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Remote Activation of Disarmed Thioglycosides in Latent-Active Glycosylation *via* Interrupted Pummerer Reaction

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ABSTRACT: *S*-glycosides, *S*-2-(2-propylthio)benzyl (SPTB) glycosides, were converted to the corresponding oxidized glycosyl donors, *S*-2-(2-propylsulfinyl)benzyl (SPSB) glycosides, by a simple and selective oxidation. Treatment of disarmed SPSB donor and various acceptors with triflic anhydride provided the desired glycosides in good to excellent yields. Meanwhile, the observation of thiosulfinate, thiosulfonate and disulfide suggested that the leaving group was activated *via* an interrupted Pummerer reaction. The disarmed SPSB thioglycosyl donors could be selectively activated in the presence of various thioglycosides with remote activation mode. Finally, two natural hepatoprotective glycosides, Leonoside E and Leonuriside B, were efficiently synthesized in a convergent manner with this newly developed method.

■ INTRODUCTION

Although 1-thioglycosides occur rarely in nature, they are widely used as important glycosylation donors in constructing a broad range of glycosidic linkages.[1] Ever since the first glycosylation reaction with a thioglycosyl donor was reported in 1973,[2] the improvement of corresponding leaving groups, various promoters, different activation conditions and strategies *etc.* has become a prominent subject in carbohydrate research.[3] In most of the reported cases, the initial activation takes place on the anomeric sulfur atom (direct activation),[4] whereas activation of thioglycosides in remote mode is rare.[5] Nearly twenty years ago, Kunz and Leuck employed *S*-pent-4-enyl thioglycosides as donors to construct *O*-glycosyl amino acids.[6] Because soft electrophiles can be either attacked by the anomeric sulfur atom or by the tethered double bond, the real mode of activation remains unsolved. In 2012, based on the success of Yu glycosylation,[7] Yu and co-workers reported an Au(I)-catalyzed glycosylation in a remote activation mode with *ortho*-alkynylphenyl thiolglycosides.[8a] Later, Zhu group succeeded in using *S*-but-3-ynyl thioglycoside as thioglycosyl donor.[8b,c] Most recently, Ragains *et al.* designed a novel *S*-butenyl glycosyl donor, 4-*p*-methoxyphenyl-3-butenylthioglucoside, for a remote activation approach.[8d] In this method, the armed and superarmed *S*-butenyl glycosyl donors could be activated efficiently under visible-light irradiation in the presence of stoichiometric amount of Umemoto's reagent.

Another milestone in this field was made in 1992 by Roy and his colleagues who introduced a latent-active glycosyl synthesis strategy arising from the investigation of *p*-acetamidophenyl thioglycosides and *p*-nitrophenyl thioglycoside.[9] In this strategy, a latent leaving group (LG) is inert to the activation condition of the active LG, and is able to be activated in the subsequent glycosylation under appropriate conditions.[10] In the past twenty years, this concept has been further enriched by Fraser-Reid,[11a] Boons,[11b,c] Kim,[11d] Huang,[11e] Wang,[11f] Demchenko,[11g] Yu[11h] and our own.[11i] The advantage of latent-active strategy may streamline the global efficiency of oligosaccharide assembly process.[10]

Recently, our research laboratories have developed an *O*-benzyl glycoside, *O*-2-(2-propylthio)benzyl (OPTB) glycoside, and an oxidized *O*-benzyl glycoside, *O*-2-(2-propylsulfinyl)benzyl (OPSB) glycoside, which can be employed in the synthesis of oligosaccharides with latent-active concept.[11i] The latent glycosides can be converted to the corresponding active oxidized glycosides by a simple and efficient oxidation.[11c, 11i, 12] Treatment of the oxidized *O*-benzyl glycosides and acceptors with triflic anhydride provided desired glycosidic linkages in good to excellent yields (Scheme 1a). We revealed that the leaving group was remotely activated by an interrupted Pummerer reaction.[13,14,15] Despite significant progress, only armed and superarmed glycosyl donors[16] bearing the oxidized *O*-benzyl leaving group can be successfully activated to unleash the desired oxocarbenium. In contrast, the disarmed glycosides usually yield unproductive side products: intermolecular Pummerer reaction adducts.[17]

