Synthesis of Di- and Trisaccharide Congeners of the (1→2)-β-Mannan from the Cell-wall Phosphomannan of Candida albicans.

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Introduction
Candida albicans is one of the most common hospital-acquired opportunistic pathogens1 and is particularly serious for immune-compromised patients or those undergoing long-term antibiotic treatment (Figure 1a,b). Anti-fungal drugs are only partially effective against this pathogen and immunotherapeutic approaches are currently under consideration. An especially attractive vaccine candidate is the unique (1→2)-β-mannan of the cell wall phosphomannan complex (Figure 1c).

Scheme 1: The synthetic strategy relies on the use of thio-glycoside donors (1, 2a and 2b) with neighbouring participation to afford the β-glucosylation product with β-mannoside acceptors (3a, 3b and 4).

Scheme 2: Thio-glucoside donors (1, 2a or 2b) were reacted with β-mannose acceptors (3a, 3b or 4) to yield the β-glucoside intermediates with high selectivity. Deprotection under Zemplén conditions followed by oxidation-reduction afforded the (1→2)-β-mannoside product.

Scheme 3: The strategy for synthesis of the (1→2)-β-mannan congeners relies on the regioselective deprotection of intermediates (7a,b and 8a,b) to access each hydroxyl group. Methylation or Barton deoxygenation will provide the mono-O-methyl or mono-deoxy congeners respectively.

Summary
The synthesis of disaccharides 7a and 8a has been secured. Mono-deoxy congener 9a has been synthesized and current efforts are focused on the remaining congeners. The acceptor 5 allows for preparation of trisaccharide congeners modified at the non-reducing residue. Regioselective protection and deprotection allows for ready access to prepare each mono-deoxy or mono-O-methyl congener.

Inhibition data from ELISA will be collected when the syntheses of these compounds are completed. The inhibitory activities of these compounds will be used to define the size and topology of the epitope’s contact surface with the binding sites of the two protective monoclonal antibodies. The epitope binding profile for trisaccharide 6 with these antibodies will also be determined by saturation transfer difference NMR (STD-NMR).

Acknowledgements
Financial support for this work was provided by research grants from the National Science and Engineering Research Council of Canada (NSERC), the University of Alberta and the Alberta Ingenuity Centre for Carbohydrate Science (AICCS).

References