl₂/acetone 95/5 to give compound 13 (69 mg).

Yield: 80%, colorless syrup. [α]D²⁰ = +2.1 (c 0.5, CHCl₃). Rf 0.67 (CH₂Cl₂/acetone 9/1). ¹H NMR (360 MHz, CDCl₃): δ = 8.05–7.79 (m, 8H, arom.), 7.55–7.23 (m, 12H, arom.), 5.92 (t, 1H, J = 9.6 Hz), 5.78 (d, 1H, J = 3.4 Hz,H-1), 5.69 (t, 1H, J = 9.7 Hz), 5.61 (t, 1H, J = 9.6 Hz), 4.72 (d, 1H, J = 3.5 Hz), 4.63 (dd, 1H, J = 3.1 Hz, J = 12.2 Hz), 4.51 (dd, 1H, J = 5.1 Hz, J = 12.1 Hz), 4.39–4.34 (m, 1H), 4.19–4.12 (m, 2H), 4.11–4.03 (m, 2H), 3.97 (dd, 1H, J = 5.1 Hz, J = 8.6 Hz), 3.35 (d, 1H, J = 3.6 Hz), 3.04–2.92 (m, 2H, SCH₂), 1.41 (s, 3H, CH₃), 1.40 (s, 3H, CH₃), 1.35 (s, 3H, CH₃), 1.22 (s, 3H, CH₃); ¹³C NMR (90 MHz, CDCl₃): δ = 166.0, 165.8, 165.3 and 165.1 (4C, 4xCOPh), 133.5–128.2 (24C, arom.), 111.8 and 109.4 (2C, 2xCq, i-propylidene), 104.7 (C-1), 86.0, 80.1, 78.7, 76.1, 74.2, 73.9, 71.8 and 69.7 (8C, skeleton carbons), 67.6 (C-7), 63.3 (C-6’), 53.2 (C-3’), 33.8 (SCH₂), 26.8, 26.5, 26.1 and 25.2 (4C, 4xCH₃); MS (ESI-TOF) m/z: [M + Na]+ Calcd for C₄₇H₄₆O₁₄NaS 891.2662; Found 891.2657 [M + Na]+.

4.2.5. Methyl-6-O-tert-butylidiphenylsilyl-2,3-(2’3’-dimethoxybutane-2’3’-diyl)-2-deoxy-2-C-methylene-α-D-arabino-hexopyranoside (16)

Compound 14 (1.989 g, 3.638 mmol) was dissolved in abs. CH₂Cl₂ (20 mL). Dess-Martin periodinane (1.855 g, 4.366 mmol, 1.2 equiv.) was added and the reaction was stirred for one hour. When TLC showed complete disappearance of the starting material, the reaction mixture was diluted...
with CH₂Cl₂, aq NaOH solution (28 mL, 1.3 M) was added and the mixture was vigorously stirred for 10 min. In the next step the organic layer was separated and washed with water, dried over MgSO₄ and concentrated in vacuo to yield 15 (1.965 g, 99%). This compound was used in the next step without further purification. Dry tetrahydrofuran (20 mL) was stirred under argon and methyltriphenylphosphonium bromide (2.062 g, 5.772 mmol, 1.6 equiv.) was added. The suspension was cooled to 0 °C and n-butyllithium in hexane (2.309 mL, 5.772 mmol, c = 2.5 M, 1.6 equiv.) was added dropwise. After stirring the mixture for 30 min., 15 (1.965 g, 3.067 mmol) dissolved in dry tetrahydrofuran (10 mL) was added dropwise. The reaction was monitored by TLC. After three hours, ethyl acetate (200 mL) was added, and the organic layer was washed three times with satd aq NH₄Cl solution and water, dried over MgSO₄, and evaporated in vacuo. The crude product was purified by column chromatography to give 16 (1.130 g).

Yield: 57% from 14, colorless syrup. [α]D²⁰ = +170.3 (c 0.1, CHCl₃). Rf 0.72 (hexane/acetic acid 7/3).

1H NMR (400 MHz, CDCl₃): δ = 7.74–7.70 (m, 4H, arom), 7.42–7.32 (m, 6H, arom), 5.27 (s, 1H, CH₂β), 5.09 (s, 1H, CH₂α), 5.00 (s, 1H, H-1), 4.60 (dt, J = 9.9, 2.2 Hz, 1H, H-3), 3.94 (ddd, J = 10.1, 6.8, 3.8 Hz, 1H, H-5), 3.90 (d, J = 3.3 Hz, 2H, H-6α and H-6β), 3.68 (t, J = 9.8 Hz, 1H, H-4), 3.36 (s, 3H, OCH₃), 3.27 (s, 3H, OCH₃), 3.17 (3H, OCH₃), 1.36 (3H, CH₃), 1.29 (3H, CH₃ butanedione), 1.03 (3H, 9H,3×CH₃, t-Bu), 13C NMR (101 MHz, CDCl₃): δ = 141.1 (C-2), 136.1, 135.7, 134.1, 133.6, 129.6, 127.7, 127.6 (arom), 109.0 (CH₂), 102.2 (C-1), 100.1, 99.8 (2×C₉, butanedione), 71.5, 69.2 and 68.3 (C-5, C-4 and C-3), 62.4 (C-6), 54.3 (OCH₃), 48.2, 48.2 (2×OCH₃, butanedione), 26.9 (3×CH₃, t-Bu), 19.5 (C₉, t-Bu), 18.0, 17.9 (2×CH₃, butanedione). MS (ESI-TOF) m/z: [M + Na]+ Calcd for C₃₉H₄₂O₂NaSSi 565.2597; Found 565.2592 [M + Na]+.

4.2.6. Methyl 6-O-tert-butyldiphenylsiloxy-2-deoxy-C-(2′,3′,4′,6′-tetro-O-acetyl-1′-thiomyethyl-β-n-glucopyranosyl)-2,3-(2′,3′,6′-dimethoxybutane-2′-3′-diyl)-α-n-glucopyranoside (17a) and Methyl 6-O-tert-butyldiphenylsiloxy-2-deoxy-2-C-(2′,3′,4′,6′-tetro-O-acetyl-1′-thiomyethyl-β-n-glucopyranosyl)-2,3-(2′,3′-dimethoxybutane-2′-3′-diyl)-α-n-mannopyranoside (17b).

Compound 16 (535 mg, 986 mmol) and 2a (431 mg, 1.183 mmol, 1.2 equiv.) were reacted, according to the general method, to give an inseparable 1:1 mixture of 17a and 17b (813 mg). The diastereoisomeric ratio was determined on the basis of 1H NMR spectrum.

Yield: 91%. Rf 0.40 (hexane/acetic acid 7/3). MS (ESI-TOF) m/z: [M + Na]+ Calcd for C₄₆H₆₂O₁₆NaSSi 929.3426; Found 929.3421 [M + Na]+.

4.2.7. Methyl 6-O-tert-butyldiphenylsiloxy-2-deoxy-C-(2′,3′,4′,6′-tetro-O-acetyl-1′-thiomyethyl-β-n-glucopyranosyl)-α-n-mannopyranoside (18) and Methyl 6-O-tert-butyldiphenylsiloxy-2-deoxy-2-C-(2′,3′,4′,6′-tetro-O-acetyl-1′-thiomyethyl-β-n-glucopyranosyl)-α-n-glucopyranoside (19).

The mixture of 17a and 17b (295 mg, 0.325 mmol) was dissolved in CH₂Cl₂ (5 mL) and 2 mL 90% v/v% trifluoroacetic acid (1.8 mL trifluoroacetic acid + 0.2 mL water) was added dropwise. After 15 min. toluene (5 mL) was added and the mixture was evaporated in vacuo. The crude product was purified by flash chromatography to give 18 (45 mg), 19 (64 mg), and a mixture of 18 and 19 (94 mg).

18. Yield: 17%, colorless syrup. [α]D²⁰ = +5.0 (c 0.06 CHCl₃). Rf 0.50 (CH₂Cl₂/MeOH 95/5). 1H NMR (400 MHz, CDCl₃): δ = 7.73–7.37 (m, 10H, arom), 5.21 (t, J = 9.3 Hz, 1H, H-3), 5.14–5.08 (m, 1H, H-4), 5.06 (t, J = 8.3 Hz, 1H, H-2), 4.75 (s, 1H, H-1), 4.48 (d, J = 10.0 Hz, 1H, H-1′), 4.27 (dd, J = 12.4, 4.4 Hz, 1H, H-6′α), 4.15–4.10 (m, 1H, H-6′β), 4.04 (dd, J = 9.0, 5.4 Hz, 1H, H-3), 3.88 (s, 1H, H-6α), 3.87 (s, 1H, H-6β), 3.72–3.67 (m, 1H, H-5), 3.62 (t, J = 9.3 Hz, 1H, H-4), 3.57–3.52 (m, 1H, H-5), 3.28 (s, 3H, OCH₃), 3.23 (dd, J = 13.9, 2.1 Hz, 1H, SCH₂α), 2.44 (dd, J = 13.6, 11.1 Hz, 1H, SCH₂β), 2.32–2.25 (m, 1H, H-2), 2.07 (s, 3H, COCH₃), 1.05 (3H, CH₃), 0.20 (s, 3H, COCH₃), 1.95 (s, 1H, 3×CH₃, t-Bu), 13C NMR (101 MHz, CDCl₃): δ = 170.9, 170.3, 169.5 and 169.5 (4×COCH₃), 135.7, 135.7, 133.0, 132.9, 130.1, 130.1, 128.0 and 128.0 (10C, arom), 100.3 (C-7), 83.8 (C-1′), 76.0, 74.0, 70.9, 70.7, 70.5, 69.9 and 68.3 (7C, skeleton carbons), 65.1 (C-6), 62.0 (C-6′), 55.0 (OCH₃), 46.2 (C-2), 27.0 (3C, 3×CH₃, t-Bu), 25.8 (3C, 3×CH₃, t-Bu).
25.9 (SCH₂), 20.8, 20.8, 20.7 and 20.7 (4C, 4×COCH₃), 19.3 (C₂, t-Bu); MS (ESI-TOF) m/z: [M + Na]+
Cald for C₃₈H₅₂O₄SiNSa 815.274; Found 815.276.

19: Yield: 25%, colorless syrup. [α]_D²⁰ = +28.6 (c = 0.07 CHCl₃). R₉ 0.56 (CH₂Cl₂/Methanol 95/5). ¹H NMR
(400 MHz, CDCl₃): δ = 7.73–7.34 (m, 10H, arom), 5.21 (t, J = 9.3 Hz, 1H, H-3′), 5.09–4.98 (m, 2H, H-2′, H-4′), 4.80 (d, J = 3.3 Hz, 1H, H-1′), 4.52 (d, J = 10.1 Hz, 1H, H-1′), 4.21 (dd, J = 12.4, 4.9 Hz, 1H, H-6′a), 4.15 (dd, J = 12.3, 2.3 Hz, 1H, H-6′b), 3.88 (s, 1H, H-6a), 3.87 (s, 1H, H-6b), 3.74–3.58 (m, 3H, H-3, H-5 and H-5′), 3.48 (t, J = 9.1 Hz, 1H, H-4), 3.28 (s, 3H, OCH₃), 3.13 (s, 1H, OH), 3.07 (dd, J = 13.6, 4.0 Hz, 1H, SCH₂a), 2.84 (s, 1H, OH), 2.74 (dd, J = 13.5, 10.0 Hz, 1H, SCH₂b), 2.06 (s, 3H, COCH₃), 2.02 (s, 3H, COCH₃), 2.00 (s, 3H, COCH₃), 1.98–1.92 (m, 1H, H-2), 1.06 (s, 9H, 3×CH₃, t-Bu),
¹³C NMR (101 MHz, CDCl₃): δ = 170.8, 170.3, 169.6 and 169.5 (4×COCH₃), 135.7, 133.0, 132.9, 130.0, 130.0 and 127.9 (10C, arom), 99.4 (C-1), 85.0 (C-1′), 77.5, 77.2, 76.8, 76.0, 74.5, 73.9, 72.9, 70.2 and 68.4 (7C, skeleton carbons), 65.5 (C-6), 62.2 (C-6′), 54.9 (OCH₃), 46.3 (C-2), 29.2 (SCH₂), 26.9 (3C, 3×CH₃, t-Bu), 20.9, 20.8, 20.7 and 20.7 (4C, 4×COCH₃), 19.3 (C₂, t-Bu). Anal. Calcd for C₃₈H₅₂O₄Si:S: C, 55.96; H, 6.61; O, 28.25; S, 4.04; Si, 3.54. Found: C, 66.0, H, 6.60; S, 4.11.

