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# Facile triflic acid-catalyzed α-1,2-*cis*-thio glycosylations: scope and application to the synthesis of *S*-linked oligosaccharides, glycolipids, sublancin glycopeptides, and $T_N$/$T_F$ antigens†

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Studies of *S*-linked glycoconjugates have attracted growing interest because of their enhanced chemical stability and enzymatic resistance over *O*-glycoside counterparts. We here report a facile approach to access α-1,2-*cis*-*S*-linked glycosides using triflic acid as a catalyst to promote the glycosylation of a series of thiols with D-glucosamine, galactosamine, glucose, and galactose electrophiles. This method is broadly applicable for the stereoselective synthesis of *S*-linked glycopeptides, oligosaccharides and glycolipids in high yield and excellent α-selectivity. Many of the synthetic limitations associated with the preparation of these *S*-linked products are overcome by this catalytic method.

## Introduction

Protein glycosylation, one of the most ubiquitous post-translational modifications, typically involves the attachment of carbohydrate chains to proteins through the hydroxyl group of serine or threonine (*O*-glycans) or the amido group of asparagine (*N*-glycans).[1–5] The resulting glycoproteins exhibit a diverse array of biological functions such as cell adhesion, protein folding, signal transduction, and immune response.[1–5] However, naturally occurring glycoproteins exist as mixtures of glycoforms, and their isolation as homogeneous species is a complicated process.[6] As such, there is a great demand for methods to efficiently access structurally defined glycoproteins. Recently, replacement of the anomeric oxygen of *O*-linked glycosides with a sulfur atom to generate *S*-linked glycosides has attracted considerable attention because of the enhanced resistance of the latter to chemical and enzymatic hydrolysis.[7,8] In addition, *S*-linked glycosides exhibit similar conformational preferences and equal or even improved biological activities compared to their native *O*-glycoside counterparts.[9–11] In this context, *S*-linked glycan analogs could be utilized as structural mimetics and serve as powerful tools for the biological study of the natural *O*-linked substrates. The recent discovery of *S*-glycosylation, the addition of carbohydrate residues to the sulfur atom of cysteine on bacterial peptides,[12–14] suggests that naturally existing *S*-linked glycoproteins may be more widespread than was previously thought and may lead to the development of new therapeutics.

Given the significant importance of thiol-containing carbohydrate molecules, methods that enable access to the challenging α-1,2-*cis* thiol glycosidic linkages are of high synthetic value. Formation of β-1,2-*trans* glycosides can be readily accomplished by employing electrophiles with C(2)-participatory groups.[15] The stereoselective formation of α-1,2-*cis* glycosides, however, has proven challenging, and a mixture of α- and β-glycosides is often obtained.[15] A variety of strategies have been reported for the synthesis of mucin-related α-thiol-containing GalNAc glycopeptide mimetics.[16–24] Representative methods include stereoselective preparation of α-GalNAc thiols followed by (1) an $S_N2$ displacement with β-bromoalanine-containing peptides,[16,17] (2) site-selective conjugation with aziridine-containing peptides,[18,19] or (3) conjugate addition to dehydroalanine-containing peptides.[20] $S_N2$ reaction of α-glycosyl thiols with 4-axial triflate glycosides[21,22] 6-iodinated glycosides,[23–25] enzymatic glycosylation,[26–29] and metal-catalyzed cross coupling,[30,31] have also been reported to generate α-1,2 *cis* *S*-linked oligosaccharides and glycopeptides. Despite these important advances over the past decades, numerous challenges remain, including the need for highly specialized coupling partners and the multistep preparation of bromoalanine-, aziridine-, and dehydroalanine-containing amino acid residues or peptides.[32] In addition, most of the current methods are limited to specific classes of thiol nucleophiles. To date, there is only one reported method that is applicable for a variety of sulfur nucleophiles, and it uses glycosyl stannane to promote *S*-linked glycoside formation.[31]

