JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

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

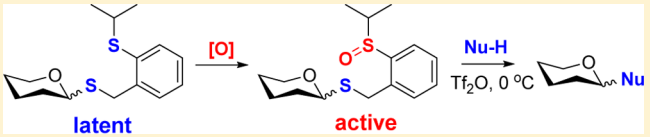
Xiong Xiao,[†] Yueqi Zhao,[†] Penghua Shu,[†] Xiang Zhao,[†] Yan Liu,[†] Jiuchang Sun,[†] Qian Zhang,[†] Jing Zeng,[†] and Qian Wan*[,†,‡]

[†]Hubei Key Laboratory of Natural Medicinal Chemistry and Resource Evaluation, School of Pharmacy, Huazhong University of Science and Technology, 13 Hangkong Road, Wuhan, Hubei 430030, People's Republic of China

[‡]Institute of Brain Research, Huazhong University of Science and Technology, 13 Hangkong Road, Wuhan, Hubei 430030, People's Republic of China

Supporting Information

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 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, 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] improvement of corresponding leaving groups (LGs), various promoters, different activation conditions and strategies, and so forth 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 20 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 attacked by either the anomeric sulfur atom or by the tethered double bond, the real mode of activation remains unsolved. In 2012, on the basis of the success of Yu glycosylation,[7] Yu and co-workers reported Au(I)-catalyzed glycosylation in a remote activation mode with *ortho*-alkynylphenyl thiolglycosides.[8a] Later, Zhu's group succeeded in using *S*-but-3-ynyl thioglycoside as the 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 a 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 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 20 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 us.[11i] The advantage of the latent-active strategy may streamline the global efficiency of the oligosaccharide assembly process.[10]

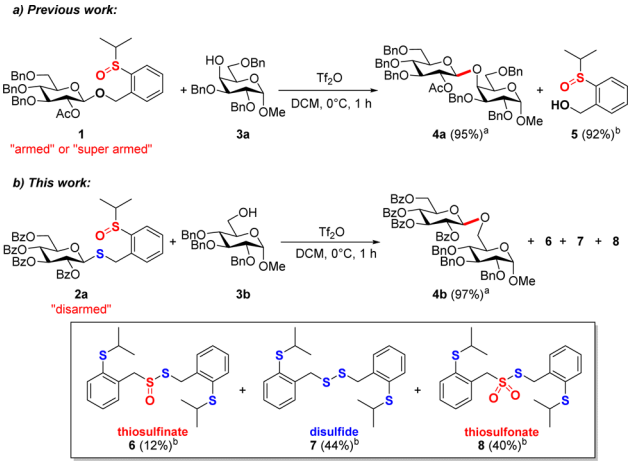
Recently, our research laboratories have developed an *O*-benzyl glycoside, *O*-2-(2-propylthio)benzyl (OPTB) glycoside, and an oxidized *O*-benzyl glycoside, *O*-2-(2-propylsulfinyl)-benzyl (OPSB) glycoside, which can be employed in the synthesis of oligosaccharides with the latent-active concept.[11i] The latent glycosides can be converted to the corresponding active oxidized glycosides by simple and efficient oxidation.[11c,i,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 LG was remotely activated by an interrupted Pummerer reaction.[13−15] Despite significant progress, only armed and superarmed glycosyl donors[16] bearing the oxidized *O*-benzyl LG 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 that 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

Received: August 9, 2016
Published: September 12, 2016

DOI: 10.1021/jacs.6b08305
J. Am. Chem. Soc. 2016, 138, 13402−13407

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.