Mixture of 18 and 19: Yield: 36%, colorless syrup.

4.2.8. Methyl-6-O-tert-butyldimethylsilyl-3,4-di-O-isopropylidene-α-D-lyxo-hexopyranoside-2-uloside (21)

A mixture of dimethyl sulfoxide (163 µL, 179 mg, 2.30 mmol, 4 equiv.) and abs. CH₂Cl₂ (2 mL) was cooled to –80 °C and oxalyl chloride (97 µL, 144 mg, 1.15 mmol, 2 equiv.) was added. After 15 min., compound 20 (200 mg, 0.57 mmol) dissolved in CH₂Cl₂ (1 mL) was added. After 30 min., N,N-diisopropylethylamine (1.000 mL, 0.742 g, 5.741 mmol, 10 equiv.) was added and the mixture was then allowed to warm to room temperature. After 2 h, when TLC showed complete conversion, the mixture was diluted with CH₂Cl₂, extracted with 1 M HCl and water. The organic layer was then concentrated in vacuo. The crude product was purified by column chromatography (hexane/ethyl acetate 7:3) to give 21 (189 mg).

Yield: 95%, colorless syrup. [α]_D²⁰ = +58.6 (c 0.1, CHCl₃). R₉ 0.52 (hexane/ethyl acetate 7:3). ¹H NMR
(400 MHz, CDCl₃): δ = 4.61 (s, 1H, H-1), 4.57 (d, J = 5.5 Hz, 1H, H-3), 4.48 (dd, J = 5.6, 1.9 Hz, 1H, H-4), 4.26 (td, J = 6.6, 1.9 Hz, 1H, H-5), 3.83 (dd, J = 10.0, 6.8 Hz, 1H, H-6), 3.77 (dd, J = 10.0, 6.5 Hz, 1H, H-6b), 3.40 (s, 3H, OCH₃), 1.35, 1.29 (2s, 6H, 2×i-Pr CH₃), 0.84 (s, 9H, 3×t-Bu CH₃), 0.03 (s, 6H, 2×Si(CH₃)₃), ¹³C NMR (101 MHz, CDCl₃): δ = 199.2 (CO), 110.6 (i-Pr CH₃), 105.0 (C-1), 77.1, 75.5, 68.2 (C-3, C-4, C-5), 61.9 (C-6), 55.3 (OCH₃), 27.2, 26.1 (2C, 2×i-Pr CH₃), 25.8 (3C, 3×t-Bu CH₃), 18.2 (C-2), -54, -5.5 (2C, Si-CH₃).

4.2.9. Methyl 6-O-tert-butyldimethylsilyl-2-deoxy-3,4-O-isopropylidene-2-C-methylene-α-D-lyxo-
hexopyranoside (22)

Methyltriphenylphosphonium bromide (332 mg, 0.929 mmol, 1.6 equiv.) was suspended in tetrahydrofuran (1.5 mL) under argon and cooled to 0 °C. n-Butyllithium (372 µL, 0.929 mmol, 1.6 equiv, 2.5 M solution in hexane) was added and the suspension was stirred. After 30 min. 21 (200 mg, 0.581 mmol) dissolved in tetrahydrofuran (1.5 mL) was added. When TLC showed the complete disappearance of 21, the mixture was diluted with ethyl acetate and washed with satd aq NH₄Cl solution. The organic layer was separated, dried over MgSO₄, and concentrated in vacuo. The crude product was purified by column chromatography (hexane/ethyl acetate 9:1) to give 22 (125 mg).

Yield: 63%, colorless syrup. [α]_D²⁰ = +71.8 (c 0.4, CHCl₃). R₉ 0.48 (hexane/ethyl acetate 9:1). ¹H NMR
(400 MHz, CDCl₃): δ = 5.52–5.48 (m, 2H, CH₂), 5.23 (s, 1H, H-1), 4.83 (d, J = 6.9 Hz, 1H, H-3), 4.34 (dd, J = 6.9, 1.5 Hz, 1H, H-4), 3.92–3.80 (m, 3H, H-5, H-6a, H-6b), 3.52 (s, 3H, OCH₃), 1.55, 1.42 (2s, 6H, 2 x i-Pr CH₃), 0.97 (s, 9H, 3×t-Bu CH₃), 0.15 (s, 6H, 2×Si(CH₃)₃), ¹³C NMR (101 MHz, CDCl₃): δ = 141.0 (C-2), 118.4 (CH₂), 110.0 (i-Pr CH₃), 99.4 (C-1), 75.5, 74.8, 70.4 (C-3, C-4, C-5), 62.3 (C-6), 54.8 (OCH₃), 26.9,
26.0 (2C, 2×-Pr CH₃), 25.7 (3C, 3×-Bu CH₃), 18.4 (C-2), -5.2, -5.4 (2C, Si-CH₃); MS (ESI-TOF) m/z: [M + Na]⁺ Calcd for C₁₇H₃₂O₅NaSi 367.1911; Found 367.1917.

4.2.10. Methyl 6-O-tert-butylidemethylsilyl-2-deoxy-3,4-O-isopropylidene-2-C-(2′,3′,4′,6′-teta-O-acetyl-1′-thiomethyl-β-D-glucopyranosyl)-α-D-galactopyranoside (23a) and Methyl 6-O-tert-butylidemethylsilyl-2-deoxy-3,4-O-isopropylidene-2-C-(2′,3′,4′,6′-teta-O-acetyl-1′-thiomethyl-β-D-glucopyranosyl)-α-D-talopyranoside (23b)

Exomethylene 22 (100 mg, 0.290 mmol), thiol 2a (127 mg, 0.348 mmol, 1.2 equiv.), and DPAP (7 mg, 0.29 mmol) were reacted with three irradiation cycles according to the general method. The crude product was purified by column chromatography (hexane/ethyl acetate 75/25) to give 23 (134 mg, 65%) as an inseparable diastereoisomeric mixture with a ratio of 23a galacto:23b talo ~ 1:2. The reaction was also carried out at −80 °C to give 23 (182 mg, 88%), with a ratio of 23a galacto:23b talo ~ 1:1. The diastereoisomeric ratios were determined on the basis of 1H NMR spectrum.

Yield (mixture of 23a and 23b): 88%, white foam. Rₚ 0.39 (hexane/ethyl acetate 75/25). ¹H NMR (400 MHz, CDCl₃): δ = 5.21 (t, J = 9.3 Hz, 1H, 5.11–4.94 (m, 4H, 1H, 4.00–3.82 (m, 2H, 1.58H), 3.84–3.61 (m, 4H, 4.32H), 3.37 (s, 3H, 1H, OCH₃), 2.14–2.97 (m, 1H, 1H, 17.42H, COOH), 1.48, 1.43, 1.32 (3s, 11.03H, 1H, tert-Pr C), 0.90, 0.89 (2s, 13.81H, 1H, tert-Pr CH₃), 0.11–0.03 (m, 3H, 1H, Si-CH₃); ¹³C NMR (101 MHz, CDCl₃): δ = 170.8, 170.7, 170.2, 170.2, 169.5, 169.4, 169.3, 169.3 (CO), 109.2, 109.0 (2×-Pr Cₙ), 101.0, 98.7 (2×C-1), 85.7, 85.4 (2×C-1'), 76.0, 75.9, 74.9, 73.9, 73.6, 71.6, 71.5, 70.5, 70.2, 68.4 67.9 (skeleton carbons), 62.7, 62.4, 62.2, 62.2 (4×C-6), 55.1, 54.9 (2×OCH₃), 43.4, 43.4, 31.3, 31.0 (2×S-CH₂), 28.6, 26.6, 26.2 (i-Pr CH₃), 25.9, 25.9, 25.1 (i-Pr CH₃), 20.8, 20.6 (COOH), 18.3, 17.1 (2×C-2), -5.3, -5.4 (2C, Si-CH₃).

4.2.11. Methyl 6-O-tert-butylidemethylsilyl-2-deoxy-3,4-O-isopropylidene-2-C-(2′,3′,4′,6′-teta-O-acetyl-1′-thiomethyl-α-D-mannopyranosyl)-α-D-galactopyranoside (24a) and Methyl 6-O-tert-butylidemethylsilyl-2-deoxy-3,4-O-isopropylidene-2-C-(2′,3′,4′,6′-teta-O-acetyl-1′-thiomethyl-α-D-mannopyranosyl)-α-D-talopyranoside (24b)

Exomethylene 22 (100 mg, 0.290 mmol), thiol 2e (127 mg, 0.348 mmol, 1.2 equiv.) and 2,2-dimethoxy-2-phenylacetophenone (7 mg, 0.029 mmol, 0.1 equiv.) were dissolved in toluene (2.3 mL) and then reacted according to the general method. The reaction mixture was concentrated in vacuo, the crude product was purified by flash chromatography (hexane/acetone 9/1 → 85/15) to give an inseparable mixture of 24a galacto and 24b talo (123 mg, 60%) as a colorless syrup. Rₚ 0.42 (hexane/acetone 75/25) in a 1:4 ratio of 24a galacto and 24b talo. The reaction was also carried out at −80 °C to give 37 (197 mg, 96%) with a ratio of 24a galacto:24b talo ~ 1:1. The diastereoisomeric ratios were determined on the basis of 1H NMR spectrum (see Supplementary Materials).

Yield (Mixture of 24a and 24b): 96%, white foam. Rₚ 0.42 (hexane/acetone 75/25).

4.2.12. Methyl 2-deoxy-2-C-(2′,3′,4′,6′-teta-O-acetyl-1′-thiomethyl-α-D-mannopyranosyl)-α-D-galactopyranoside (25) and Methyl 2-deoxy-2-C-(2′,3′,4′,6′-teta-O-acetyl-1′-thiomethyl-α-D-mannopyranosyl)-α-D-talopyranoside (26)

Compound 24 (161 mg, 0.227 mmol, 1:1 mixture of 24a galacto and 24b talo) was dissolved in CH₂Cl₂ (2 mL) and 500 µL 70 v/v% trifluoroacetic acid (350 µL trifluoroacetic acid + 150 µL water) was added dropwise. After 15 min. toluene (5 mL) was added and the mixture was evaporated in vacuo. The crude product was purified by flash chromatography to give 25 (37 mg, 29%) and a mixture of 25 and 26 (80 mg, 64%).