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We recently found that triflic acid, released from nickel triflate, can effectively promote the glycosylations of serine/threonine amino acids and hydroxyl groups of carbohydrates with the C(2)-*N*-*ortho*-(trifluoromethyl)benzylidenamino *N*-phenyl trifluoroacetimidates.[33–36] This catalytic system features several advantages such as mild conditions, short reaction time, good yields and excellent levels of α-selectivity. However, the question remains whether it will be suited for *S*-glycosylations as Lewis acid-promoted reactions are known to be incompatible with thiol nucleophiles.[37–40] Lewis acid-promoted *S*-glycosylations were underutilized with a few limited examples.[37–40] The reactions generally proceed to provide the coupling products with low yields and require stoichiometric amount of promoter. An inherent issue with the *S*-nucleophiles is their tendency to undergo oxidation to form disulfide and other side products.[38] They also react with the TMSOTf catalyst during the glycosylation process.[40] All those factors make it more challenging to handle *S*-nucleophiles than their *O*-counterparts.

Herein we report a distinct approach to *S*-linked glycosylations: a triflic acid catalyst is shown to enable the facile α-1,2-*cis* synthesis of thiol-oligosaccharides, glycopeptide of antimicrobial sublancin, *S*-linked tumor-associated $T_N$/$T_F$ antigens, and thiol-glycolipids. This strategy obviates the need for substrate prefunctionalization and can proceed by direct coupling of thiol-containing molecules or cysteine-containing peptides with *N*-phenyl trifluoroacetimidates.

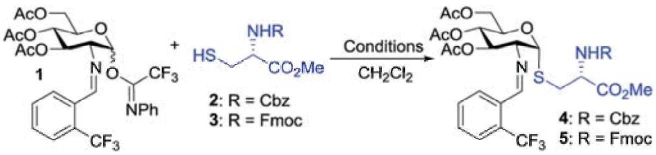
## Results and discussions

To test our hypothesis, we initiated our study by examining the glycosylation of *N*-Cbz cysteine methyl ester **2** with C(2)-*N*-*ortho*-(trifluoromethyl)benzylidene glucosamine *N*-phenyl trifluoroacetimidate **1** under previously established conditions (Table 1).[36] To our delight, the coupling of **2** with **1** was successful using 15 mol% nickel triflate, $Ni(OTf)_2$, (entry 1). As we expected based on the previously reported conditions,[36] the reaction with 5 mol% triflic acid, TfOH, proceeded to completion within 1 h at 35 °C (entry 2) to afford the desired thiol-linked glycoconjugate **4** in 68% yield with excellent selectivity (α : β > 20 : 1). This result is consistent with our recently reported mechanism of the triflic acid-catalyzed α-selective 1,2-*cis* glycosylation with *N*-phenyl trifluoroacetimidate electrophiles.[36] Specifically, triflic acid engages in the activation of electrophile **1** to generate a glycosyl triflate intermediate, which then undergoes equilibration from the stable α-anomer to the more reactive β-anomer. Subsequent $S_N2$-like displacement of the reactive β-anomer of glycosyl triflate by **2** results in the formation of **4** with exclusive α-configuration.

We observed that while the reaction proceeded to completion faster with use of triflic acid, the glycal elimination product derived from donor **1** was also detected (see Fig. S1† for details). Lowering the reaction temperature (entry 3) and catalyst loading (entry 4) provided a similar outcome (Table 1). To address the problem of **1** from undergoing elimination, the cysteine residue **2** was utilized as the limiting reagent in the presence of 1.5 equiv. of donor **1**. This modification improved the yield to 76% (entry 5). Further increasing the donor **1** to two equivalents gave the desired coupling product **4** in an enhanced 81% yield while maintaining high levels of selectivity (entry 6). Most notably, the glycosylation reached completion within 1 h at 25 °C with use of 5 mol% TfOH to provide **4** with comparable yield and α-selectivity (entry 7). The cysteine residue **3** with *N*-Fmoc protection, commonly utilized in the solid-phase peptide synthesis (SPPS), also displayed good efficiency (entry 8) to provide the desired glycoconjugate **5** (Table 1) in good yield and α-selectivity.