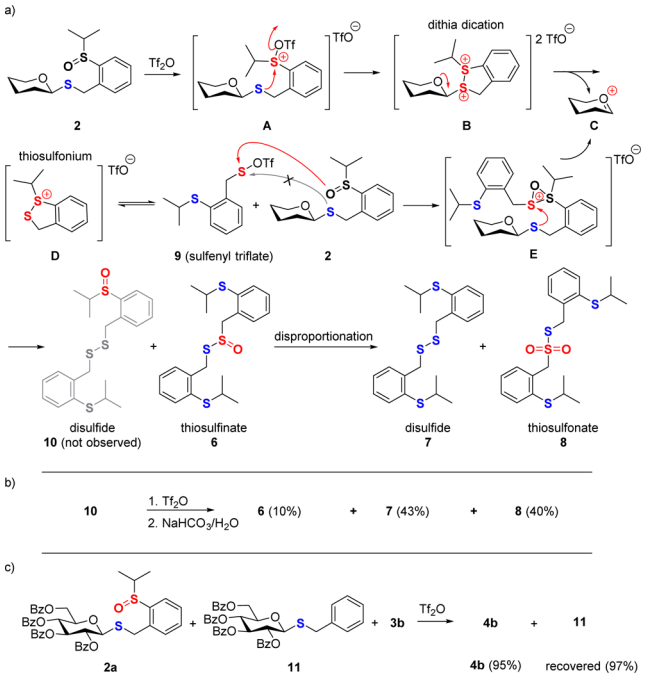
glycosyl donors. In this report, we will provide detailed information about a strategy for selective thioether oxidation, mechanistic studies of remote activation, the scope of this glycosylation, and convergent assemblies of Leonuriside B and Leonoside E.[18]

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 1 h and provided the desired disaccharide **4b** in 97% yield, along with compounds **6**–**8** derived from the glycosyl donor's LG (Scheme 1b). After 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 LG 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 compared to those of the OPSB glycosyl donor[11i] and traditional anomeric sulfoxide donors.[19−21]

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. On the basis of 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 the anomeric sulfur atom on 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

Scheme 2. Original Hypothesis for Activation

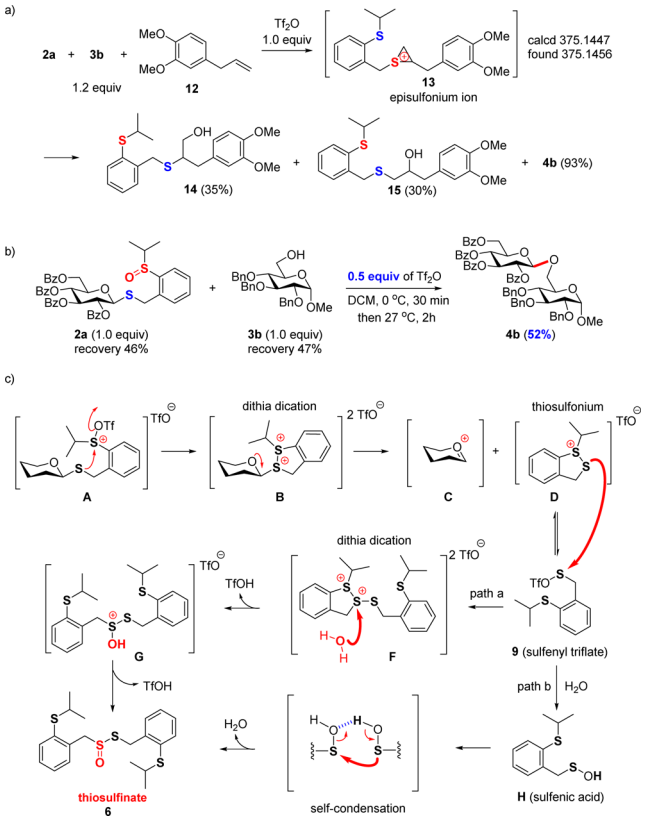


triflates are powerful electrophiles[1a] and they react with the sulfoxide more rapidly than Tf_2O.[20a] Thus, a putative sulfonium ion **E** is possibly formed. The anomeric sulfur atom of intermediate **E** then attacks the less hindered cationic sulfur, resulting in asymmetric disulfide **10** and thiosulfinate **6**, which may be accountable for the generation of disulfide **7** and thiosulfonate **8** via 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 workup, compounds **6**–**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**–**8**.[27] We then investigated 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 equiv of Tf_2O at 0 °C (Scheme 2c). As expected, disaccharide **4b** was isolated in 95% yield accompanied by 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 direct activation at the anomeric sulfur atom.

