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Review

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Stereoselective glycosylation strategies: readily available donors and synthetic applications

Stephanie Norsikian

Université Paris-Saclay, CNRS, Institut de Chimie des Substances Naturelles, UPR 2301 1, Avenue de la Terrasse, 91198, Gif-sur-Yvette, France
Email: stephanie.norsikian@cnrs.fr

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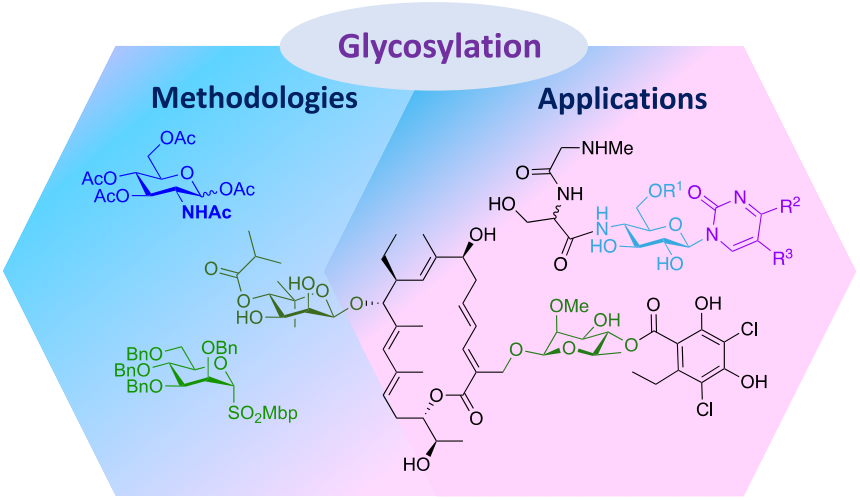
Abstract

This personal account highlights our recent efforts to develop efficient and stereoselective glycosylation methods, including applications at scale. Key advancements feature the use of readily available donors, such as peracetylated *N*-acetyl-D-glucosamine and mannosyl aryl sulfones, which are activated by metal triflates. Our work also encompasses multi-step syntheses of glycostructures, such as peptidyl nucleosides (gougerotin analogs) and a natural product, tiacumicin B, where sulfoxide donors play a pivotal role.



Keywords: Glycosylation, *N*-Acetyl glucosamine, natural product and analogs total synthesis, peptidyl nucleosides, gougerotin analogs, tiacumicin B, sulfoxide donors

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1. Introduction

Carbohydrates and carbohydrate-containing molecules have been extensively studied for their therapeutic potential, with over 50 carbohydrate-based drugs approved in the past two decades.[1] They have also been investigated for their role in plant growth control.[2] Many are either natural products or derivatives of naturally occurring carbohydrate structures. The synthesis of these compounds often relies on glycosylation, a key reaction in which a glycosyl acceptor interacts with a glycosyl donor in the presence of a promoter that activates the leaving group under appropriate conditions.[3,4] This process generates various reactive intermediates, ranging from covalent species to oxocarbenium ions. A nucleophile can attack these intermediates by exhibiting S_N1 or/and S_N2 characteristics, forming the α- or β-anomer. The exact position of the glycosylation event within this mechanistic spectrum is dictated mainly by the reactivity of both the donor and acceptor glycosides.[5] Despite significant advancements in the field, no universal method for glycosylation exists, as numerous factors influence stereoselectivity. External parameters such as temperature, concentration, and solvent choice can significantly impact the outcome. Additionally, the protecting groups on donors play a crucial role, contributing to steric hindrance, inducing conformational changes, and enabling neighboring participation or intramolecular delivery, all of which can be leveraged to control stereoselectivity.

Over the past few years, we have been developing methodologies for glycosylation reactions with an emphasis on achieving high efficiency and complete stereoselectivity, including in large-scale applications. These methods become even more valuable when they utilize readily available donors and cost-effective, non-toxic promoters. In this context, we have explored glycosylation strategies with *N*-acetyl glucosamine donors and mannosyl aryl sulfone, employing metal triflates as promotors. Additionally, our research extends to the multi-step synthesis of natural glycostructures and biologically-relevant analogs. Notably, we have synthesized peptidyl nucleosides, which are analogs of gougerotin, a natural antifungal compound.[6] Furthermore, we completed the total synthesis of tiacumicin B, a natural antibiotic,[7,8] and its analogs. In both cases, using sulfoxide donors played a critical role in ensuring the success of these syntheses.

2. Glycosylation with Metal Triflate as Promotor

2.1. *N*-acetyl glucosamine derivatives

Many naturally occurring glycoconjugates contain *N*-acetyl-D-glucosamine residues linked *via* a 1,2-*trans* glycosidic bond.[9] These compounds play crucial roles in biological systems, such as structural polysaccharides, circulating signaling molecules, tumor markers, anticoagulants, and glycoproteins.[10] Additionally, they can

serve as key components of bioactive small molecules such as tunicamycin[11] or streptozotocin,[12] two natural antibiotics. Obtaining these compounds from natural sources is often challenging. The primary difficulty in their synthesis lies in forming the glycosidic bond through glycosylation. With an *N*-acetylglucosamine donor **1a**, the glycosylation reaction typically proceeds through the formation of an oxazolinium intermediate **2a**, which promotes the selective formation of a β-glycosidic bond (Figure 1). This β-stereoselectivity, combined with the NHAc motif, is commonly found in natural glycoconjugates. However, the oxazolinium **2a** intermediate rapidly converts into oxazoline **3**, a more stable, and, therefore, less reactive species. This transformation significantly slows the reaction rate and reduces yield of **4a**, particularly when the glycosyl acceptor is sterically hindered or poorly nucleophilic. To overcome this challenge, various strategies have been developed.

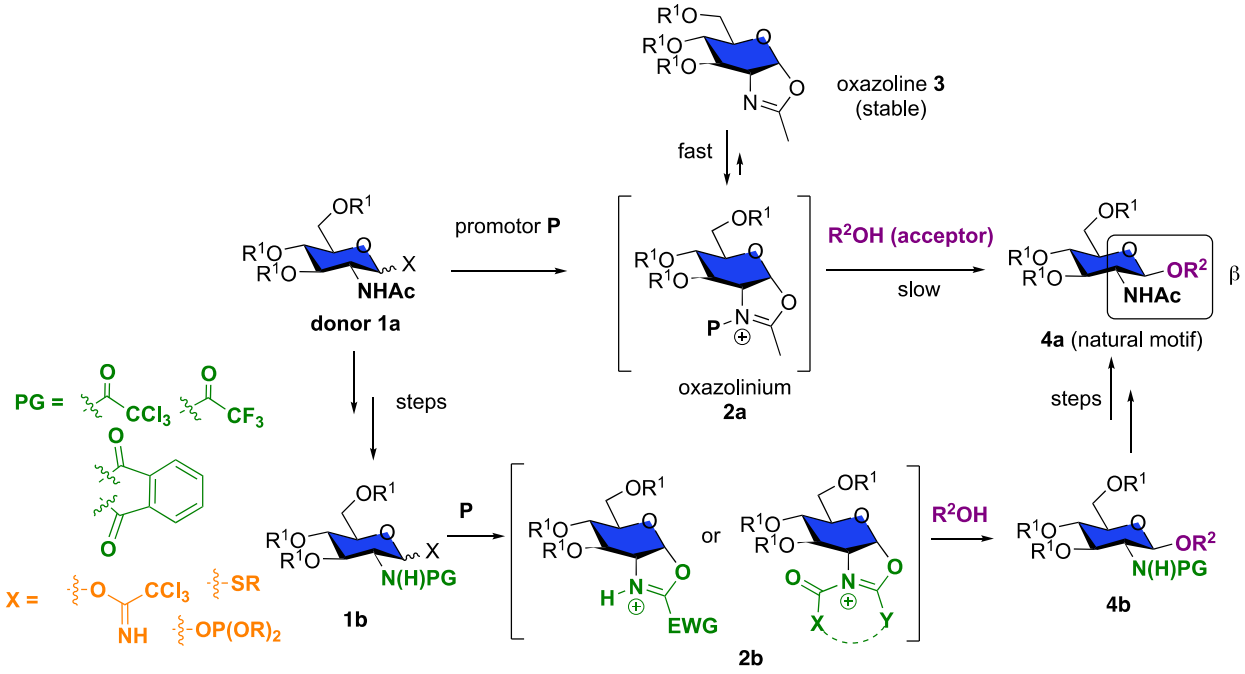
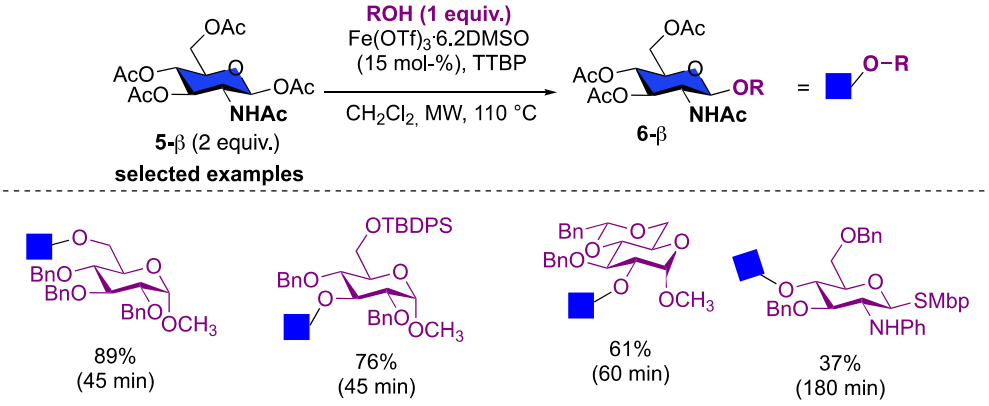


