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Synthesis and binding affinity analysis of positional thiol analogs of mannopyranose for the elucidation of sulfur in different position

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ABSTRACT

Synthetic routes towards thio-α/β-D-mannose derivatives are presented. Double parallel or double serial inversion was successfully applied in the efficient synthesis of 2-thio- or 2,4-di-thio-mannoside derivatives. The protein recognition properties of the synthesized positional thiol analogs of mannose were then evaluated in a competition binding assay with the model lectin Concanavalin A (Con A), in order to investigate the roles of thiol group in the different position of the mannopyranose ring in binding affinity. Though the substitution of oxygen atom with sulfur atom in the methyl α-D-mannoside ring usually displayed low or no binding affinity towards Con A, it was a surprise finding that the methyl 2-thio-α-D-mannoside displayed four times higher inhibition than methyl α-D-mannoside, indicating the particular importance of 2-position for modification of α-D-mannoside. Methyl 3-thio-α-D-mannoside also displayed inhibition towards Con A, indicating that the *O*-atom at the C-3 position is less important in the binding site.

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1. Introduction

Carbohydrate–protein recognitions are of great significance in many fundamental cellular processes such as adhesion, trafficking, communication, proliferation, and cell death.[1–5] The recognitions are involved in cancer and in the early stages of infection, playing roles of cell surface receptors enabling adherence of bacteria, parasites, and viruses.[6–9] New therapies and drugs would be able to be developed if these interactions are thoroughly understood and controlled. Thus, well-defined carbohydrate ligands need to be synthesized and further studied on their interactions to the corresponding proteins. Sulfur-containing glycosides are often applied in the synthesis of thio-oligosaccharides.[10–16] In comparison with nature O-linked ligands, studies have shown that various thio-oligosaccharides display increased conformational flexibility.[17–19] Generally these sulfur-containing analogs are more stable due to lower rates of both acid-catalyzed and enzymatic hydrolysis, and thus are potential candidates as glycosidase inhibitors and are of special interests in enzyme-inhibition studies.[20–26] In addition, sulfur-containing carbohydrates have special advantages in generating dynamic carbohydrate libraries based on easy oxidation of thiols to give disulfides.[27–31]

The lectins are another class of carbohydrate-specific proteins besides enzymes and antibodies. Carbohydrate-lectin interactions play important roles in cell-cell recognition.[32–34] Concanavalin A (Con A) is the most extensively studied member of the lectins and has a strong binding affinity to the α-linked mannose.[35–37] This binding to the mannose moiety of glycoproteins on cell surface is relate to the cell growth and death. For example, Con A has been found as potential *anti*-hepatoma therapeutic recently.[38] In early studies, by the analysis of affinity of various derivatives of D-mannose and other saccharides to Con A, Goldstein et al. suggested that *O*-atoms of the C-1, C-2 and C-3 hydroxyl groups and H-atoms of the C-4 and C-6 are involved in the H-bonding to the protein.[39–42] Recently, by the analysis of methyl α-mannoside-Con A complex crystal structure, it was suggested that 3-, 4- and 6-OHs of the mannoside provide the main contribution to affinity through H-bonding, whereas 2-OH and 1-OMe extend into solvent.[36,37] However, the complex in real solvent might not be exactly the same as its crystal structure. For example, as derivatives of 1- or 6-thio mannose are easy to synthesize, the affinities of 1-thio-α-D-mannose and methyl 6-thio-α-D-mannoside towards Con A have been measured.[30] Methyl 6-thio-α-D-mannoside shows no activity as expected. However, 1-thio-α-D-mannose shows lower activity compared to methyl α-D-mannoside, suggesting that 1-OMe group

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should be involved in pronounced interactions with the Con A lectin. Thus, synthesis of various derivatives of D-mannose modified at the different positions and further measurement of their affinity towards Con A in real solvent might provide additional information for the binding mechanism. Synthesises of 1- or 6-thio glycosides have been widely reported due to their distinctive reaction selectivities.[43–47] However, the synthesises of 2-, 3- or 4-thio glycosides are rarely reported likely due to the requirements of complicated multi-step reactions including selective protection/deprotection and epimerization.[48,49]

We have developed an efficient method for the synthesis of β-D-mannoside derivatives by double parallel or double serial inversion.[50] The strategy is based on multiple regioselective acylation via the respective stannylene intermediates,[51] followed by simultaneous inversion of both addressed hydroxyl groups or stepwise inversion of the hydroxyl groups. The double parallel or double serial inversion strategy was also applied in synthesis of orthogonally protected galactosamine thioglycoside building blocks.[52] Recently, we developed a multiple regioselective acetylation method using tetrabutylammonium acetate as a catalyst.[53,54] This method is more convenient and environmentally friendly than organotin method. In the present study, we developed synthetic routes towards positional thio-α/β-D-mannose derivatives (Fig. 1) using these methodologies. Especially, 2-thio- and 2,4-dithio-mannoside derivatives were efficient synthesized by the application of double parallel or double serial inversion, so as to avoid complicated multi-step reactions. The protein recognition properties of these positional thiol analogs of mannose were then evaluated in a competition binding assay with the model lectin Con A through Quartz Crystal Microbalance (QCM), in order to investigate the roles of thiol group in the different position of the mannopyranose ring in binding affinity.

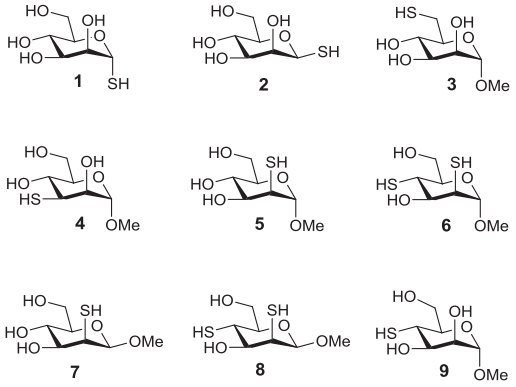
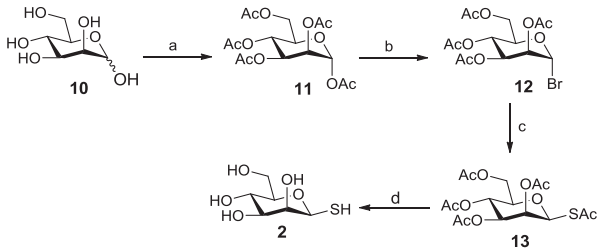


Fig. 1. The positional thio-α/β-D-mannose derivatives.