Species **9** and its equivalent, thiosulfonium **D**, were proposed as key active species in the aforementioned mechanistic proposal. Evidence for the formation of these reactive intermediates was 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 compounds **14** (35%) and **15** (30%). In this experiment, we were pleased to find that glycosidic bond generation was not disturbed by addition of the scavenger, which made **12** an excellent additive for sensitive substrates. On the basis of 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 equiv, the glycosylation proceeded in 52% yield and 46% of SPSB donor **2a** and 47% of

DOI: 10.1021/jacs.6b08305
J. Am. Chem. Soc. 2016, 138, 13402−13407

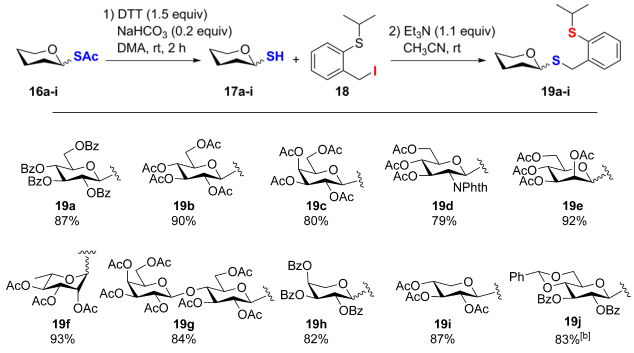
Scheme 3. Preliminary Mechanistic Proposal



acceptor **3b** were recovered (Scheme 3b). These results indicated that Tf_2O is the predominant activator in the glycosylation. Despite being highly reactive toward scavenger **12**, benzyl sulfenyl triflate **9** and thiosulfonium intermediate **D** are much less effective than Tf_2O in terms of promoting the desired glycosylation. In light of these findings, we propose that Tf_2O first activates the SPSB donor and then 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 responsible for the formation of thiosulfinate **6** upon aqueous workup. The sulfenyl triflate **9** could be also hydrolyzed during the quenching process to form corresponding sulfenic acid **H**. It is well known that sulfenic acids condense with themselves to form thiosulfinate **6** (path b).[29] The same disproportionation reaction provides symmetric disulfide **7** and thiosulfonate **8**.

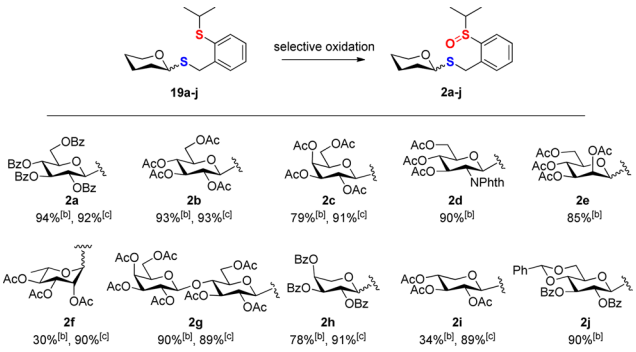
After mechanistic investigation, we turned our attention to evaluate the application potentials of our methodology. The preparation of latent *S*-2-(2-propylthio)benzyl (SPTB) glycosides **19a−j** and active SPSB glycosides **2a−j** are outlined in Tables 1 and 2. Following the procedure recently developed by our group,[30] the *S*-acetyl groups of **16a−i** were selectively removed by transthioesterification with 1.5 equiv of 1,4-dithiothreitol (DTT) in the presence of a catalytic amount of $NaHCO_3$ in DMA. Then, the resulting glycosyl thiols **17a−i** were *S*-alkylated with benzyl iodide **18** under basic conditions. 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.