Figure 1. General approaches for the synthesis of GlucNAc glycosides.

One common approach involves the introduction of a temporary amine-protecting group that destabilizes both the oxazolinium intermediate **2b** and its corresponding oxazoline.[13,14] Alternative methods modify the reaction conditions to either bypass the oxazolinium intermediate or utilize oxazoline directly as a glycosyl donor.[15] Additionally, specific activatable leaving groups—such as trichloroacetimidates, phosphites, thioalkyls or thioaryls—are often employed to enhance reactivity.[3] These strategies, however, require additional synthetic steps for donor preparation and subsequent conversion to the natural acetamide group. The most cost-effective and practical approach remains glycosylation in the presence of the acetamide group. As a result, various optimized reaction conditions have been reported in the literature to improve efficiency while maintaining the natural structural features of the glycoside.[16]

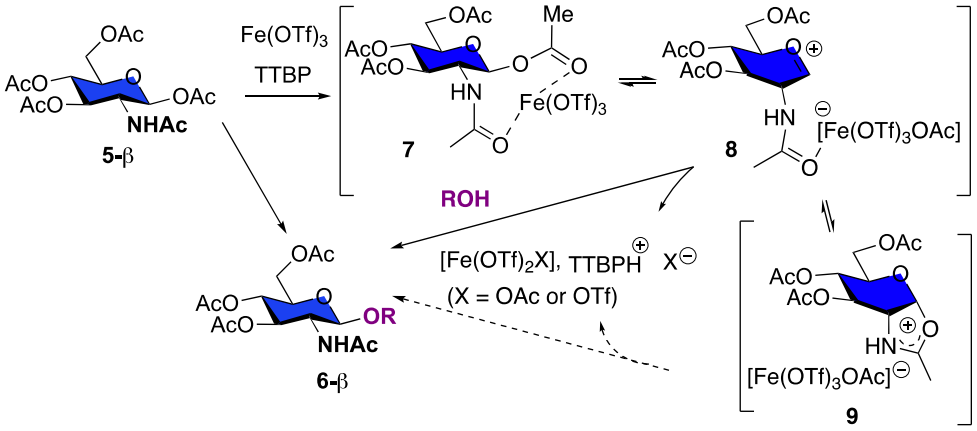
For our part, we developed a glycosylation process using peracetylated β-*N*-acetyl-D-glucosamine **5-β** as the donor in the presence of a catalytic amount of iron(III) triflate.[17,18] Under optimized conditions, the reaction occurs with an excess of the donor (2 equiv.) in anhydrous dichloromethane and 2,4,6-tri-*tert*-butylpyrimidine (TTBP). To compensate for the donor's low reactivity, the reaction is conducted at 110 °C for 45 minutes using microwave irradiation. The promoter, used at 15 mol %, can be either commercially available

iron(III) triflate or a DMSO-complexed form ($Fe(OTf)_3$•6.2DMSO). Both yielded identical results, but the complexed iron triflate was preferred due to its lower hygroscopicity and ease of preparation. The addition of TTBP,[19] as a hindered base, was found to be critical to enable reactions with acid-sensitive acceptors and prevent α-anomerization. It helps buffer the reaction medium, where triflic acid can form, and also slows the reaction rate, which otherwise proceeds via an oxycarbenium ion pathway involving either the cleavage of an exocyclic bond or the cleavage of an endocyclic bond followed by recycling to the more stable α-glycoside. These conditions enable the efficient formation of β-(1,6), β-(1,3), and β-(1,2)-linked disaccharides **6-β** bearing various functional groups from donor **5-β**. Glycosylation at position 4 proved less efficient,[20,21] yielding the corresponding disaccharides in only moderate amounts, with no successful improvements in yield. In this study, we showed that $Fe(OTf)_3$•6.2DMSO and $Fe(OTf)_3$ offered similar or even superior performance to previously described methods, including those using other Fe(III) salts and $Sc(OTf)_3$.[16]



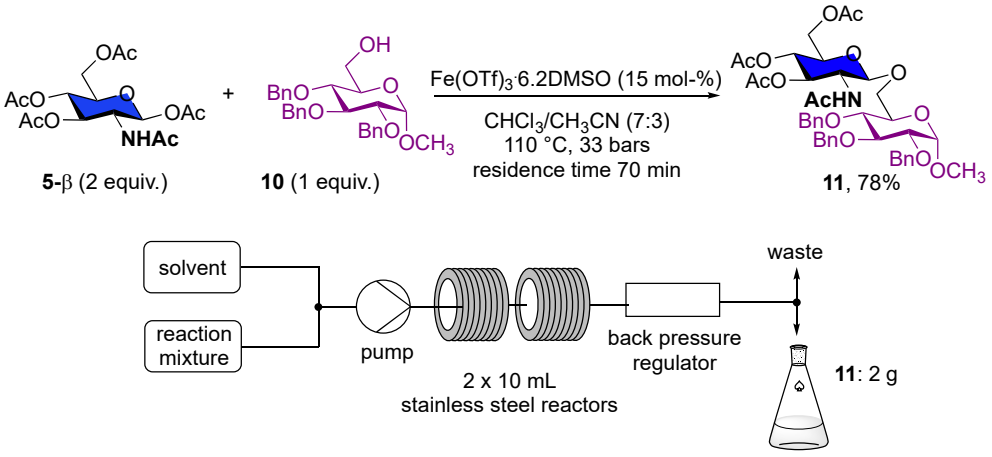
Scheme 1. Iron(III) triflate-mediated glycosylation with peracetylated β-*N*-acetyl-D-glucosamine **5-β.**

From a mechanistic perspective, the catalyst both activates the anomeric acetate, but also interacts with the acetamide-protecting group by complexation via the putative intermediate **7**. This interaction may facilitate glycosylation by allowing the acceptor to attack either the resulting ionic pair intermediate **8** or the oxazolinium species **9**. In both scenarios, the observed excellent β-stereoselectivity can be attributed to steric hindrance on the α-face, preventing the formation of the α-product.