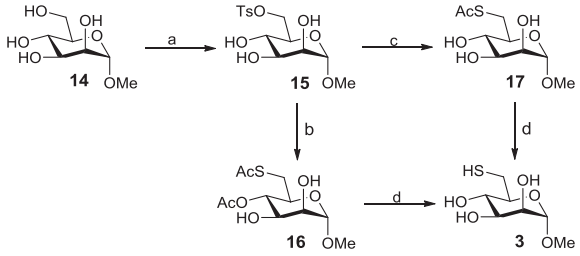
2. Results and discussion

The 1-thio-α-D-mannose compound **1** can be easily produced, starting from a fully acetylated α-D-mannose compound **11** followed by a substitution of thioacetate group at the anomeric center, in light of a reported method.[30] Synthesis of the 1-thio-β-D-mannose compound **2** has been reported in a quite low yield.[46] In the reported method, compound **11** was substituted by a bromide group at the anomeric center to form compound **12**, then treating compound **12** with KSAc in DMPU to form compound **13** in 45% yield. It is possible that the low yield of compound **13** was caused by partial formation of the five-membered acyloxonium ring arising from the 2-OAc group in the polar solvents.[55,56] In our method (Scheme 1), compound **12** was treated with TBASAc in no-polar solvent toluene for avoiding the neighboring group participation, leading to compound **13** in 85% yield.



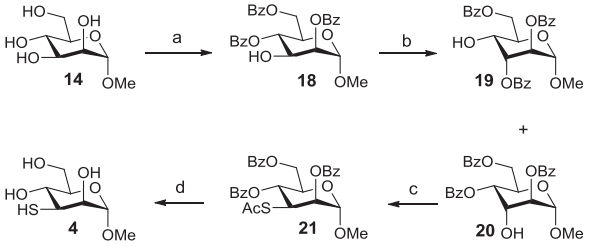
Scheme 1. Synthesis of 1-thio-α/β-D-mannopyranose **2**; (a) Ac_2O, pyridine, rt, 4h; (b) HOAc-HBr, $BF_3{\cdot}Et_2O$, CH_2Cl_2, 0 °C to rt, 2h, 90%; (c) TBASAc, toluene, 5h, 85%; (d) NaOH, MeOH, rt, 2h, then with H^+ exchange resin, 95%.

Synthesis of methyl 6-thio-α-D-mannopyranoside **3** was reported to go through compound **15** and **16** starting from free methyl mannoside **14**.[30] In this method, tosylation of compound **14** formed compound **15**, and compound **15** reacted with 5 equiv of KSAc in DMF at 70 °C to form compound **16** in 60% yield. After careful scrutinize of this reaction, we found that compound **15** reacting with 1.5 equiv of KSAc at 35 °C led to compound **17** in 70% yield (Scheme 2). Treatment of compound **15** with 5 equiv of KSAc at 35 °C also formed compound **16**. However the yield was improved by 77% in this case.



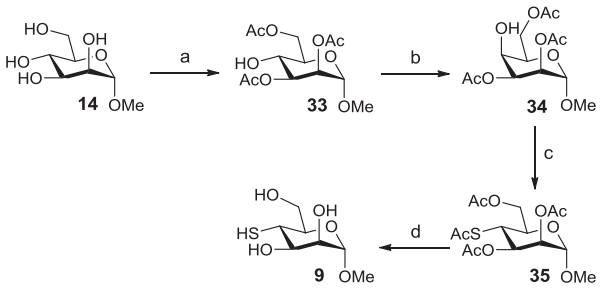
Scheme 2. Synthesis of methyl 6-thio-α-D-mannopyranoside **3**; (a) TsCl, pyridine, 0 °C to rt, (70%); (b) KSAc, DMF, 35 °C, 6h, 77%; (c) i: KSAc, DMF, 35 °C, 6h; ii: KNO_2, DMF, 35 °C, 2h, 70%; (d) NaOH, MeOH, rt, 2h, then with H^+ exchange resin; DTT, H_2O, rt, 12h, 90%.

Synthesis of methyl 3-thio-α-D-mannopyranoside **4** has never been reported. The approach to this compound we developed is showed in Scheme 3. Starting from free methyl mannoside **14**, compound **18** was easily synthesized in 70% total yield, through organotin-mediated regioselective benzylation,[57,58] pyridine-mediated benzoylation and finally debenzylation by catalytic hydrogenation. However, compound **20** was only obtained in 33% yield when inversing compound **18** using nitrite-mediated epimerization methods, owing to the neighboring group participation.[55,56] Triflation of compound **20** followed by a substitution of thioacetate group led to compound **21** in 78% yield.

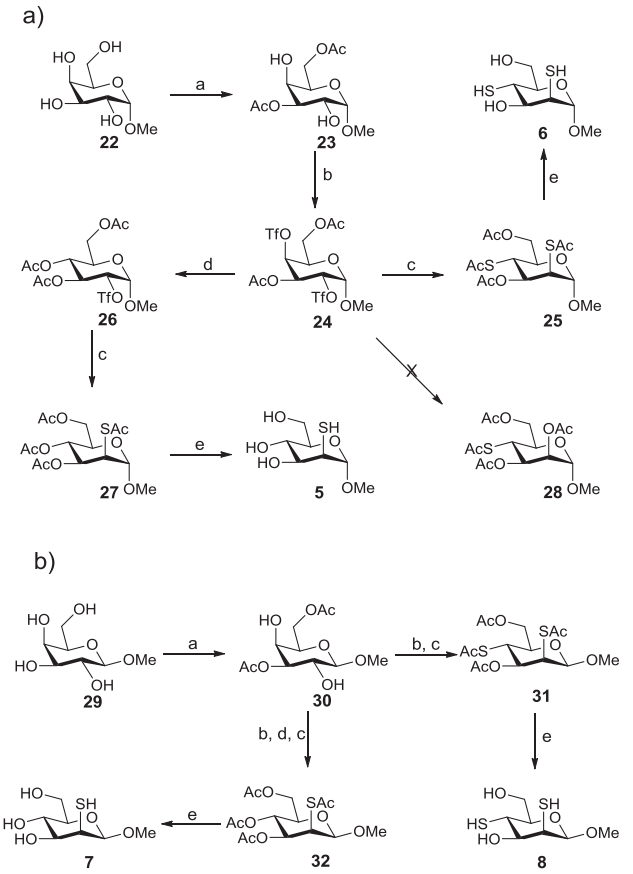


Scheme 3. Synthesis of methyl 3-thio-α-D-mannopyranoside **4**; (a) i: Bn_2SnO, toluene, reflux,4h; ii: BnBr, TBAB,100 °C, 8h; iii: BzCl, pyridine, 0 °C to rt, 12h; iiii: Pd–C, H_2, EtOH/AcOH (2:1), overnight, 60% total yield; (b) i: Tf_2O, pyridine, CH_2Cl_2, −30 to −10 °C, 4h; ii: KNO_2, DMF, 50 °C, 6h, 55% of **19** and 33% of **20**; (c) i: Tf_2O, pyridine, CH_2Cl_2, −30 to −10 °C, 4h; ii: TBASAc, toluene, rt, 5h, 78%; (d) NaOH, MeOH, rt, 4h, then with H^+ exchange resin; DTT, H_2O, rt, 12h, 90%.