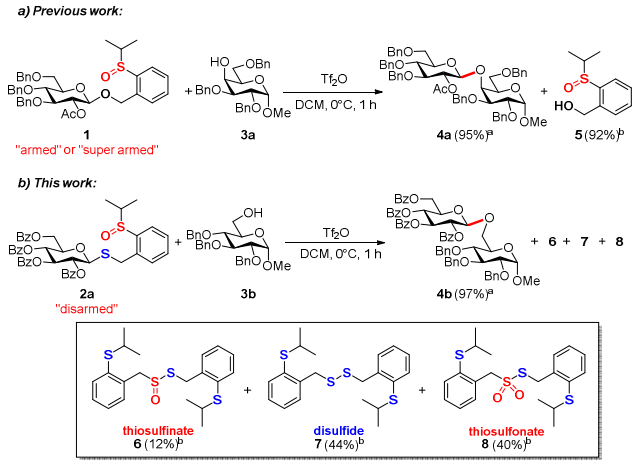
Herein, we disclose a novel strategy combines oxidized *S*-benzyl glycosides, namely *S*-2-(2-propylsulfinyl)benzyl glycosides (SPSB), and remote activation *via* interrupted Pummerer reaction to efficiently construct glycosidic bonds with disarmed glycosyl donors. In this report, we will provide detailed information about a strategy for selective thioether oxidation, mechanistic studies of remote activation, the scope of this glycosylation, and convergent assemblies of Leonuriside B and Leonoside E.[18]

■ RESULTS AND DISCUSSION

First, we evaluated the reactivity of the oxidized *S*-benzyl glycosyl donor **2a** with glycosyl acceptor **3b**. Following a previously established activation protocol for superarmed OPSB glycosyl donor **1**, triflic anhydride (Tf_2O, 1.2 equiv)

was added to a solution of **2a** (1.2 equiv) and **3b** (1.0 equiv) in CH_2Cl_2 in the presence of 4 Å molecular sieves (M.S.) at 0 °C. The reaction completed in 30 min and provided the desired disaccharide **4b** in 97% yield, along with compounds **6-8** derived from glycosyl donor's leaving group (scheme 1b). After a thorough investigation, the side products were assigned as thiosulfinate **6** (12%), symmetric disulfide **7** (44%) and thiosulfonate **8** (40%), the combined yield of these materials related to the leaving group PSB-SH is 96%. These results indicated that the disarmed SPSB glycoside is an eligible glycosyl donor, but the mechanism of activation may be much more complex compare to those of OPSB glycosyl donor[11i] and traditional anomeric sulfoxide donors.[19,20,21]

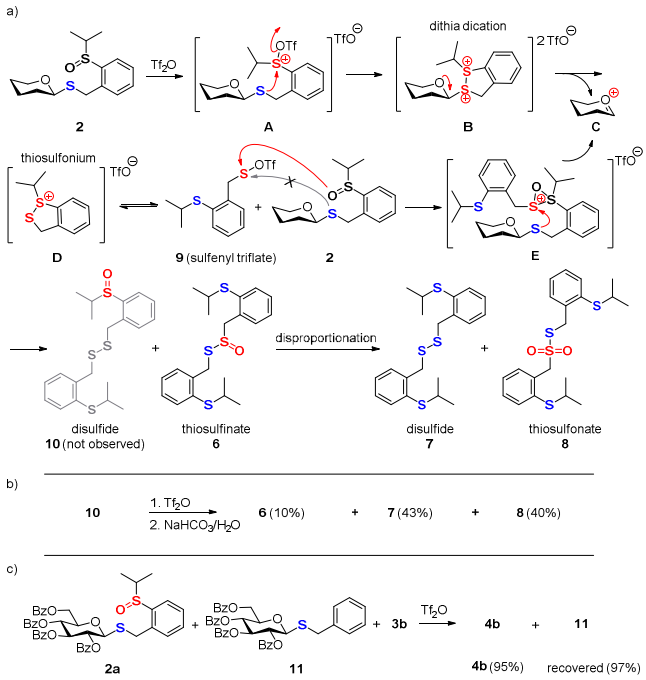
Scheme 1. Remote Activation of Oxidized *O*/*S*-benzyl Glycosides



[a] Yield of isolated product based on the amount of acceptor. [b] Yield of isolated product based on the amount of donor.