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]



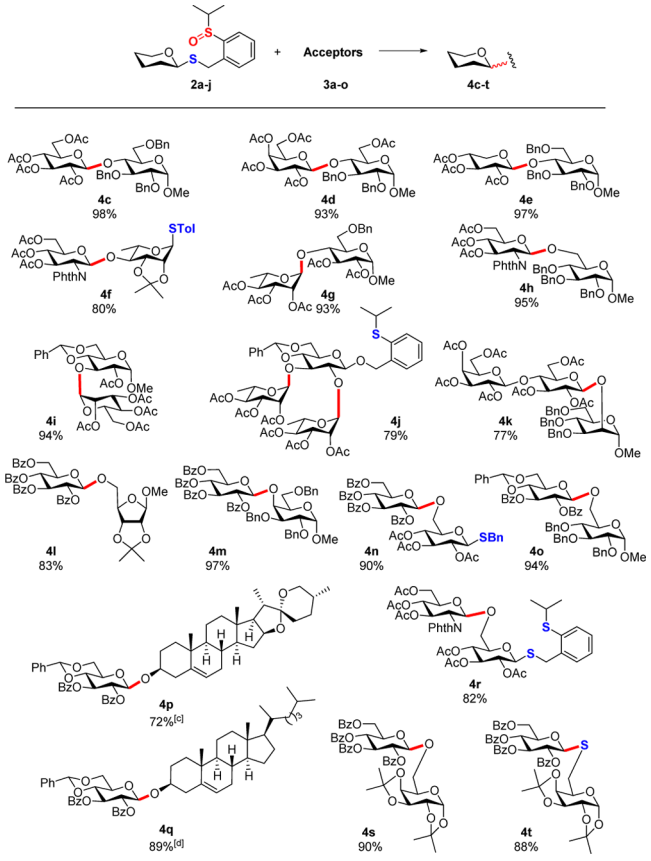
[a]Yield of isolated product. [b]PIFA (1.0−1.2 equiv), wet CH_3CN, rt, 10 min. [c]*m*-CPBA (1.0 equiv), dry CH_2Cl_2, −20 °C, 30 min. PIFA = bis(trifluoroacetoxy)iodobenzene, *m*-CPBA = 3-chloroperbenzoic acid.

With latent SPTB glycosides **19a−j** in hand, we began to investigate selective oxidation of the phenyl thioethers. In our previous work, we 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 delighted to find that the desired SPSB glycosides **2a−j** could be prepared smoothly by selective oxidation with PIFA or *m*-CPBA.[31]

Next, we investigated the scope of this new glycosylation method (see Table 3) 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 **2d**, Man **2e**, L-Rha **2f**, lactose **2g**, and Xyl **2i**) and acceptors (natural occurring steroids, $Glu^{o\text{-}2}$, $Glu^{o\text{-}3}$, $Glu^{o\text{-}4}$, $Glu^{o\text{-}6}$, $Rha^{o\text{-}4}$, $Man^{o\text{-}2}$, $Ribofuranose^{o\text{-}5}$, $Gal^{o\text{-}6}$, 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

DOI: 10.1021/jacs.6b08305
J. Am. Chem. Soc. 2016, 138, 13402−13407

Table 3. Scope of Reaction[a,b]

