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# Selective *S*-deacetylation inspired by Native Chemical Ligation: practical syntheses of glycosyl thiols and drug mercapto-analogues

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Glycosyl thiols are useful building blocks for the construction of compounds with biological and synthetic importance. Herein, we report a practical synthetic approach toward the efficient synthesis of glycosyl thiols *via* chemo- and regioselective *S*-deacetylation inspired by native chemical ligation. This strategy allows the large scale synthesis of glycosyl thiols by simple purification steps without column chromatography. In addition, deactylation reagent (DTT) could also be recovered and regenerated by a simple process. Thiol containing taxol and artemisinin analogues were successfully prepared based on this methodology. Finally, auranofin, a glucose-based oral drug used to treat rheumatoid arthritis was synthesized in concise steps and overall high yields.

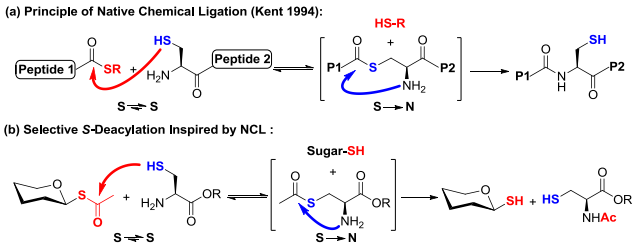
## Introduction

Oligosaccharides and glycoconjugates exhibit a wide range of utilities in the investigation of biological processes.[1] However, the acid and enzymatic sensitive nature of *O*-glycosidic bonds hamper their further applications in some circumstances. This limitation thus stimulated the development of new glycosides with exceptional stability, such as thio-linked oligosaccharides, glycopeptides and glycolipids.[2] These thioglycosides and derivatives are tolerated by most biological systems and are considered as promising molecules for the development of new therapeutics.[3] Generally, most of these thioglycosides and derivatives were prepared from glycosyl thiols (1-thio sugars) by alkylation[4], conjugate-addition or thiol-ene coupling reactions[5] that are allowed due to the retention of anomeric configuration during the synthetic transformations. In addition, glycosyl thiols have been used as precursors for the preparation of active glycosyl donors, such as glycosyl *N*-phenyltrifluorothio-acetimidate,[6] glycosyl-sulfenamides[7] and sulfonamides[8] in glycosylation reactions. The good affinity of glycosyl thiols with gold also stimulated interest in developing them as drugs (such as auranofin).[9]

A number of methods are available for the synthesis of glycosyl thiols. Conventional approaches include a two-step reaction sequence involving a substitution reaction of glycosyl halides or acetates with thiourea,[10] thioacetate[11] or thiophosphate[12] followed by hydrolysis. Bubbling hydrogen sulfide gas through a solution of glycosyl halides[13] offered an alternative method. Treatment of 1,2-anhydro sugars,[14] 1,6-anhydro sugars or glycosyltrichloro-acetimidates[15] with bis(trimethylsilyl)sulfide supplied an exclusive preparation method. Davis and co-workers found a direct and general preparation way with moderate to good selectivity by reacting glycosyl hemiacetales with Lawesson's reagent.[16] Very recently, Misra group also developed an expedient one-step pathway to *β*-glycosyl thiols by reaction of glycosyl bromides with $CS_2$ and $Na_2S\ 9H_2O$,[17] although the purity of some compounds was not satisfactory. Given the easy availability, wide applicability and absolute steric control of the anomeric configuration of peracylated glycosyl thiols, selective deacetylation of the anomeric thioacetate probably is the most convenient and practical way among all the reported synthetic methods. However, the chemo- and regioselective deprotection of the anomeric thioacetate using strong bases such as NaOH, NaOMe etc. required strict control of the reaction conditions, such as low temperature,[18] specific pH value[4d] and reaction time. In another procedure, utilization of a weaker base, for example NaSMe[11,19] or $Et_2NH$[20] could give moderate yields. Although remarkable progress has been made in the past few decades, the large-scale preparation of glycosyl thiols, especially in a greener way, to synthesize thio-linked glycosides remains inefficient. As a consequence, we intended to search for more convenient and practical synthetic methods for the stereoselective preparation of glycosyl thiols.