With the optimized conditions in hand, we evaluated the scope of the triflic acid-catalyzed *S*-glycosylations (Fig. 1) using

Table 1 Optimization of the reaction conditions[a]




| Entry | 1 (equiv.) | 2 or 3 (equiv.) | Catalyst | Temp. (°C) | Time (h) | 4 or 5 yield (α : β) |
|---|---|---|---|---|---|---|
| 1 | 1 | **2** (1.5) | 15 mol% $Ni(OTf)_2$ | 35 | 16 | **4**: 66% (>20 : 1) |
| 2 | 1 | **2** (1.5) | 5 mol% TfOH | 35 | 1 | **4**: 64% (>20 : 1) |
| 3 | 1 | **2** (1.5) | 5 mol% TfOH | 25 | 2 | **4**: 68% (>20 : 1) |
| 4 | 1 | **2** (1.5) | 1 mol% TfOH | 25 | 20 | **4**: 67% (>20 : 1) |
| 5 | 1.5 | **2** (1.0) | 3 mol% TfOH | 25 | 3 | **4**: 76% (>20 : 1) |
| 6 | 2 | **2** (1.0) | 3 mol% TfOH | 25 | 3 | **4**: 81% (>20 : 1) |
| 7 | 2 | **2** (1.0) | 5 mol% TfOH | 25 | 1 | **4**: 80% (>20 : 1) |
| 8 | 2 | **3** (1.0) | 5 mol% TfOH | 25 | 1 | **5**: 78% (>20 : 1) |

[a] The reaction was conducted with 0.1–0.2 mmol of donor **1**. Yields of the isolated product averaged two runs. The (α/β) ratios were determined by $^1H$ NMR analysis.

