Glycosides

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Interrupted Pummerer Reaction in Latent-Active Glycosylation: Glycosyl Donors with a Recyclable and Regenerative Leaving Group

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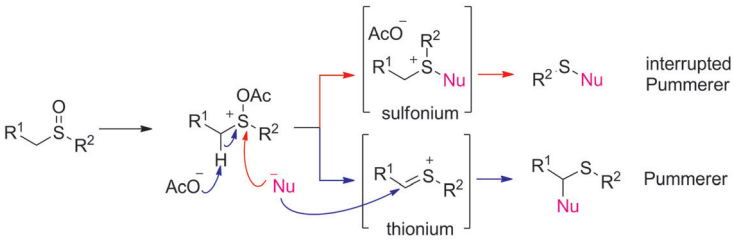
Abstract: *Latent O-glycosides, 2-(2-propylthiol)benzyl (PTB) glycosides, were converted into the corresponding active glycosyl donors, 2-(2-propylsulfinyl)benzyl (PSB) glycosides, by a simple and efficient oxidation. Treatment of the PSB donor and various acceptors with triflic anhydride provided the desired glycosides in good to excellent yields. The leaving group, which was activated by an interrupted Pummerer reaction, can be recycled (PSB-OH) and regenerated as the precursor (PTB-OH). A natural hepatoprotective glycoside, leonoside F, was efficiently synthesized in a convergent [3+1] manner with this newly developed method. The present total synthesis also led to a structural revision of this phenylethanoid glycoside.*

Carbohydrates, essential molecules of life, are involved in various important biological processes and functions.[1] It is well-known that traditional oligosaccharide synthesis is a laborious process involving multistep operations.[2] To streamline the oligosaccharide assembly process, a latent-active strategy arising from the studies of *p*-acetamidophenyl thioglycosides and *p*-nitrophenyl thioglycosides was introduced by Roy et al.[3a] in 1992. Since then, this concept has been further investigated by the groups of Fraser-Reid,[3b] Boons,[3c] Kim,[3d] Wang,[3e] Demchenko,[3f] and Yu.[3g] In this strategy,[4,2b] an active leaving group (LG) can be selectively stimulated over the latent LG in the presence of a suitable promotor. Subsequently, through a simple modification, the latent LG of the resulting glycoside can be converted into a similar but active LG. By taking advantage of this latent-active concept, the manipulation of anomeric leaving groups and tedious protection and deprotection procedures can be minimized, and is highly beneficial for complex target synthesis.[2]

In most of the reported latent-active methods, simple, efficient, and chemoselective transformation of the latent LGs into active LGs plays a crucial role. Current modifications involving reduction/acetylation,[3a] reductive debromination,[5] allyl isomerization,[3c,e] hydrogenation,[3d] deacylation,[3f] and Sonogashira coupling[3g] usually require toxic metal salts,[3a] stoichiometric amounts of Zn powder,[3a,5] transition/rare-earth metals (Ir, Sm, Pd),[3c–e,g,5] basic amide hydrolysis,[3f] or high reaction temperatures.[3a,5] Such requirements present a challenge to the practical utility of the methodology. Glycosyl sulfoxide donors and related sulfonate promoters (diphenyl sulfoxide, sulfonamide and thiolsulinate etc.) are well-studied and the literature is replete with examples of their synthesis and applications.[6] To our surprise, although significant contributions (Kahne glycosylation,[7a] Crich-type β-selective mannosylation,[7b] Gin dehydrative glycosylation,[7c] and Gin oxidative glycosylation[7d] etc.) have been made in this field, the simple transformation of sulfides into sulfoxides and utilization in latent-active approach has not been explored, as there are only a few applications in the literature.[7e–f] We became interested in using sulfoxides to remotely activate the glycosyl leaving group, particularly through the Pummerer and interrupted Pummerer reactions. In these two reactions, the thionium ion or sulfonium ion resulting from activation of the sulfoxide can react with different nucleophiles and has found great utility in organic synthesis (Scheme 1).[8] In this premise, we now report a novel active glycosyl donor, 2-(2-propylsulfinyl)benzyl (PSB) glycoside, which can be prepared by a selective oxidation of the corresponding latent 2-(2-propylthiol)benzyl (PTB) glycoside under mild reaction conditions.