Native chemical ligation (NCL) is by far the most powerful and most widely utilized ligation method for synthesizing peptides or proteins.[21] The application of NCL not only has revolutionized the total or semi-synthesis of medium sized proteins but has also been extended to other areas such as nucleic acid chemistry and glycoprotein synthesis.[22] A classical NCL involves a reversible transthioesterification between a *C*-terminal peptidyl thioester and another peptide bearing an *N*-terminal cysteine residue. A subsequent irreversible *S* to *N* acyl shift occurs on the cysteine residue, forming the peptide with concurrent release of a free thiol compound (RSH) (Scheme 1a). Given the innate character and the mild reaction conditions of native chemical ligation, we envisaged that this strategy could be further applied to selective *S*-deacetylation of glycosyl thioacetates to produce glysosyl thiols (Scheme 1b). In a literature survey, we found that early in 1974, Endo etc. utilized

cysteamine to convert thioacetates to corresponding thiols.[23] In 1988, Blanc-Muesser and Driguez achieved an *in situ* chemoselective *S*-deacetylation by using cysteamine in hexamethyl-phosphoramide (HMPA) in the presence of 1,4-dithiothreitol (DTT).[24] After these reports, Hashimoto[25a,b] and Defaye[25c] groups discovered that with a combination of DTT and cysteamine in acetonitrile at higher temperature, the efficiency of this reaction could be further increased. Considering the role of cysteamine played in these reactions, we speculate that the reaction essentially involves the native chemical ligation (NCL) mechanism. Inspired by these results, we inte nded to further develop a practical method for the synthesis of glycosyl thiols by chemo- and regioselective deacetylation reaction in a NCL mode.



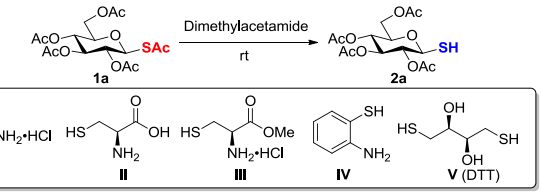

**Scheme 1**. Principle of NCL and NCL inspired *S*-deacetylation.

## Results and discussion

Initially, we examined the strategy by selective *S*-deacetylation of peracylated thioglycoside **1a** with 1.2 equiv of cysteamine hydrochloride (**I**) in DMA at room temperature, however, only 65% yield of *S*-deacetylated product **2a** was obtained with 30% of recovered thioglycoside **1a** after 24 h (Table 1, entry 1). Replacing **I** with cysteine (**II**), which is frequently used in NCL mediated peptide synthesis led to lower yields after 12 h (Table 1, entry 2). Extension of the reaction time resulted in decreased yields due to the formation of partially *O*-deacetylated products. Interestingly, when cysteine methyl ester hydrochloride (**III**) was used in the reaction, the yield increased to 80% although 12% of starting material was still recovered (Table 1, entry 3). We further considered neutralizing the hydrochloride salt of **III** with 1.2 equiv of $NaHCO_3$, in this case, the reaction proceeded fast and the desired *S*-deacetylated product **2a** was obtained in 95% yield in 1 h (Table 1, entry 4). Decreasing the amount of base to 1.0 equiv did not affect the yield much and a product yield of 94% was obtained (Table 1, entry 5). Further decrease in base loading to 0.6 equiv led to longer reaction time and lower yield (Table 1, entry 6). Other than $NaHCO_3$, the reaction with 1.0 equiv of triethylamine (TEA) also gave similar results (Table 1, entry 7). The utilization of 2-aminobenzenethiol (**IV**) with/without base did not provide useful results (Table 1, entry 8, 9).