In 1989, Kahne's group reported a successful glycosylation reaction with glycosyl sulfoxides as donors.[22a] Since then, application of sulfoxide donors and related sulfonate reagents in chemical glycosylation has become an intensely pursued research area. Many outstanding reactions (Kahne glycosylation,[22a] Crich β-mannosylation,[22b] Gin oxidative glycosylation[22c] and Gin dehydrative glycosylation[22d]) have been established in this field. Based on the elegant mechanistic investigations of the previous reports,[20] a proposed activation pathway of SPSB donors is illustrated in Scheme 2a. The first step of the reaction is the activation of phenyl sulfoxide by triflic anhydride to form a trifloxylsulfonium ion **A**. The attack of anomeric sulfur atom to the cationic sulfur atom leads to a dithia dication species[23] **B** *via* an interrupted Pummerer reaction.[24] Intermediate **B** subsequently generates the key oxocarbenium ion **C** and a thiosulfonium ion **D** which is equivalent to benzyl sulfenyl triflate **9**.[25] Usually, sulfenyl triflates are powerful electrophiles[1a] and they react with the sulfoxide more rapidly than Tf_2O.[20a] Thus, a putative sulfonium ion **E** is possibly formed. The anomeric sulfur atom of intermediate **E** then attacks the less hindered cationic sulfur, resulting asymmetric disulfide **10** and thiosulfinate **6,** which may be accountable for the generation of disulfide **7** and thiosulfonate **8** *via* a disproportionation.[26] Given no direct observation of compound **10** in the reaction mixture, we synthesized **10** according to Scheme S1. Upon treatment with Tf_2O and standard work-up, compounds **6**, **7** and **8** were isolated in a similar ratio to that in the glycosylation reaction (Scheme 2b). These observations suggested that the *in situ* produced disulfide **10** is a possible precursor of products **6**, **7** and **8**.[27] We then investigated that whether the anomeric thioether could be activated by intermediate **D** or **9** by a competitive glycosylation reaction between two thioglycosyl donors **2a** and **11** in the presence of **3b** and 1.0 equivalent of Tf_2O at 0 °C (Scheme 2c). As expects, disaccharide **4b** was isolated in 95% yield accompanied with 97% recovered **11**. These results clearly indicated that the glycosyl donor was activated in a tandem fashion initiated from the remote sulfur atom rather than directly activation at the anomeric sulfur atom.

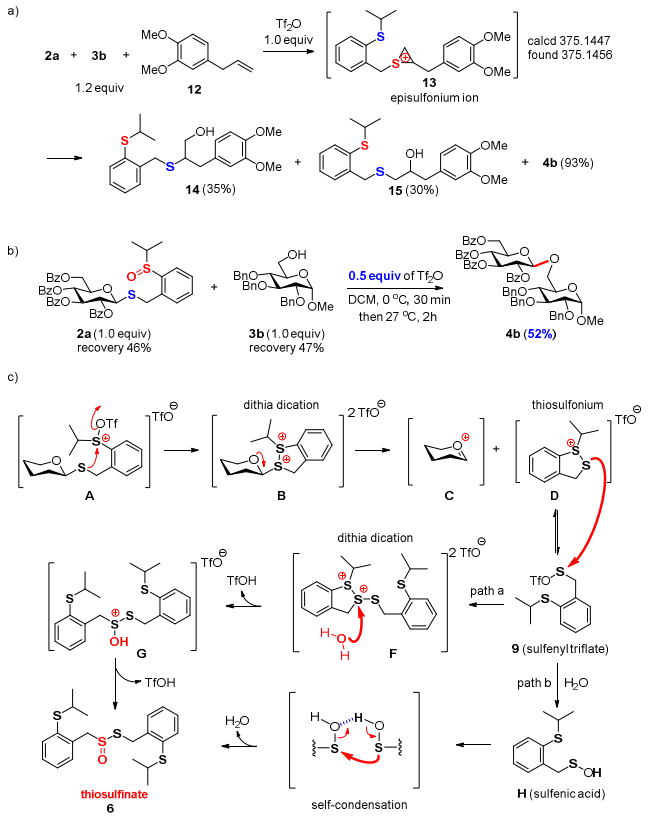
Scheme 2. Original Hypothesis for Activation



