

Synthesis of Glycoconjugate Vaccines against *Candida albicans* Using the Novel Linker Methodology

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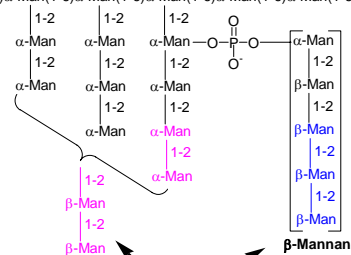
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Introduction

The cell wall phosphomannan of *Candida* species is a glycoprotein containing predominantly α -linked mannose residues. However, it is the minor β -mannan component of the phosphomannan of clinically important *Candida* strains that provides immunological protection in animal models of fungal disease and hence holds promise as a component of conjugate vaccines. This important antigen 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 Evidence from immunochemistry and solution properties of this antigen implied that (1 \rightarrow 2)- β -mannan oligomers have potential as the key epitope of conjugate vaccines.²

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



At least two forms of the β -mannan

Here, we report gram scale syntheses of the both forms of the β -mannan antigen.

References

- Shibata, N.; Fukasawa, S.; Kobayashi, H.; Tojo, M.; Yonezu, T.; Ambo, A.; Ohkubo, Y.; Suzuki, S. *Carbohydr. Res.* **1989**, 187, 239.
- Nitz, M.; Ling, C. C.; Otter, A.; Cutler, J. E.; Bundle, D. R. *J. Biol. Chem.* **2002**, 277, 3440.

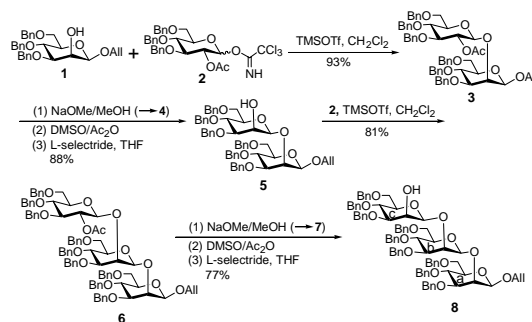
Summary

Compounds that are derivatives of the unique (1 \rightarrow 2)- β -D-mannopyranan found in the cell wall of *C. albicans* have been synthesized on a multi-gram scale employing the C2 inversion methodology. Coupling larger oligosaccharides to BSA or TT using the linear homobifunctional linker with high efficiency under very mild conditions was confirmed. Glycoconjugates **26** and **27** are being evaluated for their efficiency as anti-*C. albicans* vaccine in rabbit and mice. (see poster # 44 by Tomasz Lipinski *et al.*)

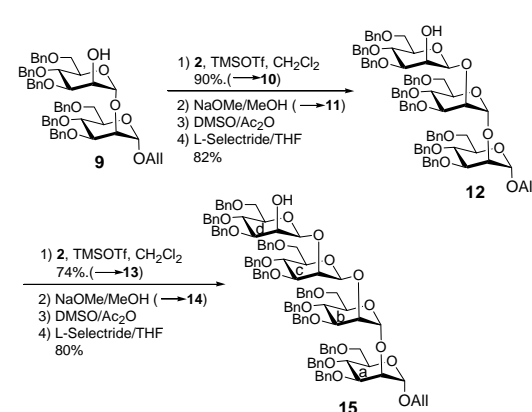
Preparation of 5, 8 and 15.

The 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**, **8** and **15** on a multi-gram scale.

Synthesis of acid labile epitope



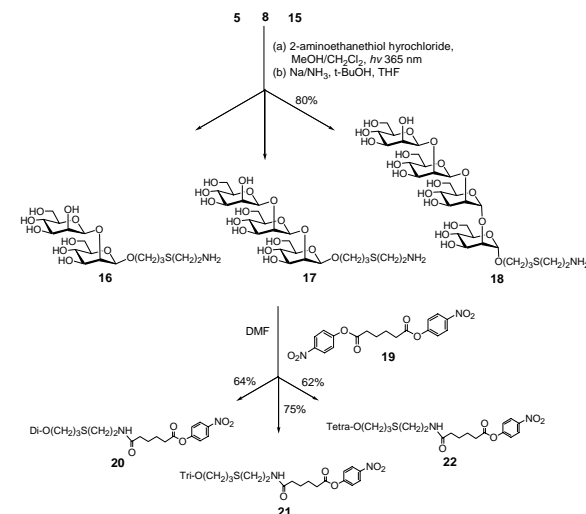
Synthesis of acid stable epitope



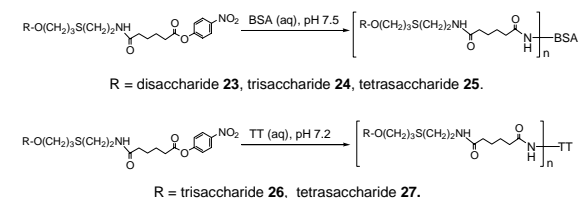
Conjugation Chemistry

Reaction of glycosides **16**, **17** and **18** with homobifunctional adipic acid p-nitrophenyl diesters in dry DMF gave the corresponding half esters in good yields, and of sufficient stability to permit chromatographic purification.

Synthesis of half esters 20, 21 and 22



Synthesis of neoglycoproteins



Acknowledgements

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