In Hashimoto's protocol, the use of 0.5 equiv of DTT as additive is supposed to prevent the disulfide bond formation.[26] Surprisingly, when we use 1.2 equiv of DTT in combination with 0.1 equiv of $NaHCO_3$ in the absence of cysteamine or any other NCL-like reagents, the reaction still proceeded smoothly and the desired *S*-deacetylation product **2a** was generated in 90% yield (Table 1, entry 10). Increasing the amount of DTT to 1.5 equiv produced the best yield (98%) (Table 1, entry 11). 0.6 equiv of DTT was less efficient and longer reaction time was needed, with lower yield observed as well (Table 1, entry 13). The addition of more base was ineffective in increasing the yield (Table 1, entry 14). The catalytic amount of base (either $NaHCO_3$ or TEA) was proved to be important; without base, only 65% yield of product was isolated after 24 h (Table 1, entry 15). A wide variety of solvents such as $CH_3OH$, $CH_3CN$, toluene, DMF and DMA were tested and found to be effective to produce good yields in this reaction (See details in ESI). Among them, DMA not only yield the best results, but most importantly also simplified the purification step. For both of the cysteine methyl ester hydrochloride (**III**) and DTT (**V**) mediated *S*-deacetylation reactions, with DMA as solvent, we found that a simple extraction of reaction mixture with toluene without further purification produced the desired product with satisfactory purity, which facilitates the large-scale synthesis of glycosyl thiols.

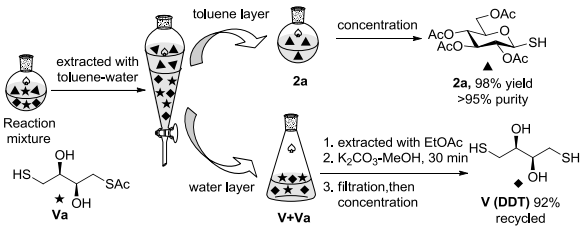
**Table 1**. Optimization of selective deacetylation reaction conditions[a,b]




| Entry | Reagent (equiv) | Addtive (equiv) | Time (h) | Yield[c] |
|---|---|---|---|---|
| 1 | **I** (1.2) | - | 24 | 65% (30%) |
| 2 | **II** (1.2) | - | 12 | 52% |
| 3 | **III** (1.2) | - | 24 | 80% (12%) |
| 4 | **III** (1.2) | $NaHCO_3$ (1.2) | 1 | 95% |
| 5 | **III** (1.2) | $NaHCO_3$ (1.0) | 1 | 94% |
| 6 | **III** (1.2) | $NaHCO_3$ (0.6) | 5 | 88% (7%) |
| 7 | **III** (1.2) | TEA (1.0) | 1 | 94% |
| 8 | **IV** (1.5) | - | 24 | 20%[d] |
| 9 | **IV** (1.5) | $NaHCO_3$ (0.1) | 5 | 30%[d] |
| 10 | **V** (1.2) | $NaHCO_3$ (0.1) | 1 | 90% |
| 11 | **V** (1.5) | $NaHCO_3$ (0.1) | 1 | 98% |
| 12 | **V** (1.5) | TEA (0.1) | 1 | 96% |
| 13 | **V** (0.6) | $NaHCO_3$ (0.1) | 24 | 75% (17%) |
| 14 | **V** (0.6) | $NaHCO_3$ (0.6) | 24 | 74% (20%) |
| 15 | **V** (1.5) | - | 24 | 65% |

[a]All of the reactions were carried out in 100 mg scale. [b]See ESI for additional information of reaction conditions optimization. [c]Isolated yield, yield in parentheses was of recovered starting material. [d]Most of the starting material degraded. TEA = triethylamine, DMA = dimethylacetamide.

In addition, we also tried to recover and regenerate DTT by extraction of the aqueous phase with ethyl acetate followed by hydrolysis with $K_2CO_3$-MeOH. (Scheme 2) With this protocol, DTT was easily recycled in 92% yield. The recycled DTT was further utilized into the next selective *S*-deacetylation reaction and produced the desired product in 94% yield. These results indicated a promising future for the industrial application.




