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Communication

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One-pot Relay Glycosylation

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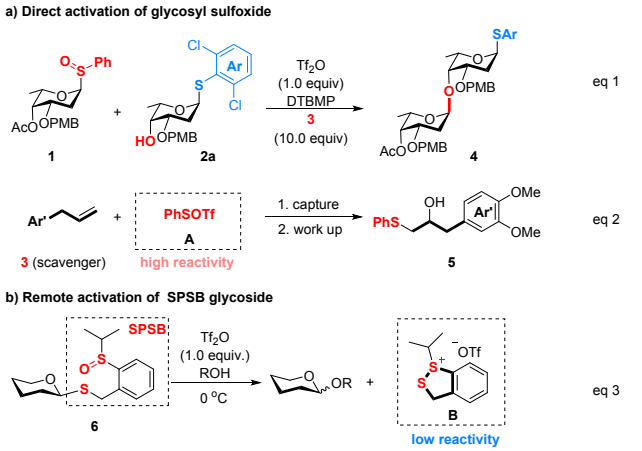
Supporting Information Placeholder

ABSTRACT: A novel one-pot relay glycosylation has been established. The protocol is characterized by the construction of two glycosidic bonds with only one equivalent of triflic anhydride. This method capitalizes on the *in situ* generated cyclic-thiosulfonium ion as the relay activator, which directly activates the newly formed thioglycoside in one-pot. A wide range of substrates are well-accommodated to furnish both linear and branched oligosaccharides. The synthetic utility and advantage of this method have been demonstrated by rapid access to naturally occurring phenylethanoid glycoside kankanoside F and resin glycoside merremoside D.

In the odyssey of carbohydrate synthesis, great efforts have been made to promote the efficiency of the glycosidic bond construction.[1] Among the tremendous achievements, activation of glycosyl sulfoxides[2] and thioglycosides[3] presented as the most popular glycosylation methods. It is well known that conventional activation of glycosyl sulfoxides with triflic anhydride inevitably generated active sulfenyl triflates (RSOTf) intermediates which are powerful activators for sulfinyl/thioglycosides.[4] To prevent these side reactions resulted from the unbridled activity of RSOTf, large excess of scavengers were usually introduced in these reactions (Scheme 1a, eq 2).[5] On the contrary, this chemistry shined a beam of light on the cascade one-pot glycosylation strategy[6,7] involving sequential activation of glycosyl sulfoxides and thioglycosides by harnessing the intermediate's reactivity, albeit it was less investigated.[4i,8]

We have recently reported an interrupted Pummerer reaction mediated (IPRm) glycosylation strategy with *S*-2-[(propan-2-yl)sulfinyl]benzyl (SPSB) glycosides as novel glycosyl donors (Scheme 1b).[9] It was observed that a cyclic thiosulfonium ion (**B**) was generated upon activation of the SPSB glycosides with Tf_2O.[9c] Compared with sulfenyl triflates, the cyclic thiosulfonium ion (**B**) was inactive under cryogenic conditions but reactive at ambient temperature as a thioglycoside activator (see the ESI). Galvanized on this observation, we hypothesized that one equivalent of Tf_2O can be used as an initial activator and the *in situ* generated thiosulfonium ion can serve as the relay activator, which would enables cascade activation of a SPSB glycoside and a thioglycoside to form two glycosidic bonds in one-pot. This hypothesis would supply a novel relay one-pot oligosaccharide assembly strategy (Scheme 1c). Compared to the classical one-pot glycosylation strategies, in which, each glycosylation step was independent, consequently, required portion-wisely addition of one and even more equivalents of activators for each glycosidic bond connection, this strategy features the advantage that two glycosidic linkages constructed by a single activator.

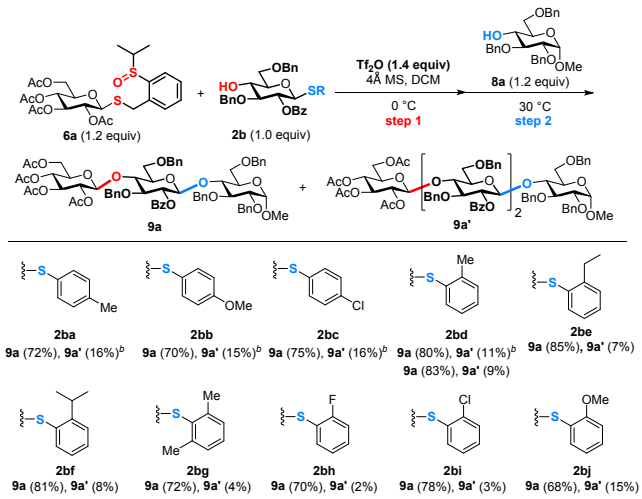
Scheme 1. Glycosylation with glycosyl sulfoxides