Scheme 1. The standard Pummerer reaction and interrupted Pummerer reaction.

O-alkyl glycosides are ideal candidates for the preparation of latent glycosides because of the rather stable C–O σ-bonds. Despite the several advantages of O-alkyl glycosides, such as easy preparation and convenient manipulation of protecting groups, they are not commonly used as glycosyl donors.[9] The groups of Fraser-Reid,[10a] Inanaga,[10b] Davis,[10c] Kim,[3d] and Hotha[10d] have succeeded in using O-alkyl groups as leaving groups. More recently, based on the success of the

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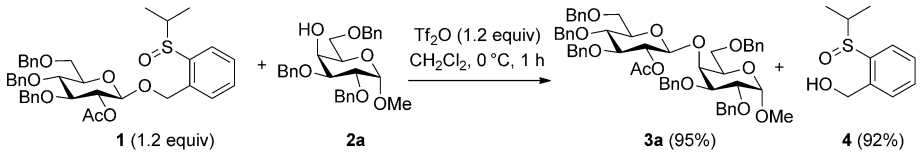
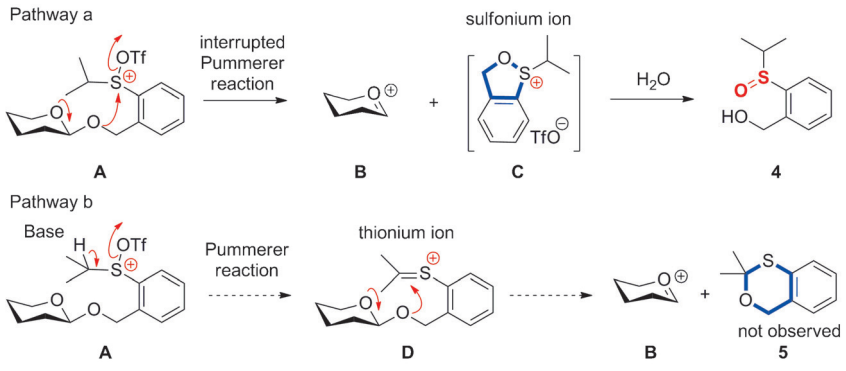
Yu glycosylation,[11] Yu and co-workers designed a novel O-benzyl glycosyl donor, *ortho*-(methyltosylaminoethynyl)benzyl glycoside, for a latent-active approach.[3g] The new glycosyl donors could be activated by a catalytic amount of TMSOTf and other Lewis acids at room temperature. Inspired by the methods of Kim and Yu, we envisioned that treatment of the PSB glycosides with Tf_2O would induce an annulation through five- or six-membered-ring formation to activate the leaving group.

Initial experiments for transglycosylation were performed with the PSB glycoside **1**[12] as a glycosyl donor and **2a** as the glycosyl acceptor (Scheme 2). In a representative procedure, trifluoromethanesulfonic anhydride (Tf_2O, 1.2 equiv) was added to a solution of **1** (1.2 equiv) and **2** (1.0 equiv) in CH_2Cl_2 in the presence of 4 Å molecular sieves (M.S.) at 0 °C. The solution was stirred at 0 °C for 1 hour and then quenched by addition of saturated aqueous $NaHCO_3$. Aqueous workup of the reaction mixture followed by silica gel column chromatography afforded the desired β-(1→4)-disaccharide **3a**[13] (95 %) and a relatively polar compound (**4**; 92 %).



Scheme 2. New glycosyl donor with recyclable leaving group.

A plausible pathway for this transformation is shown in Scheme 3. After activation of the sulfoxide **A** by Tf_2O,[7a–c,14,15] an intramolecular nucleophilic attack of the anomeric oxygen atom onto the cationic sulfur atom leads to the oxocarbenium ion **B** and cyclic benzylsulfonium ion **C** (five-membered ring).[16] The intermediate **C** then undergoes hydrolysis to form **4**. The oxocarbenium ion **B** undergoes glycosylation in the presence of nucleophiles to form the target glycoside. Pathway a (Scheme 3) would be akin to an intramolecular interrupted Pummerer reaction.[17] In contrast, the nonpolar stable compound **5** was synthesized according to literature procedure,[18] and served as a reference for monitoring the reaction. However, we did not observe any formation of **5** or its hydrolyzed form during the reaction. These observations suggested that this novel glycosylation proceeded through an interrupted Pummerer reaction rather than a Pummerer reaction. It is notable that the active leaving group **4** (PSB-OH) could be easily recovered from the reaction mixture and regenerated as the precursor (PTB-OH).[19]