Methyl β-D-mannopyranoside derivatives had been efficiently synthesized through double parallel and double serial inversion starting from methyl β-D-galactopyranoside.[50] These results inspired us to further explore if methyl 2-thio-, 4-thio- and 2,4-dithio-α/β-D-mannopyranosides can also be efficiently synthesized by the application of the double parallel and double serial inversion. The method was proven efficient for the synthesis of 2-thio-, and 2,4-thio-α/β-D-mannopyranosides (Scheme 4) but inefficient for the synthesis of 4-thio-α/β-D-mannopyranosides. 3,6-di-OAc galactosides **23** and **30** were synthesized starting from free galactosides **22** and **29** in high yields using acetate-mediated methods.[54] Triflation of compound **23** and **30** followed by substitution of thioacetate group afforded compound **25** and **31** in 63% and 81% yields, respectively. In order to obtain products where only the 2-positions were substituted by thioacetate group, the triflation intermediates of compound **23** and **30** were allowed to react with 1.1 equiv of KOAc followed by substitution of thioacetate group. As a result, compound **27** and **32** were obtained in 70% and 78% yields, respectively. The triflation intermediates of compound **23** and **30** reacting with 1.1 equiv of KSAc led to intermediates where only the 4-positions were substituted by thioacetate group in high yields. The generation of 4-thio-α/β-D-mannopyranoside derivatives were expected through following substitution by either acetate or nitrite. However, this double serial inversion didn't give any desired products where the equatorial 2-position was supposed to be inversed to an axial position. Therefore, in order to obtain 4-thio-α-D-mannopyranoside **9**, we have to design a conventional strategy though it is much more complicated (Scheme 5). It was reported that compound **14** could be regioselectively acetylated using organotin-mediated method to form compound **33**.[51] Thus, compound **33** was firstly obtained in 85% yield through this method, and then followed by a nitrite-mediated inversion,[55,59] to form taloside **34** accompanied by a side product probably caused by neighboring group participation.[55,56] Though **34** was unable to separate from the side product, triflation of the mixture followed by substitution of thioacetate group led to desired compound **35** in 33% yield over four steps after purification.



Scheme 5. Synthesis of methyl 4-thio-α-D-mannopyranoside; (a) i: Bu_2SnO, MeOH, reflux, 2h; ii: Ac_2O, MeCN, 0 °C to rt, 12h, 85%; (b) i: Tf_2O, pyridine, CH_2Cl_2, −30 to −10 °C, 4h; ii: $TBANO_2$, toluene, 50 °C, 5h; (c) i: Tf_2O, pyridine, CH_2Cl_2, −30 to −10 °C, 4h; ii: TBASAc, toluene, rt, 6h., **35**, 33% over 4 steps; (d) i: NaOH, MeOH, rt, 4h, then with H^+ exchange resin; ii: DTT, H_2O, rt, 12h, 88%.



Scheme 4. Synthesis of methyl 2-thio- and 2,4-dithio-α/β-D-mannopyranosides; (a) TBAOAc, Ac_2O, MeCN, rt −40 °C, 12h, 86%; (b) Tf_2O, pyridine, CH_2Cl_2, −30 to −10 °C, 4h; (c) KSAc, DMF, rt, 24h, over 2 steps (**25**, 63%, **31**, 81%), over 3 steps (**27**, 70%, **32**, 78%); (d) KOAc, DMF, rt, 1h; (e) i: NaOH, MeOH, rt, 4h, then with H^+ exchange resin; ii: DTT, H_2O, rt, 12h(**5**, 85%; **6**, 81%; **7**, 84%; **8**, 78%).

Deacylation of these acylated sulfur-containing mannosides can afford the desired free thio-mannosides. We recently demonstrated that using NaOH and NaOMe in methanol for deacylation are identical.[60] Thus, in this study, all the deacylation were performed in methanol using NaOH as a catalyst (Table S1). As the formed sulfhydryl group appeared much stronger acidity than hydroxyl group and would neutralize the base catalyst, a little more than a stoichiometric amount of the base is necessary for each thioacetate group. The results proved NaOH as a catalyst efficient in the deacylation of acylated sulfur-containing carbohydrates.

We have obtained positional thio-α/β-D-mannose derivatives **1**–**9**. Their relative binding affinities towards the target lectin Con A were then determined using a QCM flow-through instrumentation and mannose-functionalized sensor chips. The polystyrene surfaces were functionalized with PFPA-derivatized α-D-monomannoside by a Photo-Click functionalization methodology (Fig. S1),[61] which is because a larger binding capacity of Con A was showed towards this functionalized surface.[14] In order to maintain reducing conditions while analyzing the thiol monomers, a minimal amount of dithiothreitol (DTT), showing no influence on the binding itself, was added to the samples. The results from the binding study are presented in Fig. 2 and Table 1. The stable surfaces allowed for reproducible binding over time thus generating inhibitory response curves, which fitted well to the binding data. The EC_{50}-value of tested thio-mannosides compared with mannoside **14** and mannose are showed in Table 1.

It is well known that anomeric configuration is critical and α-conformers play important roles for the mannose/Con A binding. Thus methyl α-D-mannoside **14** displays much stronger binding towards Con A than mannose since mannose usually is a mixture of α and β-conformer. It can be seen that the measured EC_{50} values by us are 1.6 mM for methyl α-D-mannoside **14** and 8.6 mM for mannose. All β-conformer including 1-thio-β-D-mannose **2**, methyl-2-thio-β-D-mannoside **7** and methyl-2,4-di-thio-β-D-mannoside **8** display low or no binding towards Con A as expected. 1-thio-α-D-mannose **1** displayed an EC_{50} value of 8.8 mM, almost same as mannose. Methyl 3-thio-α-D-mannoside **4** towards Con A displayed an EC_{50} value of 4.1 mM, almost one-third as high inhibition as the methyl-α-D-mannoside **14**. Methyl-6-thio-α-D-mannoside **3** and methyl-4-thio-α-D-mannoside **9** displayed no