**Scheme 2**. Isolation of **2a** by simple extraction and recycle of DTT.

With these optimized reaction conditions in hand, next we investigated the reaction scope with regards to the *S*-acetylated sugars (Figure 1).

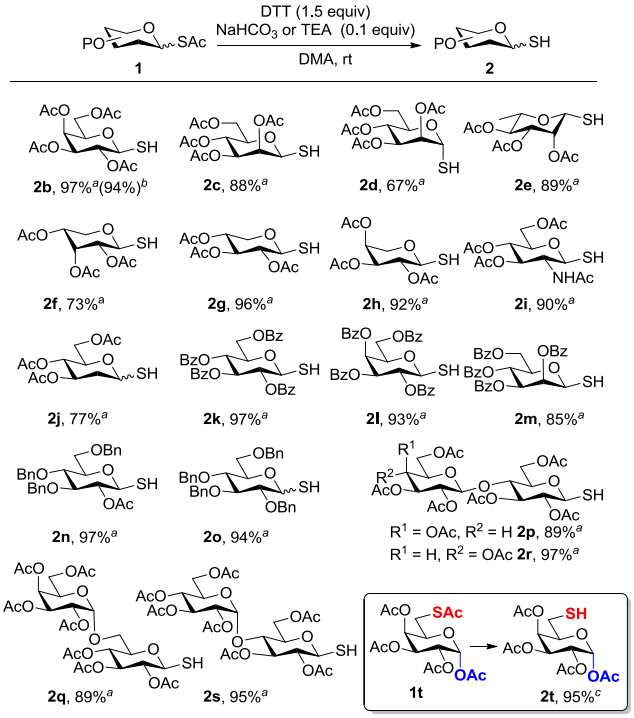
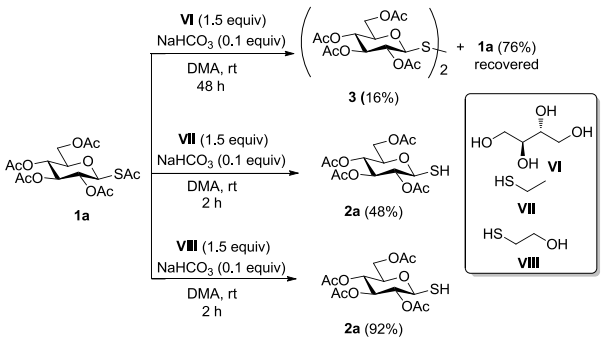



**Figure 1**. Substrate scope of DTT mediated selective *S*-deacetylation. [a]Reaction conducted on a 0.2 mmol scale. Isolated yields. [b]Yield of isolated product on a 2 gram scale. [c]2.0 equiv of DTT was used.

Given the slightly higher yields and the utilization of less amount of base in the DTT mediated *S*-deacetylation strategy, the substrate scope was examined by subjecting the substrate to 1.5 equiv of DTT with 0.1 equiv of $NaHCO_3$ in DMA at room temperature. Various *S*-acetylated sugars were examined under the optimized reaction conditions and all of them afforded the corresponding glycosyl thiols in good to excellent yields (**2b** - **2j**). Benzoyl group was tolerated in this reaction condition and was kept untouched while the *S*-acetyl group was removed smoothly (**2k** - **2m**). Benzyl protecting group also did not show any negative effect to the reactivity (**2n**, **2o**). Among all these reactions, the configurations of the anomeric C-S bond were not affected and remained exactly the same as the starting materials. The *β*-*S*-acetylated sugars gave absolute *β*-glycosyl thiols while the α-anomers gave corresponding *α*-products (**2d** and **2h**). Compounds **2j** and **2o** were obtained as α, *β*-mixtures simply due to the starting materials that were mixtures (see ESI). Besides the monosaccharides, the anomeric *S*-acetyl group of peracylated disaccharides was also removed smoothly under the optimized reaction conditions without affecting the *O*-acetyl groups (**2p** - **2s**). Most interestingly, under current reaction conditions, selective removal of C-6 *S*-acetyl group was successfully achieved without affect the anomeric *O*-acetyl group (**2t**), which is difficult to reach by most of the known selective *S*-deacylation or *O*-deacylation reaction conditions (See ESI). In addition, we also carried out the selective *S*-deacetylation of compound **1b** in a 2-gram scale, which produced **2b** in 94% yield. As we demonstrated previously, product **2b** was obtained by extraction of the reaction mixture with toluene but without further purification, and the product purity was confirmed by NMR analysis (see details in ESI).