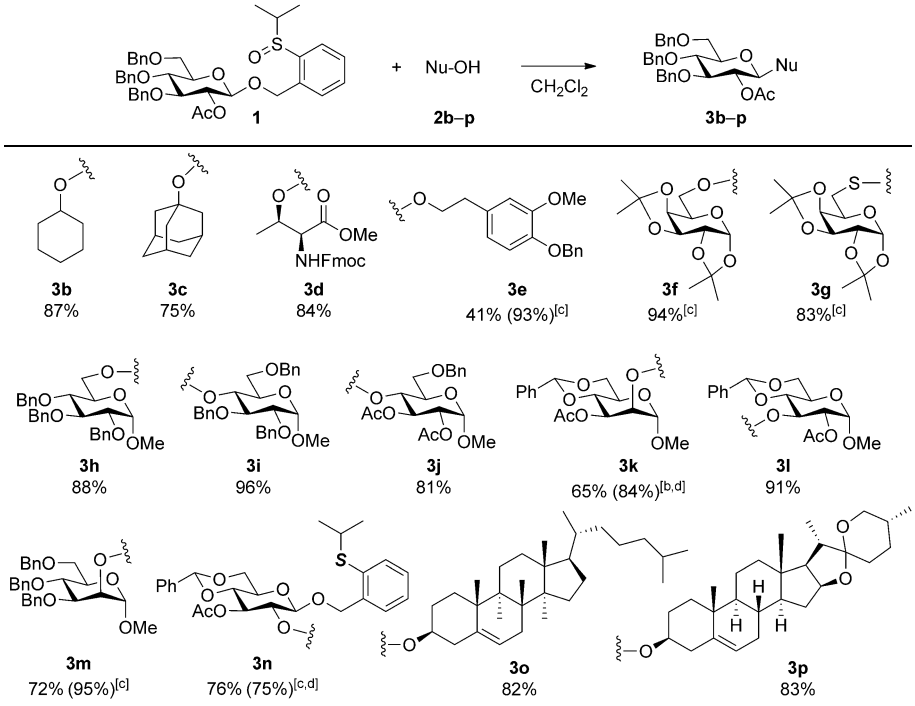
Scheme 3. Proposed mechanism for activation.

To illustrate the scope of this new glycosylation method, a variety of acceptors (**2b–p**; oxo and mercapto nucleophiles), in addition to **2a**, were coupled with **1** (Table 1). Primary, secondary, and tertiary alcohols, as well as amino acid, thiol, and even naturally occurring steroids were found to be suitable glycosyl acceptors using this protocol. From these examples, it is worth noting that: 1) a variety of β-glycoside bonds could be linked to $Gal^{O\text{-}6}$, $Gal^{S\text{-}6}$, $Gal^{O\text{-}4}$, $Glu^{O\text{-}6}$, $Glu^{O\text{-}4}$, $Glu^{O\text{-}3}$, $Glu^{O\text{-}2}$, and $Man^{O\text{-}2}$ in good to excellent yields, 2) extremely hindered nucleophiles such as the adamantine alcohols **2c**, **2i**, and **2j** could also be glycosylated in good yields, 3) gratifyingly, acid-labile groups such as benzylidene (**3l** and **3n**) and acetonide (**3f** and **3g**) were tolerated well even in the absence of acid scavenger,[20] 4) in certain cases, the preactivation procedure (see footnote [c]) increased the reaction efficiency (**3e**, **3f**, **3g**, and **3m**),[21] 5) the thiol **2g** and thiol ether groups (**2n**, **3n**, and **3g**) remained intact in the presence of the sulfoxide triflic anhydride reagent.[22] Most importantly, the successful synthesis of the β-(1→2)-disaccharide **3n** implied that the sequential glycosylation for oligosaccharide synthesis would be possible by employing this approach since the resulting PTB disaccharide **3n** could be used in the next glycosylation after a simple selective oxidation.