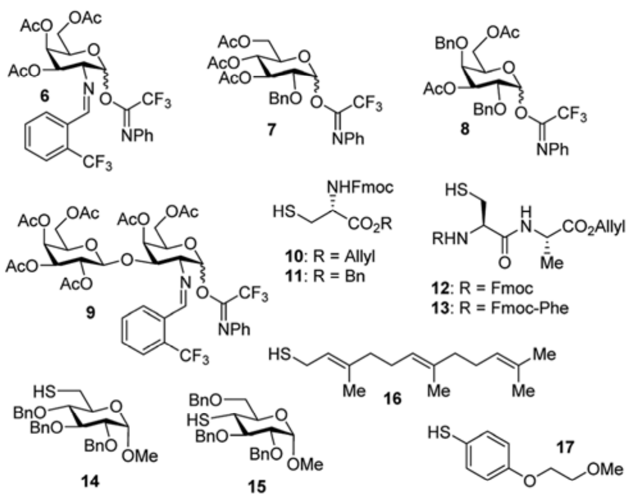


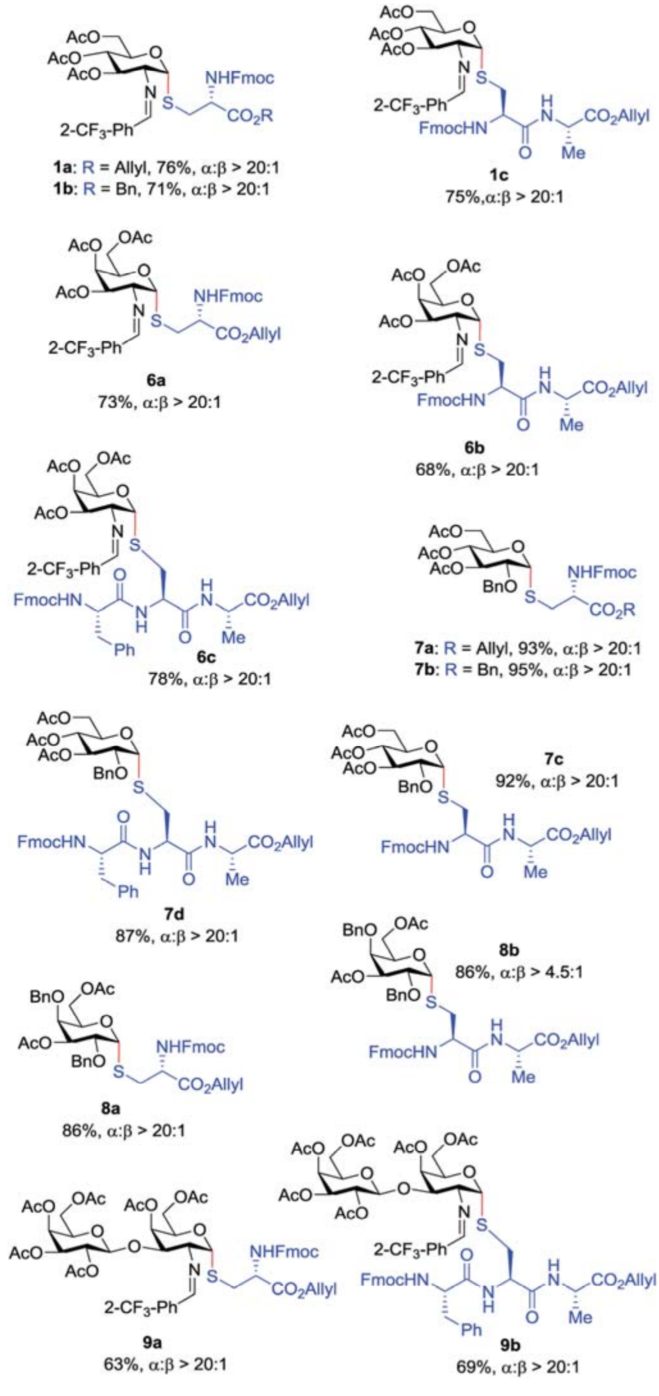

Fig. 1 Carbohydrate donors and thiol-containing acceptors.

glycosyl *N*-phenyl trifluoroacetimidate donors (**1**, **6–9**) and thiol-containing molecules (**10–17**). Based on our previous study,[36] we anticipated that *N*-phenyl trifluoroacetimidates **1**, **6** and **7** would exhibit high α-selectivity because their C(2)-*N*-benzylidene and C(2)-benzyl ether can modulate the electronic properties of the anomeric carbon, facilitating isomerization of the glycosyl triflate intermediate. Indeed, both donors **1** and **6** were effectively glycosylated to cysteine amino acids **10** and **11** to provide **1a**, **1b**, and **6a**, respectively, in good yield and with excellent α-selectivity (Table 2). There are several underlying factors that could influence the stereochemical outcome of the coupling event. To confirm that the α-selectivity arise from the directing ability of the C(2)-*N*-benzylidene group, we also coupled C(2)-azido donors **18** and **19** with cysteine residue **10** under standard conditions (Scheme 1). The desired products **18a** and **19a** were obtained with poor levels of α-selectivity (α : β = 1.6 : 1 to 2 : 1).

These results in Scheme 1 support the importance of the C(2)-*N*-benzylidene group in the triflic acid-catalyzed stereoselective α-1,2-*cis* *S*-linked glycosylation. Next, we expanded nucleophilic scope from single cysteine amino acid to more complex peptides. Both dipeptide **12** and tripeptide **13** (Fig. 1) performed well under the standard conditions with **1** and **6** to afford glycopeptides **1c**, **6b**, and **6c** (Table 2), presaging the potential utility of this transformation for access *S*-linked glycopeptides of tumor-associated mucin $T_N$ and $T_F$ antigens (*vide infra*).[11,44]