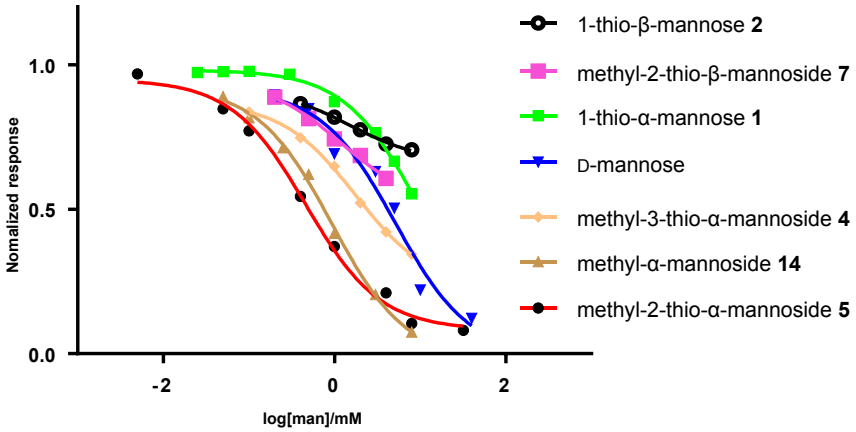


Fig. 2. Competition binding plots of seven different mannosides towards Con A. (Competition plots of methyl-6-thio-α-mannoside **3**, methyl-2,4-di-thio-α-mannoside **6**, methyl-2,4-di-thio-β-mannoside **8** and methyl-4-thio-α-mannoside **9** are not shown in this figure due to their extremely low binding affinity toward Con A).

Table 1
Estimation of EC_{50} values (50% inhibition of Concanavalin A binding) for tested carbohydrates

Carbohydrates	EC_{50} (mM)	R^2
[a]1-*S*-α-D-mannose **1**	8.8 (>5.0)[30]	0.9951
1-*S*-β-D-mannose **2**	>>30	—
[a]Methyl 6-*S*-α-D-mannoside **3**	>>30 (>>20)[30]	—
Methyl 3-*S*-α-D-mannoside **4**	4.1	0.9975
Methyl 2-*S*-α-D-mannoside **5**	0.42	0.9946
Methyl 2,4-*S*-α-D-mannoside **6**	>>30	—
Methyl 2-*S*-β-D-mannoside **7**	>10	—
Methyl 2,4-*S*-β-D-mannoside **8**	>>30	—
Methyl 4-*S*-α-D-mannoside **9**	>>30	—
Methyl α-D-mannoside **14**	1.6	0.9930
α/β-D-mannose	8.6	0.9942

[a] The values in brackets were reported in reference.

binding towards Con A. These results support that the *O*-atoms at the C-1, C-3, C-4 and C-6 positions are involved in binding,[36,40] but the *O*-atoms at the C-3 positions is less important for the binding site. The *S*-atom is both larger and considerably poorer hydrogen-bond donor than the *O*-atom. Thus the substitutions of *S*-atom with *O*-atom lead to decreased binding affinities. Since the *H*-atom at the 4-OH and 6-OH are also involved in binding,[39] the substitutions of SH with OH at C-4 and C-6 positions led to dramatically decreased binding affinities. However, a surprising result is that methyl-2-thio-α-D-mannoside **5** towards Con A displayed an EC_{50} value of 0.42 mM, almost four times as high inhibition as the methyl-α-D-mannoside **14**. Methyl-2,4-di-thio-α-D-mannoside **6** displayed no binding, indicating the importance of 4-OH in binding site. According to a previous report,[40] binding affinity sequence of their related tested sugars is D-mannose≈2-*O*-methyl-mannose <2-deoxy-2-fluoro-D-mannose. Since a fluorine atom is isosteric with a hydroxyl group and is known to be a better hydrogen-bond donor, it was suggested that the *O*-atom at the C-2 position of D-mannose is involved in non-covalent binding to con A.[40] If this is the case, the substitutions of *S*-atom with *O*-atom should lead to a decreased binding affinity, which is against our result. The study of a complex of Con A with methyl α-D-mannoside shows that the 2-OH is not hydrogen-bonded to the binding site but linked through a water bridge to an adjacent subunit.[36] The results cannot explain why methyl-2-thio-α-D-mannoside **5** displays higher binding affinity. Interestingly, it was reported recently that Meα Man(S2-3)Glc and MeαMan(S2-2)ManαMe also displayed 3–6 times as high binding constant as mannoside **14** towards Con A.[62] These results indicated that modification of 2-OH of α-D-mannoside derivatives may lead to better inhibitor toward mannoside-complexing proteins.

3. Conclusion

A range of thio-α/β-D-mannose derivatives has been successfully synthesized using the strategies of protection/deprotection patterns and inversions, especially using the double parallel or double serial inversion for the synthesis of 2-thio- and 2,4-di-thio-mannosides. The yields of 1-thio-β-D-mannose **1** and methyl-6-thio-α-D-mannoside **3** were improved. The 2-, 3-, 4-, and 2,4-thio mannosides **4**–**9** were firstly synthesized. NaOH instead of NaOMe as a catalyst catalyzing deacylation of acylated sulfur-containing glycosides proved efficient. The binding affinity of these synthesized positional thiol analogs of mannose towards Con A were evaluated, and their EC50-values were then recorded. The thio-β-mannosides and the thio-α-mannosides where the 4- and 6-positions are displaced with sulfur displayed no binding affinities towards Con A. The 3-thio-α-D-mannoside displayed almost one-third as high inhibition as methyl α-D-mannoside, indicating that the *O*-atoms at the C-3 positions is less important in binding site. It was surprisingly found that the methyl 2-thio-α-D-mannoside displayed four times as high inhibition as methyl α-D-mannoside, indicating that modification of 2-OH of α-D-mannoside derivatives may lead to better inhibitor towards mannoside-complexing proteins.

4. Experimental section

4.1. General method for multiple regioselective acylation via organotin[51]

Methyl D-glycoside and dibutyltin oxide (2.2–3.3 equiv) were refluxed in methanol for two hours. After complete removal of methanol via coevaporation with toluene, the residue was dissolved in solvent (DMF, MeCN) and followed by an addition dropwise of a solution of acetic anhydride (2.2–3.3 equiv) in dry solvent at 0 °C. The reaction proceeded at room temperature for 6–12 h. After removal of the solvent, the mixture was directly purified by flash chromatography, affording the selectively protected derivatives.

4.2. General method for multiple regioselective acylation via acetate[54]

Methyl D-glycoside (100 mg) were allowed to react with acetic anhydride (2.2 equiv) in dry acetonitrile (1 mL) at 40 °C for 8–12 h

in the presence of tetrabutylammonium acetate (0.6 equiv). The reaction mixture was directly purified by flash column chromatography (hexanes/EtOAc=2:1 to 1:1), affording the pure selectively protected derivatives.