With regards to the mechanism, if the reaction was mediated by cysteine methyl ester hydrochloride (**III**), it should involve NCL pathway. Indeed, we isolated the acylated cysteine methyl ester, in which the acetyl group is located on the nitrogen atom due to the transthioesterification and *S* to *N* acyl transfer sequence. To understand the role of DTT in the selective *S*-deacetylation reaction, we carried out several comparison studies (Scheme 3). First, DTT was replaced by *meso*-erythritol **VI**. In this reaction, we did not observe the desired glycosyl thiol compound **2a** except for the disulfide bond linked glycoside **3** (16%, and 76% recovered starting material), which implied that the thiol group in DTT not only prevented the disulfide bond formation but also played an essential role in the deacetylation step. Then, ethanthiol **VII** was used instead of DTT and only 48% yield of **2a** was isolated. This observation indicated that the hydroxyl group is also essential in this reaction. With 2-hydroxyethanthiol (**VIII**), which could be considered as truncated DTT, 92% yield of **2a** was obtained. These results further demonstrated that both the thiol group and hydroxyl group of DTT are indispensable.




**Scheme 3**. Comparison studies of *S*-deacetylation reaction.

To further investigate the mechanism of DTT mediated *S*-deacylation reaction, we monitored the reaction process by $^{13}C$-NMR study (Figure 2). Initially, compound **1n** and DTT were dissolved in DMF-$d_7$ and the $^{13}C$-NMR spectra was subsequently recorded (Figure 2a). In the spectra, peaks at [$\delta$ C 170.0, 20.7] and [$\delta$ C 193.2, 30.7] were attributed to the OAc and SAc group of **1n** respectively. The spectra did not show any obvious change after the reaction mixture was kept for 1 h. However, upon adding 0.1 equivalent of $NaHCO_3$, new peaks appeared rapidly (Figure 2b). These results indicated that the base dramatically increased the reaction speed. After 1 h, peaks at [$\delta$ C 170.0, 20.7] and [$\delta$ C 193.2, 30.7] totally disappeared and new peaks were formed concurrently (Figure 2c). The newly formed peaks at [$\delta$ C 170.1, 20.9] and [$\delta$ C 195.7, 32.9] implied that one OAc and one SAc group still remained in the reaction system. Since the *S*-acetyl group has been removed and the *C*-2 OAc group was unaffected in the isolated product **2n**, the new formed *S*-acetyl is most probably located at the *S* atom of DTT. In addition, this *S*-acylated DTT **Va** was isolated and characterized by 1D and 2D NMR. After comparing Figure 2c with Figure 2d, it is not difficult to understand that the DTT mediated *S*-deacylation

reaction should pass through transthioesterfication pathway, thus the anomeric *S*-acetyl group is transferred to the *S* atom of DTT but without occurrence of the further *S* to *O* shift. Based on this mechanism, it is easy to understand that excess of DTT was inevitable because the transthioesterification step is reversible. In addition, the vital role of trace amount of base can be explained by the fact that the transthioesterfication step is favoured in weak basic environment. Overall, the proposed mechanisms for cysteine methyl ester and DTT mediated *S*-deacetylation reactions were depicted in Scheme 4.