Obviously, the thioglycoside (**2**) played a crucial role in the one-pot relay glycosylation. It not only acted as the acceptor to couple with the SPSB donor **6** but also served as part of newly generated glycosyl donor 7 for the second glycosidic bond formation. Initially, *p*-methylbenzyl thioglycoside **2ba** was chose as first acceptor. The reaction was first carried out at – 40 °C with 1.4 equiv of Tf_2O as activator, after **2ba** was consumed completely (about 30 min), then the terminal sugar **8a** was added dropwise and the reaction temperature was warmed up to 30 °C. To our delight, this one-pot reaction proceeded smoothly. After 14 hours, the desired trisaccharide **9a** was isolated in 72% yield accompanied by 16% yield of tetrasaccharide by-product **9a'**. Occurrence of this by-product indicated that the thioglycoside **2ba** was still partially activated by the thiosulfonium ion intermediate **B** even at – 40 °C.

Further decreased the activation temperature of the first step led to an inefficient coupling.

Table 1. Tune the activity and stability of the thioglycoside 2b.[a]

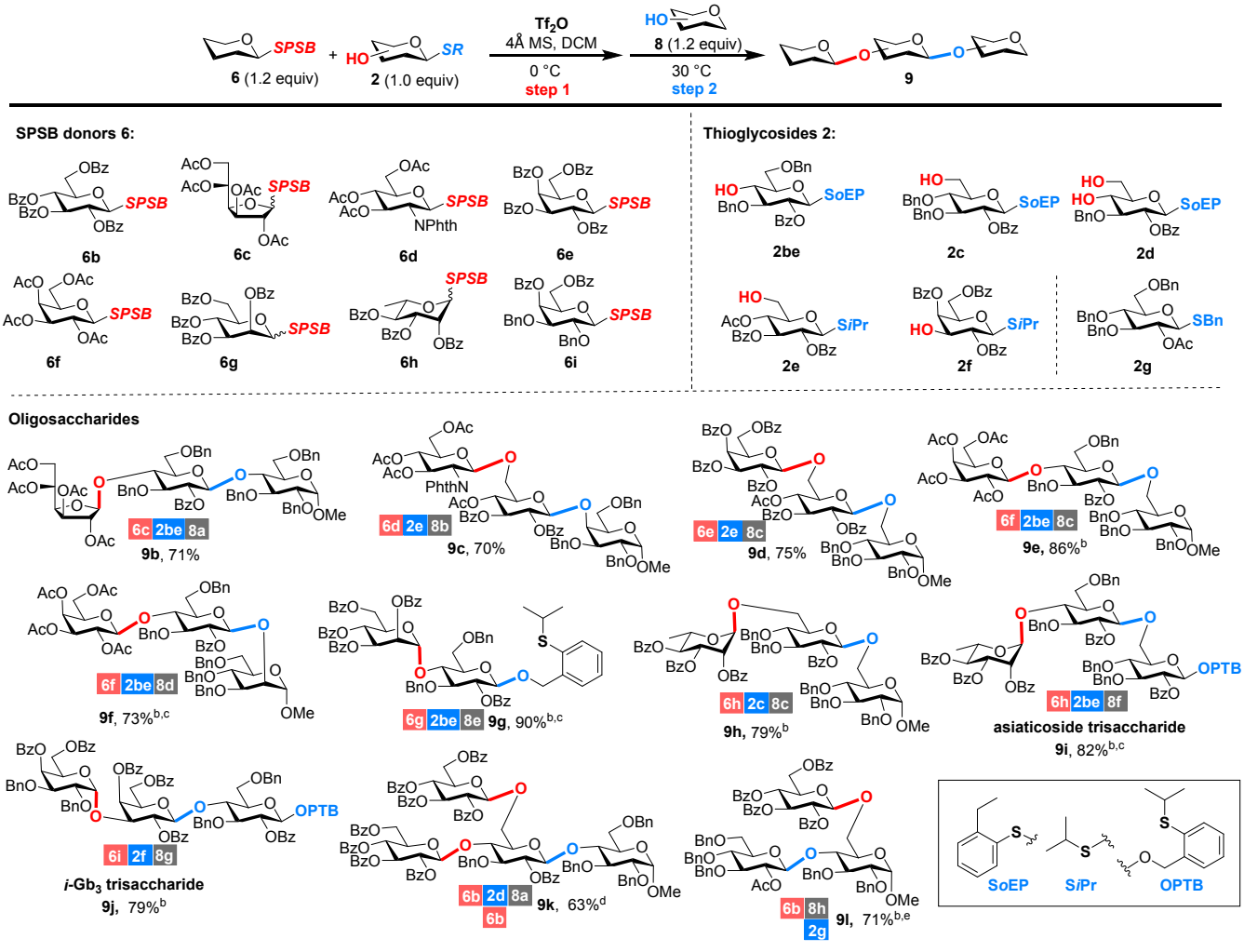


[a] **General procedure:** Tf_2O was added to the mixture of the SPSB glycoside donor **6a** and the thioglycoside **2b** at 0 °C and stirred for 30 min., followed by the addition of acceptor **8a**, then stirred at 30 °C for an appropriate time. [b] Tf_2O was added at -40 °C.

Consequently, we considered to tune the activity and stability of the thioglycoside **2b** by modification of the thiophenyl groups. It was found that steric effect of thiophenyl group had greater impact on the coupling efficiency compared to electronic effect. Introducing *ortho*-methyl group on the phenyl ring (**2bd**) increased the