

Synthesis of Glycoconjugate Vaccines on Clustered Modes

against *Candida Albicans* Using the Novel Methodology

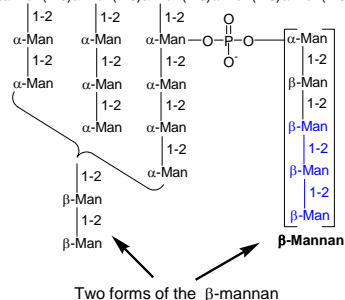
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Introduction

The cell wall phosphomannan of *Candida* species is a glycoprotein containing predominantly α -linked mannose residues. A minor β -mannan component constitutes the protective epitope of the glycoprotein and occurs in different forms linked to the α -mannan backbone via a phosphodiester bond (acid labile β -mannan) or directly via a glycosidic bond.¹ Protective monoclonal antibodies that recognize the (1 \rightarrow 2)- β -mannan are most effectively inhibited by short (1 \rightarrow 2)- β -mannose disaccharide or trisaccharide sequences.^{2,3} While simple glycoconjugates with a trisaccharide attached to tetanus toxoid are highly effective immunogens in rabbits, the same antigen is less effective in mice. In a search for a better method to present the *Candida* epitope to mice we have investigated clustering of oligosaccharide motifs. We report the synthesis of (1 \rightarrow 2)- β -mannan disaccharides clustered on a glucose core, the conjugation of these clustered epitopes to proteins and preliminary immunization data.

α -Man(1-6) α -Man(1-6) α -Man(1-6) α -Man(1-6) α -Man(1-6) α -Man(1-6)-inner core-Asn



References

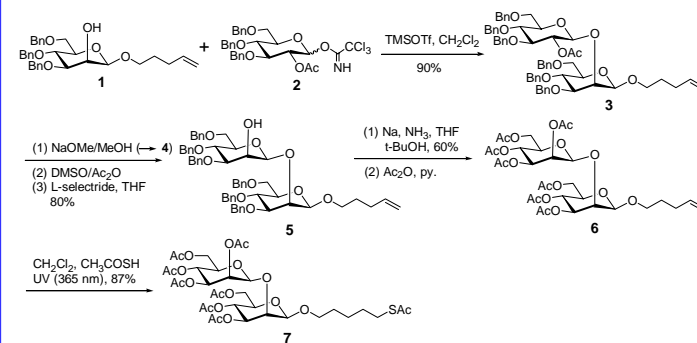
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- Nitz, M.; Ling, C. C.; Otter, A.; Cutler, J. E.; Bundle, D. R. *J. Biol. Chem.* **2002**, 277, 3440.
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Summary

Cluster **11** containing the (1 \rightarrow 2)- β -D-mannopyranan epitope of the *Candida albicans* cell wall has been synthesized and coupled to BSA or tetanus toxoid via a homobifunctional adipate linker. In Balb/c mice the glycoconjugate **12** gave an antibody response similar to those obtained with simple trisaccharide tetanus toxoid conjugates. Similar vaccination experiments are being pursued in outbred mice.

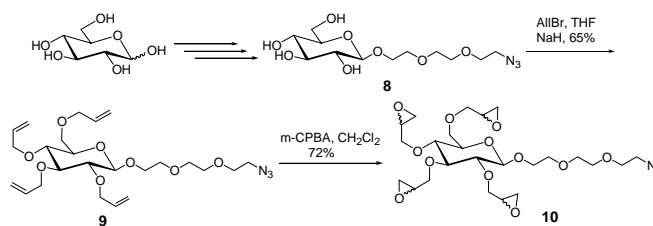
Synthesis of Building block 7

Glucosyl trichloroacetimidate donor **2** was employed to establish a β -glucopyranosyl linkage. Subsequent *Swern* oxidation and selective reduction facilitated an efficient approach to the β -mannopyranosides **5** which was transformed to compound **7** by *Birch* reaction and photochemical addition of thioacetic acid.

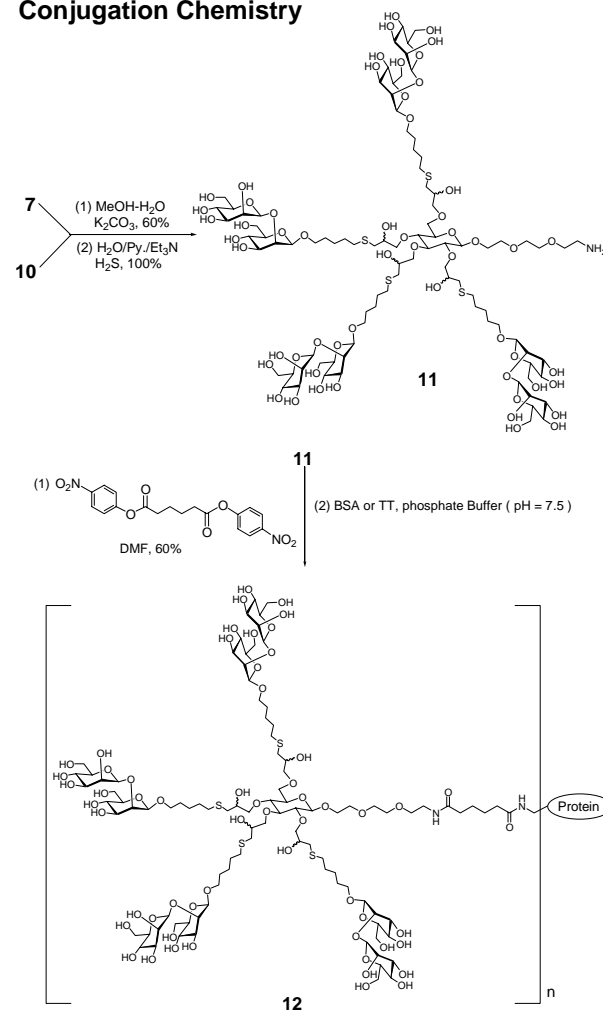


Synthesis of epoxide 10

The reaction between compound **8** and AllBr in THF with NaH afforded compound **9** in good yield. Subsequent epoxidation with *m*-CPBA furnished intermediate **10** for coupling with compound **7**.



Conjugation Chemistry



Acknowledgements

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