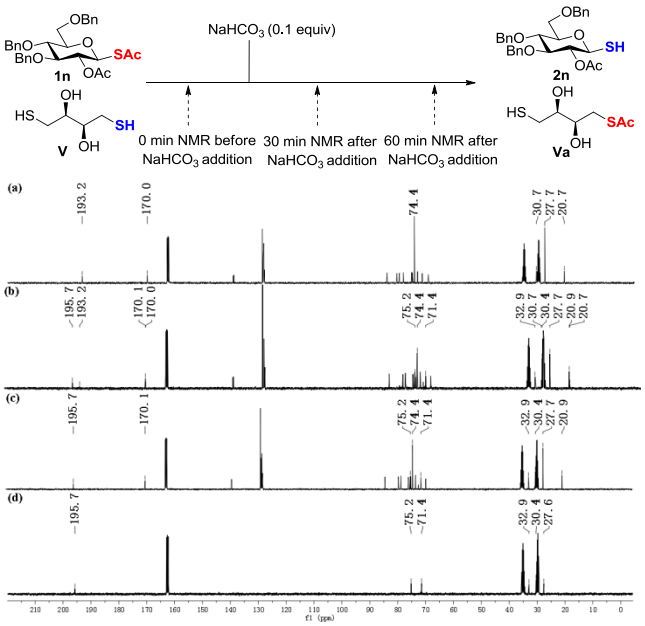
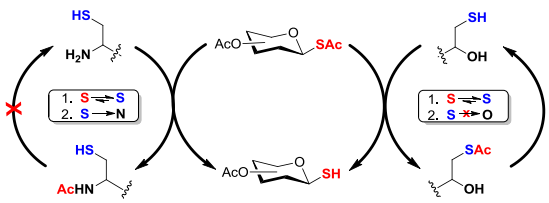
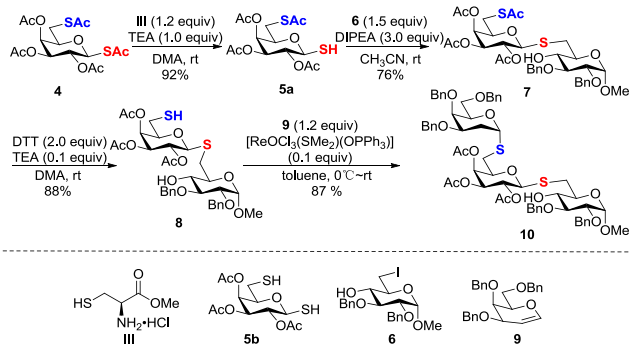



**Figure 2**. NMR study of DTT mediated deacylation reaction in DMF-$d_7$: (a) t = 1 h, without $NaHCO_3$; (b) t = 1.5 h, after adding 0.1 equiv of $NaHCO_3$ for 0.5 h; (c) t = 2 h, after adding 0.1 equiv of $NaHCO_3$ for 1 h. (d) $^{13}C$ NMR of **Va** in DMF-$d_7$.



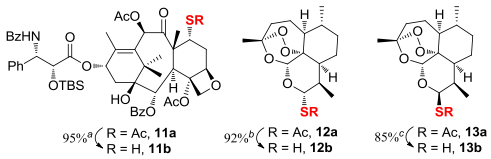

**Scheme 4**. Proposed mechanisms of *S*-deacetylation reactions.

The applicability of these selective *S*-deacetylation reactions was further demonstrated by a practical synthesis of *S*-linked trisaccharide **10** (Scheme 5). The synthesis started from the selective deacetylation of anomeric SAc group of **4** (preparation of compound **4**， see ESI). This selective deacetylation reaction is extremely challenging, as additional SAc group existing at the *C*-6 position of compound **4** besides the anomeric SAc group and other OAc groups. The originally optimized DTT mediated deacetylation reaction conditions only resulted in 64% yield of compound **5a** as well as 28% di-*S*-deacetylated compound **5b**. Further optimization of the reaction conditions revealed that use of compound L-cysteine methyl ester hydrochloride (**III**) could produce the ideal result. With 1.2 equiv of **III** and 1.0 equiv of TEA, the selective *S*-deacetylation reaction proceeded smoothly in DMA and produced the desired mono-*β*-*S*-deacetylated compound **5a** in 92% yield. Coupling of the *β*-glycosyl thiol compound **5a** with **6** offered compound **7** in 76% yield. In this reversed glycosylation reaction, the configuration of anomeric *β*-glycosidic bond was kept unchanged. The selective *S*-deacetylation of *C*-6 SAc group with 1.5 equiv of DTT and 0.1 equiv of TEA produced compound **8** in 82% yield. Increasing the amount of DTT to 2.0 equiv led to 88% yield. However, in this case, utilize of **III** is less efficient; the reaction with 1.2 equiv of **III** and 1.0 equiv of TEA generated compound **8** in a moderate yield of 56%. Finally, based on Toste's protocol,[27] the reaction of compound **8** with glycal **9** catalyzed by Rhenium reagent produced *S*-linked trisaccharide **10** in 87% yield with exclusive *α*-selectivity.