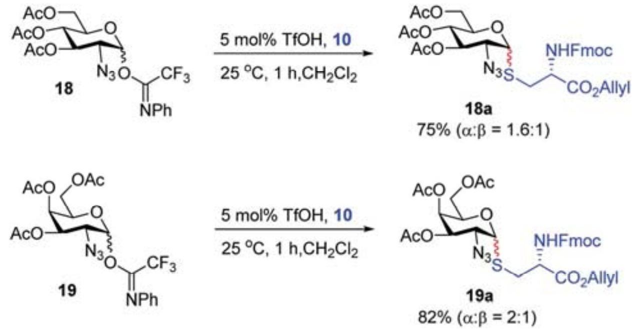
In addition to C(2)-*N*-benzylidene electrophiles **1** and **6**, the C(2)-*O*-benzyl protecting group is tolerated. Glucose donor **7** (Table 2) was an effective electrophilic partner, providing the coupling products **7a–7d** in excellent yields (87–95%) with exclusive α-configuration. More importantly, donor **7** does not generate a glycal elimination product. Employing the axial 4-*O*-benzyl protected donor **8** in place of the equatorial 4-*O*-acetyl group (**7**) slightly diminished the α-selectivity (**8a:** α : β > 20 : 1, **8b:** α : β = 4.5 : 1). Nevertheless, this result illustrates the ability of this catalytic system to overturn the inherent bias of D-galactose donors whose axial C(4)-*O*-benzyl protecting group

Table 2 Scope with respect to cysteine-containing peptides[a]




[a] All reactions were conducted with donor (2 equiv.), acceptor (1 equiv.) and 5 mol% TfOH in $CH_2Cl_2$ at 25 °C for 1 h. Yields of isolated *S*-linked glycopeptides averaged two runs. The (α/β) ratios were determined by $^1$H NMR analysis.

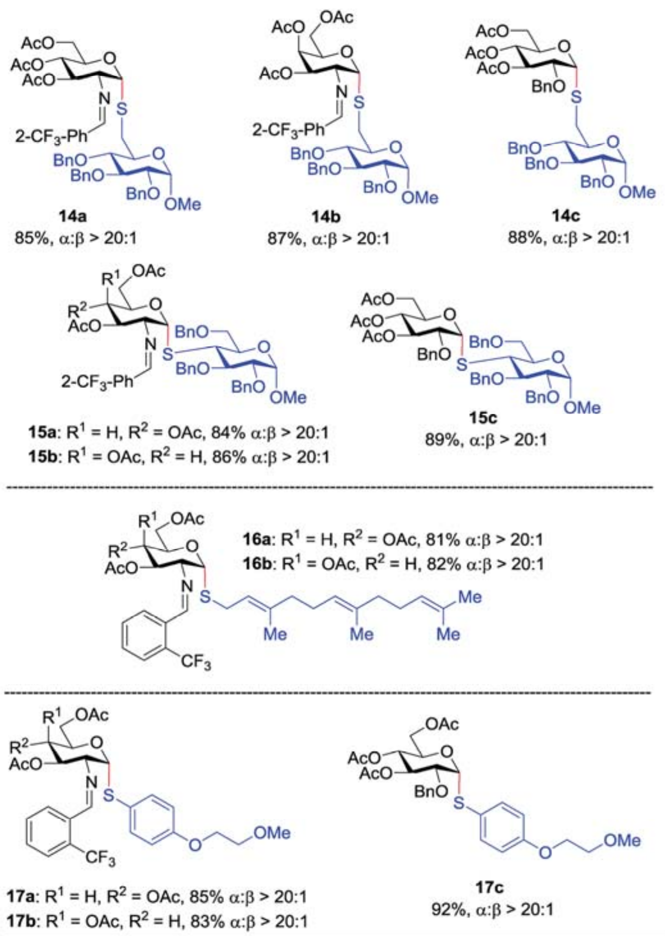
has been reported to favor β-products.[41] The difference in α-selectivity between the coupling products **8a** and **8b** could be explained by the relative rate for anomerization of the α-to the β-glycosyl triflate intermediate generated from the reaction of glycoyl electrophile **8** with triflic acid. Since a dipeptide is




Scheme 1 Glycosylation with C(2)-azido donors **18** and **19**.

a more reactive nucleophile than a cysteine amino acid residue, less time is allowed for anomerization of the α-triflate to the more reactive β-triflate, resulting in decreasing the α-selectivity observed in the coupling product **8b**. Finally, disaccharide donor **9**, a carbohydrate motif of $T_F$ antigen,[42] was readily coupled to provide the corresponding 1,2-*cis* *S*-glycoconjugates **9a** and **9b** (63–69%, α : β > 20 : 1).