yield of **9a** to 80% while slightly inhibited the occurrence of the tetrasaccharide **9a'**. Interestingly, warmed up the activation temperature of the first step to 0 °C further increase the efficiency of the one-pot reaction in this case. Among the test steric hindered thiophenyl groups, *ortho*-ethyl thiophenyl (**2be**) performed as the best. More hindered groups or halogen atoms located on *ortho* position although sufficiently prevented the side reaction but also stymied the coupling.

Having approved the concept, we then commenced to investigate the substrate scope (Table 2).[10] Various SPSB donors (**6b-i**), thioglycoside (**2b-g**) and sugar or aglycon termini (**8a-h**) were then examined. Among the tested SPSB donors, the peracylated pyranoses, furanoses, deoxysugars and 2-aminosugars were all performed very well. With respect to the thioglycoside **2**, it was found that *o*-ethylphenylsulfanyl (*So*EP) group presented as better leaving group for active thioglycosides (**2be**, **2c** and **2d**) while *i*-propylsulfanyl (*Si*-Pr) is more suitable for inactive (disarmed) thioglycosides (**2e** and **2f**). Combination of these components with the one-pot

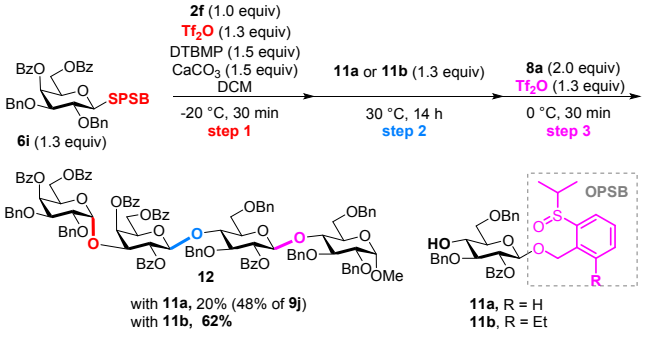
Table 2. Substrate scope[a]



[a] **General procedure**: Tf_2O (1.0 equiv. to SPSB glycosides) was added to the mixture of **6** and **2** in DCM (0.1 M), 0 °C, 15 min, followed by the addition of **8**, then stirred at 30 °C for an appropriate time. [b]DTBMP (1.5 equiv) and $CaCO_3$ (1.5 equiv) was added, SPSB donor **6** was activated at -20 °C. [c] 3.0 equiv of terminal sugar or aglycon was used. [d] 2.2 equiv of **6b** was used. [e] **6b** (1.05 equiv), **2g** (1.0 equiv), **8f** (1.0 equiv), SPSB glycoside was activated at 0 °C.