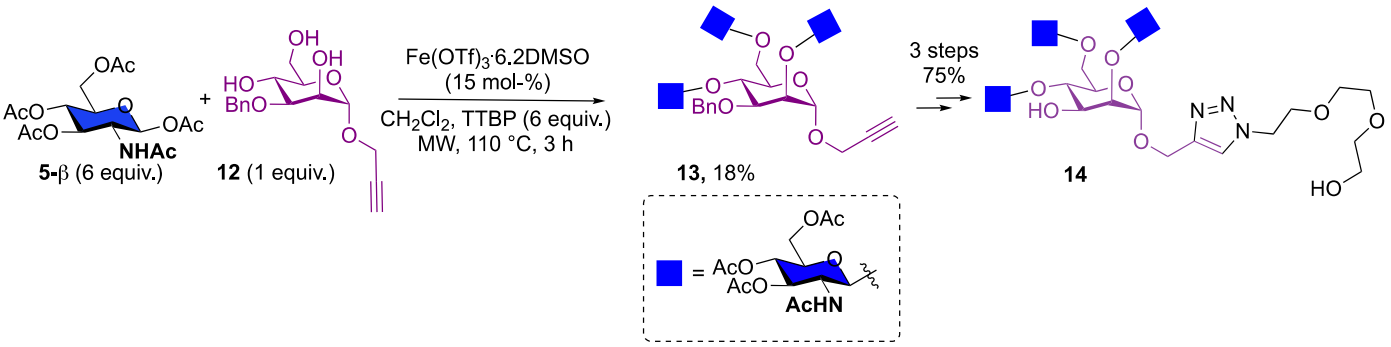
Scheme 2. Putative mechanism of the iron(III) triflate-mediated glycosylation with **5-β.**

Using donor **5-β**, the reaction was also adapted for flow chemistry with the Vapourtec R4-Unit (Scheme 3).[18] This technique has many advantages, some of which are similar to those of microwave activation, particularly regarding very efficient mass and heat transfer, and the possibility of working at a temperature higher than the boiling point of the solvent.[22] Due to the limited solubility of iron triflate in DCM, however, a direct translation was not possible. To address this, we performed the reaction in a DCM/ACN solvent mixture (7:3 ratio v/v). In this modified system, the reaction proceeded more slowly, requiring an extended reaction time of 70 minutes (compared to 45 minutes in batch) to achieve, with acceptor **10**, a 78% yield of the desired product. Notably, under these conditions, TTBP could be omitted, which is advantageous given its relatively high cost. When scaling up the reaction, DCM is replaced by chloroform, enabling the synthesis of 2 g of disaccharide **11** with a comparable yield and selectivity (>95:5).



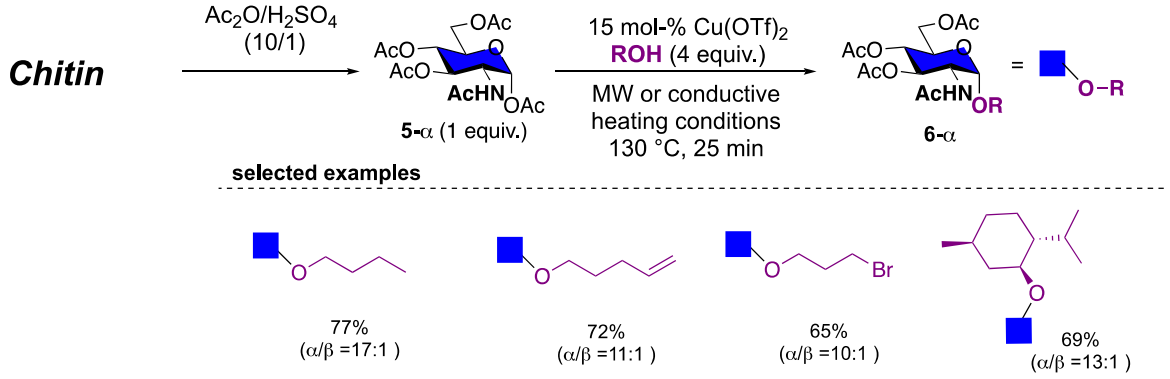
Scheme 3. Iron(III) triflate-mediated glycosylation with **5-β** in flow chemistry.

This activation method was then applied to the synthesis of complex *N*-glycan motifs. For this approach, we selected a mannoside acceptor bearing a 2-methyl-5-*tert*-butylphenylthio (SMBP) group at the anomeric position.[23] The reaction was conducted under microwave heating at 110 °C in DCM, similar to previous conditions, but with extended reaction times. Two equivalents of both the donor and TTBP were used per glycosylation site to ensure efficient glycosylation. Using differentially substituted mannoside acceptors, we successfully synthesized tri-, tetra, and pentasaccharides in a single step, with yields ranging from 16% to 28%. While these yields are moderate, this method directly utilizes the natural acetamide group of the glucosamine units, eliminating the need for conventional protection and deprotection steps. As a result, this synthetic route is significantly shorter than those typically reported in the literature.[24-26] Specifically, glycosylation of the mannoside acceptor **12** with peracetylated glucosamine **5-β** using iron triflate yielded a tetrasaccharide **13**, which was isolated with an 18% yield (Scheme 4). This tetrasaccharide was then coupled to a triethylene glycol linker containing an azide functional group via CuAAC (copper-catalyzed azide-alkyne cycloaddition) in a dichloromethane/water mixture, using a catalytic amount of copper sulfate and sodium ascorbate. Following this step, deprotections were performed resulting in the fully deprotected product **14** with an overall three-step yield of 75% from tetrasaccharide **13**.



Scheme 4. Iron(III) triflate-mediated synthesis of complex *N*-glycan motifs.

The previously described glycosylation catalyzed by iron(III) triflate proceeds, exclusively, with the β-donor, while the α-derivative remains unreactive. We also demonstrated that peracetylated α-*N*-acetyl-D-glucosamine **5-α** can be activated using a catalytic amount of Cu(II) triflate (Scheme 5).[27] The starting material was readily obtained in pure form through a one-step chitin acetolysis.[28] In the presence of 15 mol % copper(II) triflate ($Cu(OTf)_2$) and various acceptors, the reaction occurs in 1,2-dichloroethane (DCE) at 130 °C for 25 minutes, either under microwave irradiation or conventional heating in a sealed reactor (Monowave 50 reactor, Anton Paar GmbH). Additionally, we observed that the resulting glycosides predominantly show an α-selectivity, likely due to post-reaction anomerization of the initially formed β-product. While this approach does not apply to glycosyl acceptors, it complements existing methods, as synthesizing 1,2-*cis*-glycosides of GlcNAc typically requires a non-participating group at C-2, such as an azide.[13,14]