4.3. General synthesis of triflate derivatives[55]

To a solution of the suitably *O*-protected methyl D-glycoside, carrying unprotected OH groups at C-2 and C-4 (140 mg, 0.5 mmol), in DCM (5 mL) was added pyridine (0.53 mL) at −30 °C. Trifluoromethanesulfonic anhydride (705 mg, 2.5 mmol) in DCM (2 mL) was added dropwise, and the mixture was warmed to −10 °C and stirred for 4 h. The resulting mixture was subsequently diluted with DCM and washed with 1M HCl, aqueous $NaHCO_3$, water, and brine. The organic phase was dried with $MgSO_4$ and concentrated in vacuum at low temperature. The residue was used directly in the next step without further purification.

4.4. General double parallel inversion

KSAc (5 equiv) was added to a solution of the protected triflate residue (100 mg) in dry DMF (1.0 mL). After stirring at room temperature for 24–36 h under nitrogen atmosphere, the mixture was diluted by ethyl acetate, and washed with brine. The organic phase was dried with $MgSO_4$ and concentrated in vacuum. Purification of the residue by flash column chromatography (ethyl acetate/petrol, 1:4–1:7) afforded the inversion products.

4.5. General double serial inversion

KOAc (1.1 equiv) was added to a solution of the protected triflate residue (100 mg) in dry DMF (1.0 mL). After stirring at room temperature for 1 h, KSAc (3.0 equiv) was added to the mixture and kept at room temperature for 24–36 h. The mixture was diluted by ethyl acetate, and washed with brine. The organic phase was dried with $MgSO_4$ and concentrated in vacuum. Purification of the residue by flash column chromatography (ethyl acetate/petro, l:4–1:7) afforded the inversion products.

4.6. General deacylation of thio-containing carbohydrate derivatives

Sodium hydroxide (1.1 equiv for each of thioacetyl groups) was added in the solution of acylated thio-containing methyl D-glycoside derivative in methanol. The reaction mixture was stirred at room temperature for 4–8 h under nitrogen protection and monitored with TLC. Then the mixture was neutralized with Amberlite IR-120 (H^+) ion exchange resin and filtered. DTT (3.0–5.0 equiv) was added to the filtration. The mixture was stirred at room temperature for 12 h. The solvent was removed under vacuum. Purification of the residue by flash column chromatography ($CHCl_3$/MeOH 10:1–20:1) afforded the deprotected products **1**–**9**.

4.7. Binding affinity study

QCM analyses were performed using a flow-through Attana A100 *C*-Fast QCM system. The gold plated 10 MHz QCM crystals were obtained from Attana AB and further coated with polystyrene. The mannose-functionalized surface was subjected to injections of solutions containing Con A (200 mg/mL) and either of the synthesized thio-mannosides in various concentrations. A continuous flow of running buffer (PBS 10 mM, pH 7.4, 25 L/min) was used throughout the experiments, and the sample of Con A was prepared in the same buffer. The crystals were washed/equilibrated with buffer solution prior to manipulations/measurements. After equilibration of the crystals in the flowthrough system, they were subjected to three injections of bovine serum albumin (BSA, 10 mg/mL in PBS, pH 7.4), two injections of low pH buffer (pH 1.5) and finally two additional injections of BSA (10 mg/mL) to fully block any nonfunctionalized surfaces. Binding to the surfaces was monitored by frequency logging with Attester 1.1 (Attana), and adsorption/desorption to the surface recorded as the resulting frequency shifts. Solutions of the lectins were then injected into the system, where the resulting shifts in frequency correspond to binding to the surfaces. Bound lectins were released from the surfaces between measurements by two successive injections of low pH buffer (PBS 10 mM, pH 1.5). The procedure was then repeated at least two times for each carbohydrate inhibitor concentration to give an average value and determine the surface stability over time. The observed reduction in measured frequency, compared to injections with pure Con A, was taken as a measure of the competitive effect of the tested thio-mannosides. The quantitative binding was then subjected to no-linear regression analysis using Eq. 1.

$$\Delta f = \Delta f\min + \frac{\Delta fmax - \Delta fmin}{1 + 10^{(\log c - \log EC50)}} \quad (1)$$

During the binding studies, when high inhibitor concentrations were injected, an unexpected binding behavior was observed (Fig. S2a). Control injections in the absence of Con A showed the same behavior (Fig. S2b), indicating that the resulting frequency change emanated from an instrumental artifact due to the change of buffer composition. The corrected binding was obtained by the subtraction of the Con A response curves with the corresponding inhibitor response curves (Fig. S2c).

4.8. 2,3,4,6-Tetra-*O*-acetyl-1-*S*-acetyl-β-D-mannopyranose 13[46]

To a solution of penta-*O*-acetyl-D-mannopyranose **11** (1.00 g, 2.56 mmol) in DCM (10 mL) was added HBr-AcOH (33%, 15 mL) at 0 °C. After the reaction proceeded for two hours, the mixture was extracted and concentrated, giving 2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl bromide **12** (946 mg, 90%), which could be used in the next step without further purification. To a solution of **12** (700 mg, 2.6 mmol) in toluene (10 mL) was added TBASAc (1.65 g, 5.2 mmol). The reaction proceeded for 5 h at room temperature. After extracted and concentrated, the resulting residue was purified by flash chromatography (ethyl acetate/petrol; 1:2) to afford compound **13** (589 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=5.50 (m, 2H, H-1, H-2), 5.27 (t, *J*=10.0 Hz, 1H, H-4), 5.16 (dd, *J*=3.3 Hz, 10.1 Hz, 1H, H-3), 4.28 (dd, *J*=5.3 Hz, 12.4 Hz, 1H, H-6), 4.13 (dd, *J*=2.3 Hz, 12.4 Hz, 1H, H-6′), 3.83 (ddd, *J*=2.3 Hz, 5.3 Hz, 9.9 Hz, 1H, H-5), 2.38 (s, 3H, SAc), 2.20 (s, 3H, OAc), 2.09 (s, 3H, OAc), 2.06 (s, 3H, OAc), 1.99 (s, 3H, OAc).

4.9. Methyl 6-*S*-acetyl-α-D-mannopyranside 17

To a solution of **15** (200 mg) in dry DMF (2 mL) was added KSAc (100 mg). After the mixture was stirred at 35 °C under nitrogen atmosphere for 8 h, the mixture was added KNO_2 (15 mg) and stirred at 35 °C for 2 h. After removal of the solvent, the residue was purified directly by flash chromatography with solvent system DCM/MeOH 25:1 giving compound **17** (101 mg, 70%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.69 (d, 1H, *J*=0.8 Hz, 1-H), 3.95–3.96 (m, 1H, 2-H), 3.84 (dd, 1H, *J*=3.2 Hz, 9.2 Hz, 3-H), 3.73–3.77 (m, 1H, 5-H), 3.53 (t, 1H, *J*=9.2 Hz, 4-H), 3.43 (dd, 1H, *J*=4.4 Hz, 12 Hz, 6-H), 3.36 (s, 3H, OMe), 3.16 (dd, 1H, *J*=3.2 Hz, 12.0 Hz, 6-H′), 2.49 (s, 3H, SAc). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 199.3, 100.8, 70.9, 70.2, 70.0, 69.2, 55.1, 30.9, 30.5. HRMS (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd for $C_9H_{16}O_6SNa$ 275.0565; found 275.0560.