25 Yield: 29%, colorless syrup. [α]D⁰ = +91.8 (c 0.15, CHCl₃), ¹H NMR (400 MHz, CDCl₃): δ = 5.35 (d, J = 3.0, 1.4 Hz, 1H, H-2), 5.32–5.27 (m, 2H, H-4′, H-1′), 5.24 (d, J = 9.9, 3.1 Hz, 1H, H-3′), 4.91 (s, 1H, H-1), 4.34 (d, J = 9.2, 5.2, 2.3 Hz, 1H, H-5′), 4.28 (d, J = 12.1, 5.3 Hz, 1H, H-6′).
12.0, 2.2 Hz, 1H, H-6′$_b$), 4.06 (dd, $J = 4.9, 3.8$ Hz, 1H, H-3), 3.97–3.92 (m, 2H, H-4, H-6$_a$), 3.88 (dd, $J = 11.7, 4.3$ Hz, 1H, H-6$_a$), 3.77 (td, $J = 4.6, 1.8$ Hz, 1H, H-5), 3.46 (s, 1H, OH), 3.37 (s, 3H, OMe), 3.15 (dd, $J = 13.7, 3.3$ Hz, 1H, SCH$_2$)$_a$, 2.93 (dd, $J = 13.6, 11.1$ Hz, 1H, SCH$_2$)$_b$, 2.20–2.14 (m, 4H, COCH$_3$ and H-2), 2.11 (s, 3H, COCH$_3$), 2.06 (s, 3H, COCH$_3$), 2.00 (s, 3H, COCH$_3$); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 171.1, 170.2, 170.1$ and 169.9 (4C, 4×COCH$_3$), 100.8 (C-1′), 84.5 (C-1′′), 71.2, 70.1, 69.5, 69.4, 69.2, 66.9 and 66.5 (7C, skeleton carbons), 63.6 (C-6), 62.6 (C-6′), 55.2 (OCH$_3$), 44.3 (C-2), 30.3 (SCH$_2$), 21.0, 20.8, 20.8 and 20.7 (4C, 4×COCH$_3$). MS (ESI-TOF) m/z: [M + Na]$^+$ Calcd for C$_{27}$H$_{34}$O$_4$NaS 577.1567; Found 557.1560; [M + Na]$^+$.

The NMR spectra of the mixture of 25 and 26 can be found in the Supplementary Material.

4.2.13. Methyl-6-O-tert-butyldiphenylsilyl-3,4-O-isopropylidene-β-D-lyxo-hexopyranoside-2-ulose (28)

Dimethyl sulfoxide (1.135 mL, 1.248 g, 15.978 mmol, 4 equiv.) was dissolved in abs. CH$_2$Cl$_2$ (19 mL), cooled to −80 °C and oxalyl chloride (1.888 g, 3.994 mmol) dissolved in CH$_2$Cl$_2$ (19 mL) was added. After 15 min. 27 (1.888 g, 3.994 mmol) dissolved in CH$_2$Cl$_2$ (19 mL) was added. After 30 min, N,N-diisopropylethylamine (2.783 mL, 2.065 g, 15.978 mmol, 4 equiv.) was added and the mixture was then allowed to warm to room temperature. After 2 h, when TLC showed complete conversion, the mixture was diluted with CH$_2$Cl$_2$ extracted with 1 M HCl and water. The organic layer was dried over MgSO$_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography (hexane/acetone 75/25) to give 28 (1.798 g).

Yield: 96%, colorless syrup. [α]$_D^{20}$ = −13.1 (c 0.2, CHCl$_3$). R$_f$ 0.27 (hexane/acetone 8/2). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.74–7.68$ (m, 4H, arom.), 7.46–7.36 (m, 6H, arom.), 4.75 (d, $J = 0.5$ Hz, 1H, H-1), 4.68 (dd, $J = 5.6, 1.7$ Hz, 1H, H-4), 4.50 (d, $J = 5.6$ Hz, 1H, H-3), 4.15 (td, $J = 6.6, 1.6$ Hz, 1H, H-5), 4.02–3.97 (m, 2H, H-6$_a$, H-6$_b$), 3.57 (s, 3H, OCH$_3$), 1.42 (s, 3H, CH$_3$, i-Pr), 1.38 (s, 3H, CH$_3$, i-Pr), 1.08 (s, 9H, 3×CH$_3$, t-Bu); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 198.7$ (C-2), 135.7, 135.6, 133.3, 133.2, 129.9, 127.9 and 127.8 (12C, arom.), 111.2 (C$_n$ i-Pr), 100.4 (C-1′), 77.8, 77.7 and 73.3 (C-3, C-4 and C-5), 62.5 (C-6), 56.9 (OCH$_3$), 27.3 (CH$_3$, i-Pr), 26.8 (3C, 3×CH$_3$, t-Bu), 26.1 (CH$_3$, i-Pr), 19.3 (C$_n$ i-Pr). Anal. Calcd for C$_{26}$H$_{34}$O$_5$Si: C, 66.36; H, 7.28. Found: C, 66.71; H, 7.07.

4.2.14. Methyl-6-O-tert-butyldiphenylsilyl-2-deoxy-3,4-O-isopropylidene-2-C-methylene-β-D-lyxo-hexopyranoside (29)

Methyltriphenylphosphonium bromide (2.119 g, 5.932 mmol, 1.6 equiv.) was suspended in tetrahydrofuran (20 mL) under argon and cooled to 0 °C. n-Butyllithium (2.373 mL, 5.932 mmol, 1.6 equiv, 2.5 M solution in hexane) was added and the suspension was stirred. After 30 min. 28 (1.745 g, 3.708 mmol) dissolved in tetrahydrofuran (17 mL) was added. When TLC showed complete disappearance of 28 the mixture was diluted with ethyl acetate and washed with satd aq NH$_4$Cl solution. The organic layer was separated, dried over MgSO$_4$, and then concentrated in vacuo. The crude product was purified by column chromatography to give 29 (1.153 g).

Yield: 66%, colorless syrup. [α]$_D^{20}$ = +16.7 (c= 0.18, CHCl$_3$). R$_f$ 0.68 (hexane/acetone 8/2). $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 7.74–7.68$ (m, 4H), 7.44–7.34 (m, 6H), 5.47–5.45 (m, 1H, CH$_2$)$_b$, 5.44–5.42 (m, 1H, CH$_2$)$_b$, 4.84 (s, 1H, H-1), 4.69 (dt, $J = 6.3, 1.4$ Hz, 1H, H-3), 4.30 (dd, $J = 6.3, 1.9$ Hz, 1H, H-4), 3.96 (dd, $J = 10.0, 6.9$ Hz, 1H, H-6$_a$), 3.90 (dd, $J = 10.1, 6.3$ Hz, 1H, H-6$_b$), 3.74–3.70 (m, 1H, H-5), 3.50 (s, 3H, OCH$_3$), 1.46 (s, 3H, CH$_3$, i-Pr), 1.36 (s, 3H, CH$_3$, i-Pr), 1.06 (s, 9H, 3×CH$_3$, t-Bu); $^{13}$C NMR (101 MHz, CDCl$_3$): $\delta = 141.7$ (C-2), 135.8, 135.7, 133.7, 133.6, 129.8, 127.8 and 127.7 (12C arom.), 115.8 (C-2), 110.3 (C$_n$ i-Pr), 101.0 (C-1′), 75.3, 73.7 and 73.3 (C-5, C-4, C-3), 63.0 (C-6), 56.2 (OCH$_3$), 27.4 (CH$_3$, i-Pr), 26.9 (3C, 3×CH$_3$, t-Bu), 26.2 (CH$_3$, i-Pr), 19.4 (C$_n$ i-Pr); MS (MALDI-TOF) m/z: [M + Na]$^+$ Calcd for C$_{27}$H$_{36}$O$_5$NaSi 491.223; Found: 491.290.
4.2.15. Methyl 6-O-tert-butyldiphenylsilyl-2-deoxy-3,4-O-isopropylidene-2-C-(2′,3′,4′,6′-tetra-O-acetyl-1′-thiomethyl-β-D-glucopyranosyl)-β-D-galactopyranoside (30a) and Methyl 6-O-tet-tert-butyldiphenylsilyl-2-deoxy-3,4-O-isopropylidene-2-C-(2′,3′,4′,6′-tetra-O-acetyl-1′-thiomethyl-β-D-glucopyranosyl)-β-D-talopyranoside (30b)

Compound 29 (100 mg, 0.213 mmol), 2a (93 mg, 0.256 mmol, 1.2 equiv.) and 2,2-dimethoxy-2-phenylacetophenone (5 mg, 0.021 mmol, 0.1 equiv.) were dissolved in toluene (1.9 mL) and reacted according to the general method with three irradiation cycles. The crude product was purified by column chromatography (hexane/aceton 8/2→75/25) to give 30 (39 mg, 22%) in 4:1 ratio of the d-galacto and d-talo isomers (the diastereoisomeric ratio was determined on the basis of 1H NMR spectrum). The reaction was also carried out at −80 °C to exclusively give the d-galacto isomer 30a (135 mg).

30a galacto Yield: 76%, colorless syrup. [α]D20 = −37.7 (c 0.2, CHCl3). Rf 0.45 (hexane/aceton 7/3). 1H NMR (400 MHz, CDCl3): δ = 7.74–7.67 (m, 4H, arom.), 7.46–7.34 (m, 6H, arom.), 5.21 (t, J = 9.4 Hz, 1H, H-3′), 5.12–5.02 (m, 2H, H-4′, H-2′), 4.49 (d, J = 10.0 Hz, 1H, H-1′), 4.27–4.21 (m, 2H) and 4.18–4.12 (m, 2H) and 4.10 (m, 2H) and 3.99 (m, 1H, H-1’), 4.00 (dd, J = 9.8, 7.3 Hz, 1H, H-6’a), 3.92 (m, J = 9.8, 6.1 Hz, 1H, H-6b), 3.85–3.80 (m, 1H, H-5), 3.71 (dd, J = 9.9, 5.0, 2.3 Hz, 1H, H-5’), 3.46 (s, 3H, OCH3), 3.02 (dd, J = 12.7, 5.1 Hz, 1H, SCH2a), 2.95 (dd, J = 12.7, 3.6 Hz, 1H, SCH2b), 2.07 (s, 3H, COCH3), 2.03 (s, 3H, COCH3), 2.01 (s, 3H, COCH3), 1.98–1.91 (m, 1H, H-2’), 1.47 (s, 3H, CH3, i-Pr), 1.33 (s, 3H, CH3, i-Pr), 1.05 (s, 9H, 3C, tert-Bu); 13C NMR (101 MHz, CDCl3): δ = 170.7 (COCH3), 170.3 (COCH3), 169.5 (COCH3), 169.5 (COCH3), 135.7, 135.7, 133.6, 133.5, 129.8, 127.8 and 127.7 (12C, arom.), 109.7 (Cq, i-Pr), 102.4 (C-1), 84.2 (C-1′), 76.0, 75.2, 74.0, 73.4, 71.8, 70.3, 68.5, 63.0 (C-6), 62.4 (C-6′), 56.6 (OCH3), 44.8 (C-2), 28.5 (CH3, i-Pr), 28.4 (SCH2), 26.8 (3C, 3C, CH3, i-Pr), 26.6 (CH3, i-Pr), 20.8 (COCH3), 20.8 (COCH3), 20.7 (COCH2), 20.7 (COCH2), 19.3 (Cq, i-But); MS (MALDI-TOF) m/z: [M + Na]+ Calcd for C41H36NaO14Si3 855.3056; Found: 855.3055; [M + Na]+.

4.2.16. Methyl 6-O-tet-tert-butyldiphenylsilyl-2-deoxy-3,4-O-isopropylidene-2-C-(2′,3′,4′,6′-tetra-O-acetyl-1′-thiomethyl-α-D-mannopyranosyl)-β-D-galactopyranoside (31)

Compound 29 (100 mg, 0.213 mmol), 2e (93 mg, 0.256 mmol, 1.2 equiv.) and 2,2-dimethoxy-2-phenylacetophenone (5 mg, 0.021 mmol, 0.1 equiv.) were dissolved in toluene (1.9 mL) and reacted according to the general method with three irradiation cycles. The crude product was purified by column chromatography (hexane/aceton 8/2) to give 31 (69 mg, 39%) as a colorless syrup. The reaction was also carried out at −80°C to give 31 (120 mg).

