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Exploring Photoredox Catalytic Reactions as an Entry to Glycosyl-α-amino Acids

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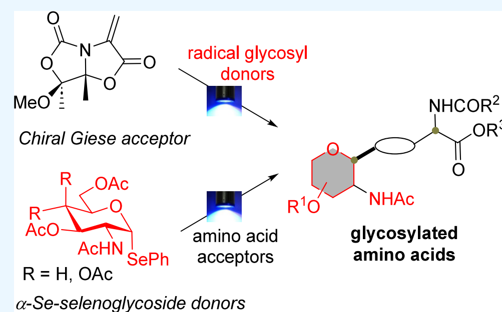
ABSTRACT: The synthesis of glycosyl-α-amino acids presents a significant challenge due to the need for precise glycosidic linkages connecting carbohydrate moieties to amino acids while maintaining stereo- and regiochemical fidelity. Classical methods relying on ionic intermediates ($2e^-$) often involve intricate synthetic procedures, particularly when dealing with 2-*N*-acetamido-2-deoxy-glycosides linked to α-amino acids—a crucial class of glycoconjugates that play important biological roles. Considering the growing prominence of photocatalysis, this study explores various photoredox catalytic approaches to achieving glycosylation reactions. Our focus lies on the notoriously difficult case of 2-*N*-acetamido-2-deoxyglycosyl-α-amino acids, which could be obtained efficiently by two methodologies that involved, on the one hand, photoredox Giese reactions using a chiral dehydroalanine (Dha) as an electron density-deficient alkene in these radical 1,4-additions and, on the other hand, photoredox glycosylations using selenoglycosides as glycosyl donors and hydroxyl groups of protected amino acids as acceptors.



INTRODUCTION

Glycopeptides and glycoproteins play crucial roles in biochemical processes[1] like molecular recognition and immune response, whose studies are essential for developing biomedical applications.[2] Therefore, the demand for homogeneous samples of glycopeptides and their minor units of glycosyl-α-amino acids for biological research has boomed in recent decades. Especially relevant are 2-*N*-acetamido-2-deoxyglycosides connected to amino acids, which are widely distributed in living organisms as glycoconjugates with important biological roles.[3]

In this context, *O*-linked-β-*N*-acetylglucosamine (β-*O*-GlcNAc), a single sugar modification of Ser and Thr residues of proteins, is an important glycosylation since, while other carbohydrates modify proteins on the cell surface, *O*-GlcNAc modifies nucleocytoplasmic proteins, which are involved in transcription, ubiquitination, cell cycle, and stress responses.[3c] In addition, *O*-linked-α-*N*-acetylgalactosamine to Ser or Thr, namely, the Tn antigen (α-*O*-GalNAc-L-Ser/Thr), has been the focus of numerous investigations due to their use in therapeutic vaccines against cancer or as powerful tools for early diagnosis of cancer.[4] However, one potential drawback in using the native Tn antigen for vaccine design is the instability of the glycosidic linkage to glycosidases and the low immunogenicity. To overcome this problem, a plethora of structural mimetics of the Tn antigen has been used.[5] Therefore, the chemical synthesis of different glycosyl-α-amino acid structures is necessary, especially α-*O*-GalNAc-L-Ser/Thr and β-*O*-GlcNAc-L-Ser/Thr along with their mimetics displaying α- or β-*C*-, *S*- or *Se*-glycosidic bonds. In this regard, the main synthetic challenge is to construct glycosidic linkages that connect monomeric carbohydrate units to amino acids with the appropriate stereo- and regiochemical orientation. In recent decades, many procedures for chemical glycosylation have been developed, making it a very active area of research.[6] In particular, several methods have been reported for the difficult case of 2-*N*-acetamido-2-deoxyglycosyl-α-amino acids but all of them use precursors that need to be prepared in multiple steps, including the specific protecting/deprotecting procedures, which decreases the efficiency of synthesis.[7] Although more and more syntheses of complex carbohydrates are becoming standardized,[8] the complete stereochemical control of glycosylation reactions remain a challenge in carbohydrate and glycoconjugate chemistry.[9]

Classical methods concerning the formation of glycosidic bonds frequently use reactions involving ionic intermediates and need a methodology that requires the activation of a glycosyl donor, with most of these activating agents being sensitive to air and humidity, so they must be used under strict

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anhydrous conditions and at low temperatures, adding another difficulty to the synthetic process.[6] Because of this, much of the interest in glycosylation reactions has therefore shifted toward the discovery of simpler procedures. In the past, some methods for carrying out this process using glycosyl radicals have also been described.[10] These processes involving radical reactions are not widely used, given the disadvantages of the use of toxic tin hydrides.[11] In addition, the development of radical processes has been challenging due to the numerous reduction, elimination, and nucleophilic substitution side reactions that compete with the labile glycosyl donors commonly used. More recently, an interesting radical methodology was established to achieve 2-amidoglycosylation of glycals.[12]

However, in recent years, due to the rise of photocatalysis[13] and given the advantages of developing radical reactions promoted by photoredox catalytic processes, some methodologies have been described to synthesize carbohydrate derivatives by photoinduced radical glycosylation reactions.[14] In this way, glycosylation reactions take place under mild reaction conditions at room temperature and do not require strict anhydrous conditions. Moreover, they use substoichiometric amounts of activating agents.[15] Despite the versatility of photoredox catalysis in organic synthesis and its fundamental role in the development of major areas of contemporary synthetic chemistry, it has not yet been addressed in depth in carbohydrate chemistry, especially in the case of important 2-deoxy-2-(acetamido)pyranose derivatives (Figure 1a).[14] In addition, although several cases have been reported for photocatalytic glycosylation reactions, very few works have