4.10. Methyl 3-thio-α-D-mannopyranoside 4

Prepared from methyl 2,4,6-tri-*O*-benzoyl-3-*S*-acetyl-α-D-mannopyranoside **21** in light of the general deacetylation of thio-containing carbohydrate derivatives procedure, 14% total yield. ^{1}H NMR (400 MHz, D_2O) δ=4.83 (d, *J*=1.2 Hz, 1H, H-1), 3.95 (m, 2H, H-6,H-2), 3.81 (dd, *J*=6.1 Hz, 12.1 Hz, 1H, H-6′), 3.70 (m, 1H, H-5), 3.56 (t, *J*=10.2 Hz, 1H, H-4), 3.48 (s, 3H, OMe), 3.19 (dd, *J*=3.8 Hz, 7.6 Hz, 1H, H-3). ^{13}C NMR (100 MHz, D_2O) δ=100.0, 73.6, 71.3, 67.8, 61.2, 54.6, 43.6. HRMS (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd for $C_7H_{14}O_5SNa$ 233.0460; found 233.0478.

4.11. Methyl 2,3,6-tri-*O*-benzoyl-α-D-altropyranoside 19 and methyl 2,4,6-tri-*O*-benzoyl-α-D-altropyranoside 20

Starting from methyl-α-D-mannopyranoside **14** (304 mg, 2 mmol), methyl 3-*O*-benzyl-α-D-mannopyranoside (369 mg, 83%) was obtained in light of the literature.[58] Benzylation with BzCl (903 μL) and pyridine (4 mL) afforded methyl 2,4,6-tri-*O*-benzoyl-3-*O*-benzyl-α-D-mannopyranoside (736 mg, 95%). After removal of benzyl group by catalytic hydrogenation, compound **18** (612 mg, 98%) was given. To a solution of compound **18** (200 mg) in DCM (5 mL) was added pyridine (210 μL) at −30 °C. Trifluoromethanesulfonic anhydride (200 μL) in DCM (2 mL) was added dropwise, and the mixture was warmed to −10 °C and stirred for 4 h. The resulting mixture was subsequently extracted and concentrated. The residue was dissolved in DMF with the addition of KNO_2 (101 mg, 3.0 equiv). The mixture was stirred at 50 °C for 6 h. After extracted and concentrated, the crude product was purified by flash chromatography with solvent system petrol/ethyl acetate 7:1 giving compound **19** (110 mg, 55%) and compound **20** (66 mg, 33%). For compound **19**: ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.13−7.32 (m, 15H, Phx3), 5.57 (t, *J*=3.3 Hz, 1H, H-3), 5.36 (d, *J*=3.3 Hz, 1H), 4.84 (s, 1H, H-1), 4.77 (dd, *J*=4.7 Hz, 12.0 Hz, 1H, H-6), 4.68 (dd, *J*=2.1 Hz, 12.0 Hz, 1H, H-6′), 4.41 (ddd, *J*=2.1 Hz, 4.5 Hz, 9.8 Hz, 1H, H-5), 4.27 (dd, *J*=3.5 Hz, 9.9 Hz, 1H, H-4), 3.48 (s, 3H, OMe), 2.84 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ=166.9, 166.4, 164.9, 133.5, 133.3, 130.2, 130.1, 130.0, 129.9, 129.8, 129.7, 129.3, 128.6, 128.5, 128.4, 98.5, 70.0, 69.8, 67.2, 64.4, 64.2, 55.7. HRMS (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd for $C_{28}H_{26}O_9Na$ 529.1475; found 529.1475.

4.12. For compound 20

^{1}H NMR (400 MHz, $CDCl_3$) δ=8.17−7.32 (m, 15H, Phx3), 5.59 (dd, *J*=3.2 Hz, 10.3 Hz, 1H, H-4), 5.30 (dd, *J*=1.1 Hz, 3.6 Hz, 1H, H-2), 4.96 (s, 1H, H-1), 4.72 (dd, *J*=2.3 Hz, 11.8 Hz, 1H, H-6), 4.59 (ddd, *J*=2.3 Hz, 4.9 Hz, 10.3 Hz, 1H, H-5), 4.52 (dd, *J*=5.0 Hz, 11.8 Hz, 1H, H-6), 4.45 (t, *J*=3.3 Hz, 1H, H-3), 3.53 (s, 3H, OMe), 3.42 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ=166.4, 165.7, 165.3, 133.9, 133.8, 133.7, 133.3, 130.4, 130.1, 130.0, 129.9, 129.6, 129.5, 129.3, 128.8, 128.7, 128.6, 99.1, 70.5, 68.1, 67.5, 64.5, 63.8, 56.2. HRMS (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd for $C_{28}H_{26}O_9Na$ 529.1475; found 529.1470.

4.13. Methyl 2,4,6-tri-*O*-benzoyl-3-*S*-acetyl-α-D-mannopyranoside 21

To a solution of compound **20** (66 mg) in DCM (2 mL) was added pyridine (68 μL) at −30 °C. Trifluoromethanesulfonic anhydride (66 μL) in DCM (0.5 mL) was added dropwise, and the mixture was warmed to −10 °C and stirred for 4 h. The resulting mixture was extracted and concentrated. The residue was dissolved in toluene (1.5 mL) with the addition of TBASAc (20 equiv, 827 mg). After being stirred at rt for 5 h, the mixture was extracted and concentrated. The crude product was purified by flash chromatography with solvent system petrol/ethyl acetate 8:1 giving compound **21** (57 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=8.06−7.31 (m, 15H, Phx3), 5.74 (t, *J*=10.6 Hz 1H, H-4), 5.31 (dd, *J*=1.6 Hz, 2.9 Hz, 1H, H-2), 4.89 (d, *J*=1.5 Hz, 1H, H-1), 4.66 (dd, *J*=3.0 Hz, 11.3 Hz, 1H, H-3), 4.63−4.56 (m, 1H, H-6), 4.47−4.35 (m, 2H, H-5, H-6′), 3.51 (s, 3H, OMe), 2.13 (s, 3H, SAc). ^{13}C NMR (100 MHz, $CDCl_3$) δ=193.4, 166.2, 165.7, 165.5, 133.7, 133.6, 133.1, 130.1, 130.0, 129.8, 129.3, 129.2, 128.8, 128.7, 128.5, 97.7, 73.3, 69.7, 67.3, 63.6, 55.6, 44.2, 30.6. HRMS (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd for $C_{30}H_{28}O_{9S}Na$ 587.1352; found 587.1348.