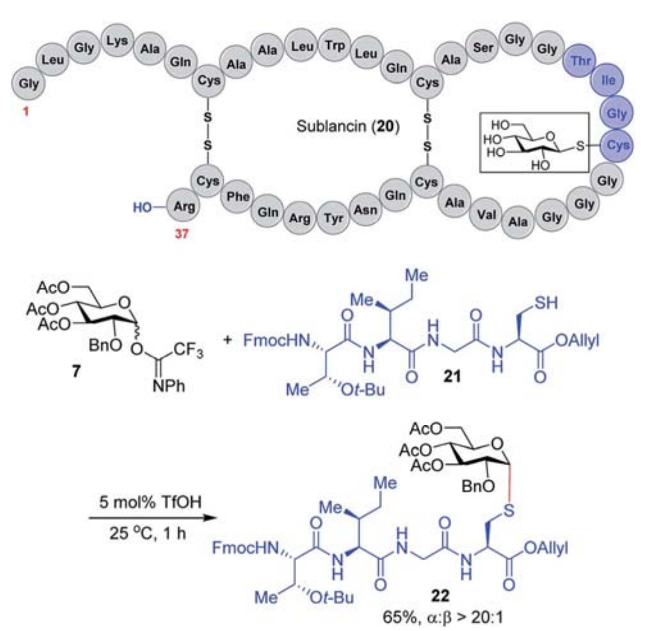
Table 3 Scope with respect to thiol-containing acceptors[a]




[a] See Table 2.

Inspired by the above discovery, we next examined the scope with respect to nucleophilic coupling partners **14–17**. As illustrated in Table 3, the glycosylations of primary (**14**) and secondary (**15**) thiol acceptors with donors **1**, **6**, and **7** proceeded smoothly to produce the desired *S*-linked disaccharides **14a–c** and **15a–c** in good yields (84–89%) with exclusive α-selectivity. The *trans*,*trans*-farnesyl mercaptan **16** was also a suitable nucleophile (**16a**, **b**), revealing the potential utility of this method for preparation of *S*-linked glycolipids. Recently, Messaoudi and co-workers reported the Pd-mediated cross coupling of aryl iodides with β-glycosyl thiols to generate *S*-linked glycosides with exclusive β-configuration.[30] For comparison, we examined the coupling efficiency of our method with aryl thiol **17**. To our delight, the reaction compared favorably with excellent α-stereoselectivity and yield (**17a–c**).

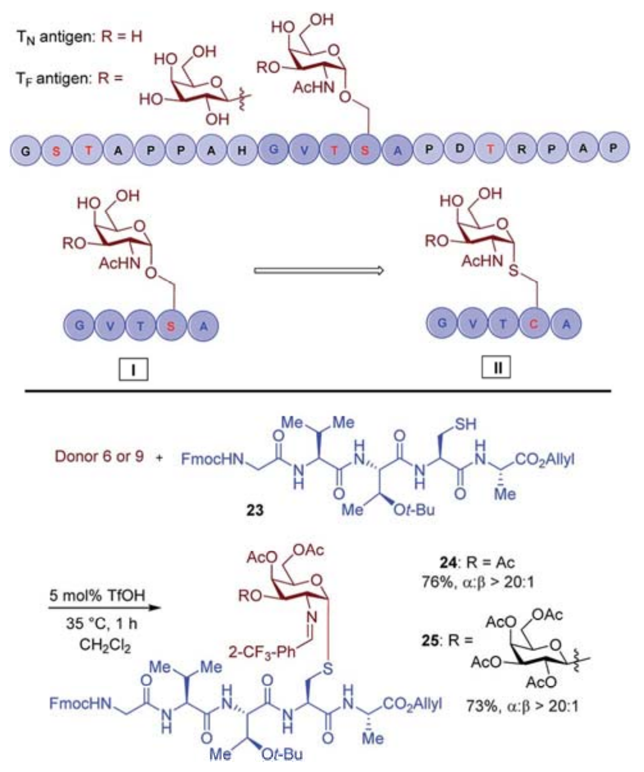
We expect that the triflic acid-catalyzed α-1,2-*cis* *S*-linked glycosylation method will be particularly useful when applied to the synthesis of bioactive glycopeptides. To establish the potential of a late-stage glycosylation approach, we prepared the tetrapeptide sequence surrounding the β-linked D-glucose unit in sublancin **20** (Scheme 2). This *S*-linked glycosyl unit is essential for antimicrobial activity.[12] SunS, the recently discovered *S*-glycosyl transferase enzyme, is responsible for the unusual glycosylation of cysteine residues with carbohydrates.[12] It has a relaxed substrate specificity and is able to glycosylate other hexose sugars, which has allowed its use in the preparation of sublancin analogs bearing other β-linked glycans.[12,13] However, to the best of our knowledge, the activity of α-1,2-*cis* *S*-linked sublancin analogs has not been investigated,[10] presumably because of the difficulty of α-1,2-*cis* *S*-glycosylations. Our current catalytic method would provide an ideal approach for the assembly of such analogs. Accordingly, we investigated the coupling of tetrapeptide **21** with glucose donor **7** in the presence of 5 mol% triflic acid. The




