Synthesis of phosphomannan antigens found in the *Candida albicans* cell wall

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Introduction

Candida albicans is the most common etiologic agent in candidiasis, a serious infection that affects immunocompromised patients or those undergoing long-term antibiotic treatment.

The cell wall phosphomannan of *C. albicans* (Figure 1) is a promising target for the induction of immunity by development of a conjugate vaccine. It contains a unique antigen, a β1,2-mannan, that affords active protection to mice following immunization and subsequent challenge with live organisms.

We are investigating the use of short oligosaccharides conjugated to suitable carriers [1,2] as viable conjugate vaccines since oligosaccharides of this size are sufficiently well organized to induce mannan specific antibodies. The ordered solution three-dimensional structure determined for oligo β1,2-mannan shows that the oligosaccharide approximates a helix with three hexose residues per turn (Figure 2). This helical conformation has been observed in solution by NOE NMR experiments and the trisaccharide segment corresponds with the most potent trisaccharide inhibitor [3].

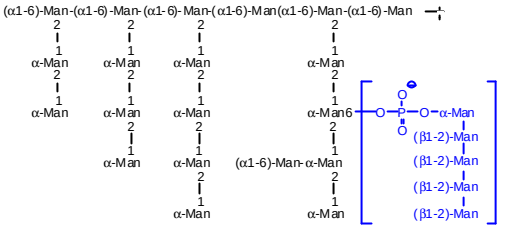


Figure 1 *Candida albicans* phosphomannan (side chain lengths vary)

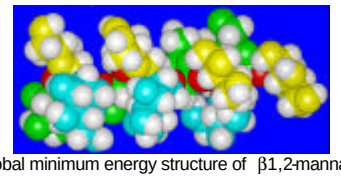


Figure 2 Global minimum energy structure of β1,2-mannan

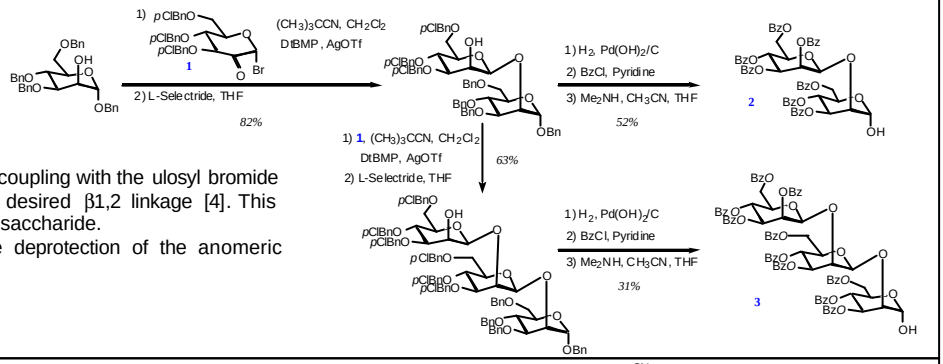
Synthesis

The phosphodiester bridge between the β-mannan and the α-mannan could be an essential element of a vaccine construct. Here we report our efforts towards the chemical synthesis of di- and trisaccharide epitopes attached via a phosphodiester linkage that mimics a portion of the phosphomannan.

β1,2-mannans

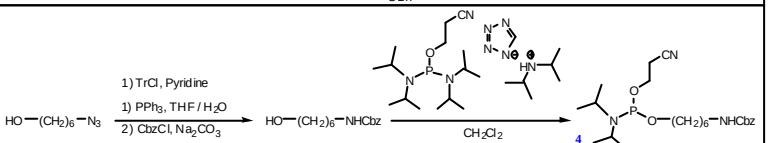
The glycosylation procedure is based on the coupling with the ulosyl bromide **1**, followed by a selective reduction to give the desired β1,2 linkage [4]. This process was repeated to give the corresponding trisaccharide.

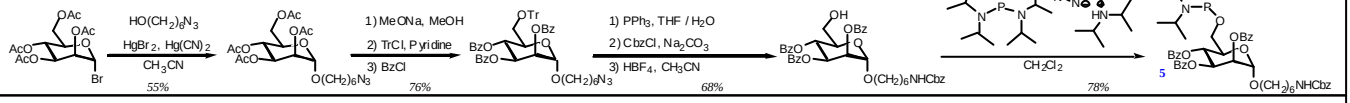
Protecting group exchange and a selective deprotection of the anomeric position gave access to the hemiacetals **2** and **3**.



Phosphoramidite synthesis

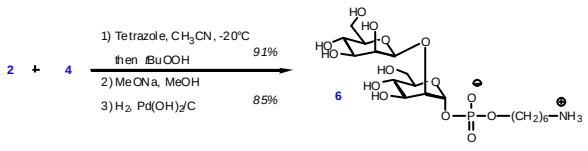
Phosphoramidites **4** and **5** were obtained using standard conditions. Benzyl carbamate was found to be a suitable protecting group because of its stability and its ease of removal under hydrogenation conditions.

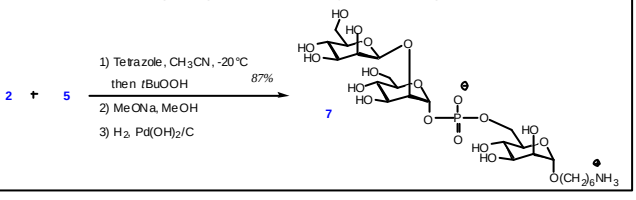




Coupling procedures

Tetrazole catalysis followed by oxidation provided the desired phosphodiester bridges on compounds **6** and **7**.





Conclusion and perspectives

We have demonstrated the efficiency of the phosphoramidite coupling for obtaining phosphodiester linkages under mild reaction conditions at the reducing end of a β1,2-mannan motif.

The synthesis remains to be optimized. In addition, coupling of trisaccharide hemiacetal **3** to phosphoramidites **4** and **5** will be performed.

Following deprotection of the carbamate, the free amines will be used to couple the synthesized antigens to a protein carrier to generate conjugate vaccines.

Acknowledgments

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References

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