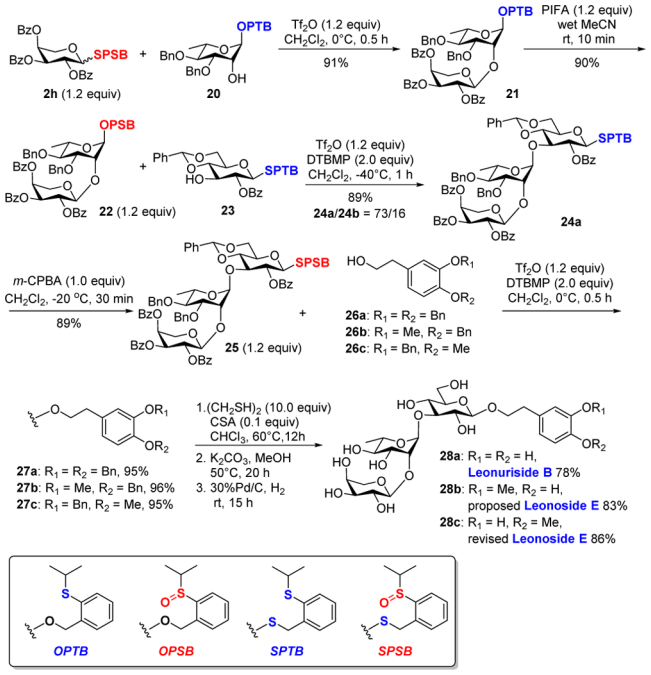


[a]Yield of isolated product, **2** (1.2 equiv). [b]Tf_2O (1.2 equiv) was added to the mixture of the glycosyl donor and the acceptor in DCM, 0 °C, 30 min. [c]Tf_2O (1.2 equiv) was added to the solution of glycosyl donor, ADMB (3.0 equiv), and DTBMP at 0 °C, followed by the addition of acceptor. [d]Additional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

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, 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.

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

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



aglycon. Recently, we 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 were 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 conditions 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%), respectively. 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 that can be efficiently activated in a tandem remote mode. The SPSB glycoside can be derived from the corresponding SPTB glycoside by efficient and selective oxidation. By employing the SPSB group as a new LG, glycosylations of disarmed glycosyl donors are successfully achieved. Integration of OPSB LG and this newly discovered SPSB LG allows rapid oligosaccharide assembly by the latent-active strategy. Finally, we have demonstrated that this novel

DOI: 10.1021/jacs.6b08305
J. Am. Chem. Soc. 2016, 138, 13402−13407

methodology is applicable to natural product syntheses in a convergent manner.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b08305.

Experimental details, ^{1}H and ^{13}C NMR spectra for all new compounds, and 2D NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*wanqian@hust.edu.cn

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This research is partially supported by the National Natural Science Foundation of China (21272082, 21402055, 21472054), the State Key Laboratory of Bio-organic and Natural Products Chemistry (SKLBNPC13425), Natural Science Funds of Hubei Province for Distinguished Young Scholars (2015CFA035), "Thousand Talents Program" Young Investigator Award, Wuhan Creative Talent Development Fund, the Fundamental Research Funds for the Central Universities, and Huazhong University of Science and Technology (2014ZZGH015). We thank Professor Suwei Dong (Peking University) and Professor Yu Yuan (University of Central Florida) for helpful discussions. This paper is dedicated to Professor Samuel J. Danishefsky on the occasion of his 80th birthday.

■ REFERENCES

(1) (a) Lian, G.; Zhang, X.; Yu, B. *Carbohydr. Res.* **2015**, *403*, 13−22. (b) Pachamuthu, K.; Schmidt, R. R. *Chem. Rev.* **2006**, *106*, 160−187. (c) Zhong, W.; Boons, G.-J. In *Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance*; Demchenko, A. V., Ed.; Wiely-VCH: Weiheim, Germany, 2008; pp 261−303.

(2) Ferrier, R. J.; Hay, R. W.; Vethaviyasar, N. *Carbohydr. Res.* **1973**, *27*, 55−61.

(3) Selected reviews: (a) Zhu, X. M.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900−1934. (b) Codée, J. D. C.; Litjens, R. R. J. N.; van den Bos, L. J.; Overkleeft, H. S.; van der Marel, G. A. *Chem. Soc. Rev.* **2005**, *34*, 769−782.

(4) Selected references: (a) Yu, Y.; Xiong, D.-C.; Mao, R.-Z.; Ye, X.-S. *J. Org. Chem.* **2016**, *81*, 7134−7138. (b) Mao, R.-Z.; Xiong, D.-C.; Guo, F.; Li, Q.; Duan, J.; Ye, X.-S. *Org. Chem. Front.* **2016**, *3*, 737−743. (c) Goswami, M.; Ashley, D. C.; Baik, M.-H.; Pohl, N. L. B. *J. Org. Chem.* **2016**, *81*, 5949−5962. (d) Mao, R.-Z.; Guo, F.; Xiong, D.-C.; Li, Q.; Duan, J.; Ye, X.-S. *Org. Lett.* **2015**, *17*, 5606−5609. (e) Chu, A.-H. A.; Minciunescu, A.; Bennett, C. S. *Org. Lett.* **2015**, *17*, 6262−6265. (f) Goswami, M.; Ellern, A.; Pohl, N. L. B. *Angew. Chem., Int. Ed.* **2013**, *52*, 8441−8445.