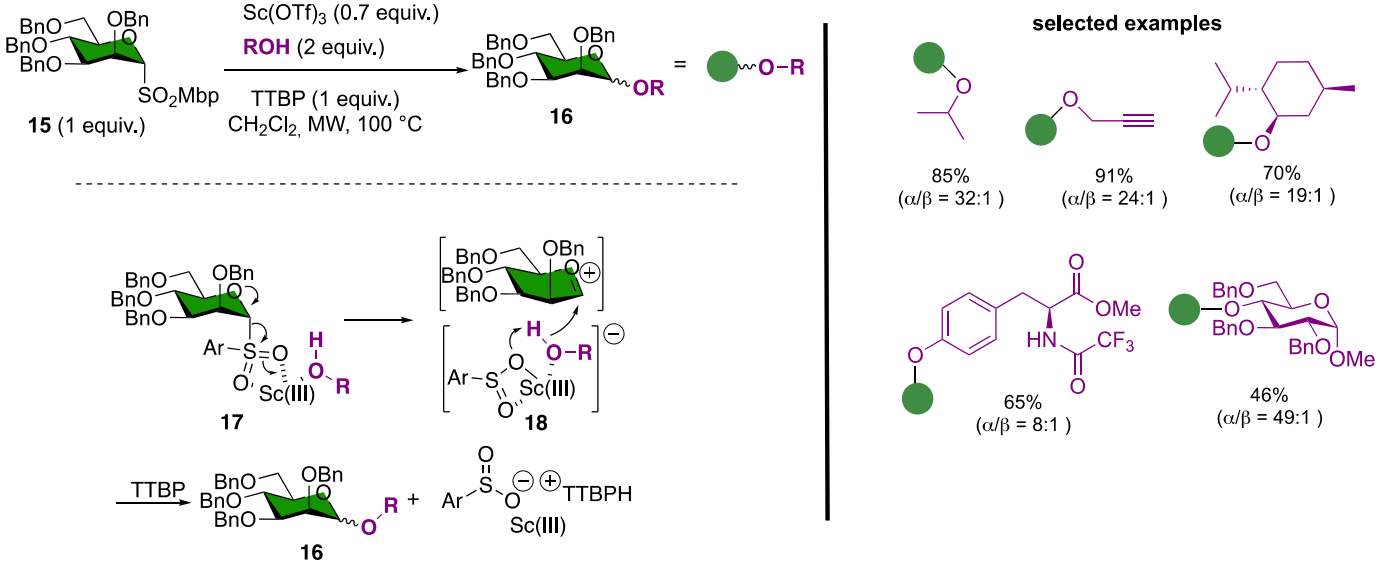
Scheme 5. Copper(II) triflate-mediated glycosylation with peracetylated α-*N*-acetyl-D-glucosamine **5-α.**

2.2. Activation of mannosyl aryl sulfone derivatives

Various methods for α-mannosylation have been described in the literature, with stereoselectivity typically attributed to the participation of the donor's C2 group or, in some cases, remote participation from the C3 or C6 positions.[3,4,29] Fully α-stereoselective mannosylations without a participating group, however, are far less common. In many cases, the selectivity observed depends on multiple factors, including reaction conditions and the nature of the acceptor. Some of the most effective methods rely on post-anomerization, where an initially formed β-product is converted into the α-product under the reaction conditions. Regarding glycosyl sulfones, the use of activatable sulfonyl groups for *O*-glycoside synthesis is extremely rare, with only two reported examples. The first, developed by Ley's team, involves deoxyglycoside or glycal donors activated with magnesium bromide etherate and sodium bicarbonate under sonication or reflux heating.[30,31] The second

example, reported by Chang and Lowary, involved the use of an activatable pyridyl sulfone group in the presence of samarium(III) triflate.[32] While this method produced mono- and disaccharides in good yields, the stereoselectivity was only moderate (2:1 to 10:1).

In our work, we observed that the armed mannosyl sulfone donor **15** could be effectively activated using iron(III) triflate in the presence of one equivalent of TTBP under microwave irradiation at 100 °C.[33] In dichloromethane, the reaction required 0.7 equivalents of the promoter. When isopropanol was used as the acceptor, the glycosylation product was obtained after 90 minutes with a good yield of 71% and an α/β ratio of 49:1. During this reaction, we detected the presence of a benzylmannoside by-product, likely due to the partial deprotection of benzylic protecting groups on the donor. This deprotection generated benzyl alcohol, which, being more reactive than isopropanol, acted as an alternative acceptor. We then explored glycosylation with other metal triflates, but found that they resulted in lower conversion rates and reduced stereoselectivity compared to $Fe(OTf)_3$. Scandium(III) triflate ($Sc(OTf)_3$), however, proved to be an effective promoter, yielding glycosylation adducts in 85% yield with an α/β ratio of 32:1, while also eliminating the formation of the benzylmannoside by-product (Scheme 6).



Scheme 6. Scandium(III) triflate-mediated glycosylation with mannosyl aryl sulfone derivatives. Mbp = 2-methyl-5-*tert*-butylphenyl.

$Sc(OTf)_3$ is known for its strong oxophilicity and higher Lewis acidity, which can be attributed to its small ionic radius compared to other rare earth triflates.[34] A possible mechanism for glycoside formation involves complexation, where both the donor and acceptor interact with Sc(III) via the donor's sulfone oxygen atoms and the acceptor's hydroxyl group. Cleavage of the C–S bond generates an oxacarbenium ion **18** and an arenesulfinate ion. The glycosylation reaction then proceeds through a nucleophilic attack by the alcohol, leading to a mixture of α- and β-C-glycosides. The observed selectivity is partially attributed to a post-anomerization process occurring during prolonged heating, although further experimental studies are required to confirm this mechanism. With $Sc(OTf)_3$ as the standard activator, we also explored glycosylation with various functionalized acceptors to produce simple glycosides and disaccharides with yields ranging from moderate to excellent (43-91%). This method is compatible with a wide range of functional groups (NHFmoc, NHCbz, NHTFA, NHTCA, NPhth, N_3, OTBDPS, Br, alkene, alkyne) and with gluco- and galactosyl sulfone donors, albeit with significantly lower α/β selectivities (1.7:1 and 1.6:1 respectively). This study demonstrates that our

method offers a complementary strategy to existing approaches for achieving α-mannosylation in the absence of participating groups.[3,4,29]

3. *N*- and *O*-glycosylation with Sulfoxide Donors for Access to Natural Products or Analogs

Since Kahne introduced sulfoxide as a glycosyl donor in 1989,[35] its significance in glycosylation reactions, especially for total synthesis, has been firmly established.[36] In the following part, we will present two examples of complex target preparation in which sulfoxide donors played a key role. The discussion will focus on the glycosylation strategies rather than the whole synthesis.

3.1. Preparation of gougerotine analogs

Gougerotin was first isolated in 1962 from *Streptomyces gougerotii* and is classified as a peptidylnucleoside.[6] Its structure features a glucan-type pyranose saccharide motif with a carboxamide group at the C-5 position (Figure 2). Additionally, a dipeptide composed of D-serine and sarcosine is attached at the C-4 position, while the anomeric center is *N*-linked to a cytosine base by a β-glycosidic bond. Gougerotin exhibits broad biological activity, including antiviral,[37] antifungal,[38] antiparasitic, and antibacterial properties.[39] Its mechanism of action involves inhibiting protein synthesis in both prokaryotic and eukaryotic systems. While effective in preventing and treating plant diseases, its phytotoxicity limits its direct agricultural application.[40] To enhance crop specificity, we focused on developing gougerotin analogs **19**.[41]