The species **9** and its equivalent, thiosulfonium **D**, were proposed as key active species in the aforementioned mechanistic proposal. The evidences for the formation of these reactive intermediates were obtained by a trapping experiment (Scheme 3a).[20c] When scavenger **12** was added to the glycosylation mixture, episulfonium **13** was detected by high-resolution MS and subsequent hydrolysis led to the formation of compound **14** (35%) and **15** (30%). In this experiment, we were pleased to find that the glycosidic bond generation was not disturbed by addition of the scavenger, which made **12** an excellent additive for sensitive substrates. Based on the proposed activation mode (scheme 2a), it would be possible to use substoichiometric Tf_2O for the glycosylation reaction.[28] However, when triflic anhydride was reduced to 0.5 equivalent, the glycosylation proceeded in 52% yield, and 46% of SPSB donor **2a** and 47% of acceptor **3b** were recovered (Scheme 3b). These results indicated that Tf_2O is the predominant activator in the glycosylation. Despite highly reactive towards scavenger **12**, benzyl sulfenyl triflate **9** and thiosulfonium intermediate **D** are much less effective than Tf2O in terms of promoting the desired glycosylation. In light of these findings, we propose that Tf_2O first activates the SPSB donor and the resulting dithia dication ion **B** decomposes to generate oxocarbenium ion **C** and thiosulfonium ion **D** (Scheme 3c). Subsequent condensation between thiosulfonium ion **D** and sulfenyl triflate **9** provides a new dithia dication ion **F** (path a), which is respon-

sible for the formation of thiosulfinate **6** upon aqueous work-up. The sulfenyl triflate **9** could be also hydrolyzed during the quenching process to form corresponding sulfenic acid **H**. It is well know that sulfenic acid condense with themselves to form thiosulfinate **6** (path b).[29] The same disproportionation reaction provides symmetric disulfide **7** and thiosulfonate **8**.

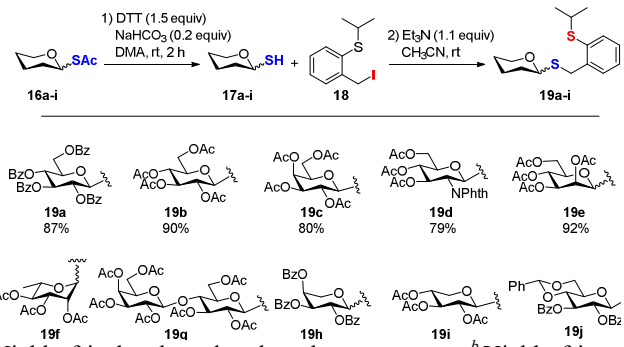
Scheme 3. Preliminary Mechanistic Proposal



After mechanistic investigation, we turned our attention to evaluate the application potentials of our methodology. The preparation of latent *S*-2-(2-propylthio)benzyl (SPTB) glycosides **19a-j**, and active SPSB glycosides **2a-j** were outlined in table 1 and table 2. Following the procedure recently developed by our group,[30] the *S*-acetyl group of **16a-i** was selectively removed by transthioesterification with 1.5 equivalent of 1,4-dithiothreitol (DTT) in the presence of catalytic amount of $NaHCO_3$ in DMA. Then the resulting glycosyl thiols **17a-i** was *S*-alkylated with benzyl iodide **18** under basic condition. In two steps, the disarmed SPTB glycosides **19a-i** were prepared with good to excellent yields. The benzylidene acetal protected SPTB glycoside **19j** was prepared from **19b** following routine protecting group manipulations in three steps.