(5) Selected Reviews: (a) Ranade, S. C.; Demchenko, A. V. *J. Carbohydr. Chem.* **2013**, *32*, 1−43. (b) El Ashry, E. S. H.; Awad, L. F.; Atta, A. I. *Tetrahedron* **2006**, *62*, 2943−2998. Selected references: (c) Kaeothip, S.; Pornsuriyasak, P.; Rath, N. P.; Demchenko, A. V. *Org. Lett.* **2009**, *11*, 799−802. Note: in the literature, the remote activating sites are usually less than 3 bonds far away from the anomeric position.

(6) Leuck, M.; Kunz, H. *J. Prakt. Chem./Chem.-Ztg.* **1997**, *339*, 322−334.

(7) Li, Y.; Yang, Y.; Yu, B. *Tetrahedron Lett.* **2008**, *49*, 3604−3608.

(8) (a) Yang, F.; Wang, Q.; Yu, B. *Tetrahedron Lett.* **2012**, *53*, 5231−5234. (b) Adhikari, S.; Baryal, K. N.; Zhu, D.; Li, X.; Zhu, J. *ACS Catal.* **2013**, *3*, 57−60. (c) Adhikari, S.; Li, X.; Zhu, J. *J. Carbohydr. Chem.* **2013**, *32*, 336−359. (d) Spell, M. L.; Deveaux, K.; Bresnahan, C. G.; Bernard, B. L.; Sheffield, W.; Kumar, R.; Ragains, J. R. *Angew. Chem., Int. Ed.* **2016**, *55*, 6515−6519. The active sites are located at least 3 bonds far away from the anomeric position.

(9) Roy, R.; Andersson, F. O.; Letellier, M. *Tetrahedron Lett.* **1992**, *33*, 6053−6056.

(10) Shiao, T. C.; Roy, R. *Top. Curr. Chem.* **2011**, *301*, 69−108.

(11) (a) A similar approach, sidetracking the glycosyl synthesis strategy, was introduced in 1990: Fraser-Reid, B.; Wu, Z.; Udodong, U. E.; Ottosson, H. *J. Org. Chem.* **1990**, *55*, 6068−6070. (b) Boons, G.-J.; Isles, S. *Tetrahedron Lett.* **1994**, *35*, 3593−3596. (c) Fang, T.; Mo, K.-F.; Boons, G.-J. *J. Am. Chem. Soc.* **2012**, *134*, 7545−7552. (d) Kim, K. S.; Kim, J. H.; Lee, Y. J.; Lee, Y. J.; Park, J. *J. Am. Chem. Soc.* **2001**, *123*, 8477−8481. (e) Huang, L.; Wang, Z.; Huang, X. *Chem. Commun.* **2004**, 1960−1961. (f) Wang, P.; Haldar, P.; Wang, Y.; Hu, H. *J. Org. Chem.* **2007**, *72*, 5870−5873. (g) Hasty, S. J.; Kleine, M. A.; Demchenko, A. V. *Angew. Chem., Int. Ed.* **2011**, *50*, 4197−4201. (h) Chen, X.; Shen, D.; Wang, Q.; Yang, Y.; Yu, B. *Chem. Commun.* **2015**, *51*, 13957−13960. (i) Shu, P.; Xiao, X.; Zhao, Y.; Xu, Y.; Yao, W.; Tao, J.; Wang, H.; Yao, G.; Lu, Z.; Zeng, J.; Wan, Q. *Angew. Chem., Int. Ed.* **2015**, *54*, 14432−14436.

(12) (a) Sliedregt, L. A. J. M.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1994**, *35*, 4015−4018. (b) He, X.; Chan, T. H. *Synthesis* **2006**, *2006*, 1645−1651.

