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ABSTRACT BOOK

Synthesis of Tn Antigen β-Mimetics by Photoredox Catalysis

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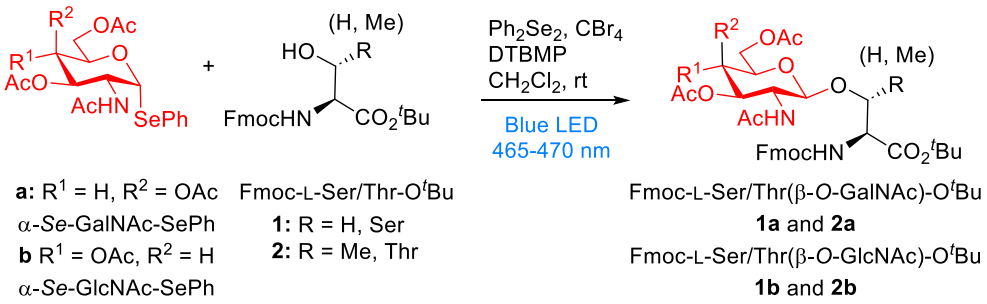
The synthesis of glycosyl α-amino acids presents a significant challenge due to the need for precise glycosidic linkages connecting carbohydrate moieties to amino acids, while maintaining stereo- and regiochemical fidelity. Classical methods relying on ionic intermediates often involve intricate synthetic procedures, particularly when dealing with 2-*N*-acetamido-2-deoxyglycosides linked to α-amino acids—a crucial class of glycoconjugates that play important biological roles. For instance, *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. 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. However, one potential drawback in using the native Tn antigen for cancer vaccine design is the instability of the glycosidic linkage to glycosidases. To overcome this problem, a plethora of structural mimetics of the Tn antigen has been used.[1] In this field, β-*O*-GalNAc-L-Ser/Thr and β-*O*-GlcNAc-L-Ser/Thr are also considered as β-mimetics of the Tn antigen. It is important to note that although different photoredox glycosylations have been published, the notoriously difficult case of 2-*N*-acetamido-2-deoxyglycosyl-α-amino acids has been largely unexplored.

In this work, the synthesis of Tn antigen β-mimetics **1a,b** and **2a,b** could be obtained efficiently by photoredox glycosylations using α-*Se*-selenoglycosides **a** and **b** as glycosyl donors and hydroxyl groups of protected amino acids Ser **1** and Thr **2** as acceptors, in the presence of diphenyldiselenide as an organophotocatalyst, tetrabromomethane and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) as a base.



a: R^1 = H, R^2 = OAc
α-*Se*-GalNAc-SePh
b R^1 = OAc, R^2 = H
α-*Se*-GlcNAc-SePh

Fmoc-L-Ser/Thr-O^{t}Bu
1: R = H, Ser
2: R = Me, Thr

Fmoc-L-Ser/Thr(β-*O*-GalNAc)-O^{t}Bu
1a and **2a**
Fmoc-L-Ser/Thr(β-*O*-GlcNAc)-O^{t}Bu
1b and **2b**

Figure 1: Structures of the different Tn antigens synthesized in this work. a) β-O-GalNAc-Thr/Ser; b) β-O-GlcNAc-Thr/Ser.

In the future, these Tn antigen mimetics will be incorporated into non-natural peptides to develop therapeutic vaccines to treat cancer or diagnostic tools.

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