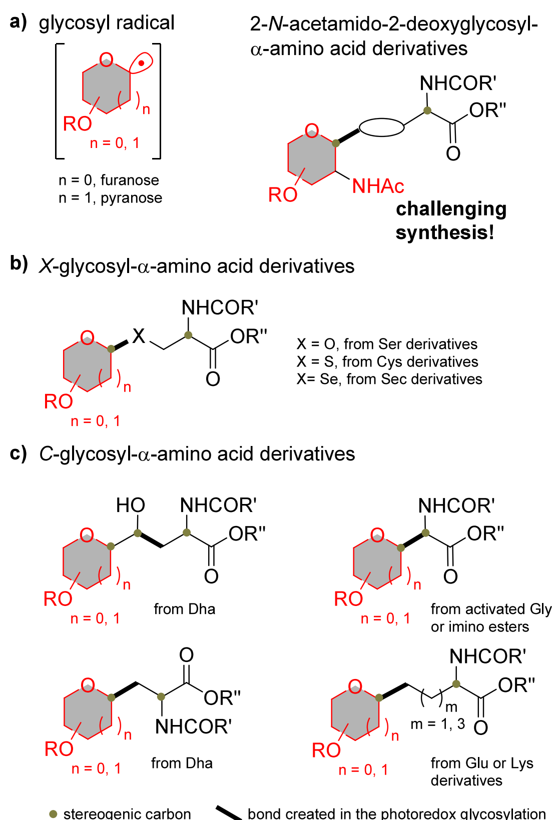


Figure 1. (a−c) Furanosyl and pyranosyl radicals, 2-N-acetamido-2-deoxyglycosyl-α-amino acid derivatives, and some O-, S-, and C-glycosyl-α-amino acids synthesized using photocatalytic glycosylation reactions.

been published concerning the synthesis of glycosyl-α-amino acids.[16−25]

In this field, only two O-glycosyl-α-amino acids[16−18] and some examples of S-glycosyl-α-amino acids[19] have been reported (Figure 1b). However, it is important to note that in this last work about the synthesis of S-glycosylated derivatives, the authors described a limitation of this method since when N-(acyl)glucosamines (protected GlcNAc bromide, for instance) are used as substrates for the C−S coupling reaction, the desired products (α-S-GlcNAc-L-Cys among others) are not formed, probably due to the lability of these reactants.[19] In fact, the reaction with such substrates is not described in any of the S-glycosides formed, suggesting challenging access to this type of 2-N-acetamido-2-deoxy-glycosyl-α-amino acid.

This drawback was not observed in the synthesis of α-S-GalNAc-Cys derivatives using allyl glycosyl sulfones as precursors to glycosyl radicals.[20a] The abovementioned drawback was also not detected for the case of α-Se-GalNAc-Sec included in peptides and proteins using a photocatalytic method for the rapid and efficient dimerization of $(\alpha\text{-}Se\text{-}GalNAcSe)_2$ and peptide diselenides in the presence of an iridium photocatalyst and a phosphine. However, this method uses substantial quantity of the starting diselenide $(\alpha\text{-}Se\text{-}GalNAcSe)_2$, which is challenging to synthesize.[20b]

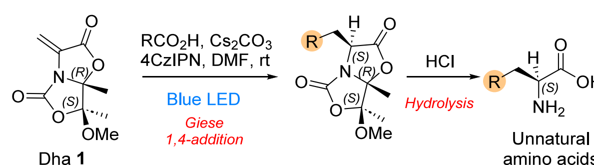
The most explored photoredox glycosylation reactions of this type of compound involve the synthesis of C-glycosyl-α-amino acids from a radical generated in the glycosyl moiety, in most of the cases in anomeric positions, which is captured with different electrophiles in chemoselective addition reactions (Figure 1c). For instance, protected dehydroalanines (Dha)—via a Giese-type reaction—,[21] α-imino esters,[22] or activated glycines[23] have been used as good electrophiles with nucleophilic glycosyl radicals. In other cases, the radical is generated in the amino acid moiety, and it reacts with glycosyl halides to generate the corresponding C-glycosyl-α-amino acids via a photoinduced, nickel-catalyzed reaction.[24,25]

Considering this background, we focused on the synthesis of glycosyl-α-amino acids, especially 2-N-acetamido-2-deoxyglycosides linked to α-amino acids, by means of some published methodologies that use photoredox catalytic processes. Thus, we envisioned the use of chiral bicyclic dehydroalanine derivatives, already reported by our group, to construct these glycosyl-α-amino acid derivatives via photoredox catalysis (Scheme 1).[26]

■ RESULTS AND DISCUSSION

α-Glycosyl-α-amino Acids by Photoredox 1,4-Additions. Initially, we focused on the challenging synthesis of important glycosyl-α-amino acids derived from C2-N-acetyl pyranoses following the above commented photoredox strategy.[26] In particular, and to be used for their application

Scheme 1. Photocatalytic Giese-Type 1,4-Additions of Carboxylic Acids to Dha 1 as an Entry to a Variety of Enantiomerically Pure Unnatural Amino Acids



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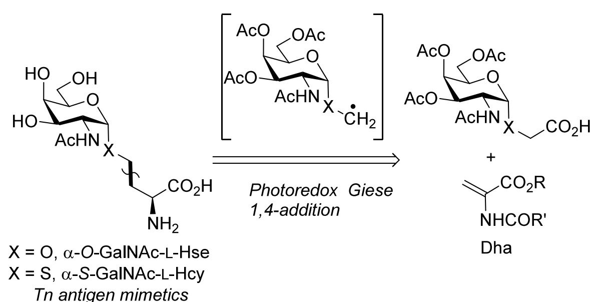
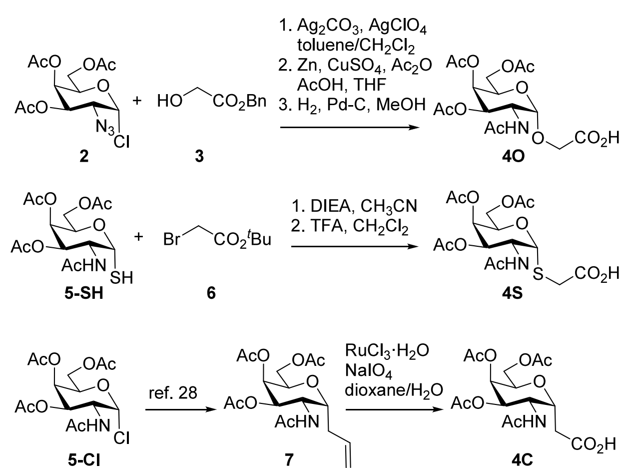
in cancer vaccines,[5] we are interested in the synthesis of three mimetics of the Tn antigen α-*O*-D-GalNAc-L-Ser incorporating nonproteinogenic α-amino acids: α-*O*-D-GalNAc-L-Hse, α-*S*-D-GalNAc-L-Hcy, and α-*C*-D-GalNAc-L-Abu. One of them displays a homologue of Ser amino acid, homoserine (Hse), the other one incorporates homocysteine (Hcy), and the third one corresponds to the α-*C*-GalNAc-glycosylated 2-aminobutanoic acid (Abu).