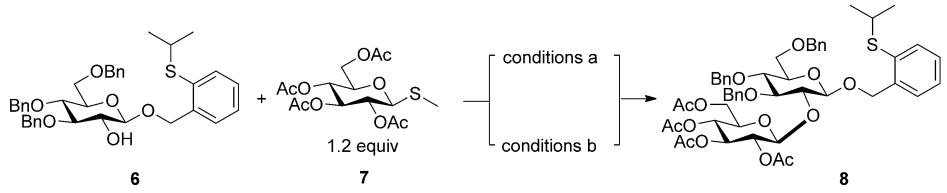
Having investigated the preparation and applicability of the PSB glycosyl donor for chemical glycosylations, we next investigated the stability of the PTB glycoside under reaction conditions commonly used for the activation of thioglycosides. Experiments were performed with 2-hydroxy PTB glycoside **6** as an acceptor and disarmed methyl peracetylated 1-thio-β-D-glycopyranoside **7** as a low reactivity donor, which usually requires strong promoters to activate (Scheme 4). Interestingly, both NIS/TfOH and MeOTf could promote the glycosylation reactions to produce the PTB disaccharide **8** in excellent yield. These preliminary studies indicated that the PTB glycosides are relatively stable under the conditions for activation of thioglycosides.

To further demonstrate the potential of this new glycosyl donor in the synthesis of complex oligosaccharides, we initiated a total synthesis of hepatoprotective Leonoside F,[23a,b] which was recently isolated from Chinese motherwort

Table 1: β-Selective glycosylation with a variety of acceptors.[a,b]



[a] Yield is that of the isolated product. Used 1.2 equiv **1**. [b] Tf_2O (1.2 equiv) was added to the mixture of the glycosyl donor and the acceptor in CH_2Cl_2, 0 °C, 1 h. [c] Tf_2O (1.2 equiv) was added to the solution of glycosyl donor at −40 °C, followed by the addition of acceptor. [d] Additional DTBMP (1.0 equiv) was used. DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