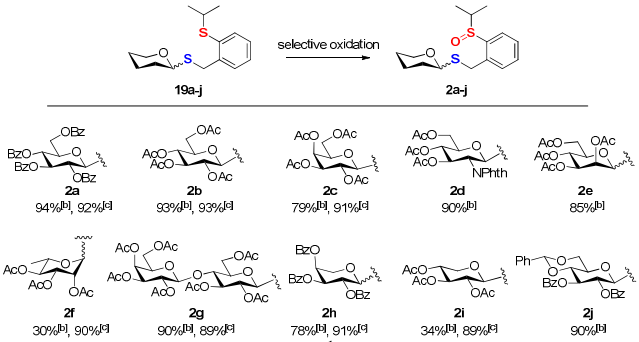
With latent SPTB glycosides **19a-j** in hand, we began to investigate selective oxidation of the phenyl thioethers. In our previous work, we have demonstrated that OPTB glycoside could be selectively oxidized to the corresponding OPSB glycosyl donor leaving an *S*-methyl group intact by PIFA (1.2 equiv).[17] Although it is a daunting task to differentiate a phenyl thioether group from an anomeric methyl thioether group, we were delight to find that the desired SPSB glycosides **2a-j** could be prepared smoothly by selective oxidation with PIFA or *m*-CPBA.[31]

Table 1. Preparation of Thiobenzyl Glycosides: *S*-2-(2-propylthio)benzyl Glycosides.[a]



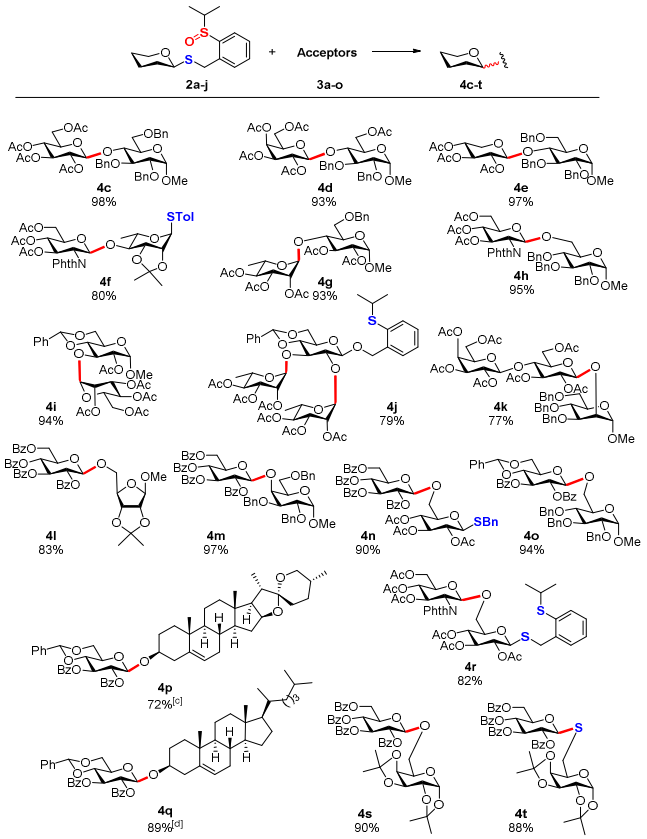
[a] Yield of isolated product based on two steps. [b] Yield of isolated product based on three steps from **19b**: 1) K_2CO_3 (0.3 equiv), MeOH, rt, 1 h, 2) CSA (0.2 equiv), $PhCH(OCH_3)_2$ (1.2 equiv), dry CH_3CN, overnight, 3) BzCl (2.4 equiv), NEt_3 (3.0 equiv), DMAP (0.1 equiv), dry CH_2Cl_2. DTT = 1,4-dithiothreitol, DMA = dimethylacetamide, CSA = camphorsulfonic acid, BzCl = benzoyl chloride.

Table 2. Preparation of Oxidized Thiobenzyl Glycosides: *S*-2-(2-propylsulfinyl)benzyl Glycosides.[a]



[a] Yield of isolated product. [b] PIFA (1.0-1.2 equiv), wet CH_3CN, rt, 10 min. [c] *m*-CPBA (1.0 equiv), dry CH_2Cl_2, -20 °C, 30 min. PIFA = bis(trifluoroacetoxy)iodobenzene, *m*-CPBA = 3-chloroperbenzoic acid.