Based on retrosynthetic analysis, we considered the disconnection of a hitherto little explored linkage (marked in bold in Scheme 2a) to address the synthesis of the aforementioned glycosyl-α-amino acids involving 1,4-additions of alkyl radicals to dehydroalanines (Dha) mediated by photoredox processes. We prepared starting materials incorporating carboxylic acid groups to generate the corresponding decarboxylative alkyl radicals. Thus, in the first case, we installed an -O-CH_2-CO_2H group at the anomeric position of α-GalNAc by a well-known Koenigs−Knorr glycosylation reaction[27] between 3,4,6-tri-*O*-acetyl-2-azido-2-deoxy-α-*O*-D-galactopyranosyl chloride **2** and benzyl hydroxyacetate **3** followed by conversion of azide to the *N*-acetyl group and further debenzylation using a hydrogenolysis reaction (Scheme 2b).

Scheme 2. Retrosynthesis of α-GalNAc-α-Amino Acids by a Photocatalytic Giese Process (a) and Synthesis of Adequate GalNAc Precursors (b)

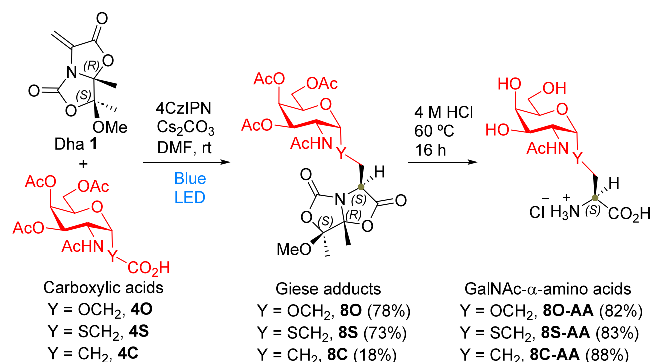




Once compound **4O** was obtained, we synthesized its partner **4S** that incorporates a sulfur atom instead of oxygen at the anomeric position but now using a different methodology. Thus, the nucleophilic substitution reaction between α-*S*-D-GalNAc-SH **5-SH** and *tert*-butyl bromoacetate **6** in the presence of diisopropylethyl amine (DIEA) as a base and using acetonitrile as a solvent followed by acid hydrolysis of the *tert*-butyl ester group with trifluoracetic acid (TFA) afforded the corresponding acid **4S** (Scheme 2b).

In the third case, oxidative cleavage of the alkene group of the corresponding α-*C*-D-GalNAc-allyl derivative **7** by using ruthenium tetraoxide *in situ* generated from $RuCl_3 \cdot H_2O$ and $NaIO_4$ gave the (α-*C*-GalNAc)acetic acid **4C**. Compound **7** was obtained from GalNAc chloride **5-Cl** following the published synthetic procedure for its GlcNAc partner (Scheme 2).[28] With the starting material in our hands (**4O**, **4S**, and **4C**), we tested these carboxylic acids in photocatalytic Giese-type reactions with chiral Dha **1**, using the optimized conditions[26] previously commented in Scheme 1. The reactions work very well when using Dha **1** (1.0 equiv), carboxylic acid **4O** or **4S** (1.2 equiv), Cs_2CO_3 (1.5 equiv) as a base, and 4CzIPN (0.05 equiv) as an organophotocatalyst in *N*,*N*-dimethylformamide (DMF) as a solvent at room temperature. Once reactions were completed after 16 h under blue-light-emitting diode (LED) irradiation, we observed the clean formation of a single diastereomer in each case, corresponding to adducts **8O** and **8S**, respectively (Scheme 3).

Scheme 3. α-GalNAc-α-Amino Acids by Photocatalytic Giese-Type 1,4-Additions of GalNAc-Carboxylic Acids to Chiral Dha 1



However, when **4C** was used in the same conditions, we found the expected adduct **8C** in very low yield and accompanied by several nonidentified products. This fact is probably due to the instability of the corresponding alkyl radical intermediate (Scheme 3). These adducts **8O**, **8S**, and **8C** can be regarded as protected α-glycosyl-α-amino acids in which hydroxyl groups of the carbohydrate moiety are protected as acetates, carboxylic acid group as a cyclic ester (lactone), and amino group as a cyclic carbamate, since—as described in our previous work[26]—all of them can be easily deprotected by acid hydrolysis. In fact, Giese adducts **8O**, **8S**, and **8C** were hydrolyzed using a 4 M aqueous solution of HCl at 40 °C for 16 h to give glycosyl-α-amino acids **8O-AA**, **8S-AA**, and **8C-AA**, respectively (Scheme 3). The substructure of some of these new glycosyl amino acids appear included in some peptides, and the most related one is GalNAc-L-homoserine protected as the Fmoc derivative, which was incorporated in an antitumor neoglycopeptide vaccine as a novel homoserine Tn antigen.[29]