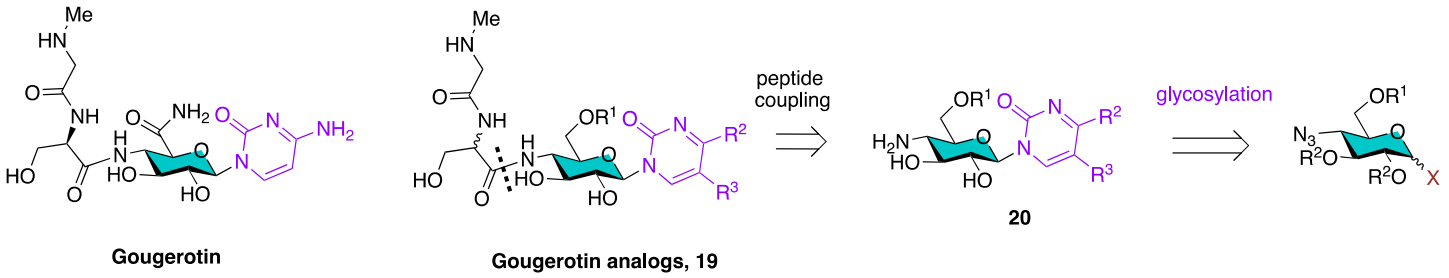


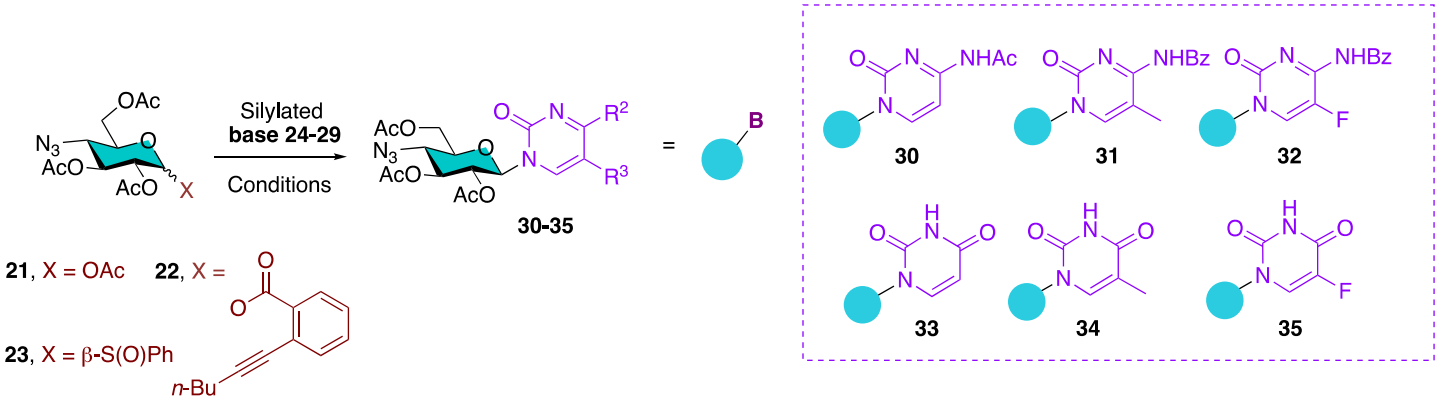
Figure 2. Retrosynthetic pathway to gougerotin analogs.

Our approach involves replacing the natural nucleic base with alternative pyrimidine bases while maintaining the glucopyranosyl core. The C-5 carboxamide group has also been replaced with a free hydroxymethyl group. The synthetic approach for these analogs relies on peptide coupling between the target dipeptide and the corresponding amine **20**. To assess the potential impact of the dipeptide motif on bioactivity, compounds incorporating L-serine instead of D-serine or a modified peptide have also been synthesized. The amine **20** was produced by reducing the corresponding azide, which was obtained after glycosylation of various bases and a donor carrying an azide at the C-4 position.

We began by glycosylating *N4*-Ac-cytosine **24**, the naturally occurring nucleobase in gougerotin, using the classical Vorbrüggen conditions with peracetylated donor **21** (Table 1).[42] The reaction was carried out in DCE or MeCN with the corresponding silylated cytosine, employing TMSOTf or $SnCl_4$ as promoters for 12 h at 55 °C. The best result with this base was obtained with 3 equiv. of $SnCl_4$, yielding the expected product **30** in 69% as a single β-anomer, facilitated by the anchimeric assistance of the 2-OAc group. When extending the reaction to other pyrimidine bases, however, lower yields were obtained. In particular, 5-Me-*N4*-Bz-cytosine

25 and 5-F-*N4*-Bz-cytosine **26** gave only 45% and 51% yields, respectively, which were expected outcomes given that pyranosyl donors rarely glycosylate these bases efficiently. The yield was even lower with silylated uracil **27**, producing only 25% of the desired product. To explore alternative glycosylation strategies, we tested compound **22** bearing *ortho*-hexynyl benzoate at the anomeric position. These donors were found to be highly effective for *N*-glycosylation of nucleobases under gold catalysis with mild conditions.[43] While uracil **27** afforded a good yield of 78%, other bases produced moderate yields ranging from 9% to 49%. Finally, we investigated the use of sulfoxide donors, which have been rarely applied to *N*-glycosylation with furanosyl or pyranosyl derivatives with only three examples reported in the literature.[44-46] Using six different silylated pyrimidine bases, the sulfoxide donor in combination with TMSOTf (1.5 equiv.) as a promoter generally provided the highest yields at 55 °C in MeCN (48-94%), demonstrating its potential as an effective alternative for *N*-glycosylation.

Table 1. *N*-Glycosylation of different pyrimidine bases with donors **21-23**



Bases	24	25	26	27	28	29
Donors						
21	69%[a]	45%[a]	51%[a]	25%	74%[a]	71%[b]
22	49%[c]	30%[c]	9%[c]	78%[c]	48%[c]	40%[c]
23	82%	88%	75%	94%	89%	48%[b]
Products	**30**	**31**	**32**	**33**	**34**	**35**

General conditions: N,O-bis(trimethylsilyl)acetamide (BSA) was used as a silylating agent. Unless otherwise stated, the reaction was performed with TMSOTf (1.5 equiv.) as the promoter for 12 h at 55 °C in MeCN. a) The reaction was performed with $SnCl_4$ (3 equiv.) in DCE for 12 h at 55 °C. b) HMDS (1.8 eq.) was used as a silylating agent with saccharine (5 mol %). c) BSTFA (N,O-bis(trimethylsilyl) trifluoroacetamide was used as a silylating agent, and the reaction was performed with Ph3PAuNTf2 (10 mol %) for 48 h at r.t.

After the glycosylation step, the azide group at C-4 position of the obtained compound was reduced to an amine, enabling peptide coupling with the dipeptide synthesized in parallel. Subsequent deprotection of the protective groups yielded various gougerotin analogs **19a-d** (Figure 3). Additionally, the presence of the azide group was exploited to perform a CuAAc reaction, providing access to a triazole-containing analog **19e**.

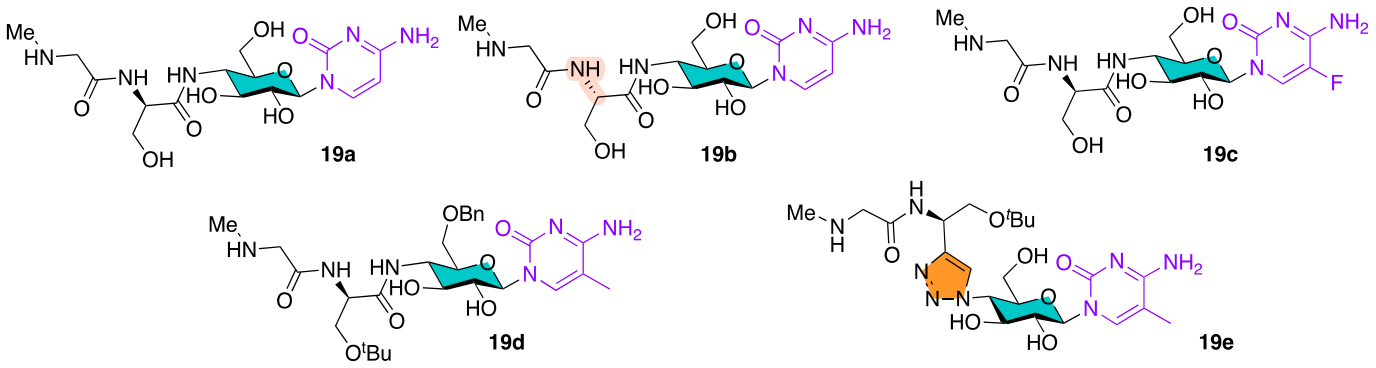


Figure 3. Examples of the obtained gougerotin analogs.

The antifungal activities of the synthesized analogs were evaluated in preventive tests against a panel of agriculturally-relevant pathogens, including *Podosphaera fuliginea* (SPHRFU), *Uromyces appendiculatus* (UROMAP), *Puccinia triticina* (PUCCRT), *Alternaria brassicae* (ALTEBA), *Botrytis cinerea* (BOTRCI), and *Zymoseptoria tritici* (SEPPTR). While some analogs exhibited promising bioactivity, none outperformed gougerotin itself. These results underscore the critical role of the carboxamide function and the dipeptide chain in maintaining full biological activity.