Compound 31: Yield: 68%, [α]D20 = +84.7 (c 0.2, CHCl3). Rf 0.41 (hexane/aceton 7/3). 1H NMR (400 MHz, Acetone-d6): δ = 7.81–7.75 (m, 4H, arom.), 7.51–7.41 (m, 6H, arom.), 5.35–5.32 (m, 2H, H-1′, H-2′), 5.29 (t, J = 10.0 Hz, 1H, H-4′), 5.21 (dd, J = 10.1, 3.0 Hz, 1H, H-3′), 4.40 (ddd, J = 8.3, 5.6, 2.2 Hz, 1H, H-5′), 4.33–4.24 (m, 4H, H-6′a, H-4′, H-3′, H-1′), 4.15–4.08 (m, 2H, H-6′b, H-5), 4.00 (dd, J = 9.8, 6.3 Hz, 1H, H-6a), 3.92 (dd, J = 9.8, 6.7 Hz, 1H, H-5), 3.44 (s, 3H, OCH3), 3.01 (dd, J = 12.9, 4.8 Hz, 1H, CH2a), 2.92 (dd, J = 12.9, 3.5 Hz, 1H, CH2b), 2.13 (s, 3H, COCH3), 2.05 (s, 6H, 2×COCH3), 1.96 (s, 3H, COCH3), 1.94–1.87 (m, 1H, H-2), 1.42 (s, 3H, CH3, i-Pr), 1.31 (s, 3H, CH3, i-Pr), 1.26 (s, 3H, CH3, tert-Bu); 13C NMR (101 MHz, Acetone-d6): δ = 170.7, 170.4, 170.4 and 170.2 (4C, 4×COCH3), 136.4, 134.2, 130.7, 128.7 and 128.6 (12C, arom.), 110.0 (Cq, i-Pr), 103.0 (C-1), 83.6 (C-1′), 76.3, 74.2, 72.9, 71.5, 70.3, 70.1, 66.9, 64.2 and 63.0 (C-6′ and C-6), 56.4 (OCH3), 46.0 (C-2), 29.6 (SCH2) 28.7 (CH3, i-Pr), 27.1 (3C, 3C, CH3, i-But), 26.7 (CH3, i-Pr), 20.7, 20.7, 20.6 and 20.5 (4C, 4×COCH3), 19.7 (i-But, Cq). MS (ESI-TOF) m/z: [M + Na]+ Calcd for C41H36O14Si3Na 855.3058; Found 855.3055; [M + Na]+.

4.2.17. 1,2,4,6-Tetra-O-acetyl-3-deoxy-3-C-methylene-β-D-ribo-hexopyranose (33)

Compound 32 (1.613 g, 6.293 mmol) was dissolved in 5 mL 95/5 v/v% trifluoroacetic acid (4.5 mL trifluoroacetic acid + 0.5 mL water) and the mixture was stirred at room temperature. After 15 min., toluene (12 mL) was added and the mixture was concentrated in vacuo. Acetic anhydride (4.73 mL,
50.1 mmol, 8 equiv.) and sodium acetate (825 mg, 10.020 mmol, 1.6 equiv.) were added to the residue and the suspension was stirred at 70 °C. After 1.5 h the mixture was allowed to cool down, ethyl acetate was added, and the mixture was washed with water, satq NaHCO₃, and water. The organic layer was dried over MgSO₄, filtered, and evaporated in vacuo. The crude product was purified by column chromatography (hexane/ethyl acetate 7/3) to give 33 (1.755 g).

Yield: 81% over two steps, colorless syrup. [α]D²⁰ = +6.1 (c 0.2, CHCl₃). Rf 0.47 (hexane/ethyl acetate 6/4). ¹H NMR (400 MHz, CDCl₃): δ = 5.62 (d, J = 7.5 Hz, 1H, H-1), 5.42-5.34 (m, 2H, H-2 and H-4), 5.14 (t, J = 1.7 Hz, 1H, CH₂a), 5.11 (t, J = 1.6 Hz, 1H CH₂b), 4.32 (dd, J = 12.3, 4.7 Hz, 1H, H-6a), 4.14 (dd, J = 12.2, 2.8 Hz, 1H, H-6b), 3.78 (dd, J = 9.0, 4.7, 2.8 Hz, 1H, H-5), 2.16 (s, 3H, COCH₃), 2.13 (s, 3H, COCH₃), 2.09 (s, 3H, COCH₃); ¹³C NMR (101 MHz, CDCl₃): δ = 169.1 and 169.0 (4×COCH₃), 137.5 (CH₂), 109.8 (C-3), 93.4 (C-1), 75.8, 70.6 and 68.0 (3C, C-5, C-4, C-2), 62.2 (C-6), 21.0 (COCH₃), 20.8 (COCH₃), 20.7 (COCH₃), 20.7 (COCH₃). Anal. Calcd for C₁₅H₂₀O₇: C, 52.32; H, 5.85. Found: C, 57.06; H, 6.01.

4.2.18. 1,2,4,6-Tetra-O-acetyl-3-deoxy-3-C-(2′,3′,4′,6′-tetra-O-acetyl-1′-thiomethyl-β-D-glucopyranosyl)-β-D-glucopyranosyl (34)

Compound 33 (200 mg, 0.581 mmol) and thiol 2a (254 mg, 697 mmol, 1.2 equiv.) were reacted according to the general method with three irradiation cycles. The crude product was purified by flash chromatography to give 34 (332 mg).

Yield: 82%, white foam. [α]D²⁰ = −30.7 (c 0.1, CHCl₃). Rf 0.23 (hexane/acetone 7/3). ¹H NMR (400 MHz, CDCl₃): δ = 5.67 (d, J = 7.9 Hz, 1H, H-1), 5.21 (t, J = 9.4 Hz, 1H) and 5.11-4.91 (m, 4H) (H-4, H-4′, H-3′, H-2, H-2′), 4.40 (d, J = 10.0 Hz, 1H, H-1′), 4.27 (dd, J = 12.4, 4.8 Hz, 1H), 4.18 (dd, J = 12.4, 4.9 Hz, 1H) and 4.12-4.04 (m, 2H) (H-6a, H-6a′, H-6b, H-6b′), 3.77 (dd, J = 9.5, 4.7, 2.3 Hz, 1H, H-5), 3.72 (dd, J = 10.0, 4.7, 2.1 Hz, H-5′), 2.86-2.76 (m, 2H, CH₂), 2.38-2.30 (m, 1H, H-3), 2.12 (s, 3H), 2.10 (s, 6H), 2.08 (s, 6H), 2.06 (s, 3H), 2.03 (s, 3H) and 2.00 (s, 3H) (8×COCH₃); ¹³C NMR (101 MHz, CDCl₃): δ = 170.7, 170.5, 170.0, 169.6, 169.5, 169.4, 169.3 and 169.2 (8C, 8×COCH₃), 93.3 (C-1), 82.5 (C-1′), 76.0 (C-5′), 75.4 (C-5), 73.7, 69.6, 69.2, 68.2 and 67.5 (C-4, C-4′, C-3′, C-2′), 62.0 (2C, C-6, C-6′), 43.8 (C-3), 26.3 (CH₂), 20.9, 20.8, 20.7, 20.7 and 20.6 (8C, 8×COCH₃). Anal. Calcd for C₇₀H₄₀O₃₄S: C, 49.14; H, 5.69; S, 4.51. Found: C, 48.93; H, 5.65; S, 4.62.

4.2.19. 1,2,4,6-Tetra-O-acetyl-3-deoxy-3-C-(2′,3′,4′,6′-tetra-O-acetyl-1′-thiomethyl-α-D-mannopyranosyl)-β-D-glucopyranosyl (35)

Compound 33 (100 mg, 0.290 mmol) and thiol 2e (127 mg, 0.349 mmol, 1.2 equiv.) dissolved in toluene (2.3 mL) were reacted according to the general method with three irradiation cycles. The reaction mixture was concentrated in vacuo and the crude product was purified with column chromatography (hexane/acetone 65/35) to give 35 (162 mg).

Yield: 80%, colorless syrup. [α]D²⁰ = +77.8 (c 0.3, CHCl₃). Rf 0.33 (hexane/acetone 65/35). ¹H NMR (400 MHz, Acetone-d₆): δ = 5.73 (d, J = 8.0 Hz, 1H, H-1), 5.31 (d, J = 1.4 Hz, 1H, H-1′), 5.29 (dd, J = 3.3, 1.4 Hz, 1H, H-2′), 5.29-5.24 (m, 1H, H-4′), 5.19 (dd, J = 10.1, 3.4 Hz, 1H, H-3′), 5.03 (t, J = 9.3 Hz, 1H, H-4), 4.98 (dd, J = 10.1, 7.2 Hz, 1H, H-2), 4.29 (dd, J = 9.5, 5.5, 2.3 Hz, 1H, H-5′), 4.25 - 4.16 (m, 2H, H-6a, H-6a′), 4.11 (dd, J = 12.0, 2.3 Hz, 1H, H-6b′), 4.03 (dd, J = 12.3, 2.5 Hz, 1H, H-6b), 3.97 (dd, J = 9.6, 5.0, 2.5 Hz, 1H, H-5), 2.84 (dd, J = 13.9, 3.8 Hz, 1H, SCH₂a), 2.75 (dd, J = 13.9, 5.5 Hz, 1H, SCH₂b), 2.53 (dd, J = 10.8, 5.4, 3.9 Hz, 1H, H-3), 2.12 (s, 3H, COCH₃), 2.11 (s, 3H, COCH₃), 2.07 (s, 3H, COCH₃), 2.05 (s, 3H, COCH₃), 2.04 (s, 3H, COCH₃), 2.00 (s, 3H, COCH₃), 1.94 (s, 3H, COCH₃); ¹³C NMR (101 MHz, Acetone-d₆): δ = 170.8, 170.8, 170.4, 170.3, 170.2 and 169.6 (8C, 8×COCH₃), 93.9 (C-1), 82.6 (C-1′), 75.8, 71.2, 70.7, 70.3, 70.2, 69.3 and 66.8 (7C, skeleton carbons), 63.1 and 62.9 (2C, C-6 and C-6′), 45.0 (C-3), 29.2 (SCH₂), 21.1, 20.8, 20.7, 20.7 and 20.6 (8C, 8×COCH₃); MALDI-TOF m/z: [M + Na]+ Calcd for C₂₉H₄₀O₁₈Na 731.183; Found 731.135.
4.2.20. Methyl-6-O-tert-butyldiphenylsilyl-2,3-(2′,3′-dimethoxybutane-2′,3′-diyl)-4-deoxy-4-C-methylene-α-n-xylol-hexopyranoside (37)

Compound 36 (2.862 g, 5.235 mmol) was dissolved in abs. CH₂Cl₂ (29 mL). Dess-Martin periodinane (2.669 g, 6.282 mmol, 1.2 equiv.) was added and the reaction was stirred for one hour. When TLC showed complete disappearance of the starting material, the reaction mixture was diluted with CH₂Cl₂, aq NaOH solution (28 mL, 1.3 M) was added and the mixture was vigorously stirred for 10 min. In the next step, the organic layer was separated and washed with water, dried over MgSO₄, and concentrated in vacuo. The crude product 4-ulose (2.822 mg, 99%) was used in the next step without further purification. Dry tetrahydrofuran (30 mL) was stirred under argon and methyltriphenylphosphonium bromide (2.961 g, 8.289 mmol, 1.6 equiv.) was added. The suspension was cooled to 0 °C and n-butyllithium in hexane (3.316 mL, c = 2.5 M, 8.289 mmol) was added dropwise. After stirring the mixture for 30 min., 4-ulose dissolved in dry tetrahydrofuran (15 mL) was added dropwise. The reaction was monitored by TLC. After three hours, ethyl acetate (200 mL) was added, and the organic layer was washed three times with satd aq NH₄Cl solution and water, dried over MgSO₄, and evaporated in vacuo. The crude product was purified by column chromatography to give 37 (1.831 g).