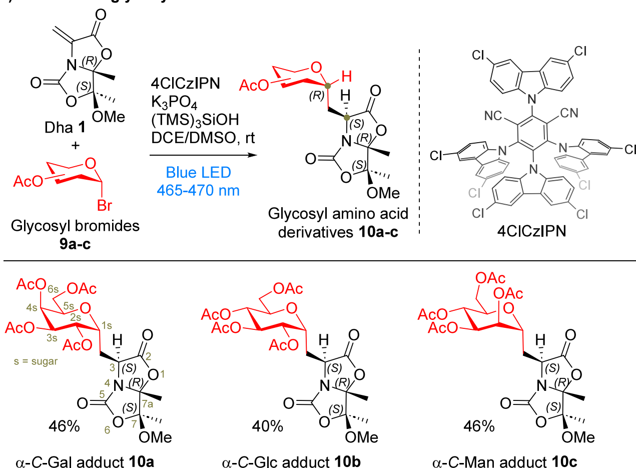
The stereochemical outcome of these photocatalytic reactions between Dha **1** and carboxylic acids **4O**, **4S**, and **4C** follows a stereoinduction mechanism similar to that previously described by us.[26] As in this case, the absolute

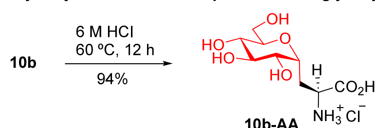
configurations (*S*) of the new stereocenter (carbon atom marked as a green dot in Scheme 3) corresponding to the Cα of the amino acid moiety of the glycosyl-α-amino acid derivatives **8O**, **8S**, and **8C** formed on Giese additions were confidently assigned based on 2D NOESY experiments. These results likely indicate that reactions follow a mechanism similar to that described in our previous work (Supporting Information).

As a next step, we selected the procedure described by Wang and co-workers[19] to generate *S*-glycosyl-α-amino acids attending to the fact that the authors developed a radical trapping study with methyl acrylate to confirm the radical engaged process. In our case, we aim to apply this method to *C*-glycosylation reactions. Starting from the optimized conditions used in that work, we tested different organophotocatalysts (4ClCzIPN and 4CzIPN), bases (K_3PO_4 and Cs_2CO_3), solvents (DMF and CH_2Cl_2), and proportions. The best conditions, which matched precisely with those described in that work, were selected to assay the photoredox reactions. Thus, some glycosyl bromides (**9a**–**9c**) were used to generate visible light-mediated anomeric glycosyl radicals by the action of 4ClCzIPN as organophotocatalyst—avoiding the use of a transition metal—and $(TMS)_3SiOH$ as a halogen atom transfer (XAT) reagent in the presence of K_3PO_4, as a base, and a mixture of dichloroethane (DCE) and dimethyl sulfoxide (DMSO) as a solvent. This process took place at room temperature under irradiation of blue LEDs in an inert atmosphere, and the radical was trapped with chiral Dha **1** as an acceptor alkene (Scheme 4a).

First, we evaluated the performance using galactosyl bromide (**9a**) as a radical donor for coupling with chiral Dha **1**. When the reaction was irradiated with 16 W Kessil blue LEDs in an inert atmosphere at room temperature for 16 h, α-*C*-galactosyl adduct **10a** was obtained as a solely diastereoisomer in 46% yield after purification by column chromatography (β-anomer was not detected). The process serves as a general approach since α-*C*-glucosyl and α-*C*-mannosyl-α-amino acid derivatives **10b** and **10c** were also obtained in 40 and 46% yield, respectively.

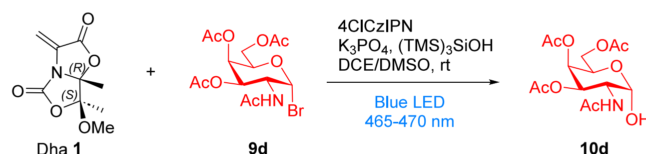
Scheme 4. Organophotocatalytic Radical *C*-Glycosylation Reactions Using Glycosyl Bromides 10a–10c and Dha 1 (a) and Deprotection of α-*C*-Glc Adduct 10b by Acid Hydrolysis to Give α-*C*-Glucosyl-α-amino Acid 10b-AA (b)





Unfortunately, the reaction did not take place when 3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-α-*O*-D-galactopyranosyl bromide $(OAc)_3$GalNAc-α-Br **9d** was used, probably due to the lability of the anomeric radical formed. In these conditions, we only detected, isolated (75%), and characterized the known product **10d**, corresponding to the addition of one hydroxyl group to the anomeric carbon (Scheme 5 and Scheme S10 in the Supporting Information).

Scheme 5. Organophotocatalytic Reaction of Glycosyl Bromide 9d and Dha 1



Interestingly, total axial selectivity was observed for the three adducts **10a**–**10c** and, most importantly, the absolute configurations of the two new stereogenic centers created in the photoredox radical reaction (highlighted as green dots in Scheme 4a) were totally controlled. As in the previous cases (Scheme 3), adducts **10a**, **10b**, and **10c** can be regarded as protected glycosyl-α-amino acids. To illustrate this characteristic, one of these adducts—specifically, adduct **10b**—underwent hydrolysis in an acidic environment, resulting in the acquisition of the corresponding fully deprotected α-*C*-glucosyl-α-amino acid, denoted as **10b-AA** (Scheme 4b).

These absolute configurations were assessed by 2D NOESY experiments for the case of the new stereocenter (C3) corresponding to Cα of the amino acid moiety of adduct **10a** formed in the Giese addition and attending to the study of the coupling contants (*J*) values observed for the case of anomeric carbon (C 1s). Similar structural characteristics were found in adducts **10b** and **10c** (Supporting Information). Alternatively, these structural features were also determined by X-ray analysis of a single crystal of compound **10a** (Figure 2 and Figure S88 of the Supporting Information).

Therefore, the stereochemical outcome of these photocatalytic reactions between Dha **1** and glycosyl bromides **9a**–**9c** indicates a highly conserved stereoinduction mechanism, not only at the amino acid level created in the Giese reaction[26]—as demonstrated in our previous work—but also at the anomeric carbon C 1s of the carbohydrate moiety, possibly due to the stabilizing anomeric effect on the anomeric radical formed in the process.[30] That is, this photoredox process allows stereochemical control of the two stereogenic centers created in the photoredox radical reaction.

Based on the above-described results, we propose that these photoredox catalytic Giese reactions proceed via the mechanism shown in Scheme S10 of the Supporting Information.