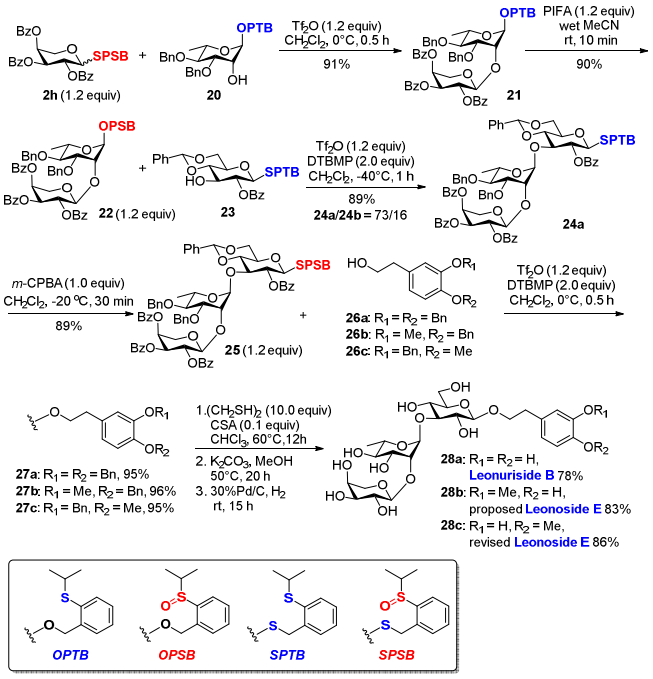
Table 3. Scope of Reaction.[a,b]



[a] Yield of isolated product, **2** (1.2 equiv). [b] Tf_2O (1.2 equiv) was added to the mixture of the glycosyl donor and the acceptor in DCM, 0 °C, 30 min. [c] Tf_2O (1.2 equiv) was added to the solution of glycosyl donor, ADMB (3.0 equiv) and DTBMP at 0°C, followed by the addition of acceptor. [d] Additional DTBMP (1.2 equiv) was used. DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine, ADMB = 4-allyl-1,2-dimethoxybenzene.

Next, we investigated the scope of this new glycosylation method by coupling of a variety of disarmed SPSB donors **2a-j** with different acceptors (oxo- and mecapto-nucleophiles, table S4). Many glycosidic bonds could be formed between the newly developed disarmed glycosyl donors (Glu **2b**, Gal **2c**, 2-amino-Glu 2**d**, Man **2e**, *L*-Rha **2f**, lactose **2g** and Xyl **2i**) and acceptors (natural occurring steroids, Glu$^{o\text{-}2}$, Glu$^{o\text{-}3}$, Glu$^{o\text{-}4}$, Glu$^{o\text{-}6}$, Rha$^{o\text{-}4}$ and Man$^{o\text{-}2}$, Ribofuranose$^{o\text{-}5}$, Gal$^{o\text{-}6}$ and even Gal$^{s\text{-}6}$) in good to excellent yields. From these examples, it is worth noting that: I) there are some acetyl group migrations between the donors and acceptors (primary alcohols), and replacement of the acetyl groups by benzoyl groups inhibited these side reactions (**4l**, **4n**, **4o**, **4s** and **4t**); II) the less reactive nucleophiles such as **3a**, **3e** and **3g** could be glycosylated in excellent yields; III) acid sensitive groups such as acetonide (**4f**, **4l**, **4s** and **4t**) and benzylidene (**4i**, **4j** and **4o**) were tolerable under current conditions; IV) the thioether groups (**4f**, **4j**, **4n**, **4r** and **4t**) remained intact during the glycosylation; V) the formation of **4t** represented a rare but efficient transthioglycosylation which was hard to achieve by traditional methods;[32,1b] VI) in certain cases, when the acceptors were highly sensitive to electrophiles (diosgenin and cholesterol etc.), the sulfenyl triflate scavenger **12** was required for optimal yield (**4p**); VII) most reactions were carried out at 0 °C rather than -78 °C, a common practice for complex carbohydrate synthesis;[21] and VIII) there was no unpleasant odor released from the reaction. Most importantly, the oxidized SPSB glycosyl donors were able to couple with thioglycoside, *O*-PTB glycoside and *S*-PTB glycoside to yield corresponding new glycosyl donors (**4f** and **4n**) or latent *O/S* benzyl glycosides (**4j** and **4r**), which could be used in the subsequent glycosylation.