Yield: 65% (over two steps), colorless syrup. [α]D²⁰ = +21.8 (c 0.1, CHCl₃). Rf 0.73 (hexane/acetone 8/2). ¹H NMR (400 MHz, CDCl₃): δ = 7.72-7.67 (m, 4H, arom), 7.46-7.33 (m, 6H arom), 5.27 (s, 1H, C-2), 4.95 (s, 1H, C-2α), 4.80 (d, J = 3.6 Hz, 1H, H-1), 4.52 (d, J = 10.3 Hz, 1H, H-3), 4.23 (t, J = 5.5 Hz, 1H, H-5), 4.03 (dd, J = 10.7, 4.9 Hz, 1H, H-6α), 3.88 (dd, J = 10.7, 6.4 Hz, 1H, H-6β), 3.69 (dd, J = 10.3, 3.6 Hz, 1H, H-2), 3.41 (s, 3H, OCH₃), 3.26 (s, 3H, OCH₃), 3.23 (s, 3H, OCH₃), 1.36 (s, 3H, CH₃ butanedione), 1.34 (s, 3H CH₃ butanedione), 1.06 (d, J = 7.0 Hz, 9H, 3×CH₃-t-Bu); ¹³C NMR (101 MHz, CDCl₃): δ = 141.4(C-4), 135.8, 135.8, 134.9, 133.6, 133.6, 129.8, 127.9, 127.8 and 127.8 (arom), 106.2 (CH₂), 100.0 and 99.9 (2×Cq butanedione), 98.1 (C-1), 71.9, 69.7, 66.4 and 63.8 (C-5, C-3, C-2), 55.0 (C-1-OCH₃), 48.0 (2×OCH₃ butanedione), 26.9 (3×CH₃, t-Bu), 19.4 (Cq, t-Bu), 18.0 and 17.9 (2×CH₃ butanedione). Anal. Calcd for C₃₀H₄₂O₇Si: C, 66.39; H, 7.80. Found: C, 67.88; H, 7.63.

4.2.21. Methyl-6-O-tert-butyldiphenylsilyl-4-deoxy-4-C-(2′,3′,4′,6′-tetra-O-acetyl-1′-thiomethyl-β-D-glucopyranosyl)-2,3-(2′,3′-dimethoxybutane-2′,3′-diyl)-α-n-glucopyranoside (38a) and Methyl-6-O-tert-butyldiphenylsilyl-4-deoxy-4-C-(2′,3′,4′,6′-tetra-O-acetyl-1′-sulfanyl methyl-β-D-glucopyranosyl)-2,3-(2′,3′-dimethoxybutane-2′,3′-diyl)-α-n-glucopyranoside (38b)

4-Exomethylene 37 (1.380 g, 2.543 mmol), thiol 2a (1.112 g, 3.051 mmol, 1.2 equiv.) and DPAP (65 mg, 0.254 mmol, 0.1 equiv.) were reacted according to the general method with one irradiation cycle to provide compounds 38a and 38b (2.056 g, 38a: 38b ~ 3.2 on the basis of ¹H NMR spectrum, see supplementary file). The two products cannot be separated and used as a mixture in the next step.

Rf 0.27 (hexane/acetone 8/2). ¹H NMR (360 MHz, CDCl₃) Characteristic peaks: δ 4.76 (d, J = 3.5 Hz, 1H, H-1major), 4.74 (d, J = 3.9 Hz, 0.6H, H-1minor), 4.49 (d, J = 10.1 Hz, 0.6H, H-1'minor), 4.26 (d, J = 9.8 Hz, 1H, H-1'major).

MS (ESI-TOF) m/z: [M + Na]+ 38a: Calcd for C₄₄H₆₂O₁₆SiNa 929.3420; Found 929.3430; [M + Na]+ 38b: Calcd for C₄₄H₆₂O₁₇SiNa 945.3569; Found 945.3575.

4.2.22. Methyl-4-deoxy-4-C-(2′,3′,4′,6′-tetra-O-acetyl-1′-thiomethyl-β-D-glucopyranosyl)-2,3-(2′,3′-dimethoxybutane-2′,3′-diyl)-α-n-glucopyranoside (39a) and Methyl-4-deoxy-4-C-(2′,3′,4′,6′-tetra-O-acetyl-1′-sulfanyl methyl-β-D-glucopyranosyl)-2,3-(2′,3′-dimethoxybutane-2′,3′-diyl)-α-n-glucopyranoside (39b)

The mixture of 38a and 38b (2.056 g, 2.3 mmol) were dissolved in tetrahydrofuran (20 mL), 1M tetrabutyl-ammonium-fluoride in tetrahydrofuran (3.400 mL, 3.400 mmol, 1.5 equiv.) was added and the solution was stirred for 12 h. When TLC showed complete disappearance of the starting material the mixture was evaporated in vacuo, the crude product was purified by flash chromatography (hexane/acetone 75/25 → 65:35) to give 39a, b as an inseparable mixture (877 mg).
39a,b: R₂ 0.12 (hexane/acetone 7/3).¹H NMR (360 MHz, CDCl₃) Characteristic peaks: δ 4.78 (d, J = 3.5 Hz, 1H, H-1major), 4.72 (d, J = 3.9 Hz, 0.5H, H-1minor), 4.55 (d, J = 10.1 Hz, 0.5H, H-1’minor), 4.48 (d, J = 9.8 Hz, 1H, H-1’major).

MS (ESI-TOF) m/z: [M + Na]+ 39a,b: Calcd for C₂₈H₄₄O₁₆Na 691.225; Found 691.240; [M + Na]+ 39b: Calcd for C₂₈H₄₄O₁₇Na 707.220; Found 707.224.

4.2.23. Methyl-4-deoxy-4-(2′,3′,4′,6′-tetra-O-acetyl-1′-thiomethyl-β-D-glucopyranosyl)-α-D-glucopyranoside (40)

The mixture of 39a,b (850 mg) was dissolved in CH₂Cl₂ and 3 mL 90 v/v% trifluoroacetic acid (2.7 mL trifluoroacetic acid + 0.3 mL water) was added dropwise. After 15 min, toluene (5 mL) was added and the mixture was evaporated in vacuo. The crude product was purified by flash chromatography to provide 40 (443 mg).

Yield: 31% for three steps, colorless syrup. R₂ 0.13 (CH₂Cl₂/acetone 7/3).¹H NMR (360 MHz, CDCl₃): δ = 5.23 (t, J = 9.3 Hz, 1H), 5.07 (t, J = 9.8 Hz, 1H) and 5.07 (t, J = 9.7 Hz, 1H) (H-2’, H-3’, H-4’), 4.81 (d, J = 3.8 Hz, 1H, H-1), 4.51 (d, J = 10.0 Hz, 1H, H-1’), 4.27–4.17 (m, 8H), 4.12 (dt, J = 10.1, 4.9, 2.3 Hz, 1H), 3.38 (s, 2H), 3.37 (s, 2H). MS (MALDI-TOF) m/z: [M + Na]+ Calcd for C₄₃H₆₁O₂₈Na 759.434; Found 759.436.

4.2.24. Methyl-2,3,6-tri-O-acetyl-4-deoxy-4-(2′,3′,4′,6′-tetra-O-acetyl-1′-thiomethyl-β-D-glucopyranosyl)-α-D-glucopyranoside (41a) and Methyl-2,3,6-tri-O-acetyl-4-deoxy-4-(2′,3′,4′,6′-tetra-O-acetyl-1′-sulfinylmethyl-β-D-glucopyranosyl)-α-D-glucopyranoside (41b)

Compound 40 (430 mg) was dissolved in CH₂Cl₂, acetic anhydride (0.141 mL, 1.487 mmol, 3.6 equiv.) and pyridine (0.100 mL, 1.237 mmol, 3.0 equiv.) was added. The mixture was stirred overnight. When TLC showed the complete disappearance of the starting material, the solvent was evaporated in vacuo, and the crude product was purified by column chromatography to give 41a and 41b (223 mg). 41a and 41b cannot be separated from each other.

Yield: 69%, colorless syrup. R₂ 0.82 (CH₂Cl₂/acetone 7/3).

¹H NMR (400 MHz, CDCl₃): δ 5.41 (dd, J = 10.9, 9.7 Hz, 1H, H-3), 5.28 (dd, J = 5.3, 1.7 Hz, 0.3H), 5.21 (t, J = 9.4 Hz, 1H), 5.08 (t, J = 9.7 Hz, 1H), 5.01 (td, J = 9.8, 3.6 Hz, 2H), 4.96–4.91 (m, 1H), 4.89 (d, J = 3.6 Hz, 1H), 4.82 (dd, J = 9.7, 3.6 Hz, 1H), 4.40 (d, J = 9.8 Hz, 2H), 4.36–4.15 (m, 8H), 4.12 (dt, J = 10.7, 3.5 Hz, 1H), 3.81 (dd, J = 10.1, 4.3, 2.2 Hz, 1H), 3.70 (dd, J = 10.1, 4.9, 2.3 Hz, 1H), 3.38 (s, 2H), 3.37 (s, 3H), 2.99 (dd, J = 13.1, 3.3 Hz, 1H), 2.84 (dd, J = 13.1, 7.7 Hz, 1H), 2.78 (d, J = 3.9 Hz, 2H), 2.56 (q, J = 4.1 Hz, 1H), 2.22 (ddt, J = 14.9, 11.8, 3.8 Hz, 1H), 2.11 (s, 3H), 2.10 (s, 1H), 2.01 (s, 3H), 2.01 (s, 3H), 2.01 (s, 1H), 2.00 (s, 3H), 2.00 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 170.78, 170.75, 170.69, 170.21, 170.15, 169.68, 169.49, 169.47, 169.45, 97.24, 97.02, 83.84, 82.52, 76.05, 73.80, 72.67, 69.83, 69.58, 69.12, 68.41, 68.28, 68.12, 67.82, 67.15, 64.13, 63.25, 62.04, 61.90, 55.35, 55.15, 41.26, 40.48, 25.54, 22.44, 21.04, 20.92, 20.77, 20.68. MS (MALDI-TOF) m/z: [M + Na]+ 41a: Calcd for C₂₈H₄₀O₁₈Na 719.183; Found 719.195.

4.2.25. Methyl-6-O-tert-butyldiphenylsilyl-2,3-di-O-methyl-α-D-glucopyranoside (42)

Methyl-2,3-di-O-methyl-α-D-glucopyranoside [69] was dissolved in abs. CH₂Cl₂ (5 mL) and pyridine (0.653 mL, 6.75 mmol 2 equiv.). tert-Butyl-diphenylsilyl chloride (1.038 mL, 4.050 mmol, 1.2 equiv.) was added and the mixture was stirred overnight. When the reaction was complete, CH₂Cl₂ was added and the mixture was extracted with 1M HCl, satd aq NaHCO₃ solution and water. The
organic phase was dried over MgSO₄ and then concentrated; the crude product was purified by flash chromatography to give 42 (1.180 g).