4.14. Methyl 2-thio-α-D-mannopyranoside 5

prepared from 3,4,6-tri-*O*-acetyl-2-*S*-acetyl-α-D-mannopyranoside **27** according to the general deacetylation of thio-containing carbohydrate derivatives procedure, 51% total yield. ^{1}H NMR (400 MHz, D_2O) δ=4.94 (s, 1H, H-1), 4.04 (dd, *J*=4.9 Hz, 8.8 Hz, 1H, H-3), 3.88 (dd, *J*=2.0 Hz, 12.3 Hz, 1H, H-6), 3.78 (dd, *J*=5.3 Hz, 12.3 Hz, 1H, H-6′), 3.73−3.60 (m, 2H, H-4, H-5), 3.45 (d, *J*=5.0 Hz, 1H, H-2), 3.41 (s, 3H, OMe). ^{13}C NMR (100 MHz, D_2O) δ=102.4, 72.9, 69.0, 66.5, 60.7, 54.8, 44.4. HRMS (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd for $C_7H_{14}O_5SNa$ 233.0460; found 233.0460.

4.15. Methyl 2-*S*-acetyl-3,4,6-tri-*O*-acetyl-α-D-mannopyranoside 27

Prepared from methyl 3,6-di-*O*-acetyl-α-D-galactoside **23** according to the general synthesis of triflate derivatives and general double serial inversion procedure. The yield over three steps is 70%. Compound **23** was obtained in 86% yield starting from methyl α-D-galactoside **22** in light of the literature.[54] ^{1}H NMR (400 MHz, $CDCl_3$) δ=5.54 (dd, *J*=4.8 Hz, 9.9 Hz, 1H, H-3), 5.05 (t, *J*=10.0, 1H, H-4), 4.73 (s, 1H, H-1), 4.24 (dd, *J*=1.1 Hz, 4.7 Hz, 1H, H-2), 4.18 (dd, *J*=4.9 Hz, 12.2 Hz, 1H, H-6), 4.07 (dd, *J*=2.4 Hz, 12.2 Hz, 1H, H-6′), 3.93 (ddd, *J*=2.4 Hz, 4.8 Hz, 9.9 Hz, 1H, H-5), 3.37 (s, 3H, OMe), 2.34 (s, 3H, SAc), 2.08 (s, 3H, OAc), 2.00 (s, 3H, OAc), 1.93 (s, 3H, OAc). ^{13}C NMR (100 MHz, $CDCl_3$) δ=193.5, 170.7, 169.8, 169.7, 101.0, 68.7, 68.6, 66.9, 62.4, 55.5, 47.2, 30.6, 20.8, 20.7. HRMS (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd for $C_{15}H_{22}O_9SNa$ 401.0882; found 401.0879.

4.16. Methyl 2,4-di-thio-α-D-mannopyranoside 6

Prepared from 3,6-di-*O*-acetyl-2,4-di-*S*-acetyl-α-D-mannopyranoside **25** according to the general deacetylation of thio-containing carbohydrate derivatives procedure procedure, 44% total yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ=4.86 (s, 1H, H-1), 3.93−3.79 (m, 3H, H-3, H-6, H-6′), 3.60−3.51 (m, 1H, H-5), 3.35 (ddd, *J*=1.2 Hz, 4.5 Hz, 9.7 Hz, 1H, H-2), 3.31 (s, 3H, OMe), 3.03 (td, *J*=8.3 Hz, 10.5 Hz, 1H, H-4), 2.78 (s, 2H, OH), 1.75 (d, *J*=9.7 Hz, 1H, SH), 1.58 (d, *J*=8.3 Hz, 1H, SH). ^{13}C NMR (100 MHz, $CDCl_3$) δ=102.5, 74.4, 70.3, 62.8, 55.4, 45.6, 39.9. HRMS (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd for $C_7H_{14}O_4S_2Na$ 249.0231; found 249.0228.

4.17. Methyl 2,4-di-*S*-acetyl-3,6-di-*O*-acetyl-α-D-mannopyranoside 25

Prepared from compound **23** according to the general synthesis of triflate derivatives and general double parallel inversion procedure. The yield over two steps is 63%. ^{1}H NMR (400 MHz, $CDCl_3$) δ=5.52 (dd, *J*=4.4 Hz, 11.5 Hz, 1H), 4.83 (d, *J*=1.3 Hz, 1H, H-1), 4.34 (dd, *J*=5.2 Hz, 12.1 Hz, 1H, H-6), 4.25 (dd, *J*=1.6 Hz, 4.4 Hz, 1H, H-2), 4.18 (dd, *J*=2.1 Hz, 12.1 Hz, 1H, H-6′), 3.99 (ddd, *J*=2.0 Hz, 5.2 Hz, 11.2 Hz, 1H, H-5), 3.81 (t, *J*=11.4 Hz, 1H, H-4), 3.40 (s, 3H, OMe), 2.39 (s, 3H, SAc), 2.35 (s, 3H, SAc), 2.13 (s, 3H, OAc), 1.97 (s, 3H, OAc). ^{13}C NMR (100 MHz, $CDCl_3$) δ=193.7, 192.9, 170.9, 169.8, 101.1, 70.0, 67.2, 63.6, 55.5, 47.8, 41.8, 30.8, 30.7, 20.9, 20.8. HRMS (ESI-TOF) *m*/*z*: $[M+Na]^+$ Calcd for $C_{15}H_{22}O_8S_2Na$ 417.0654; found 417.0655.

4.18. Methyl 2-thio-β-D-mannopyranoside 7

Prepared from methyl 2-*S*-acetyl-3,4,6-tri-*O*-acetyl-β-D-mannopyranoside **32** according to the general deacetylation of thio-containing carbohydrate derivatives procedure, 56% total yield. ^{1}H NMR (400 MHz, D_2O) δ=4.79 (d, J=1.8 Hz, 1H, H-1), 3.97–3.85 (m, 2H, H-3, H-6), 3.75 (dd, J=6.1 Hz, 12.3 Hz, 1H, H-6′), 3.65–3.57 (m, 2H, H-2, H-4), 3.55 (s, 3H, OMe), 3.45–3.37 (m, 1H, H-5). ^{13}C NMR (100 MHz, D_2O) δ=100.3, 76.8, 71.9, 66.5, 60.9, 56.7, 46.3. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_7H_{14}O_5SNa$ 233.0460; found 233.0455.