β-*O*-Glycosyl-α-amino Acids from Selenoglycosides. Regarding the synthesis of *O*-GalNAc-α-amino acids using photoredox strategies, we tested the methodology published by Ragains and co-workers that involves a photocatalytic glycosylation of alcohols with selenoglycosides promoted by

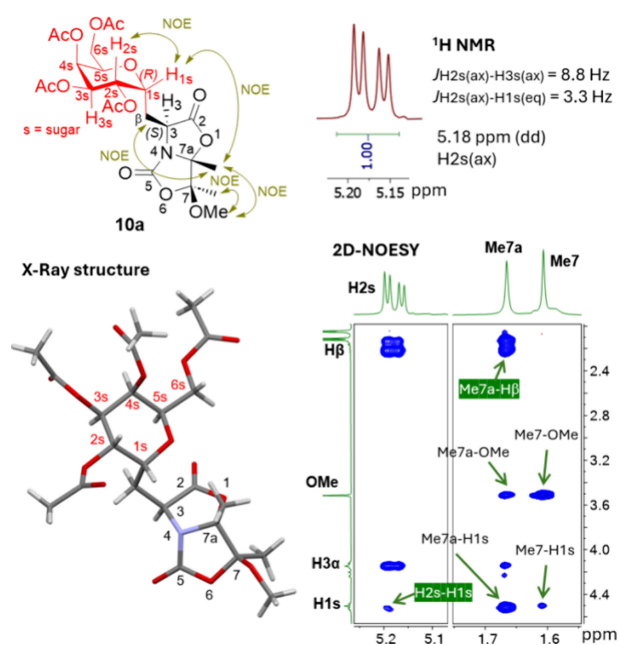


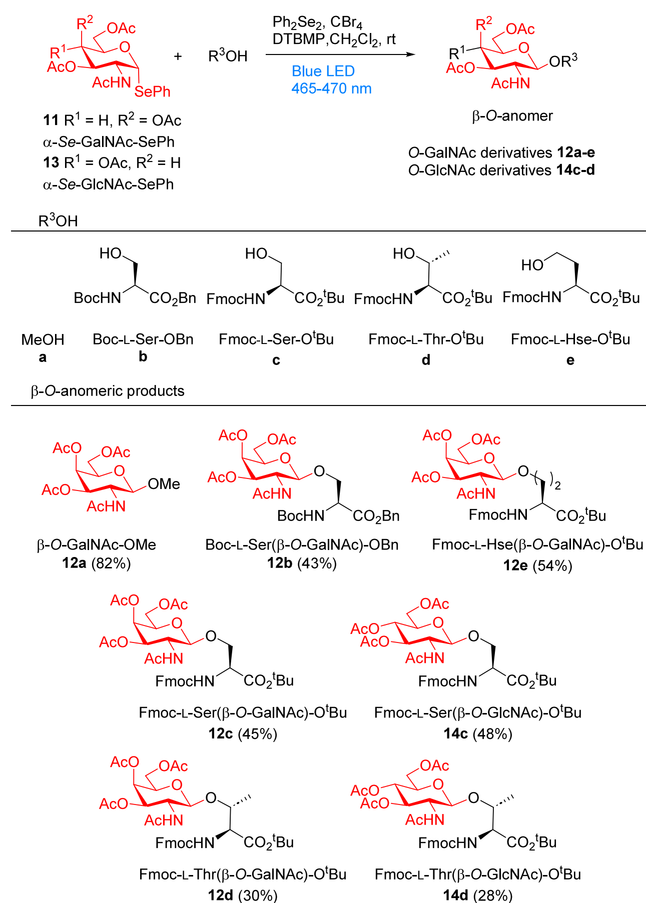
Figure 2. ^{1}H NMR and 2D NOESY spectra as well as X-ray structure to determine the absolute configurations of the stereogenic centers created in the photoredox reaction for compound **10a**.

visible light.[31] We envisioned that this mild procedure would be applied to the synthesis of challenging *O*-GalNAc-*α*-amino acids by using the visible light photocatalytic activation of easily available phenyl 3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-1-seleno-*α*-D-galactopyranoside[32] **11**—abbreviated as *α*-*Se*-GalNAc-SePh—as a selenoglycoside donor and hydroxyl groups of protected Ser and Thr as acceptors. Starting from the optimized conditions used in that work, we tested different organophotocatalysts—$(PhSe)_2$ and 4CzIPN—, bases (TEA and DTBMP), and proportions. The best conditions that matched those described in that work were selected. Therefore, we used diphenyldiselenide [$(PhSe)_2$, 10 mol %] as an organocatalyst in the presence of tetrabromomethane (CBr_4, 1.1 equiv) as an electron acceptor and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP, 1.2 equiv) as a base in dichloromethane as a solvent under blue LED irradiation. The corresponding compounds displaying hydroxyl groups were selected as glycosyl acceptors: MeOH (**a**) or Boc-L-Ser-OBn (**b**), Fmoc-L-Ser-O^{t}Bu (**c**), Fmoc-L-Thr-O^{t}Bu (**d**), and Fmoc-L-Hse-O^{t}Bu (**e**) were used in excess (3.0 equiv) with respect to selenoglycoside donor **11**. We obtained acceptable yields of glycosylation products **12a**−**12e** after irradiation and subsequent purification by column chromatography (Scheme 6).

Reactions afford, in all cases, *β*-anomers with high selectivities since we do not detect the corresponding *α*-anomers in the crude reactions. This result is contrary to that obtained by the authors since they observed preferentially *α*-selectivity, but probably is due to the fact that they used *β*-*Se*-$(OBn)_4$Gal-SePh or *β*-*Se*-$(OBn)_4$Glc-SePh as selenoglycosides, in which the lack of 2-acetate or 2-acetamido groups as an anchimeric support does not favor *β*-selectivity, attending to the proposed mechanism (Supporting Information).