(13) For the concept of interrupted Pummerer reaction, see: (a) Bates, D. K.; Winters, R. T.; Picard, J. A. *J. Org. Chem.* **1992**, *57*, 3094−3097. (b) Bates, D. K.; Xia, M. *J. Org. Chem.* **1998**, *63*, 9190−9196. (c) Bates, D. K.; Sell, B. A.; Picard, J. A. *Tetrahedron Lett.* **1987**, *28*, 3535−3538.

(14) Selected reviews: (a) Bur, S. C.; Padwa, A. *Chem. Rev.* **2004**, *104*, 2401−2432. (b) Smith, L. H. S.; Coote, S. C.; Sneddon, H. F.; Procter, D. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 5832−5844. (c) Akai, S.; Kita, Y. *Top. Curr. Chem.* **2007**, *274*, 35−76. (d) Feldman, K. S. *Tetrahedron* **2006**, *62*, 5003−5034. (e) De Lucchi, O.; Miotti, U.; Modena, G. *Organic Reactions* **1991**, *40*, 157−405. (f) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717−1760.

(15) Selected recent applications: (a) Fernández-Salas, J. A.; Eberhart, A. J.; Procter, D. J. *J. Am. Chem. Soc.* **2016**, *138*, 790−793. (b) Eberhart, A. J.; Shrives, H.; Zhang, Y.; Carrër, A.; Parry, A. V.; Tate, D. J.; Turner, M. L.; Procter, D. J. *Chem. Sci.* **2016**, *7*, 1281−1285. (c) Eberhart, A. J.; Shrives, H. J.; Álvarez, A.; Carrër, A.; Zhang, Y.; Procter, D. J. *Chem. - Eur. J.* **2015**, *21*, 7428−7434. (d) Murakami, K.; Yorimitsu, H.; Osuka, A. *Angew. Chem., Int. Ed.* **2014**, *53*, 7510−7513. (e) Huang, X.; Maulide, N. *J. Am. Chem. Soc.* **2011**, *133*, 8510−8513. (f) Eberhart, A. J.; Procter, D. J. *Angew. Chem., Int. Ed.* **2013**, *52*, 4008−4011. (g) Eberhart, A. J.; Cicoira, C.; Procter, D. J. *Org. Lett.* **2013**, *15*, 3994−3997. (h) Kobatake, T.; Fujino, D.; Yoshida, S.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2010**, *132*, 11838−11840.

(16) For the concept of armed−disarmed glycosyl donors, see: (a) Mydock, L. K.; Demchenko, A. V. *Org. Lett.* **2008**, *10*, 2107−2110. (b) Fraser-Reid, B.; López, J. C. *Top. Curr. Chem.* **2011**, *301*, 1−29.

(17) Shu, P.; Yao, W.; Xiao, X.; Sun, J.; Zhao, X.; Zhao, Y.; Xu, Y.; Tao, J.; Yao, G.; Zeng, J.; Wan, Q. *Org. Chem. Front.* **2016**, *3*, 177−183.

(18) (a) Sugaya, K.; Hashimoto, F.; Ono, M.; Ito, Y.; Masuoka, C.; Nohara, T. *Food Sci. Technol. Int., Tokyo* **1998**, *4*, 278−281. (b) Li, Y.; Chen, Z.; Feng, Z.; Yang, Y.; Jiang, J.; Zhang, P. *Carbohydr. Res.* **2012**, *348*, 42−46.

(19) Selected reviews: (a) Crich, D.; Lim, L. B. L. *Organic Reactions* **2004**, *64*, 115−251. (b) Aversa, M. C.; Barattucci, A.; Bonaccorsi, P. *Tetrahedron* **2008**, *64*, 7659−7683. (c) Crich, D.; Bowers, A. A. In *Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance*; Demchenko, A. V., Ed.; Wiely-VCH: Weiheim, Germany, 2008; pp 303−329.