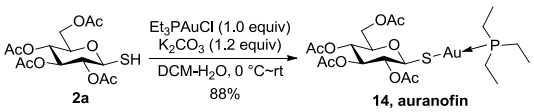

**Scheme 5**. Synthesis of thiolinked trisaccharide.

In addition, this strategy was able to expand to other thiol containing compounds[28] other than carbohydrates, which might be useful to the structural modification of natural products and drugs (Scheme 6). Taxol is one of the most important anti-cancer natural drugs， modification at 7-position has lead to several promising taxol analogues, including the compounds with sulfur group at 7-position.[29] However, the selective *S*-deacetylation of **11a** with ammonia only produced moderate yield, stronger base such as DBU caused epimerisation.[29d] In contrast, our attempt to generate thiol group at C-7 position was successfully achieved by DTT mediated *S*-deacetylation (**11b**).[30] Artemisinin and its derivatives are important antimalarial and potential anti-cancer agents. Lee and co-workers have reported that 10-mercapto-dihydroartemisinin exhibit much better activities than artemisinin and dihydroartemisinin.[31] However, only 10-*α*-mercapto-dihydroartemisinin was prepared and tested, while the preparation of *β*-isomer was failed by the common deacetylation conditions due to isomerization. In our case, both *α*- and *β*-isomer were perfectly produced without isomerisation from the corresponding *α*- and *β*-thioacetate under the DTT mediated deactylation reaction conditions (**12b**, **13b**).[32]




**Scheme 6**. Modification of natural products and drugs. [a]DTT (3.0 equiv, $NaHCO_3$ (0.1 equiv), DMA, rt. 10 h; [b]DTT (1.5 equiv), $NaHCO_3$ (0.1 equiv), DMA, rt. 1.5 h; [c]DTT (1.5 equiv), $NaHCO_3$ (0.1 equiv), DMA, rt. 2 h, longer reaction time lead to isomerisation.

The significance of this selective *S*-deacetylation reaction is finally demonstrated by the synthesis of auranofin (**14**).[33] (Scheme 7) Auranofin, a US FDA-approved drug used therapeutically for rheumatoid arthritis, was identified recently as new lead compound against *E. histolytica*, the causative agent of human amebiasis. Amebiasis is estimated to cause more than 70000 deaths per year worldwide.[34] The synthesis of this antiarthritic drug is shown in Scheme 7. Given the easy availability of glycosyl thiol **2a** according to our *S*-deacetylation strategy, auranofin could be obtained in one step by direct coupling of **2a** and $Et_3PAuCl$,[33a,35] the yield was up to 88% after recrystallization. The analytic data was coincided with those reported in literature.[36] It could be imagined that auronofin was able to synthesized in large scale with this method.