It is crucial to note that while *β*-*O*-GalNAc-Ser/Thr derivatives are rare in nature, this isomer of the Tn antigen (*α*-*O*-GalNAc-Ser/Thr), differing only in anomeric configuration, has been used as a mimic of the natural Tn antigen in the development of cancer vaccines,[33] showing improved

Scheme 6. Organophotocatalytic *O*-Glycosylation Reactions Using Selenoglycosides 11 and 13 as Donors and Alcohols a−e as Acceptors to Generate Protected *β*-*O*-GalNAc- or *β*-*O*-GlcNAc-*α*-Amino Acids



immunological potential with respect to the natural one. This observation underscores the idea that a straightforward alteration in the stereochemistry of the glycosidic linkage between carbohydrate and amino acid moieties could serve as a viable strategy for designing anticancer vaccines. In this sense, both a synthetic approach and a deep conformational study comparing *α*- and *β*-anomers of the Tn antigen have been carried out in the past by us.[34]

To validate the viability of this synthetic process and recognize the significance of this Tn antigen mimetic (*β*-*O*-GalNAc-Thr), we opted to scale up this methodology. Notably, previously reported synthetic approaches relying on classical ionic methods necessitate multiple steps or the use of harsh conditions, including mercury salts.[33,34] Thus, we could obtain derivative **12d** in a 23% yield on a scale of hundreds of milligrams from readily available raw material **11** (Supporting Information). These glycosylation reactions offer distinct advantages over classical ionic synthetic methodologies as they exhibit tolerance toward diverse functional groups and enable precise stereochemical control.

Considering the above results, we focus on the synthesis of important glycosylated building blocks[3c] consist of *N*-acetylglucosamine *β*-*O*-linked to Ser and Thr residues (*β*-*O*-GlcNAc-Ser/Thr). Initially, we synthesized easily available phenyl 3,4,6-tri-*O*-acetyl-2-acetamido-2-deoxy-1-seleno-*α*-D-galactopyranoside **13**, abbreviated as *α*-*Se*-GlcNAc-SePh, using a modified procedure already described.[35] Following

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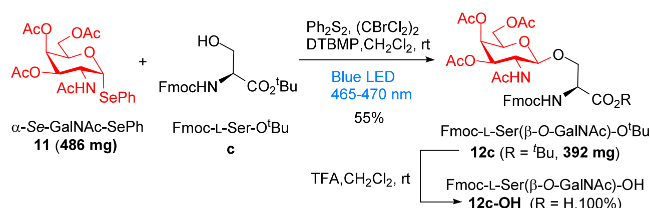
similar glycosylation conditions used for their GalNAc-counterparts [$(PhSe)_2$, CBr_4, and DTBMP in CH_2Cl_2 under blue LEDs, the reaction of selenoglycoside donor **13** with Fmoc-L-Ser-O^{t}Bu (**c**) and Fmoc-L-Thr-O^{t}Bu (**d**) as glycosyl acceptors gave the required adequately protected *β*-*O*-GlcNAc-*α*-amino acids Fmoc-L-Ser[*β*-*O*-$(OAc)_3$GlcNAc]-O^{t}Bu **14c** and Fmoc-L-Thr[*β*-*O*-$(OAc)_3$GlcNAc]-O^{t}Bu **14d** in acceptable yields (48 and 28%, respectively, Scheme 7). It is important to mention that all synthesized *O*-Ac, $CO_2{}^tBu$, and NHFmoc-protected GalNAc-glycosylated *α*-amino acids are important building blocks adequately prepared, once the quantitatively transformed $CO_2{}^tBu$ group is transformed to $-CO_2H$ with TFA, to be used in solid phase peptide synthesis (SPPS), allowing the obtention of interesting glycopeptides.

Scheme 7. Visible Light-Promoted *O*-Glycosylation Reactions, in the Presence of Ph_2S_2 and $(CBrCl_2)_2$, Using Selenoglycoside 11 as a Donor with Fmoc-L-Ser-O^{t}Bu (c) as Glycosyl Acceptors to Generate Protected *β*-*O*-GalNAc-L-Ser 12c and Deprotection of the ^{t}Bu Group



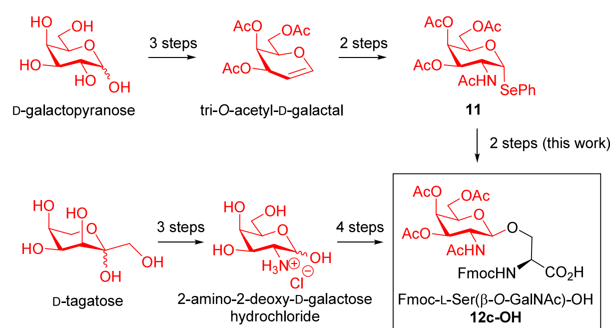
Building upon the proposed mechanism for this specific reaction,[31] irradiation with blue LEDs initiates the homolysis of $(PhSe)_2$,[36] yielding phenylselenyl radicals ($PhSe^\bullet$). These radicals subsequently engage with CBr_4, affording PhSeBr. Notably, this compound converts selenoglycosyl donor **11** into the active selenium specie **11-SePh**$^+$.[37] The latter would further evolve into the corresponding oxonium intermediate, which undergoes conversion to a dihydrooxazolium species, although none of them species have been detected by mass spectrometry of the crude reactions. These reactive intermediates, under a basic medium, then engages the alcohol group of the Thr-derivative **d** via a *β*-attack, ultimately leading to the formation of the *β*-*O*-glycosyl-*α*-amino acid **12d** (Scheme S11 of the Supporting Information). When the same reaction conditions were used but without blue LED irradiation or without CBr_4, no reaction takes place. We emphasize that this proposed mechanism remains the subject of an ongoing investigation.

Although there is no disputing the efficacy of the CBr_4[38] and $(PhSe)_2$[39] agents in the aforementioned radical *β*-*O*-glycosylation protocol, the replacement of $(PhSe)_2$ with the less toxic and cheaper $(PhS)_2$ and CBr_4 with $(CBrCl_2)_2$, which is less harmful and similarly priced, is warranted.[40,41] These substitutions address economic, toxic, and environmental concerns in the radical *β*-*O*-glycosylation protocol. To the best of our knowledge, $(CBrCl_2)_2$ has never been used as a reagent in photoredox reactions.