4.19. Methyl 2-*S*-acetyl-3,4,6-tri-*O*-acetyl-β-D-mannopyranoside 32

Prepared from methyl 3,6-di-*O*-acetyl-β-D-galactoside **30** according to the general synthesis of triflate derivatives and general double serial inversion procedure. The yield over three steps is 78%. Compound **30** was obtained in 90% yield starting from methyl β-D-galactoside **29** in light of the literature.[54] ^{1}H NMR (400 MHz, $CDCl_3$) δ=5.20 (dd, J=4.3 Hz and 9.6 Hz, 1H, H-3), 5.09 (t, J=9.5 Hz, 1H, H-4), 4.68 (d, J=1.7 Hz, 1H, H-1), 4.38 (dd, J=1.7 Hz, 4.3 Hz, 1H, H-2), 4.20 (dd, J=4.9 Hz, 12.2 Hz, 1H, H-6), 4.13 (dd, J=2.9 Hz, 12.2 Hz, 1H, H-6′), 3.64 (ddd, J=2.9 Hz, 4.9 Hz, 9.3 Hz, 1H, H-5), 3.50 (s, 3H, OMe), 2.36 (s, 3H, SAc), 2.07 (s, 3H, OAc), 2.02 (s, 3H, OAc), 1.94 (s, 3H, OAc).

4.20. Methyl 2,4-thio-β-D-mannopyranoside 8

Prepared from methyl 2,4-di-*S*-acetyl-3,6-di-*O*-acetyl-β-D-mannopyranoside **31** according to the general deacetylation of thio-containing carbohydrate derivatives procedure, 54% total yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ=4.51 (s, 1H, H-1), 3.94 (dd, J=12.2, 2.1, 1H, H-6), 3.83 (dd, J=4.6 Hz and 12.2 Hz, 1H, H-6′), 3.57 (m, 2H, H-2, H-3), 3.48 (s, 3H, OMe), 3.35 (s, 1H, OH), 3.29–3.21 (m, 1H, H-5), 3.12–2.97 (m, 1H, H-4), 2.77 (s, 1H, OH), 1.72 (d, J=6.3 Hz, 1H, SH), 1.59 (d, J=8.2 Hz, 1H, SH). ^{13}C NMR (100 MHz, $CDCl_3$) δ=100.8, 78.6, 74.0, 62.6, 57.1, 47.3, 39.4. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_7H_{14}O_4S_2Na$ 249.0231; found 249.0226.

4.21. Methyl 2,4-di-*S*-acetyl-3,6-di-*O*-acetyl-β-D-mannopyranoside 31

Prepared from compound **30** according to the general synthesis of triflate derivatives and general double parallel inversion procedure. ^{1}H NMR (400 MHz, $CDCl_3$) δ=5.22 (dd, J=4.1 Hz, 10.9 Hz, 1H, H-3), 4.62 (d, J=1.6 Hz, 1H, H-1), 4.36 (dd, J=1.5 Hz, 4.1 Hz, 1H, H-2), 4.30 (dd, J=12.1 Hz, 4.9 Hz, 1H, H-6), 4.21 (dd, J=2.1 Hz, 12.1 Hz, 1H, H-6′), 3.76 (ddd, J=2.2 Hz, 4.9 Hz, 10.7 Hz, 1H, H-5), 3.68 (t, J=10.8 Hz, 1H, H-4), 3.49 (s, 3H, OMe), 2.36 (s, 3H, SAc), 2.31 (s, 3H, SAc), 2.08 (s, 3H, OAc), 1.94 (s, 3H, OAc). ^{13}C NMR (100 MHz, $CDCl_3$) δ=194.2, 192.9, 170.8, 169.9, 100.3, 73.8, 69.8, 63.4, 57.2, 49.4, 41.6, 30.8, 30.7, 20.8, 20.7. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{22}O_8S_2Na$ 417.0654; found 417.0658.

4.22. Methyl 4-thio-α-D-mannopyranoside 9

Prepared from 2,3,6-tri-*O*-acetyl-4-*S*-acetyl-α-D-mannopyranoside **35** according to the general deacetylation of thio-containing carbohydrate derivatives procedure, 29% total yield. ^{1}H NMR (400 MHz, D_2O): δ=4.90 (d, J=1.6 Hz, 1H, H-1), 4.07 (dd, J=2.2 Hz, 12.4 Hz, 1H, H-6), 4.02–3.92 (m, 2H, H-6′,H-2), 3.77 (m, 2H, H-3,H-5), 3.50 (s, 3H, OMe), 3.03 (t, J=10.8 Hz, 1H, H-4) ^{13}C NMR (100 MHz, D_2O): δ=101.0, 74.3, 71.4, 69.0, 61.9, 54.8, 38.3. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_7H_{14}O_5SNa$ 233.0460; found 233.0455.

4.23. Methyl 2,3,6-tri-*O*-acetyl-4-*S*-acetyl-α-D-mannopyranoside 35

Starting from methyl α-D-mannopyranoside **14**, methyl 2,3,6-tri-*O*-acetyl-α-D-mannopyranoside **33** was obtained in 85% yield in light of the literature.[51] Compound **33** (160 mg, 0.5 mmol) was triflated in general procedure, following an inversion by $TBANO_2$ (417 mg) in toluene (4 mL) at 50 °C for 5 h. The crude product was purified by flash chromatography with solvent system Hex: EtOAc 2:1 giving 141 mg of a mixture of methyl 2,3,6-tri-*O*-acetyl-α-D-talopyranoside **34** and its side products. The mixture was triflated in general procedure, following an inversion by TBASAc (419 mg) in toluene (2 mL) at rt for 6 h. The mixture was extracted and concentrated. Purification of the residue by flash column chromatography (ethyl acetate/petrol: 1:5) afforded the desired product compound **35** (62 mg, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ=5.24 (dd, J=3.0 Hz, 11.2 Hz, 1H, H-3), 5.13 (dd, J=1.9 Hz, 3.2 Hz, 1H, H-2), 4.72 (d, J=1.7 Hz, 1H, H-1), 4.33 (dd, J=5.3 Hz, 12.1 Hz, 1H, H-6), 4.17 (dd, J=1.4 Hz, 12.1 Hz, 1H, H-6′), 4.01–3.88 (m, 2H, H-5, H-4), 3.36 (s, 3H, OMe), 2.30 (s, 3H, SAc), 2.13 (s, 3H, OAc), 2.06 (s, 3H, OAc), 1.94 (s, 3H, OAc). ^{13}C NMR (100 MHz, $CDCl_3$) δ=193.1, 170.9, 170.3, 169.9, 98.8, 69.9, 68.7, 67.6, 63.9, 55.4, 40.7, 30.9, 21.0, 21.0, 20.8. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{22}O_9SNa$ 401.0882; found 401.0879.

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Supplementary data

General methods, Fig. **S1** and **S2**, ^{1}H and ^{13}C NMR-spectra of compounds **4**, **5**, **6**, **7**, **8**, **9**, **19**, **20**, **21**, **25**, **27**, **31**, and **35**. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.04.060.

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