Protected Tn antigen: an efficient gram-scale synthesis

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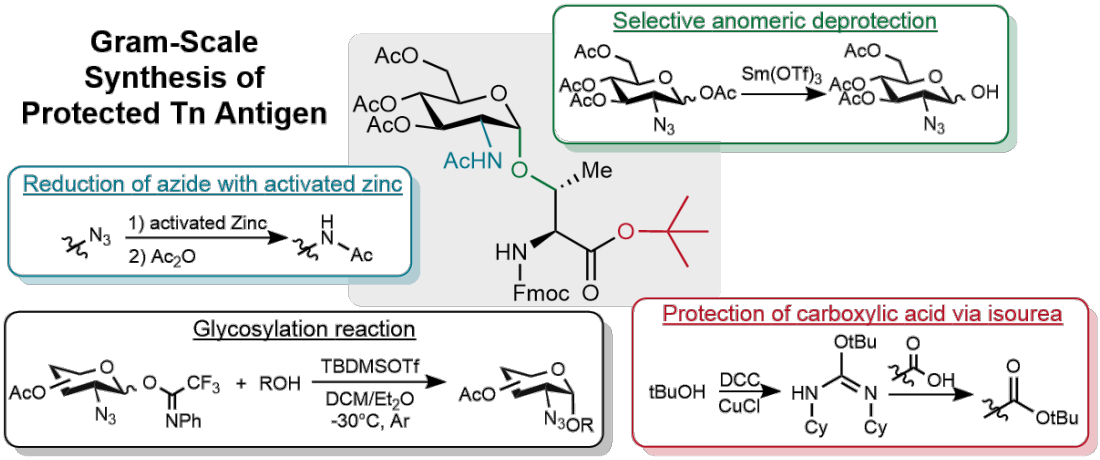
T antigens (T, Tn or sTn) were reported at the surface of numerous tumour cells and constitute an important target for cancer research. As such, an efficient method to access the molecule at a large scale is required. Although many syntheses have been reported [1,2,3], some steps fail to be reproduced or necessitate complex strategies.

Herein is proposed an efficient gram-scale synthesis of protected Tn antigen (*N*-acetyl-*O*-threonine-galactosamine), that will be introduced afterwards in a supported peptide synthesis. This seven steps synthesis utilises L-threonine and galactosamine as starting materials with an overall yield of 34%. The key glycosylation relies on coupling 2-azido-2-deoxy-galactose with the protected threonine using optimised conditions to yield the alpha anomer. Proper selection of the leaving group for the glycosylation was also undertaken to maximise the yield of this step.

Important steps were optimised for large-scale and time-efficient synthesis. Particularly, the selective protection of the carboxylic acid of threonine via an isourea was performed at a shorter reaction time (1 day) compared to previously reported methods (5 days) [3]. A replicable protocol for zinc activation was optimized to reduce the azide and add an acetyl group in a one-pot reaction. Additionally, condition screening was performed to adapt selective anomeric deprotection of the 2-azido-2-deoxy-galactosamine moiety using lanthanide triflate [4]. Overall, this strategy afforded gram-scale quantities of the protected antigen.



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Bibliographic references:

[1] S. M. Piazza, et al. (2021), New J. Chem. (45) 19224-19227
[2] J. M. Wojnar, et al. (2011), Aust. J. Chem. (64) 723–731
[3] I. Tavernaro, et al. (2015), Org. Biomol. Chem. (13) 81-97
[4] A. T. Tran, et al. (2008), Tetrahedron Lett. (49) 2163–2165