Yield: 76%, colorless syrup. [α]D²⁰ = +48.7 (c 0.2, CHCl₃). Rₙ 0.77 (CH₂Cl₂/acetonitrile 8/2). ¹H NMR (400 MHz, CDCl₃): δ = 7.73–7.35 (m, 10H, arom), 4.82 (d, J = 3.5 Hz, 1H, H-1), 3.93–3.83 (m, 2H, H-α and H-β), 3.69–3.63 (m, 1H, H-5), 3.64 (s, 3H, OCH₃), 3.56 (dt, J = 9.4, 1.6 Hz, 1H, H-4), 3.50 (s, 3H, OCH₃), 3.50–3.45 (m, δ = 8.5, 4.5 Hz, 1H, H-3), 3.39 (s, 3H, OCH₃), (dd, J = 9.4, 3.6 Hz, 1H, H-2), 2.77 (d, J = 2.0 Hz, 1H, OH), 1.06 (s, 9H, 3×CH₃, t-Bu). ¹³C NMR (101 MHz, CDCl₃): δ = 185.5, 135.7, 133.3, 129.9 and 127.8 (12C, arom), 97.6 (C-1), 84.6, 82.7 and 74.3 (C-2, C-3 and C-5), 59.5 (OC₃), 57.3.

4.2.26. Methyl-6-O-tert-butyldiphenylsilyl-2,3-di-O-methyl-α-D-xylo-hexopyranoside-4-ulose (43)

Dess–Martin periodinane (1.239 g, 2.915 mmol, 1.2 equiv.) was added and the mixture was stirred for one hour to a solution of 42 [46] (1.119 g, 2.429 mmol) dissolved in abs. CH₂Cl₂ (10 mL). The mixture was diluted with CH₂Cl₂, aq NaOH solution (19 mL, 1.3M) was added and vigorously stirred for 10 min. The organic phase was separated and washed with water, over MgSO₄ concentrated to give 43 (1.056 g). The crude 43 was used in the next step without further purification.

Yield: 94%, colorless syrup. Rₙ = 0.56 (hexane/ethyl acetate 6/4). ¹H NMR (400 MHz, CDCl₃): δ = 7.74–7.34 (m, 10H, arom), 5.03 (d, J = 3.4 Hz, 1H, H-1), 4.19 (dd, J = 6.4, 3.1 Hz, 1H), 4.11–4.06 (m, 2H, H-α and H-β), 3.89 (dd, J = 11.3, 6.4 Hz, 1H), 3.58 (s, 3H, OCH₃), 3.56 (s, 3H, OCH₃), 3.54 (s, 3H, OCH₃), 3.53–3.50 (m, J = 6.2, 2.1 Hz, 1H), 1.04 (s, 9H, 3×CH₃, t-Bu). ¹³C NMR (101 MHz, CDCl₃): δ = 135.8, 135.7, 133.5, 133.3, 129.8, 127.8, 127.8 (12C, arom), 97.6 (C-1), 84.6, 82.7 and 74.3 (C-2, C-3 and C-5), 62.1 (C-6), 60.3 (OCH₃), 59.8 (OCH₃), 56.0 (OCH₃), 26.8 (3C, 3×CH₃, t-Bu), 19.3 (C₆t, t-Bu). Anal. Calcd for C₁₃₀H₁₉₀O₅Si: C, 65.19; H, 7.88. Found: C, 67.02; H, 7.65.

4.2.27. Methyl-6-O-tert-butyldiphenylsilyl-4-deoxy-4-methylene-2,3-di-O-methyl-α-D-xylo-hexopyranoside (44)

Dry tetrahydrofuran (10 mL) was stirred under argon and methyltriphenylphosphonium bromide (1.255 g, 3.513 mmol) was added. The suspension was cooled to 0 °C and n-butyllithium in hexane (1.405 mL, c = 2.5 M, 3.513 mmol) was added dropwise. After stirring the mixture for 30 min., 43 (1.007 g, 2.196 mmol) dissolved in dry tetrahydrofuran (5 mL) was added dropwise. The reaction was monitored by TLC. After three hours, ethyl acetate (100 mL) was added, and the organic layer was washed three times with satd aq NH₄Cl solution and water, over MgSO₄ evaporated in vacuo. The crude product was purified by column chromatography to give 44 (920 mg).

Yield: 92%, colorless syrup. [α]D²⁰ = +95.0 (c 0.2, CHCl₃). Rₙ 0.46 (hexane/ethyl acetate 7/3). ¹H NMR (400 MHz, CDCl₃): δ = 7.73–7.35 (m, 10H, arom), 5.20 (s, 1H, =CH₂a), 4.96 (s, 1H, =CH₂b), 4.88 (d, J = 3.6 Hz, 1H, H-1), 4.17 (t, J = 5.7 Hz, 1H, H-5), 4.02–3.94 (m, 2H, H-α and H-β), 3.88 (dd, J = 10.6, 6.6 Hz, 1H, H-6a), 3.53 (s, 3H, OCH₃), 3.53 (s, 3H, OCH₃), 3.42 (s, 3H, OCH₃), 3.18 (dd, J = 9.5, 3.6 Hz, 1H, H-2), 1.05 (s, 9H, 3×CH₃, t-Bu). ¹³C NMR (101 MHz, CDCl₃): δ = 142.5 (C-4), 135.8, 135.8, 133.6, 132.6, 129.9, 127.8 and 127.8 (12C, arom), 107.4 (=CH₂), 97.9 (C-1), 83.8, 81.2 and 69.6 (C-2, C-3 and C-5), 63.9 (C-6), 59.5 (OCH₃), 59.4 (OCH₃), 55.2 (OCH₃), 26.9 (3C, 3×CH₃, t-Bu), 19.4 (C₆t, t-Bu). Anal. Calcd for C₁₃₀H₁₉₀O₅Si: C, 68.39; H, 7.95. Found: C, 66.74; H, 8.18.

4.2.28. Methyl-6-O-tert-butyldiphenylsilyl-4-deoxy-4-C′-(2′,3′,4′,6′-tetro-O-acetyl-1′-thiomethyl-β-D-glucopyranosyl)-2,3-di-O-methyl-α-D-glucopyranoside (45)

Preparation by photoinduced free radical hydrothiolation: 44 (106 mg, 0.232 mmol), and 2a (100 mg, 0.278 mmol, 1.2 equiv.) were reacted according to the general method with two irradiation cycle, to give compound 45 (153 mg, 81%).

The preparation by Et₃B-catechol initiated free radical hydrothiolation: 44 (100 mg, 0.262 mmol) and 2a (95 mg, 0.182 mmol, 1.2 equiv.) were dissolved in CH₂Cl₂ (2 mL) and catechol (29 mg,
After 1 h, the solvents was evaporated and the crude product was purified by column chromatography to give 45 (116 mg, 78%).

Yield: 81%, $[\alpha]_{D}^{20} = +1.30$ (c = 0.23, CHCl₃). $R_{f}$ 0.33 (CH₂Cl₂/acetone 95/5). ¹H NMR (400 MHz, CDCl₃): $\delta$ = 7.74–7.35 (m, 10H, arom), 5.19 (t, $J = 9.4$ Hz, 1H, H-3′), 5.03 (t, $J = 9.7$ Hz, 1H, H-4′), 4.95 (t, $J = 9.7$ Hz, 1H, H-2′), 4.86 (d, $J = 3.5$ Hz, 1H, H-1), 4.38 (d, $J = 10.1$ Hz, 1H, H-1′), 4.17 (dd, $J = 12.4, 4.9$ Hz, 1H, H-6′a), 4.01 (dd, $J = 12.4, 2.2$ Hz, 1H, H-6′b), 3.89 (dd, $J = 11.2, 2.2$ Hz, 1H, H-6b), 3.74 (dd, $J = 11.3, 4.7$ Hz, 1H, H-6a), 3.68 (ddd, $J = 10.5, 4.4, 2.2$ Hz, 1H, H-5), 3.62–3.59 (m, 1H, H-5′), 3.58 (s, 3H, OCH₃), 3.52 (s, 3H, COCH₃), 3.46–3.39 (m, 1H, H-3), 3.39 (s, 3H, OCH₃), 3.23 (dd, $J = 9.2, 3.5$ Hz, 1H, H-2), 2.82 (dd, $J = 13.1, 4.6$ Hz, 1H, SCH₂), 2.71 (dd, $J = 13.1, 2.8$ Hz, 1H, SCH₂), 2.02 (s, 3H, COCH₃), 2.01 (s, 3H, COCH₃), 2.00 (s, 3H, COCH₃), 1.98–1.94 (m, 1H, H-4), 1.93 (s, 3H, COCH₃), 1.06 (s, 9H, 3xCH₃, t-Bu), ¹³C NMR (101 MHz, CDCl₃): $\delta$ = 170.5, 170.2, 169.3 and 169.1 (4xCOCCH₃), 135.7, 135.7, 135.5, 133.4, 129.8, 129.7, 127.7 and 127.7 (10C, arom), 97.6 (C-1), 83.6 (C-2), 83.4 (C-1′), 78.7 (C-3), 75.8 (C-5′), 73.9 (C-3′), 71.1 (C-5), 69.8 (C-2′), 68.3 (C-4′), 64.1 (C-6), 62.0 (C-6′), 61.1, 58.5 and 55.0 (3xOCH₃), 43.3 (C-4), 26.8 (4C, 3xCH₃, t-Bu and SCH₂), 20.6, 20.6, 20.6 and 20.5 (4C, 4xCOCCH₃), 19.3 (C₆t, t-Bu). Anal. Calcd for C₅₀H₅₀O₁₄S₁₁: C, 58.53; H, 6.88; S, 3.89. Found: C, 59.90; H, 7.05; S, 3.60.

4.2.29. 2,3,4-Tri-O-acetyl-α-D-xylo-hex-5-enopyranosyl-(1→1)-2,3,4-tri-O-acetyl-α-D-xylo-hex-5-enopyranoside (47)

To a solution of 46 (1.63 g, 2 mmol) in pyridine (50 mL) AgF (3.16 g, 25 mmol) was added and the mixture was stirred in the dark overnight, and then the completion of the reaction was controlled by TLC (CH₂Cl₂/acetone 95:5). Et₂O (320 mL) was added to the mixture and the organic layer was washed with 10% aq Na₂S₂O₃ solution and water. The organic phase was dried over Na₂SO₄, evaporated under reduced pressure, and the residue was purified by column chromatography to give 47 (608 mg).

Yield: 54%, white needles. m.p.: 214.3 °C $[\alpha]_{D}^{20} = +11.2$ (c = 0.08, CHCl₃). $R_{f}$ 0.35 (hexane/acetone 7:3). ¹H NMR (400 MHz, CDCl₃): $\delta$ = 5.52 (d, $J = 3.6$ Hz, 1H, H-1), 5.50–5.55 (m, 2H, H-3 and H-4), 5.02 (dd, $J = 8.6, 3.6$ Hz, 1H, H-2), 4.66 (t, $J = 2.0$ Hz, 1H, =CH₂), 4.55 (t, $J = 1.8$ Hz, 1H, =CH₂), 2.11 (s, 3H, CH₂CO), 2.06 (s, 3H, CH₂CO), 2.04 (s, 3H, CH₂CO). ¹³C NMR (101 MHz, CDCl₃): $\delta$ = 170.1, 169.5, 169.3, (3C, 3 x CO) 149.7 (C-5), 97.7 (C-6), 90.3 (C-1), 69.7, 69.3, 69.2 (3C, C-2, C-3 and C-4), 20.7, 20.7, 20.6 (3C, 3 x CH₂CO). MS (MALDI-TOF) m/z: [M + Na]⁺ Calcd for C₂₃H₂₃O₁₄S₁₁: 581.1482; Found: 581.323.