Scheme 4. Completion of Total Synthesis of Leonuriside B (28a) and Leonoside E (28c)



To further demonstrate the power of this new glycosyl donor in the synthesis of complex oligosaccharides, we embarked the total synthesis of Leonoside E, and Leonuriside B (scheme 4). Leonoside E, F and Leonuriside B were isolated from Chinese motherwort (*Leonurus japonicus* Houtt).[18] These three natural products bear a trisaccharide moiety and a phenylethanoid aglycon. Recently, we have reported a total synthesis and structural revision of leonoside F, a branched trisaccharide, with latent and active *O*-benzyl glycosides.[11i] Unfortunately, we failed to prepare leonoside E, a linear trisaccharide, with the same strategy because disarmed oxidized *O*-benzyl donor was not able to be activated properly. This time, a convergent [3+1] approach and two pairs of latent-active glycosides are incorporated into our retrosynthesis design. First, the active L-arabinosyl SPSB glycoside **2h** was coupled with the latent L-rhamnosyl OPTB glycoside **20** under the standard reaction condition to form the α-(1-›2)-disaccharide **21** (91%), which was then oxidized to the active armed OPSB glycosyl donor **22** (90%) by the hypervalent iodine reagent. The resulting active OPSB donor **22** was coupled with the latent SPTB glycoside **23** in the presence of triflic anhydride and a bulky base (DTBMP) to give α-(1-›3)-trisaccharide **24a** (73%) along with an unwanted β-(1-›3)-trisaccharide **24b** (16%). The latent trisaccharide **24a** was then selectively oxidized to SPSB donor **25** (89%) by treatment of *m*-CPBA at -20°C. Subsequent glycosylations between the active SPSB donor **25** and aglycons (**26a-c**) in a convergent manner produced the phenylethanoid trisaccharides **27a** (95%), **27b** (96%) and **27c** (95%), respec-

tively. Finally, global deprotection furnished the leonuriside B (**28a**, 78%), proposed leonoside E (**28b**, 83%) and revised leonoside E (**28c**, 86%) in three steps.[33]

■ CONCLUSIONS

We have discovered *S*-2-(2-propylsulfinyl)benzyl (SPSB) glycoside as a novel glycosyl donor which can be efficiently activated in a tandem remote mode. The SPSB glycoside can be derived from the corresponding SPTB glycoside by an efficient and selective oxidation. By employing *S*-2-(2-propylsulfinyl)benzyl (SPSB) group as a new leaving group, glycosylations of disarmed glycosyl donors are successfully achieved. Integration of OPSB leaving group and this newly discovered SPSB leaving group allows rapid oligosaccharide assembly by latent-active strategy. Finally, we have demonstrated that this novel methodology is applicable to natural product syntheses in a convergent manner.

ASSOCIATED CONTENT

Experimental details, ^{1}H and ^{13}C NMR spectra for all new compounds, and 2D NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Author Contributions

All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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(27) A plausible mechanism was proposed. For details, see the Supporting Information (Scheme S2).

(28) In a seminal work reported by Kahne *et al*., only substoichiometric Tf_2O was required for the fully consumption of glycosyl phenylsulfoxide donor. See reference 20c.

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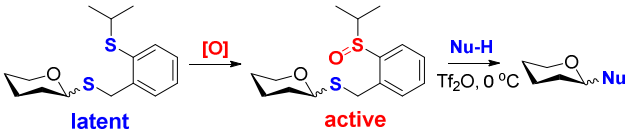
(32) Crich, D.; Li, H. *J. Org. Chem.* **2000**, *65*, 801-805.

(33) Detailed comparisons of NMR data see the Supporting Information (Table S5 and Table S6).



- remote activation
- latent-active synthesis strategy
- odorless
- intramolecular interrupted Pummerer reaction