Scheme 2 Synthesis of the sublancin glycopeptide fragment.

glycosylation proceeded to completion within an hour to provide glycopeptide **22** in 65% yield with exclusive α-selectivity (Scheme 2).

Another important application of this method is the preparation of *S*-linked glycopeptides as analogs of MUC1 type tumor-associated $T_N/T_F$ antigens. MUC1 is a glycoprotein that consists of a tandem 20 amino acids repeating unit, with five possible *O*-glycosylation sites (serine or threonine) (Scheme 3).[43] In normal cells, the protein backbone is decorated with complex oligosaccharides, while the glycosylation is incomplete in cancer cells. As such, multiple epitopes such as $T_N/T_F$ antigens are exposed to the immune system and can be targeted for the development of antitumor vaccines. A therapeutic vaccine employing multivalent $T_N$-antigen clusters and CS4+ T-cell epitopes (MAG-Tn3) has entered to clinical trials.[44] It has been reported that anti-$T_N$ monoclonal antibodies (mAbs) have a binding preference for $T_N$-Ser antigen, and the short MUC1 pentapeptide, GVTSA, is a suitable binding motif for mAbs.[43] Since the *S*-linked $T_N$ antigen has been proved to enhance the immunogenicity,[11] we sought to prepare *S*-linked $T_N/T_F$ antigen mimetics by exchanging the GVTSA sequence (I) for the GVTCA sequence (II) (Scheme 3). Accordingly, we investigated the coupling of GVTCA pentapeptide **23** with both monosaccharide donor **6** and disaccharide donor **9** in the presence of 5 mol% TfOH. The coupling proceeded smoothly at 35 °C for 1 h to provide the corresponding 1,2-*cis* *S*-linked glycopeptides **24** ($T_N$) and **25** ($T_F$) in 76% and 73% yield, respectively, with exclusive α-selectivity (Scheme 3).




Scheme 3 Substrate synthesis of *S*-linked $T_N$ and $T_F$ glycopeptide fragments.

## Conclusions

In conclusion, we have illustrated the utility of the triflic acid-catalyzed α-1,2-*cis* thiol glycosylation reaction using stable glycosyl *N*-phenyl trifluoroacetimidates and thiol-containing molecules. This catalytic system obviates the need for substrate prefunctionalization and furnishes a diverse collection of synthetically valuable *S*-linked glycopeptides, oligosaccharides, and glycolipids with excellent α-selectivity under mild and operationally simple conditions. Notably, the facile nature of this reaction have also successfully applied to the synthesis of *S*-linked glycopeptides of antimicrobial sublancin and tumor-associated mucin $T_N/T_F$ antigens. Our future investigations will focus on transforming the current method to automated synthesis for the synthesis of the α-1,2-*cis* *S*-linked glycosides.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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