4.2.30. 2,3,4-Tri-O-acetyl-6-thio-6′-S-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)-α-D-glucopyranosyl-(1→1)-2,3,4-tri-O-acetyl-α-D-xylo-hex-5-enopyranoside (48) and 2,3,4-Tri-O-acetyl-6-thio-6′-S-(2,3,4,6-tetra-O-acetyl-α-D-mannopyranosyl)-α-D-glucopyranosyl-(1→1)-2,3,4-tri-O-acetyl-α-D-xylo-hex-5-enopyranosyl (49)

Diene 47 (100 mg, 0.18 mmol), thiol 2e (195 mg, 0.54 mmol, 3.0 equiv.) and DPPA (5 mg, 0.1 equiv.) were reacted according to the general method in DMF/toluene 3:1 (3 mL) with four irradiation cycles. The crude product was purified by column chromatography (hexane/acetone 6/4) to give compound 48 (44 mg, 27%) as a colorless foam. The reaction was also carried out in the same scale in DMF/toluene 3:1 at -80 °C to give compounds 48 (55 mg, 33%) and 49 (41 mg, 18%). The reaction was repeated while using 4.5 equiv. of thiol 2e in DMF/toluene 3:1 at -80 °C to give compounds 47 (7 mg, 4%) and 49 (135 mg, 60%). The reaction was repeated using 4.5 equiv. of thiol 2e in dichloromethane to give compound 49 (164 mg, 74%).

48: Yield: 33%, colorless foam. $[\alpha]_{D}^{20} = +196.6$ (c = 0.18, CHCl₃). $R_{f}$ 0.40 (hexane/acetone 6:4). ¹H NMR (400 MHz, CDCl₃): $\delta$ (ppm) 5.51 (d, 1H, J = 3.6 Hz, 1H, H-1enoside), 5.47–5.43 (m, 2H), 5.41 (d, 1H, J = 3.6 Hz, 1H, H-1GlcP), 5.34 (dd, $J = 3.2, 1.4$ Hz, 1H), 5.33–5.25 (m, 5H), 5.16 (ddd, $J = 9.2, 3.6, 0.8$ Hz, 1H), 5.06–4.99 (m, 1H), 4.91 (dd, $J = 10.2, 3.9$ Hz, 1H), 4.67 (t, $J = 1.9$ Hz, 1H, =CH₂), 4.55 (t, $J = 1.8$ Hz, 1H, =CH₂), 4.33 (dd, $J = 12.2, 5.0$ Hz, 1H, H-6aManc), 4.26 (dd, $J = 9.5, 4.9, 2.1$ Hz, 1H, H-5Manc), 4.07 (dd, $J = 12.2, 2.2$ Hz, 1H, H-6bManc), 3.95 (ddd, $J = 10.0, 6.9, 3.0$ Hz, 1H, H-5GlcP), 2.81 (dd, $J = 14.0,
3.1 Hz, 1H, SCH₂a), 2.65 (dd, J = 14.0, 7.0 Hz, 1H, SCH₂b), 2.18 (s, 3H, CH₃CO), 2.13 (s, 3H, CH₃CO), 2.12 (s, 3H, CH₃CO), 2.11 (s, 3H, CH₃CO), 2.05 (s, 3H, CH₃CO), 2.05–2.04 (m, 9H, 3×CH₂CO), 2.03 (s, 3H, CH₃CO), 2.00 (s, 3H, CH₃CO). ¹³C NMR (101 MHz, CDCl₃) δ 170.7, 170.247, 169.9, 169.9, 169.8, 169.7, 169.7, 169.4 (10C, 10×CO), 149.8 (C-5), 98.0 (C-6), 91.4, 90.9 (2C, 2×C-1-trehalose), 82.6 (C-1₅mannp), 71.2, 70.9, 70.0, 69.6, 69.8, 69.7, 69.5, 69.4, 69.2 (2×), 66.2 (11C, skeleton), 62.3 (C-6₅mannp), 31.3 (SCH₂), 21.0, 20.9 (2×), 20.8 (5×), 20.7 (2×) (10C, 10×CH₃CO). MS (MALDI-TOF) m/z: [M + Na]+ Calcd for C₈₃H₇₀NaO₄₂S 945.231; Found: 945.230.

49: Yield: 74%, colorless foam. [α]D = +49.3 (c = 0.15, CHCl₃). R₁ 0.24 (hexane:acetone 6/4). ¹H NMR (400 MHz, CDCl₃) δ (ppm) 5.46 (t, J = 9.8 Hz, 1H), 5.36–5.21 (m, 5H), 5.05 (dt, J = 9.6, 6.9 Hz, 2H), 4.39–4.23 (m, 2H), 4.14–3.96 (m, 2H), 2.82 (dd, J = 13.9, 3.0 Hz, 1H, SCH₂a), 2.67 (dd, J = 14.0, 6.6 Hz, 1H, SCH₂b), 2.17 (s, 3H, CH₃CO), 2.11 (s, 6H, 2×CH₂CO), 2.06 (s, 6H, 2×CH₂CO), 2.03 (s, 3H, CH₃CO), 1.99 (s, 3H, CH₃CO). ¹³C NMR (101 MHz, CDCl₃) δ 170.6, 170.0, 169.9, 169.8, 169.7, 169.7 (2×) (7×CO), 92.1 (1C, C-1-trehalose), 82.4 (C-1₅mannp), 71.1, 70.8, 70.0, 69.9, 69.5, 69.4, 69.2 (8C, skeleton), 62.4 (C-6₅mannp), 31.3 (SCH₂), 20.9, 20.8, 20.7 (3×), 20.6 (7C, 7×CH₃CO). MS (MALDI-TOF) m/z: [M + Na]+ Calcd for C₅₂H₇₀NaO₃₃₅S 1309.314; Found: 1309.319.

4.2.3.1. Methyl (5-acetamido-4,7,8,9-tetra-O-acetyl-3,5-dideoxy-2-thio-D-galacto-non-2-ulpynorosyl)-onate-(2→7)-6′-deoxy-1′,2′:3′,4′-di-O-isopropylidene-7′-α-D-galacto-heptopyranose (S1)

Exomethylene 50 (22 mg, 0.11 mmol) and thiol 2f (66 mg, 0.13 mmol) were reacted according to the general method at −80 °C with three irradiation cycles to give compound 51 (65 mg).

Yield: 69%, colorless syrup. [α]D = −4.0 (c = 0.5, CHCl₃). R₁ 0.29 (CH₂Cl₂/acetone 8/2). ¹H NMR (500 MHz, CDCl₃) δ (ppm) 5.49 (d, J = 5.0 Hz, 1H, H-1′′), 5.38 (ddd, J = 8.0, 5.1, 2.7 Hz, 1H, H-8), 5.31 (dd, J = 8.5, 2.2 Hz, 1H, H-7′), 5.16 (d, J = 10.1 Hz, 1H, NH), 4.86 (ddd, J = 11.7, 10.5, 4.6 Hz, 1H, H-4′), 4.59 (dd, J = 7.9, 2.3 Hz, 1H, H-3′′), 4.32–4.27 (m, 2H, H-9a, H-2′′), 4.17 (dd, J = 7.9, 1.8 Hz, 1H, H-4′′), 4.11 (dd, J = 12.5, 5.2 Hz, 1H, H-9b), 4.04 (q, J = 10.4 Hz, 1H, H-5′), 3.86 (ddd, J = 8.9, 4.0, 1.4 Hz, 1H, H-5′′), 3.82 (dd, J = 10.8, 2.2 Hz, 1H, H-6′), 3.80 (s, 3H, OCH₃), 2.84–2.68 (m, 3H, H-7′′, H-7′, H-3a), 2.14 (s, 6H, 2×COCH₃), 2.03 (s, 3H, COCH₃), 2.03 (s, 3H, COCH₃), 2.01–1.96 (m, 1H, H-3b), 1.93–1.88 (m, 1H, H-6′′a), 1.87 (s, 3H, COCH₃), 1.81–1.74 (m, 1H, H-6′′b), 1.59 (s, 3H, CH₃-i-Pr), 1.44 (s, 3H, CH₃-i-Pr), 1.34 (s, 3H, CH₃-i-Pr), 1.32 (s, 3H, CH₃-i-Pr). ¹³C NMR (91 MHz, CDCl₃) δ (ppm) 171.1, 170.8, 170.3 and 170.0 (6C, 6×CO), 109.2 and 108.6 (2C, 2×C₄, i-Pr), 96.6 (C-1′), 83.4 (C-2), 74.3 (C-6′), 72.7 (C-4′), 71.1 (C-3′), 70.7 (C-2′), 69.8 (C-4), 68.6 (C-8), 67.4 (C-7), 66.3 (C-5′), 62.3 (C-9), 53.1 (OCH₃), 49.5 (C-5), 38.2 (C-3), 30.8 (C-6′), 26.2 (CH₃-i-Pr), 26.1 (CH₃-i-Pr), 25.4 (CH₃-i-Pr), 25.2 (CH₃-i-Pr), 24.5 (CH₃-i-Pr), 23.4, 21.2, 21.0 and 20.9 (5C, 5×COCH₃); MS (ESI-QTOF) m/z: [M+Na]+ Calcd for C₉₅H₉₀NaO₂S 786.2619; Found: 786.2616.

Supplementary Materials: Supplementary materials can be found at http://www.mdpi.com/1422-0067/21/2/573/s1.

Author Contributions: Conceptualization, A.B. and Y.Y.; methodology, A.B., L.L. and M.C.; investigation, M.C., D.E., E.M., L.L., N.D., M.T.; writing—original draft preparation, A.B.; writing—review and editing, A.B.; funding acquisition, A.B., M.C., L.S., M.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the National Research, Development and Innovation Office of Hungary under the projects K119509 (M.C.), K132870 (A.B.) and FK 128766 (M.T.). The project was also supported by the EU and co-financed by the European Regional Development Fund under the projects GINOP-2.3.3-15-2016-00008, GINOP-2.3.3-15-2016-00004 and GINOP-2.3.3-15-2016-00021. “Developing Pharmaceutical Technology R&D Infrastructure on the University of Debrecen” project. The publication was supported by the János Bolyai Fellowship (M.C. and L.L.) of the Hungarian Academy of Sciences and the ÚNKP-19-4 New National Excellence Program of the Ministry for Innovation and Technology (M.C.). The author acknowledges the support from EFOP-3.6.1-16-2016-00022 “Debrecen Venture Catapult Program” (N.D.).

Acknowledgments: The authors acknowledge the excellent technical assistance of Mártá Bodza and Dóra Fekete.