**Scheme 7**. Synthesis of Auranofin.

## Conclusions

In conclusion, we have developed efficient and practical strategies toward the synthesis of glycosyl thiols by selective *S*-deacetylation reactions. In our discovery, both of the NCL–like strategy mediated by cysteine methyl ester hydrochloride and transthioesterification strategy mediated by DTT allowed the chemoselective *S*-deacetylation proceed efficiently. Most importantly, the challenging regioselective *S*-deacetylation between two different *S*-acetyl groups has been achieved by NCL strategy. In addition, it is found that keeping the reaction environment weakly basic is vital to the efficiency of both strategies. Furthermore, we also disclosed that with DMA as reaction solvent in the DTT mediated deacetylation strategy, not only is the best yields provided, but the purification step is also greatly simplified since only an extraction with toluene is required, which coincides the fundamental of large-scale synthesis. In this case, DTT could also be recovered and regenerated by a simple process. Based on this methodology, we further synthesized an S-linked trisaccharide containing both $\alpha$ and $\beta$ linkages. This methodology was also applied to the modification of taxol, artemisinin and synthesis of drug molecule auranofin. We believe that these methods will find wide utilities in the synthesis of thio-linked oligosaccharides and glycol-conjugates as well as thiol containing natural products and drug analogues.

## Experimental

### General information

All reactions were monitored by thin-layer chromatography over silica-gel-coated TLC plates (Yantai Chemical Industry Research Institute). The spots on TLC were visualized by warming 10% $H_2SO_4$ (10% $H_2SO_4$ in ethanol) sprayed plates on a hot plate. Column chromatography was performed using silica gel (Qingdao Marine Chemical Inc., China). 1,4-Dithiothreitol (DTT), paclitaxel (taxol) and dihydroartemisinin were purchased from Adamas and used without purified. NMR spectra were recorded on a Bruker AM-400 spectrometer (400 MHz), and the $^1H$ and $^{13}C$ NMR chemical shifts were referenced to the solvent or solvent impurity peaks for $CDCl_3$ at $\delta_H$ 7.24 and $\delta_C$ 77.23, for DMF-$d_7$ at $\delta_H$ 8.02 and $\delta_C$ 163.15. Optical rotations were measured on a Perkin-Elmer 341LC polarimeter using a quartz cell with 3 mL capacity and a 1 dm path length. Concentrations (*c*) are given in g/100 ml. High resolution mass spectra were recorded on a Bruker micrOTOF II spectrometer using electrospray ionization. Commercially available grades of organic solvents of adequate purity were used in all reactions.

### Gram-scale synthesis of 2b and recycle of DTT

To a 0.15 M solution of **1b** (2.0 g, 4.92 mmol, 1.0 equiv) and **V** (1.14 g, 7.38 mmol, 1.5 equiv) in DMA was added $NaHCO_3$ (41 mg, 0.492 mmol, 0.1 equiv). The mixture was stirred at room temperature for 1 h then poured into water and extracted with toluene for three times. The combined organic layers were washed successively with water, brine and concentrated to furnish the product **2b** (1.68 g, 94%, >95% purity confirmed by NMR analysis). The aqueous phase was added NaCl until it was saturated. Then it was extracted with ethyl acetate for three times. The organic layers were combined and concentrated. The residue was dissolved in MeOH (contains 0.1‰(*w*/*w*) $K_2CO_3$) and stirred at room temperature for 30 min. Then the mixture was filtered with celite and washed with MeOH. The filtrate was concentrated to give **V** (1.05 g, recoverd yield 92%). The recycled DTT was further utilized into the next selective *S*-deacetylation reaction and produced the **2b** in 94% yield.

## Acknowledgements

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## Notes and references

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† Electronic supplementary information (ESI) available: Detailed experimental procedures, structural proofs, and spectral data for all new compounds are provided. See DOI: 10.1039/b000000x/

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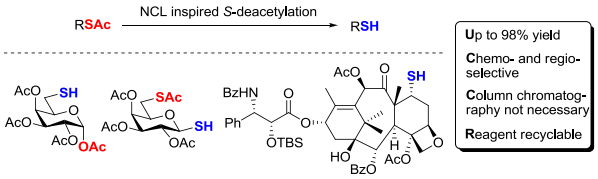
**Entry for the Table of Content**




High efficient selective *S*-deacetylations were achieved by simple transthioesterification under mild basic conditions.