3.2. Total synthesis of tiacumicin B and analogs

Tiacumicine B (Tcn-B) represents a class of hybrid molecules composed of a polyketide backbone and sugar moieties (Figure 4).[47,48] Tcn-B, also known as clostomicin B1, fidaxomicin, and lipiarmycin A3, was initially isolated through the fermentation of actinobacteria.[7,8] This compound was granted marketing authorization in the USA in 2011 to treat nosocomial diarrhea caused by *Clostridium difficile*. Additionally, it has demonstrated activity against drug-resistant strains of *Mycobacterium tuberculosis*. Tiacumicin B exerts its antibacterial effects by inhibiting RNA polymerase (RNAP), binding to the "switch" region, and blocking RNA synthesis, ultimately leading to bacterial cell death.[49,50]

A distinctive structural feature of Tcn-B is its aglycone ring, which is conjugated with two rare sugars, D-noviose and D-rhamnose, via two 1,2-*cis* glycosidic linkages. Notably, the D-noviose unit carries an isobutyric ester at the C-4 position, while the D-rhamnose unit bears a homodichloroorsellinate ester at C-4, and a methoxy group at C-2 position. These two sugars can both be structurally related to D-mannose derivatives, characterized by an axial C–O bond at the C-2 position. In these sugars, the hydroxymethyl group at C-5 is replaced by a methyl group in D-rhamnose and by a gem-dimethyl group in D-noviose, respectively. For this class of sugars, glycosylation reactions leading to 1,2-*trans* derivatives are relatively straightforward, especially when a participating group is present. Achieving 1,2-*cis* linkages is significantly more challenging, however, as the formation of the α-anomer is favored due to steric effects and stabilization via the anomeric effect.[51,52]

Until 2020, the only total synthesis of Tcn-B was completed by the Gademann's group.[53,54] Their synthesis faced challenges in directly noviosylating the complete macrolide, which primarily produced the α-anomer. To circumvent this issue, D-noviose residue was introduced at an earlier stage, after glycosylation of aglycone fragment **36** (Figure 4). For this purpose, D-noviosyl bromide donor **37** was activated with HgO/$HgBr_2$,[55] leading to the formation of the desired β-anomer with a selectivity ratio of 1:3. The resulting intermediate was then subjected to a Suzuki cross-coupling reaction with **38**, followed by a ring-closing metathesis step and selective deprotection. The resulting acceptor **39** was subsequently glycosylated using D-

rhamnoside donor **40** bearing an anomeric imidate to afford the desired β-linked product with a selectivity ratio of 1:4. Tcn-B was then obtained after the removal of all protecting groups.

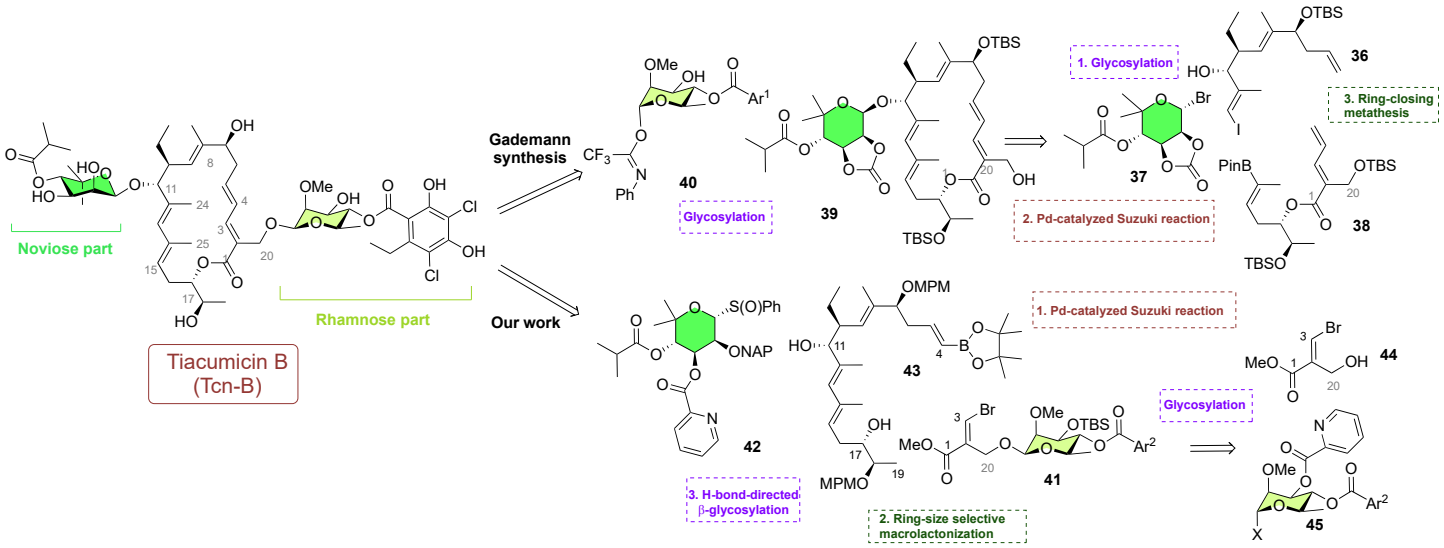
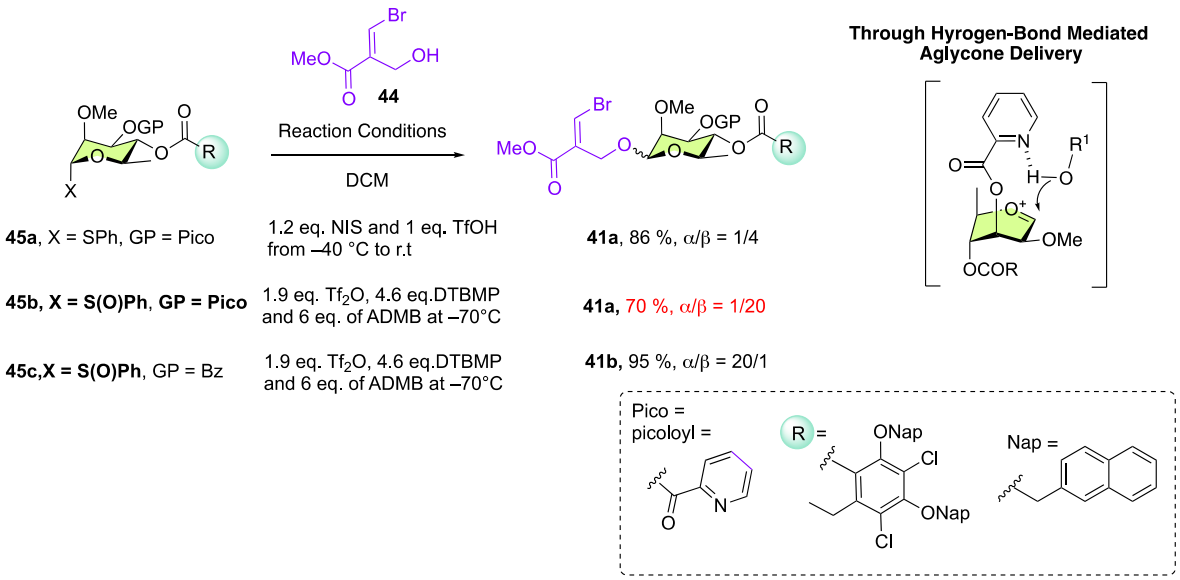


Figure 4. Retrosynthetic pathways for the total synthesis of tiacumicin B.

For our part, we chose to introduce the rhamnose derivative first, following an approach we had previously developed for aglycone synthesis,[56,57] specifically, a Suzuki reaction between boronic ester **43** and brominated derivative **41** (Figure 4).[58,59] After this step, ring-size selective macrolactonization will produce a monoglycosylated aglycone with a free hydroxyl group at C-11, ready for noviosylation. Since the macrolactone is known to be a poor glycosyl acceptor, however, this late-stage β-glycosylation posed a significant risk of failure.