relay glycosylation protocol auspiciously provided various trisaccharides. It is worth noting that in certain cases, small amount of tetrasaccharidal side-products composed of two repeated tethering sugars (glycosyl part of thioglycoside **2**) were still observed. Lowering the activation temperature of the first step and addition of 1.5 equiv of DTBMP as well as 1.5 equiv of $CaCO_3$ was able to suppress this type of side products and provided **9e-j** in good to excellent yield. The combination of these organic base and inorganic base is essential to suppress the side reaction as which was presumed to be resulted from the strong acid conditions. Considering that the first step of the one-pot protocol was a fast reaction and the second step is a slow reaction, the organic base was used to speedily neutralize the acidity of the first step while the inorganic base was used to buffer the acidity of the second step. Undoubtedly, these conditions should augur well for acid-labile substrates. Simply increasing the amount of DTBMP to 3.0 equiv although was amenable to reduce the side reaction but at the expense of attenuated overall yield because of the formation of the orthoester by-products. In addition, 1,6-anhydro by-products were observed when C6-benzyl substituted thioglycosides employed as tethering sugars (see the ESI). It could be avoided by rising the amount of the terminal sugar to 3.0 equiv (**9f**, **9g** and **9i**). Extended this protocol to synthesize sugar moieties of natural occurring glycoconjugates successfully offered asiaticoside[11] and *i*-Gb_3[12] trisaccharides (**9i**, **9j**). Most importantly, the latent 2-[(propan-2-yl)sulfanyl]benzyl (OPTB) group located at the reducing terminus would allow the downstream installation of the aglycons by means of IPRm glycosylation. By employing **2d** possessing two free hydroxy groups as tethering sugar, the assembling of a desired tetrasaccharide **9k** with three newly formed glycosidic bonds was achieved in 63% yield. This success stimulated us to take chances to assembly a branched sugar, that is activation of disarmed **6b** with Tf_2O to couple at *O*-6 position of **8h** followed by subsequent activation of armed **2g** to link at *O*-4 position of newly formed disaccharide. To our delight, this protocol effectively furnished the branched trisaccharide **9l** in 71% yield.

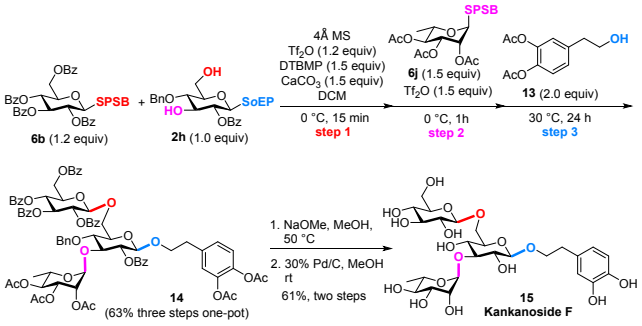
Scheme 2. Construction of three different glycosidic linkages in one-pot



Encouraged by the successes on the construction of two glycosidic linkages in one-pot by virtue of the relay-glycosylation strategy, we then embarked on the building of three linkages in one-pot. We conjectured that 2-[(propan-2-yl)sulfinyl]benzyl (OPSB) glycosides would be orthogonal to the one-pot relay glycosylation conditions. Consequently, employing OPSB glycoside (such as **11**) as the third sugar in the one-pot relay glycosylation sequence would successfully create trisaccharide with an OPSB terminal which could be activated by additional of Tf_2O for the formation of the third glycosidic bond. With this idea in mind, SPSB glycoside **6i**, thioglycoside **2f** and OPSB glycoside **11a** was then coupled sequentially under the one-pot relay glycosylation conditions. Subsequently, additional Tf_2O as well as **8a** was introduced into the reaction system. Unfortunately, although the first three sugars linked smoothly, the desired tetrasaccharide **12** was only isolated in 20% yield, along with 48% yield of **9j**, in which, the terminal OPSB group of **11a** was reduced to OPTB group. This unexpected side product was possibly raised form a competitive reduction reaction of the sulfoxide group by a disulfide compound (**10**) released from the SPSB group (see the ESI), because of the slow cyclization rate in the OPSB activation step. A lot of efforts have been made to suppress this side reaction. Finally, it was found that installing an ethyl group on the ortho position of the OPSB (**11b**) auspiciously increased the yield of tetrasaccharide **12** to 62%.

Having established the general applicability of the relay one-pot glycosylation protocol in the efficient assembly of oligosaccharides, we turned our attention to the synthesis of natural carbohydrates. Kankanoside F (**15**) which showed vasorelaxant activity was isolated from the Orobanchaceae parasitic plant (*Cistanche tubulosa*).[13] Kankanoside F bears a branched trisaccharide moiety and a phenylethanoid aglycon. A regioselective glycosylation and relay glycosylation approach was incorporated into the synthesis of this molecular. Initially, two SPSB glycosides **6b** and **6j** was regioselectivity coupled with 3,6-diol acceptor **2h** successively, then phenylethanoid aglycon **13** was introduced. This procedure afforded trisacchridal glycoconjugate **14** in 63% yield in one-pot. The global deprotection of **14** eventually furnished kankanoside F efficiently.