Conflicts of Interest: The authors declare no conflict of interest.
Abbreviations

| Abbreviation | Full Form |
|--------------|-----------|
| DPAP         | 2,2-dimethoxy-2-phenylacetophenone |
| BDA          | butane-2,3-diacetal |
| DIPEA        | N,N-diisopropylethylamine |
| TBDMS        | tert-butyldimethylsilyl |
| TBDPS        | tert-butyldiphenylsilyl |
| TFA          | trifluoroacetic acid |
| TBAF         | tetrabutylammonium fluoride |

References

1. Bertozzi, C.R.; Kiessling, L.L. Chemical glycobiology. *Science* 2001, **291**, 2357–2364. [CrossRef] [PubMed]
2. Varki, A.; Cummings, R.D.; Esko, J.D.; Freeze, H.H.; Stanley, P.; Bertozzi, C.R.; Hart, G.W.; Etzler, M.E. *Essentials of Glycobiology*; Cold Spring Harbor Laboratory Press: Cold Spring Harbor, NY, USA, 2009.
3. Varki, A. Biological roles of glycans. *Glycobiology* 2017, **27**, 3–49. [CrossRef] [PubMed]
4. Ernst, B.; Magnani, J.L. From carbohydrate leads to glycomimetic drugs. *Nat. Rev. Drug. Discov.* 2009, **8**, 661–677. [CrossRef] [PubMed]
5. Cipolla, L.; Araujo, A.C.; Bini, D.; Gabrielli, L.; Russo, L.; Shaikh, N. Discovery and design of carbohydrate-based therapeutics. *Expert Opin. Drug Discov.* 2010, **5**, 721–737. [CrossRef]
6. Driguez, H. Thiooligosaccharides as tools for structural biology. *ChemBioChem* 2001, **2**, 311–318. [CrossRef]
7. Koester, D.C.; Holkenbrink, A.; Werz, D.B. Recent advances in the synthesis of carbohydrate mimetics. *Synthesis* 2010, **2010**, 3217–3242. [CrossRef]
8. Szilágyi, L.; Varela, O. Non-conventional glycosidic linkages: Syntheses and structures of thiooligosaccharides and carbohydrates with three-bond glycosidic connections. *Curr. Org. Chem.* 2006, **10**, 1745–1770. [CrossRef]
9. Pachamuthu, K.; Schmidt, R.R. Synthetic routes to thiooligosaccharides and thioglycopeptides. *Chem. Rev.* 2006, **106**, 160–187. [CrossRef]
10. Yang, Y.; Yu, B. Recent advances in the chemical synthesis of C-glycosides. *Chem. Rev.* 2017, **117**, 12281–12356. [CrossRef]
11. Kitamura, K.; Ando, Y.; Matsumoto, T.; Suzuki, K. Total synthesis of aryl C-glycoside natural products: Strategies and tactics. *Chem. Rev.* 2017, **118**, 1495–1598. [CrossRef]
12. André, S.; Pei, Z.; Siebert, H.-C.; Ramström, O.; Gabius, H.-J. Glycosyl disulfides from dynamic combinatorial libraries as O-glycoside mimetics for plant and endogenous lectins: Their reactivities in solid-phase and cell assays and conformational analysis by molecular dynamics simulations. *Bioorg. Med. Chem.* 2006, **14**, 6314–6326. [CrossRef] [PubMed]
13. Adinolfi, M.; Capasso, D.; Di Gaetano, S.; Iadonisi, A.; Leone, L.; Pastore, A. A straightforward synthetic access to symmetrical glycosyl disulfides and biological evaluation thereof. *Org. Biomol. Chem.* 2011, **9**, 6278–6283. [CrossRef]
14. Szilágyi, L.; Illéys, T.-Z.; Herzegh, P. Elaboration of a novel type of interglycosidic linkage: Syntheses of disulfide disaccharides. *Tetrahedron Lett.* 2001, **42**, 3901–3903. [CrossRef]
15. Morais, G.R.; Falconer, R.A. Efficient one-pot synthesis of glycosyl disulfides. *Tetrahedron Lett.* 2007, **48**, 7637–7641. [CrossRef]
16. Illéys, T.Z.; Balla, S.; Bényei, A.; Kumar, A.A.; Timári, I.; Kövér, K.E.; Szilágyi, L. Exploring the Syntheses of Novel Glycomimetics. Carbohydrate Derivatives with Se-S-or Se-Se-Glycosidic Linkages. *ChemistrySelect* 2016, **1**, 2383–2388. [CrossRef]
17. Lázár, L.; Csávás, M.; Tóth, M.; Somsák, L.; Borbás, A. Thio-click approach to the synthesis of stable glycomimetics. *Chem. Pap.* 2015, **69**, 889–895. [CrossRef]
18. Bege, M.; Berczki, I.; Herzegh, M.; Kicsák, M.; Eszenyi, D.; Herzegh, P.; Borbás, A. A low-temperature, photoinduced thiol-ene click reaction: A mild and efficient method for the synthesis of sugar-modified nucleosides. *Org. Biomol. Chem.* 2017, **15**, 9226–9233. [CrossRef] [PubMed]
19. Smellie, I.A.; Moggach, S.A.; Paton, R.M. Synthesis of novel amidoxime-linked pseudodisaccharides. *Tetrahedron Lett.* 2011, **52**, 95–97. [CrossRef]
20. Gong, Y.; Sun, H.; Xie, J. Synthesis of oligosaccharide mimetics with glycoaminoxy acids. *Eur. J. Org. Chem.* 2009, **2009**, 6027–6033. [CrossRef]
21. Lopez, M.; Bornaghi, L.F.; Driguez, H.; Poulsen, S.-A. Synthesis of sulfonamide-bridged glycomimetics. J. Org. Chem. 2011, 76, 2965–2975. [CrossRef]
22. Bokor, E.; Kun, S.; Goyard, D.; Toth, M.; Praly, J.-P.; Vidal, S.; Somsátk, L. C-Glycopyranosyl arenes and hetarenes: Synthetic methods and bioactivity focused on antidiabetic potential. Chem. Rev. 2017, 117, 1687–1764. [CrossRef] [PubMed]
23. Cramer, N.B.; Reddy, S.K.; O’Brien, A.K.; Bowman, C.N. Thiol-ene photopolymerization mechanism and rate limiting step changes for various vinyl functional group chemistries. Macromolecules 2003, 36, 7964–7969. [CrossRef]
24. Hoyle, C.E.; Lee, T.Y.; Roper, T. Thiol–enes: Chemistry of the past with promise for the future. J. Polym. Sci. A Polym. Chem. 2004, 42, 5301–5338. [CrossRef]
25. Dondoni, A.; Marra, A. Recent applications of thiol-ene coupling as a click process for glycoconjugation. Chem. Soc. Rev. 2012, 41, 573–586. [CrossRef] [PubMed]
26. McSweeney, L.; Dénès, F.; Scanlan, E.M. Thiol-Radical Reactions in Carbohydrate Chemistry: From Thiosugars to Glycoconjugate Synthesis. Eur. J. Org. Chem. 2016, 2016, 2080–2095. [CrossRef]
27. Lázár, L.; Csávács, M.; Herczegh, M.; Herczegh, P.; Borbás, A. Synthesis of S-linked glycoconjugates and S-disaccharides by thiol-ene coupling reaction of enones. Org. Lett. 2012, 14, 4650–4653. [CrossRef]
28. Lázár, L.; Csávács, M.; Hadzási, Á.; Herczegh, M.; Tóth, M.; Somsátk, L.; Barna, T.; Herczegh, P.; Borbás, A. Systematic study on free radical hydrothiolation of unsaturated monosaccharide derivatives with exo-and endocyclic double bonds. Org. Biomol. Chem. 2013, 11, 5339–5350. [CrossRef]
29. Eszenyi, D.; Kelemen, V.; Balogh, F.; Bege, M.; Csávács, M.; Herczegh, P.; Borbás, A. Promotion of a Reaction by Cooling: Stereoselective 1, 2-cis-α-Thioglycoconjugation by Thiol-Ene Coupling at ~80° C. Chem. Eur. J. 2018, 24, 4532–4536. [CrossRef]
30. Eszenyi, D.; Lázár, L.; McCourt, R.O.; Borbás, A. Synthesis of thiodisaccharides by photoinduced hydrothiolation of 2-acetoxy glycols. In Carbohydrate Chemistry: Proven Synthetic Methods; Kováč, P., Vogel, C., Murphy, P., Eds.; CRC Press: Boca Raton, FL, USA, 2017; Volume 4, pp. 33–44.
31. Kelemen, V.; Bege, M.; Eszenyi, D.; Debreczeni, N.; Bényei, A.; Stürzer, T.; Herczegh, P.; Borbás, A. Stereoselective thiocation by photoinduced thiol-ene coupling reactions of hexo-and pentopyranosyl D-and L-glycals at low temperature–Reactivity and stereoselectivity study. Chem. Eur. J. 2019, 25, 14555–14571. [CrossRef]
32. Lázár, L.; Juhasz, L.; Batta, G.; Borbás, A.; Somsátk, L. Unprecedented β-manno type thiodisaccharides with a C-glycosyl function by photoinitiated hydrothiolation of 1-C-substituted glycols. New J. Chem. 2017, 41, 1284–1292. [CrossRef]
33. Fiore, M.; Marra, A.; Dondoni, A. Photoinduced Thiol-Ene Coupling as a Click Ligation Tool for Thiodisaccharide Synthesis. J. Org. Chem. 2009, 74, 4422–4425. [CrossRef] [PubMed]
34. József, J.; Juhasz, L.; Illyés, T.Z.; Csávács, M.; Borbás, A.; Somsátk, L. Photoinitiated hydrothiolation of pyranoid exo-glycals: The D-galacto and D-xylo cases. Carbohydr. Res. 2015, 413, 63–69. [CrossRef] [PubMed]
35. József, J.; Juhasz, L.; Somsátk, L. Thio-click reaction of 2-deoxy-exo-glycals towards new glycomimetics: Stereoselective synthesis of C-2-deoxy-d-glycopyranosyl compounds. New J. Chem. 2019, 43, 5670–5686. [CrossRef]
36. Tóth, M.; Somsátk, L. Exo-Glycals from glycosyl cyanides. First generation of C-glycosylmethylene carbenes from 2, 5-and 2, 6-anhydroaldose toslyhydrzones. J. Chem. Soc. Perkin Trans. 2001, 9, 942–943. [CrossRef]
37. Tóth, M.; Kóvé, K.E.; Bényei, A.; Somsátk, L. C-Glycosylmethylene carbenes: Synthesis of anhydro-aldose tosylhydrzones as precursors; generation and a new synthetic route to exo-glycals. Org. Biomol. Chem. 2003, 1, 4039–4046. [CrossRef] [PubMed]
38. Tóth, M.; Kun, S.; Somsátk, L.; Goyard, D. Preparation of exo-glycals from 2, 6-anhydro-aldose-tosylhydrzones. In Carbohydrate Chemistry: Proven Synthetic Methods; Kováč, P., Ed.; CRC Press: Boca Raton, FL, USA, 2011; pp. 365–373.
39. Móker, J.; Thiem, J. Synthesis and hydrolysis studies of novel glyco-functionalized platinum complexes. Carbohydr. Res. 2012, 348, 14–26. [CrossRef]
40. Dess, D.B.; Martin, J.C. Readily Accessible 12-I-5 Oxidant for the Conversion of Primary and Secondary Alcohols to Aldehydes and Ketones. J. Org. Chem. 1983, 48, 4155–4156. [CrossRef]
41. Yoshida, K.; Fujino, Y.; Iitsu, Y.; Inoue, H.; Kanoko, Y.; Takao, K.-i. Amine-free silylation of alcohols under 4-methylpyridine N-oxide-catalyzed conditions. Tetrahedron Lett. 2016, 57, 627–631. [CrossRef]
66. Risbood, P.A.; Phillips, T.S.; Goodman, L. The thiocyanate route to derivatives of 3-thio-\(\text{d}\)-glucose and 3-thio-\(\text{d}\)-allose. *Carbohydr. Res.* **1981**, *94*, 101–107. [CrossRef]

67. Matta, K.L.; Girotra, R.N.; Barlow, J.J. Synthesis of p-nitrobenzyl and p-nitrophenyl 1-trioglycopyranosides. *Carb. Res.* **1975**, *43*, 101–109. [CrossRef]

68. Hasegawa, A.; Nakamura, J.; Kiso, M. Studies on the thioglycosides of N-acetylneuraminic acid 1: Synthesis of alkyl \(\alpha\)-glycosides of 2-thio-N-acetylneuraminic acid. *J. Carbohydr. Chem.* **1986**, *5*, 11–19. [CrossRef]

69. Nicoll-Griffith, D.A.; Weiler, L. Introduction of a chiral centre on C-6 of a carbohydrate unit: Application to the synthesis of the C-2 to C-15 fragment of lonomycin. *Tetrahedron* **1991**, *47*, 2733–2750. [CrossRef]