To achieve the preparation of **41**, we focused on glycosylating acceptor **44** with donor **45a**, which bears a picoloyl group (Pico) at *O*-3 (Scheme 7). This glycosylation method, described by Demchenko,[60,61] involves a remotely positioned Pico group that can direct, through intermolecular H-bonding, a selective facial attack on the glycosyl donor. Activation of **45a** using dimethyl(methylthio)sulfonium triflate (DMTST) or *N*-iodosuccinimide (NIS) with catalytic TfOH was unsuccessful, as no glycosylation products were detected. Similarly, the 1-benzenesulfinyl piperidine (BSP)/Tf_2O activation method[62] at –60 °C in the presence of TTBP resulted in the degradation of the acceptor rather than successful glycosylation. Ultimately, increasing the amount of TfOH (1 equivalent) in combination with NIS (1.2 equivalents) in CH_2Cl_2 at –40 °C to room temperature, led to the successful formation of the desired compound **41a** in an 86% yield, although as a mixture of anomers (α/β = 1:4). Despite extensive optimization efforts - including variations in temperature, promoter, donor equivalents, and dilution - no significant improvements in selectivity were achieved.

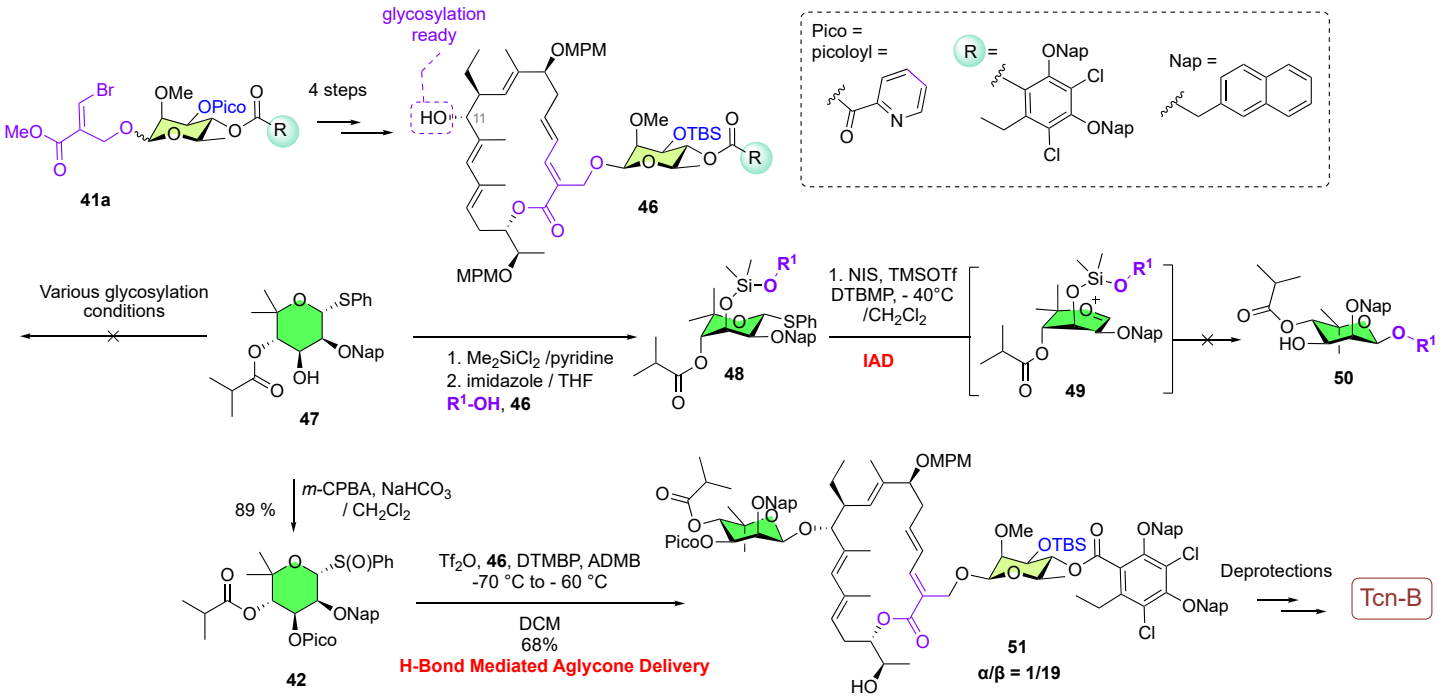


Scheme 7. Glycosylation of acceptor **44** with donors **45.**

To enhance β-selectivity, we explored the use of a sulfoxide anomeric leaving group, an approach that, to our knowledge, had never been applied in combination with a directing picoloyl group. Donor activation of **45b** was first carried out in CH_2Cl_2 at –50 °C using Tf_2O as the promoter, 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as the base, and 4-allyl-1,2-dimethoxybenzene (ADMB). The latter scavenges phenylsulfenyl triflate, a highly reactive byproduct, which forms after activation of anomeric sulfoxides with Tf_2O.[63] Under these conditions, we obtained the glycosylated product **41a** in 52% yield and a significantly improved facial selectivity (α/β = 1:12). Higher yield (70%) and selectivity (α/β = 1:20) could be further attained by lowering the temperature of the activation at –70 °C. To evaluate the role of the remote picoloyl group in directing the nucleophilic attack, we repeated the reaction using donor **45c**, in which the picoloyl group was replaced with a benzoyl group. This modification resulted in the exclusive formation of the α-glycosylation product **41b**, strongly suggesting that the Pico group promotes a hydrogen-bond-mediated Aglycone Delivery (HAD) mechanism.

After glycosylation, the Pico group was selectively removed and replaced with a TBS-protecting group. The resulting intermediate then underwent a Pd-catalyzed Suzuki cross-coupling reaction with boronic ester **43**, affording the corresponding ester in an excellent yield. Subsequent hydrolysis (Me_3SnOH)[64] yielded the seco-acid, which was then subjected to Shiina macrolactonization,[65] producing the target compound **46** with a free C-11 hydroxyl ready for the next noviosylation step (Scheme 8).