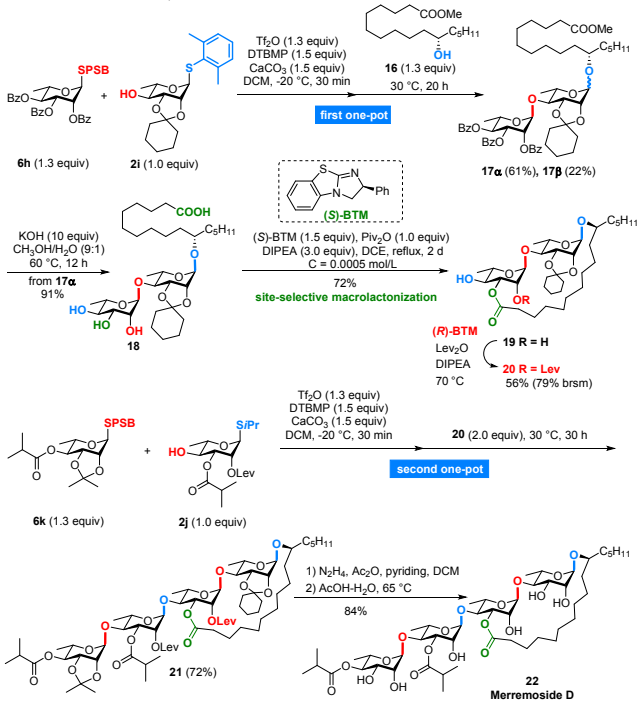
Scheme 3. Total synthesis of kankanoside F



As a final endeavor to demonstrate the utilitarian potential of the protocol, a structurally more complex resin glycoside merremoside D[14] was chose as synthetic target. Merremoside D displayed significant activity capable of transporting Na^+, K^+, and Ca^{2+} ions across human erythrocyte membranes and antiserotonic activity.[15] It possesses a tetra-rhamnose backbone which were connected by 1,4-α-linkages and a 21-membered macrolactone. O'Doherty and co-workers have reported an elegant synthetic route toward the first total synthesis and the structural refinement of Merremoside D by virtue of the *de novo* synthetic strategy.[16] We intended to synthesize this molecular with two key one-pot relay glycosylations. The first one-pot comprised the coupling of SPSB glycoside **6h**, thioglycoside **2i** and a long-chained alcohol, 11(*s*)-jalapinolate **16**. This protocol furnished **17** in overall 83% yield albeit in an α to β ratio of 2.8:1. Further hydrolyzation of the ester groups of **17α** produced acid **18** possessing three continuous free hydroxy groups. The ensuing site-selective macrolactonization of **18** presented as a

large obstacle as witnessed by the failures of known macrolactonization conditions (see the ESI). Draw inspiration from the cation-π interaction mediated site-selective acylation reaction reported by Tang et al,[17] utilization of 1.5 equiv of (*S*)-BTM (benzotetramisole) along with 1.0 equiv of Piv_2O as esterification reagents surprisingly accomplished the site-selective macrolactonization to afford **19** in 72% yield. The following site-selective installing levulinoyl (Lev) group on C2' position was relied on the (*R*)-BTM mediated acylation reaction, which produced **20** readied for the second one-pot reaction. Subsequent second one-pot glycosylation promisingly produced the desired tetrasccharide **21** in 72% yield. Global deprotection eventually furnished the merremoside D (**22**) in 84% yield.

Scheme 4. Total synthesis of merremoside D



In conclusion, we have developed a novel one-pot relay oligosaccharide and glycoconjugate assembly strategy. This strategy relied on the hypothesis that an *in situ* generated cyclic thiosulfonium ion (**B**) from the activation of SPSB glycosides was a mild activator for thioglycosides. Compared to the classical one-pot sequential glycosylation strategies, this strategy highlighted the advantage that only one equivalent of exogenous activator was required for construction of two glycosidic linkages. In a typical activation process, the exogeneous activator Tf_2O activated SPSB glycosides to construct the first glycosidic linkage accompanied by the *in situ* generation of cyclic thiosulfonium ion **B**. The cyclic sulfonium ion then acted as a relay activator for the subsequent activation of thioglycoside at a warmer temperature, consequently created the second glycosidic linkage. Wide range of SPSB glycosides, thioglycosides and terminal sugars or aglycones were well accommodated to the protocol to furnish various liner or branched oligosaccharides. The comprehensively application of this protocol and a sites-elective macrolactonization reaction allowed the expedient synthesis of resin glycoside merremoside D, which extensively demonstrated the potential of this protocol.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website. Experimental procedure, optimization tables and characterization data for all products.

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Notes

The authors declare no competing financial interests.

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