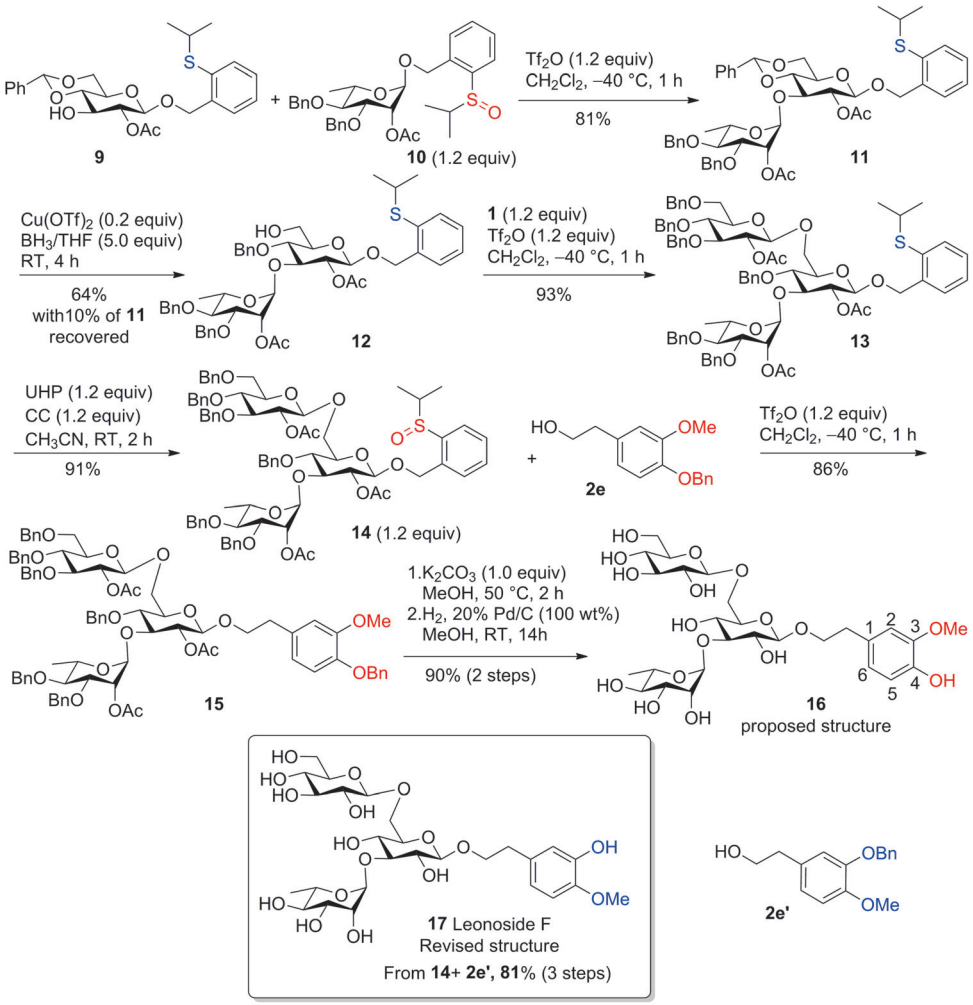


Scheme 4. Stability of PTB glycoside. Reaction conditions a: **7** (1.2 equiv), NIS (2.4 equiv), TfOH (0.24 equiv), 0 °C, CH_2Cl_2, 3 h. 92%. Reaction conditions b: **7** (1.2 equiv), MeOTf (1.2 equiv), RT, CH_2Cl_2, 24 h, 65%, with 25% of **6** recovered. NIS = *N*-iodosuccinimide.

(*Leonurus japonicus* Houtt)[23c] and Chinese foxglove (*Rehmannia glutinosa*), and collectively form two of the fifty fundamental herbs of traditional Chinese medicine. Leonoside F bears a branched trisaccharide moiety and a phenylethanoid aglycon.[23a,b] In this work, a convergent [3+1] approach is incorporated into our newly developed glycosylation, mediated by an interrupted Pummerer reaction, to synthesize this natural product (Scheme 5). To prove the possibility of using the present glycosylation method in the latent-active assembly strategy, the active PSB glycoside **10** (1.2 equiv) was coupled with the latent PTB glycoside **9** in the presence of Tf_2O to give the β-(1→3)-disaccharide **11** (81%), which was then converted into the acceptor **12** (64%, with 10% of **11** recovered) by a selective reductive opening of the 4,6-benzylidene acetal. The active PSB donor **1** was coupled with **12** under similar glycosylation conditions to produce the β-(1→6)-trisaccharide **13** (93%), which was then selectively oxidized into the corresponding active PSB donor **14** (91%).[24] Subsequent glycosylation between **14** and **2e** in a convergent [3+1] manner yielded the phenylethanoid glycoside **15** (86%). Final removal of acetate and benzyl groups furnished the target trisaccharide **16** (90% over two steps).

The synthetic compound **16** was apparently not the natural leonoside F.[25] After carefully examining the four different synthetic attempts[26] and structural data from isolations, we suspected that the methoxy group might be located at the *para*-position of phenyl group instead of at the *meta*-position as proposed in the previous assignments. As such, a replacement of **2e** by **2e′** was made, and a straightforward synthesis of the revised structure **17** (81% over three steps) from the PSB glycosyl donor **14** was achieved after another [3+1] glycosyl coupling and routine global deprotection. The NMR spectra of the synthetic **17** were virtually identical to those reported in the literature.[23a,27] Other relevant reported structures of phenylethanoid glycosides, cistanoside E,[23a,28a,b] leonoside E,[23a] leonoside F,[23b] and scrophuside[28c] will be re-examined accordingly.[29]

In conclusion, we have discovered the 2-(2-propylthiol)-benzyl (PTB) anomeric moiety as a new leaving group, which allows rapid oligosaccharide assembly through latent-active and convergent synthetic concepts. The PSB glycoside donor can be converted from the corresponding stable PTB glycoside by an efficient oxidation. After coupling, the leaving group is recycled as PSB-OH, which can be used in the synthesis of the latent PTB glycoside after a simple reduction. We have demonstrated the potential of the new approach in a complex natural product synthesis. The present total synthesis has led to the revision of the structure of leonoside F from **16** to **17**.



Scheme 5. Total synthesis of revised leonoside F using a latent-active strategy. CC = cyanuric chloride, THF = tetrahydrofuran, UHP = urea–hydrogen peroxide.

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