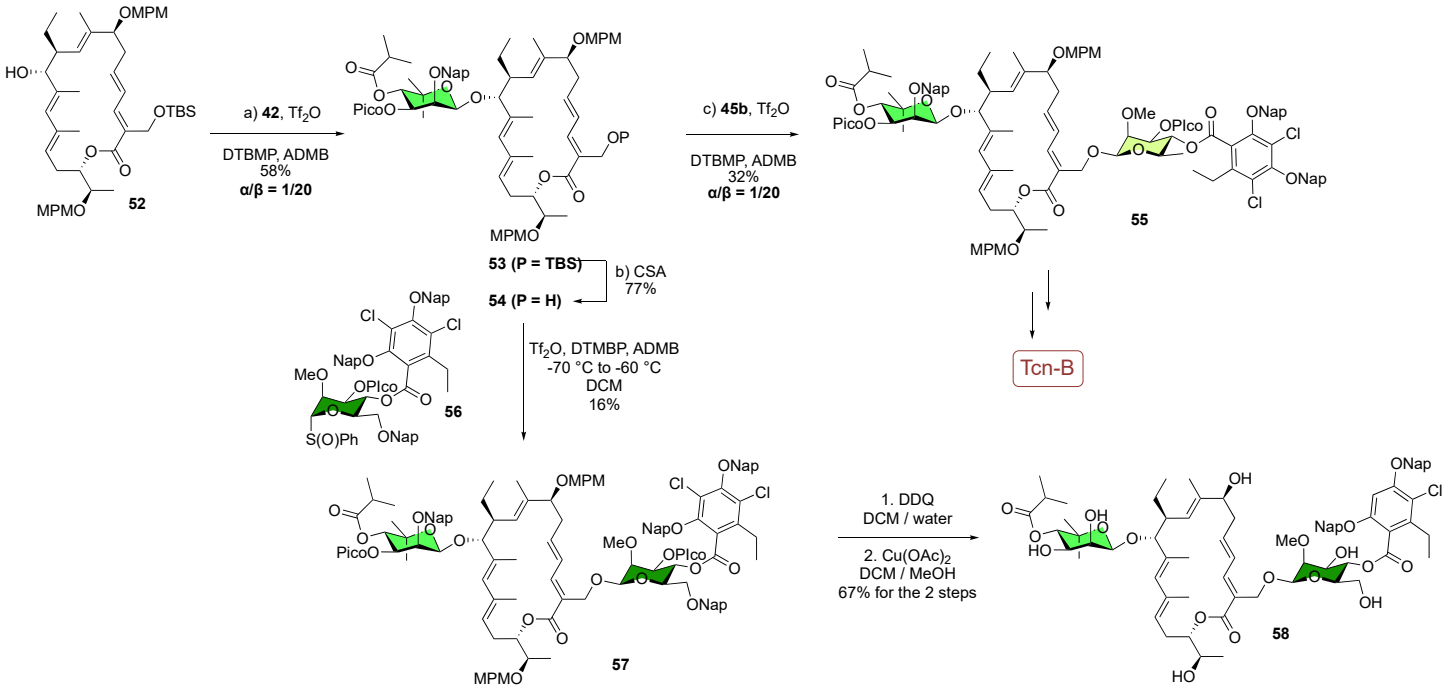
Given the challenges associated with this step, we first opted for an Intramolecular Aglycone Delivery (IAD)[66-69] using a silicon tether, anchoring **46** to the 3-*O* position of the noviosyl moiety **47** (Scheme 8). This strategy relies on the fact that silylated compound **48** adopts a $^1C_4$ chair conformation, exclusively. Consequently, the oxonium-ion intermediate **49**, in its half-chair conformation, favorably orients the transferring alcohol, thereby facilitating the formation of the desired β-isomer. We previously tested the reaction with (–)-menthol using NIS and TMSOTf in CH_2Cl_2 at –40 °C, followed by an HCl treatment, which led to the desired product in good yield, and complete selectivity in favor of the β-product. Unfortunately, with alcohol **46**, these conditions led to degradation of the compound **48** without evidence of the formation of the targeted glycosylated adduct **50**.



Scheme 8. Preparation and glycosylation of acceptor **46.**

We then shifted to another strategy based on the HAD approach involving the use of the donor **47** bearing a Pico group at the 3-position and the thiophenyl group at the anomeric position. However, either with DMTST or NIS/TfOH, the reaction turned out unsuccessful with macrolactonic acceptor **46** since no glycosylated adduct was detected. On the other hand, derivative **42** with a picoloyl in *O*-3 and a sulfoxide at the anomeric position was prepared and tested in the glycosylation reaction. Using the conditions developed with the rhamnose donor (Tf_2O activation at –70 °C) allowed us to obtain the desired product **51** in 68% yield and high selectivity in favor of the β product (α/β =1/19). The final steps, which proved to be among the most challenging, involved removing all protecting groups (2 MPM, 3 Nap, 1 Pico, and 1 TBS) from compound **51**, resulting in the formation of Tcn-B.

Employing donors equipped with a phenyl sulfoxide leaving group, together with a 3-*O*-picoloyl directing group, enables also the successive installation of two glycosides onto the tiacumicin B aglycone with high β-selectivity.[70] This strategy has led to a formal total synthesis of tiacumicin B, featuring an efficient initial noviosylation step with **42** in 58% yield and an α/β selectivity ratio of 1:20 (Scheme 9). Although the second glycosylation with **45b** proceeds with a lower yield, it still maintains excellent selectivity. Despite this limitation, the approach reduces the number of steps and improves both convergence and modularity. Furthermore, we have shown that this method allows access to structural analogs, such as a derivative **58** in which the native rhamnoside has been replaced with a mannose unit, a modification challenging to achieve through semi-synthesis. This glycosylation-based strategy not only diversifies the tiacumicinone core, but also offers a straightforward route to complex glycosylated molecules, potentially valuable for investigating how glycosylation impacts pharmacological properties.



Scheme 9. Successive glycosylation of the tiacumicin B aglycone **52** and access to the analog **58.**

Conclusions

Glycosylation is a fundamental reaction in which a glycosyl donor reacts with an acceptor to form α- and/or β-anomers. The stereochemical outcome is influenced by multiple factors, including the reactivity of both donor and acceptor, as well as reaction conditions such as temperature, solvent, and the nature of protecting groups. Our recent research has focused on developing efficient and stereoselective glycosylation strategies using readily available donors, and environmentally benign promoters like metal triflates. Specifically, we have employed peracetylated β-*N*-acetyl-D-glucosamine as the donor, activated with catalytic amounts of iron(III) triflate. These reactions were performed using unconventional activation methods, including microwave irradiation and flow chemistry, resulting in scalable protocols with excellent β-selectivity. Additionally, α-anomers were accessed by activating peracetylated α-*N*-acetyl-D-glucosamine with copper(II) triflate. In this case, the methodology was not extendable to various glycosyl acceptors, and the observed α-selectivity was attributed to post-reaction anomerization of the initially formed β-anomer under the reaction conditions. We also investigated the use of benzylated mannosyl aryl sulfone donors, which are rarely applied in *O*-glycosylation. Here, scandium triflate was the most effective promoter, providing access to α-linked products.

Beyond methodological development, our work encompasses the synthesis of complex natural glycoconjugates and analogs. We presented two examples where using sulfoxide donors proved essential for the efficient construction of complex glycostructures. In the first case, analogs of gougerotin, a peptidyl nucleoside with antifungal activity, were synthesized via *N*-glycosylation using various silylated pyrimidine bases. Among the conditions tested, the sulfoxide donor activated by TMSOTf consistently yielded the highest results. In the second example, the total synthesis of tiacumicin B, a natural antibiotic, and analog **58** were achieved using a glycosylation strategy based on hydrogen-bond-mediated aglycone delivery. Here, the association of a Pico group at C-3 position of a noviosyl or rhamnosyl donor bearing a sulfoxide as the activatable group led to excellent stereoselectivity.

Our findings highlight important emerging trends in modern glycosylation. Mild Lewis acid promoters and unconventional activation methods, such as microwave and flow chemistry, are enabling more efficient, scalable, stereoselective transformations. Donor–promoter matching and controlled anomerisation are important tools for accessing challenging α- and β-linkages. Meanwhile, the revival of underused donor classes, including mannosyl aryl sulfones, is broadening the scope of *O*-glycosylation. Sulfoxide donors are becoming increasingly prominent due to their high reactivity and reliable stereocontrol, and are proving especially effective in the construction of complex glycoconjugates, such as gougerotine analogs and tiacumicin B. Collectively, these trends emphasize the growing importance of practical, selective and broadly applicable glycosylation strategies.

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Authors' Biographies

S. Norsikian carried out her Ph.D. from the Université de Paris VI in 1999, under the supervision of Professors J.-F. Normant and I. Marek. Following her doctorate, she completed postdoctoral research in the laboratories of Professor D.M. Hodgson (Oxford, U.K.), Professor G. Guillaumet (Orléans, France), and Professor H. Kagan (Orsay, France). In 2002, she was appointed as a Research Scientist by the CNRS, joining the group of Professor A. Lubineau in Orsay. In January 2007, she became a member of Professor J.-M. Beau's group at the Institut de Chimie des Substances Naturelles (ICSN) in Gif-sur-Yvette. Since January 2015, she has been part of the "Probes and Modulators for Biological Targets" team within ICSN's Chemical Biology Department. In 2022, she was promoted to Research Director and also took on the role of Deputy Coordinator of the Chemical Biology Department. Her research primarily focuses on glycochemistry and biomolecule synthesis, with additional interests in organometallic chemistry, multicomponent reactions, and fluorescent probes.