We tested these new conditions in the reactions of selenoglycoside donor **11** with Fmoc-L-Ser-O^{t}Bu (**c**) as a glycosyl acceptor to obtain a similar (even improved) yield of glycosylation product **12c** after irradiation for 16 h and subsequent purification by column chromatography (Scheme 7). In addition, to demonstrate the feasibility of this synthetic process to afford *β*-*O*-glycosyl-*α*-amino acids, we scaled up (1 mmol) the synthesis of the *β*-*O*-GalNAc-L-Ser **12c**, including the synthetic procedure to obtain the selenoglycoside **11** (on a gram scale) from readily available raw materials (Supporting Information). Thus, using this new methodology and starting from **11** (1 mmol), *β*-*O*-GalNAc-L-Ser derivative **12c** was obtained in 55% yield (392 mg). This protected glycosylamino acid **12c** could be transformed easily and quantitatively to the required Fmoc-L-Ser[*β*-*O*-$(OAc)_3$GalNAc]−OH **12c−OH**, ready to be used in SPPS, by treatment with TFA in dichloromethane for 3 h at room temperature (Scheme 7). It is important to note that although several methodologies have been reported for their congeners (*α*-*O*-GalNAc-Ser, *α*-*O*-GlcNAc-Ser, or *β*-*O*-GlcNAc-Ser), very little attention has been paid to the synthesis of this protected *β*-*O*-GalNAc-Ser derivative **12c−OH**.

We can conclude that this photoredox methodology can compete with the classical glycosylation methodology used in the past to obtain, in particular, glycosylamino acid **12c−OH** since this compound is obtained from D-galactopyranose in seven steps with a 22% overall yield (Supporting Information and Scheme 8).

Scheme 8. Two Synthetic Methodologies of Protected *β*-*O*-GalNAc-L-Ser 12c−OH



By contrast, Fmoc-L-Ser(*β*-*O*-D-GalNAc)−OH **12c−OH** was previously obtained from 2-amino-2-deoxy-D-galactose hydrochloride in four steps that involved peracetylation, treatement with AcCl and HCl (g) to give *α*-GalNAc-$(OAc)_3$-Cl, glycosylation of this derivative with Fmoc-L-Ser-OBn, and further debenzylation by hydrogenolysis. 2-Amino-2-deoxy-D-galactose hydrochloride was previously synthesized from commercially available D-tagatose via the Heyns rearrangement. In summary, **12c−OH** was synthesized by classical methods starting from commercially available D-tagatose using seven steps in a 10% overall yield (Supporting Information and Scheme 8).

This highly efficient strategy has advantages such as high functional group tolerance, biocompatible reaction conditions, and stereochemistry control to obtain important, adequately protected *β*-*O*-2-*N*-acetamido-2-deoxyglycosyl-*α*-amino acids. Special relevance shows GalNAc-glycosylated *α*-amino acids **8O-AA**, **8S-AA**, **8C-AA**, and **12c−12e**, and in the future, we will explore their behavior as mimetics of the Tn antigen by incorporation into peptides to develop cancer vaccines or diagnostic tools.

■ CONCLUSIONS

The ability to selectively functionalize biologically relevant structures such as amino acids with carbohydrates underlines the synthetic power of a synthetic methodology. In this sense,

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it is particularly noteworthy that the protocol based on the use of glycosyl bromides and the chiral dehydroalanine (Dha) electrophile **1** is amenable for the synthesis of α-*C*-linked carbohydrates to amino acids scaffolds, a synthetic challenge in glycosylation, as demonstrated in common hexoses to afford glucosyl-, galactosyl-, and mannosyl-α-amino acids **10a−10c**, with a total stereocontrol of the two stereogenic carbon generated in the photoredox process. In addition, taking into account that the synthesis of 2-*N*-acetamido-2-deoxyglycosyl-α-amino acids represents a special challenge in photoredox carbohydrate chemistry, we report here a photoredox Giese reaction based on the use of the same Dha **1** with carbohydrates bearing a carboxylic acid group that allowed to synthesize α-linked *O*-, *S*-, and *C*-2-*N*-acetamido-2-deoxyglycosyl-α-amino acids **8O-AA**, **8S-AA**, and **8C-AA**. Finally, adequately protected β-*O*-GalNAc- and β-*O*-GlcNAc-α-amino acids **12b−12e** and **14c−14d**, respectively, could be efficiently constructed, using α-selenoglycoside donors and $(PhSe)_2$ or $(PhS)_2$ as an organophotocatalyst in the presence of CBr_4 or $(CBrCl_2)_2$, respectively. In summary, the results presented here demonstrate that 2-*N*-acetamido-2-deoxyglycosyl-α-amino acid derivatives could be obtained by photoredox methods with high stereochemistry control. We believe that the broad scope, functional group tolerance, and modularity of these photoredox synthetic approaches are likely to be of great use to chemists in both academia and industry.

■ EXPERIMENTAL SECTION

General and Experimental Methods. Commercial reagents were used without further purification. Analytical thin layer chromatography (TLC) was performed on Macherey-Nagel precoated aluminum sheets with a 0.20 mm thickness of silica gel 60 with the fluorescent indicator UV254. TLC plates were visualized with UV light and by staining with a potassium permanganate solution (0.75 g $KMnO_4$, 5 g K_2CO_3, and 0.63 mL 10% NaOH in 100 mL of water) or a ninhydrin solution (1.5 g ninhydrin in 100 mL of *n*-butanol and 3.0 mL of acetic acid). Column chromatography was performed on a silica gel (230−400 mesh). ^1H and $^{13}C\{^1H\}$ NMR spectra were measured with a 300 or 400 MHz spectrometer with TMS as the internal standard. Multiplicities are quoted as singlet (s), broad singlet (br s), doublet (d), doublet of doublets (dd), triplet (t), or multiplet (m). Spectra were assigned using the COSY and HSQC experiments. The results of these experiments were processed with the MestreNova software. High-resolution electrospray mass (ESI) spectra were recorded on a microTOF spectrometer; accurate mass measurements were achieved by using sodium formate as an external reference.