(20) Selected mechanistic studies: (a) Crich, D.; Sun, S. *J. Am. Chem. Soc.* **1997**, *119*, 11217−11223. (b) Gildersleeve, J.; Pascal, R. A.; Kahne, D. *J. Am. Chem. Soc.* **1998**, *120*, 5961−5969. (c) Gildersleeve, J.; Smith, A.; Sakurai, K.; Raghavan, S.; Kahne, D. *J. Am. Chem. Soc.*

1999, *121*, 6176−6182. (d) Crich, D. *Acc. Chem. Res.* **2010**, *43*, 1144−1153. (e) Huang, M.; Garrett, G. E.; Birlirakis, N.; Bohé, L.; Pratt, D. A.; Crich, D. *Nat. Chem.* **2012**, *4*, 663−667. (f) Fascione, M. A.; Brabham, R.; Turnbull, W. B. *Chem. - Eur. J.* **2016**, *22*, 3916−3928.

(21) In preliminary comparison experiments with **2a** and corresponding anomeric *S*-phenyl/benzyl sulfoxide compounds as glycosyl donors, we found that **2a** provided the best results at 0 °C. For details, see the Supporting Information (Tables S1−S3).

(22) (a) Kahne, D.; Walker, S.; Cheng, Y.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 6881−6882. (b) Crich, D.; Sun, S. *J. Org. Chem.* **1996**, *61*, 4506−4507. (c) Di Bussolo, V.; Kim, Y.-J.; Gin, D. Y. *J. Am. Chem. Soc.* **1998**, *120*, 13515−13516. (d) Garcia, B. A.; Poole, J. L.; Gin, D. Y. *J. Am. Chem. Soc.* **1997**, *119*, 7597−7598.

(23) Selected dication reviews: (a) Musker, W. K. *Acc. Chem. Res.* **1980**, *13*, 200−206. (b) Furukawa, N.; Kobayashi, K.; Sato, S. *J. Organomet. Chem.* **2000**, *611*, 116−126. (c) Nenajdenko, V. G.; Shevchenko, N. E.; Balenkova, E. S.; Alabugin, I. V. *Chem. Rev.* **2003**, *103*, 229−282.

(24) In 1987, Furukawa and co-workers proposed a similar pathway during preparation of a stable bicyclic dithia dication salts; see: (a) Fujihara, H.; Akaishi, R.; Furukawa, N. *J. Chem. Soc., Chem. Commun.* **1987**, 930−931. (b) Naka, H.; Maruyama, T.; Sato, S.; Furukawa, N. *Tetrahedron Lett.* **1999**, *40*, 345−348.

(25) Cai, F.; Yang, F. *J. Carbohydr. Chem.* **2014**, *33*, 1−19.

(26) (a) Kice, J. L.; Large, G. B. *Tetrahedron Lett.* **1965**, *6*, 3537−3541. (b) Moore, T. L.; O'Connor, D. E. *J. Org. Chem.* **1966**, *31*, 3587−3592. (c) Ju, T.-L.; Kice, J. L.; Venier, C. G. *J. Org. Chem.* **1979**, *44*, 610−614. (d) Freeman, F. *Chem. Rev.* **1984**, *84*, 117−135. We also observed that compound **6** was gradually decomposed to compounds **7** and **8** upon standing.

(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 full consumption of glycosyl phenylsulfoxide donor. See ref 20c.

(29) (a) Davis, F. A.; Jenkins, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 7967−7971. and references cited therein. (b) Graber, D. R.; Morge, R. A.; Sih, J. C. *J. Org. Chem.* **1987**, *52*, 4620−4622. We thank one reviewer for calling our attention to the possibility of "path b".

(30) Shu, P.; Zeng, J.; Tao, J.; Zhao, Y.; Yao, G.; Wan, Q. *Green Chem.* **2015**, *17*, 2545−2551.

(31) The synthesis of armed SPSB glycosides was much more challenging than that of disarmed SPSB glycosides due to the unwanted overoxidation reaction.

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

(33) For a detailed comparisons of NMR data, see the Supporting Information (Tables S5 and S6).

DOI: 10.1021/jacs.6b08305
J. Am. Chem. Soc. 2016, 138, 13402−13407