General Procedure for Photoredox Giese Reactions to Obtain *α-O-*, *α-S-*, and *α-C*-Glycosyl-*α*-amino Acid Derivatives 8O, 8S, and 8C. Chiral bicyclic Dha **1** (0.1 mmol, 1.0 equiv), carboxylic acids **4O**, **4S**, or **4C** (0.12 mmol, 1.2 equiv), Cs_2CO_3 (0.15 mmol, 1.5 equiv), and 4CzIPN (0.005 mmol, 0.05 equiv) were added in sample vials. The tube was evacuated and backfilled with N_2 (three times). Then, deoxidized DMF (1 mL, final concentration 0.1 M) was added by using a syringe. The solution was then stirred at room temperature under irradiation of blue LEDs (30 W) for 16 h. Once completed, water (1 mL) was added and extracted by ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. The crude mixture was purified by column chromatography (hexane/ethyl acetate) on silica gel to afford desired products **8O**, **8S**, and **8C**.

General Procedure for the Photoredox Giese Reaction to Obtain *α-C*-Glycosyl-*α*-amino Acid Derivatives 10a−10c. Glycosyl bromide **9a−9c** (0.2 mmol), chiral bicyclic Dha **1** (0.1 mmol), 4ClCzIPN (0.005 mmol), and K_3PO_4 (0.4 mmol) were added to sample vials. The vial was evacuated and backfilled with N_2. Then, anhydrous dichloroethane (0.5 mL) and DMSO (0.5 mL) were added using a syringe, and the solution was degassed. After degassing, $(TMS)_3SiOH$ (0.15 mmol) was added through a syringe. The solution was then stirred at room temperature under irradiation with blue LEDs (16 W) for 16 h. Once completed, water (1 mL) was added, and the mixture was extracted with ethyl acetate. The combined organic layer was dried over anhydrous Na_2SO_4, and the solvent was removed under vacuum. The crude mixture was purified by column chromatography (hexanes/ethyl acetate) on silica gel to afford the desired products **10a−10c**.

General Procedure for Photoredox *β-O*-Glycosylation of Selenoglycosides with Alcohols. A dried 5 mL Pyrex reactor vial was charged with the α-*Se*-glycosyl donor **11** or **13** (0.074 mmol, 1 equiv), $(PhSe)_2$ (0.0074 mmol, 0.1 equiv), CBr_4 (0.081 mmol, 1.1 equiv), 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) (0.088 mmol, 1.2 equiv), the glycosyl acceptor (0.22 mmol, 3 equiv), and 1 mL of dry CH_2Cl_2 as a solvent under a nitrogen atmosphere. The vial was sealed with a Teflon cap, and the reaction was stirred at room temperature under irradiation with 30 W blue LEDs. Reaction progress was monitored by TLC. After consumption of the glycosyl donor (16−72 h), the crude products were concentrated and then purified by silica gel chromatography (ethyl acetate/hexanes, 7:3) to obtain β-*O*-glycosyl derivatives **12a−12e** and **14c** and **14d**.

Note: $(PhSe)_2$ can be replaced by $(PhS)_2$ and CBr_4 by $(CBrCl_2)_2$, and the procedure has been scaled up to 1 mmol of selenoglycoside **11** to obtain 392 mg (55%) of Fmoc-L-Ser(β-*O*-D-GalNAc)-O^{t}Bu **12c**, after purification by column chromatography.

2D NMR Experiments. Spectra were assigned using COSY and edited-HSQC experiments (blue for CH_2 and red for CH and CH_3 groups). NOESY experiments were recorded on a 400 MHz spectrometer at 298 K. The experiments were conducted by using phase-sensitive ge-2D NOESY spectra. The number of scans used was 16, and the mixing time was 800 ms.

X-ray Diffraction Analysis. X-ray diffraction data of compound **10a** were collected on a VENTURE Bruker diffractometer using Cu Kα (λ = 1.54178 Å). A colorless arrowhead single crystal was mounted on a MiTeGen support and cooled to 100(2) K with open-flow nitrogen gas. Data were collected using ω and φ scans with a narrow frames strategy. Diffracted intensities were integrated and corrected from absorption effects with SAINT[42] and SADABS[43] programs, included in the APEX4 package.[44] The crystal structure was solved and refined using SHELXS[45] and SHELXL[46] included in the Olex2 program.[47] Hydrogen atoms were observed in difference Fourier maps; however, to increase the data/parameter ratio, most of them were included in the model in calculated positions and refined with a riding model. Hydrogen atoms bound to stereogenic centers were included in the model in the observed positions and freely refined. The absolute configuration was determined based on

previously known internal references, and this assignment was confirmed using the Flack parameter.[48]

Crystal Data of ***10a***. $C_{23}H_{31}NO_{14}$; M_r = 545.49; colorless arrowhead 0.025 × 0.10 × 0.11 mm^3; monoclinic $P2_1$; a = 8.3147(3) Å, b = 7.0757(2) Å; c = 22.2102(6) Å, β = 92.107(2)°; V = 1305.79(7) $Å^3$; Z = 2; D_c = 1.387 g/cm^3; μ = 0.998 mm^{-1}; min and max. absorption correction factors: 0.5584 and 0.7538; $2\theta_{max}$ = 149.268°; 46291 reflections measured, 5348 unique; R_{int} = 0.0.0539; number of data/restraint/parameters: 5348/1/374; R_1 = 0.0330 [5084 reflections, $I > 2\sigma(I)$], $wR(F^2)$ = 0.0871 (all data); largest difference peak: 0.29 e $Å^{-3}$; Flack parameter: −0.14(10).[49]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.4c07412.

Experimental procedures, characterization data, and copies of the NMR spectra (PDF)

FAIR Data is available as Supporting Information for Publication and includes the primary NMR FID files for compounds: [**4C**, **4O**, **4O-OBn**, **4S**, **4S-tBu**, **8C**, **8O**, **8S**, **10a**, **10b**, **10b-AA**, **10c**, **10d**, **12a**, **12b**, **12c**, **12c−OH**, **12d**, **12e**, **14c**, **14d**]. See FID for Publication for additional information.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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